Harikesh Bahadur Singh
Chetan Keswani · Surya Pratap Singh
Editors

Intellectual Property Issues in Microbiology

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ISBN 978-981-13-7465-4 ISBN 978-981-13-7466-1 (eBook)
https://doi.org/10.1007/978-981-13-7466-1

This Springer imprint is published by the registered company Springer Nature Singapore Pte Ltd.
The registered company address is: 152 Beach Road, #21-01/04 Gateway East, Singapore 189721, Singapore

Foreword

सत्यमेव जयते
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The extremely fast technological progress *in the field of microbiology* has brought about new legislative and judicial attempts to restructure the global regulatory regime especially with regard to intellectual property rights, trying to balance the interests of both rights-holders and consumers. The success of the microbial-biotechnology industry *was not achieved spontaneously*. On the contrary, it *was the result of several influencing* and *favourable government policies* toward the sector Debates and concerns about the need to regulate the disruptive potential of biological manipulation were apparent almost from the moment when genetic engineering became feasible in the 1970. *The emergence of all these concerns has also* shed light on the problem of how to regulate the use, access, distribution and appropriation of essential public knowledge assets in the life sciences.

The proposed book focuses on the integrated approach for sustained innovation in various areas of microbiology. The outlook of this book is based to a great extent on industrial and socio-legal implications of IPR in microbiological advances. The book takes a comprehensive look not only on the implications of IPR in 'omics based research' but on what are the ethical and intellectual standards and how these can be developed for sustained innovation. I congratulate the editors for synchronizing with global authorities on the subject to underline the upcoming challenges and present most viable options for translating commercially viable ideas into easily affordable products and technologies.

New Delhi
August 7, 2018

[Girish Sahni]

Preface

The current era of incredible innovations toward the zeal to chase the heights of development has made microbial biotechnology one of the most powerful tools to accomplish the tasks of incremental prosperity for human welfare and sustainable development. The development of microbiology-based industries in any given country is shaped by the characteristics of technology, particularly its close relation to scientific knowledge, and by country-specific factors, the level and nature of the scientific knowledge base, the institutional setup, and the role assumed by the government, which influence the country's ability to exploit the new opportunities and appropriate the respective results.

This volume focuses on the integrated approach for sustained innovation in various areas of microbiology. The outlook of this book is based, to a great extent, on industrial and socio-legal implications of IPR in microbiological advances. The book takes a comprehensive look not only on the implications of IPR in omics-based research but also on the ethical and intellectual standards and how these can be developed for sustained innovation. This book attempts to collate and organize information on current attitudes and policies in several emerging areas of microbial biotechnology.

Adopting a unique approach, this book integrates science and business for an inside view on the microbiology industry. Peering behind the scenes, it provides a thorough analysis of the foundations of the present-day industry for students and professionals alike.

Varanasi, Uttar Pradesh, India

Harikesh Bahadur Singh
Chetan Keswani
Surya Pratap Singh

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Part I

Recent Interventions of Intellectual Property Rights in Microbiology

Patent-Eligible Subject Matter in the United States: An Evolving Landscape

1

Michael S. Mireles

Abstract

The scope of patent-eligible subject matter has been evolving since the early 1980s in the United States. The US Supreme Court has attempted to restrict the doctrine in recent years; however the US Court of Appeals for the Federal Circuit has reinterpreted the Supreme Court case law to arguably cause confusion in the doctrine. The US Patent and Trademark Office attempted to clarify the doctrine, but some of the cases may be irreconcilable. Notably, interested groups are attempting to change the doctrine to return to a more expansive time. The doctrine lacks clarity and will likely continue to evolve. This paper explores the evolution of the patent-eligible subject matter doctrine, especially in the biotechnology field.

Keywords

USPTO · Biotechnology patents · Patent-eligible subject matter · Federal circuit

1.1 Introduction

This article examines the ever changing scope of the patent-eligible subject matter doctrine in the United States. In particular, this doctrine is examined in the general context of all technological fields with particular emphasis on biotechnology. The general premise of the article is that the doctrine will continue to evolve (because it has to) and is very much a moving target. Indeed, even the current state of the doctrine has been characterized as a "quagmire."[1]The doctrine clearly fails to provide

[1] See John M. Golden, *Flook Says One Thing, Diehr Says Another: A Need for Housecleaning in the Law of Patentable Subject Matter*, 82 Geo. Wash. L. Rev. 1765, 1767 (2014).

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H. B. Singh et al. (eds.), *Intellectual Property Issues in Microbiology*,
https://doi.org/10.1007/978-981-13-7466-1_1

certain boundaries and perhaps operates to discourage investment in some technological fields in the United States.

Patent rights are provided to incentivize invention in the United States. Indeed, the US Constitution essentially provides that exclusive rights in the form of patents are provided for limited times to inventors to promote the progress of the useful arts. While the incentive to invent theory is an important theory underlying US patent rights, the incentive to commercialize theory and incentive to disclose theory also underlie the grant of patent rights. The incentive to commercialize theory provides that patent rights provide an ex post incentive to bring an invention to market, for example, by paying for the costs to move a pharmaceutical through clinical trials. The incentive to disclose theory provides that patent rights give an incentive to disclose an invention; otherwise an inventor may decide to keep an invention secret and possibly exploit it indefinitely.

Notably, patent rights do not arise automatically, but must be granted by the US Patent and Trademark Office (USPTO). To receive a patent, several requirements must be met: (1) patent-eligible subject matter, (2) novelty, (3) nonobviousness, (4) utility, and (5) disclosure and claim requirements. This article reviews the patent eligibility requirement. However, before reviewing the eligibility requirement, there is a historical context that must be discussed, including the Bayh-Dole Act.

In the United States, there was a massive increase in patenting and licensing since the early 1980s. There are arguably several causes of this rise in patenting and licensing, particularly in the field of biotechnology. First, the Congress passed the Bayh-Dole Act in 1980 which allowed nonprofits, including universities, to take title to government-funded invention.[2] This arguably placed universities and other nonprofits in the position to create technology transfer offices dedicated to ensuring that university-created and government-funded inventions were disclosed, possibly patented, and then licensed for the benefit of the university.[3] The primary justification for the Bayh-Dole Act is the ex post commercialization theory. The Bayh-Dole Act sets the stage for additional patenting and licensing by increasing the number of entities involved in the endeavor. Second, the US Supreme Court issued the *Diamond v. Chakrabarty* decision which allowed the patenting of a man-made microorganism.[4] This decision pushed the envelope on what could be patented and included the citation of the famous Congressional language: "anything under the sun made by man" is patentable.[5] Third, the US Court of Appeals for the Federal Circuit (Federal Circuit) was formed. This Court was formed to address forum shopping and provide a consistent and stable patent law. Some criticize or laud the Court for expressing a pro-patent bent. Fourth, the Federal Circuit issued the *In re Brana* decision which modified patent utility law allowing for patenting closer to the laboratory bench and further from the marketplace. Finally, science in the biotechnology field was advancing relatively rapidly. In the early 1980s, Cohen and Boyer's revolutionary patents

[2] 35 USCS § 200.

[3] *Id.*

[4] *Diamond v. Chakrabarty*, 447 U.S. 303, 309 (1980).

[5] *Id.*

on gene splicing were issued by the USPTO.[6] These patents are often credited with providing the basis for the biotechnology industry.

These five influences arguably led the way to an increase in patenting and licensing in the United States. And, that patenting and licensing has continued to increase by universities since the 1980s, even during years when the US Supreme Court has attempted to curb patent-eligible subject matter doctrine. In several cases, including *In re Bilski*, *Mayo v. Prometheus*, *Alice Corp. v. CLS Bank*, and *Association for Molecular Pathology v. Myriad Genetics*, the US Supreme Court has restricted patent-eligible subject matter. Notably, *Mayo* and *Myriad* directly deal with medical-related and biotechnology patents. Since the issuance of those decisions, the US Court of Appeals for the Federal Circuit has pushed back with a number of decisions finding patent eligibility by clarifying the *Mayo/Alice* test. US District Courts have struggled with applying *Mayo/Alice* in the context of the Federal Circuit decisions interpreting it. The USPTO has also attempted to provide guidance to patent seekers by releasing numerous documents and resources intended to help navigate the new case law. Despite the USPTO's efforts, several prominent organizations concerned with intellectual property in the United States have argued that the Congress should legislatively overrule the Supreme Court's recent patent-eligible subject matter jurisprudence because it has led to arguably inconsistent results.

1.2 Patent-Eligible Subject Matter Decisions in the United States

This section discusses the cases developing to the broadening of the patent eligibility requirement. This section also analyzes how patent eligibility has narrowed through the case law and the USPTO approach to patent-eligible subject matter and discusses the path forward on eligibility.

Most, if not all, patent eligibility cases start with analyzing Section 101 of the Patent Act. That section provides:

> Whoever invents or discovers any new and useful process, machine, manufacture, or composition of matter, or any new and useful improvement thereof, may obtain a patent thereof, subject to the conditions and requirements of this title.[7]

As discussed by numerous US Supreme Court cases, the language of the Patent Act in Section 101 is very broadly worded. The terms "process," "machine," "manufacture," and "composition of matter" are very broad.[8] Indeed, it is hard to imagine something that is not either a process or a composition of matter. Additionally, the statute also includes patent-eligible subject matter to include "improvements" of the

[6] See Rajendra K. Bera, *The Story of the Cohen-Boyer Patents*, 96 Current Science 760, 760 (March 25, 2009).

[7] 35 USC § 101.

[8] *Id.*

prior categories. To emphasize the breadth of the categories, the statute qualifies those categories with the term "any." Additionally, the US Supreme Court has repeatedly pointed to legislative history stating that "anything under the sun made by man" is patentable, although the full quote of that language may not indicate an intent that is quite so broad.[9]

Section 101 patent eligibility categories are limited by the terms "new" and "useful," although those are often viewed as separate limitations on patentability, novelty (along with other statutory provisions) and utility, which are dealt with in other sections, respectively.[10] The main limitations to these categories have been judicial-made exceptions: laws of nature, natural phenomena/products of nature, and abstract ideas.[11] Claims on those categories are generally not patentable. The common examples cited by courts include "a new mineral discovered in the earth or a new plant found in the wild is not patentable subject matter.[12] Likewise, Einstein could not patent his celebrated $E=mc^2$; nor could Newton have patented the law of gravity." Importantly, courts have not clearly distinguished these categories from one another.[13] And, there is a struggle to define exactly what constitutes an abstract idea.[14]

Part of a concern with patenting these prohibited categories includes thwarting the purpose of patent law stated in the US Constitution: promoting the progress of the arts. Those concepts are "basic tools of scientific and technological work."

1.2.1 US Supreme Court and Federal Circuit Broadening Eligibility

There are several patent eligibility decisions which signaled broadening patentable subject matter. Indeed, these decisions added some confusion to the scope of preexisting patent-eligible subject matter.[15] The two primary decisions from the US Supreme Court include *Diamond v. Chakrabarty* and *Diamond v. Diehr*. Importantly, the case often contrasted with *Diamond v. Chakrabarty* is the *Funk Brothers* deci-

[9] *Bilkski v. Kappos*, 561 U.S. 593, 642–643 (2010).

[10] *Id*.

[11] See *infra*.

[12] See *infra*.

[13] See Alan L. Durham, *Two Models of Unpatentable Subject Matter*, 31 Santa Clara Comp. & High Tech. L.J. 251, 261–264 (2014–2015) ("The discussion typically begins with a list of three types of unpatentable subject matter – natural laws, natural phenomena, and abstract ideas – and by the end, if a patent is denied, it is not always clear which forbidden category has been adopted").

[14] See Kristen Osenga, Debugging Software's Schemas, 82 Geo. Wash. L. Rev. 1832, 1839–1840 (2014) (quoting Judge Richard Linn's observations concerning "the abstractness of the 'abstract ideas' test to patent eligibility").

[15] See Jeffrey A. Lefstin, *The Three Faces of Prometheus: A Post-Alice Jurisprudence of Abstractions*, 16 N.C. J.L. & Tech. 647, 656 (2015) ("Even as each new case has recast the test for patent eligibility, as well as its underlying rationales, the Court has maintained the pretense that all its historical and modern subject-matter cases are coherent with each other").

sion. The two cases are used in the biotechnology space to define what falls within the scope of the product of nature exception to general patent eligibility. There are also several Federal Circuit cases confirming broad patent-eligible subject matter, such as *State Street Bank and Trust Co. v. Signature Financial Group, Inc.*, and *AT&T v. Excel Communications*, which followed Chakrabarty and Diehr.

The Supreme Court issued the *Diamond v. Chakrabarty* case in 1980, which indicated that patent-eligible subject matter is very broad. In that decision, the Supreme Court held that a living man-made microorganism is patent-eligible subject.[16] The patent was directed to a microorganism that "is capable of breaking down multiple components of crude oil."[17] Apparently, a microorganism with this characteristic did not exist in nature. In analyzing the issue, the Supreme Court focused on the statutory language concerning "composition of matter" or "manufacture."[18] The Supreme Court noted the broad language of the categories. For example, manufacture is defined as "the production of articles for use from raw or prepared materials by giving to these materials new forms, qualities, properties, or combinations, whether by hand-labor or by machinery."[19] Composition of matter is defined as "all compositions of two or more substances and … all composite articles, whether they be the result of chemical union, or of mechanical mixture, or whether they be gases, fluids, powders or solids."[20] The Supreme Court apparently also considered legislative history indicating an "expansive" consideration of what is patent-eligible subject matter.[21] In examining the exceptions to patentability, the Supreme Court noted that the microorganism is clearly patent-eligible subject matter—it is clearly not something that is found in nature.[22]

The Supreme Court distinguished the *Funk Brothers* case which held that discovering that certain strains of bacteria did not mutually inhibit the nitrogen fixing of various legumes strains was naturally occurring and thus not patentable.[23] Those particular strains were not mutually inhibitive, and all that the patentee did was discover that fact. The act of mixing those strains together to treat various legume strains did not result in a patent-eligible invention.[24] The invention in *Chakrabarty* did not involve a discovery of something already existing in nature, but was the result of human intervention. The Supreme Court stated: "Here, by contrast, the patentee has produced a new bacterium with markedly different characteristics from any found in nature and one having the potential for significant utility."[25] Importantly, future courts and the USPTO have focused on the "markedly different characteris-

[16] *Chakrabarty*, 447 U.S. at 309.

[17] *Id.* at 305.

[18] *Id.* at 307.

[19] *Id*.

[20] *Id*.

[21] *Id.* at 308.

[22] *Id.* at 309.

[23] *Id.* at 310.

[24] *Id.*

[25] *Id.*

tics" language in examining whether a particular invention is naturally occurring or a product of nature.

The Supreme Court further rejected arguments based on the living status of the microorganisms. The Court decided that the Congress through passage of various acts concerning plants, the Plant Patent Act and the Plant Variety Protection Act, did not have an intention to limit Section 101 to nonliving matter.[26] Additionally, the Supreme Court discarded an argument essentially that the Congress did not consider the patentability of living matter when passing Section 101 and that the Court should "proceed cautiously when … asked to extend patent rights into areas wholly unforeseen by Congress."[27] The Supreme Court rejected the judicial restraint argument as basically abdicating the Court's responsibility to "say what the law is."[28] This decision is often credited as one of the foundational building blocks of the biotechnology industry in the United States.

Also, in 1981, the Supreme Court issued the decision in *Diamond v. Diehr*. The Supreme Court in that case held that a process including a mathematical algorithm and a programmed digital computer was patent-eligible subject matter and did not fall within the exception to patentability concerning abstract ideas.[29] The patent was directed to solving the problem of inaccurate cure times for rubber molded in a press. Apparently, it was difficult to accurately know when to open a press to extract molded cured rubber. If removed too early or late, the molded rubber exhibited undesired characteristics. The problematic variable was the unknown temperature in the press. The patent solved the problem by using a mathematical equation and certain inputs with a computer to calculate the exact optimal time for opening the press. This also apparently involved a sensor in the press to gauge temperature.[30]

The Supreme Court examined the language of Section 101 and focused on the definition of "process."[31] The Court stated that a "process is a mode of treatment of certain materials to produce a given result. It is an act, or a series of acts, performed upon the subject-matter to be transformed and reduced to a different state or thing."[32] Notably, the Court further quoted language from a prior case stating, "Transformation and reduction of an article 'to a different state or thing' is the clue to the patentability of a process claim that does not include particular machines."[33] The Court noted that this process was clearly patentable. It was an "industrial" process that historically has been patentable. Indeed, there are multiple steps which resulted in the "transformation of raw, uncured synthetic rubber" into cured rubber.[34]

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[26] *Id.* at 313.

[27] *Id.* at 314–315.

[28] *Id.* at 315.

[29] *Diamond v. Diehr*, 450 U.S. 175 (1981).

[30] *Diehr*, 450 U.S. at 177–178.

[31] *Id.*

[32] *Id.* at 183.

[33] *Id.*

[34] *Id.* at 184.

The Court noted that the invention was patentable even though the claim included a mathematical algorithm and a programmed computer.[35] The Court arguably limited prior case law by stating that nothing in those cases essentially meant that any computer-implemented invention could not be patentable because of the presence of a computer. The Court further essentially indicated that the claimed invention did not foreclose the use of the algorithm—the preemption argument. The patent is directed to the claimed invention as a series of steps using the algorithm.[36] However, it is unclear what else this particular formula could be used for except in connection with these particular steps. Importantly, the Court stated that a patent directed to cover the algorithm in the "abstract" is unpatentable subject matter.[37] The Court also warned against insignificant post-solution activity in claims as well as noting that "attempting to limit the use of the formula to a particular technological environment" will not carry patentability.[38]

After these two decisions, the Federal Circuit moved to broaden eligibility. In perhaps the high-water mark of broad patent eligibility, Judge Giles Rich authored the *State Street Bank and Trust Co. v. Signature Financial Group, Inc.*, decision.[39] In that case the Federal Circuit determined that claims directed to a data processing system including pooling of mutual funds to lessen costs and taxes that is implemented through a computer calculating various amounts relevant to the pool.[40] In examining the patentability of the claim in light of the abstract idea exception, the Federal Circuit stated:

> We hold that the transformation of data, representing discrete dollar amounts, by a machine through a series of mathematical calculations into a final share price, constitutes a practical application of a mathematical algorithm, formula, or calculation, because it produces "a useful concrete and tangible result"—a final share price momentarily fixed for recording and reporting purposes and even accepted and relied upon by regulatory authorities and in subsequent trades.[41]

The Federal Circuit further rejected the Freeman-Walter-Abele test which was used to determine if an abstract idea rendered a claim patent ineligible. The Court stated that post-*Chakrabarty* and *Diehr*, the test was no longer applicable.[42] Judge Rich further stated that patent eligibility inquiries should be directed to "practical utility" and not whether the claimed invention fits within one of the statutory categories under Section 101.[43] Judge Rich also rejected the business method

[35] *Id.* at 185.

[36] *Id.* at 187.

[37] *Id.* at 191.

[38] *Id.*

[39] *State Street Bank & Trust Co. v. Signature Fin. Group*, 149 F.3d 1368, 1373 (1998).

[40] *Id.*

[41] *Id.*

[42] *Id.* at 1374.

[43] *Id.* at 1375.

exception.[44] This case was followed with approval by *AT&T v. Excel Communications*, which involved a process claim. These cases arguably led to a substantial increase in the patenting of business methods and software. Again, this is the high-water mark of patent-eligible subject matter.

1.2.2 US Supreme Court Narrowing Eligibility, Federal Circuit Response, and USPTO Guidance

In reversing the broadening patent eligibility trend, the US Supreme Court has issued numerous important decisions narrowing the scope of patentable subject matter. The Federal Circuit has issued decisions interpreting the US Supreme Court's decisions and, in some decisions, arguably is responding to the US Supreme Court by pushing for broader eligibility again. The USPTO has tried to respond to the US Supreme Court and the Federal Circuit by producing materials designed to aid applicants for patents. Importantly, the US Supreme Court's majority decisions are binding on the Federal Circuit, but the Federal Circuit may interpret those decisions based on the individual facts of cases in ways that may ultimately and practically limit or expand the impact of the Supreme Court's rules. District Courts are also bound by the decisions of the US Supreme Court and the Federal Circuit. The USPTO is also bound by the decisions of the US Supreme Court and the Federal Circuit. However, the USPTO has rule-making authority in some circumstances which may receive deference from courts. Moreover, the USPTO in the past has created rules impacting patent-eligible subject matter.

1.2.2.1 US Supreme Court Narrows Eligibility

The US Supreme Court has issued numerous patent-eligible subject matter decisions which restrict patent eligibility. Professor Holman has stated that the US Supreme Court has not spent so much concentrated attention on any other patent law doctrine, particularly within such a short time frame.[45] The decisions include *In re Bilski*, *Mayo v. Prometheus*, *Alice Corp. v. CLS Bank*, and *Association for Molecular Pathology v. Myriad Genetics*. *Mayo* and *Myriad* both specifically involve patent eligibility in the biotechnology space. The decisions all involve interpretation and application of Section 101 of the Patent Act.

In re Bilski

The *In re Bilski* case is the US Supreme Court's first attempt to provide some guidance in limiting patent-eligible subject matter by defining the general contours of the inquiry and rejecting a prohibition on the patentability of business methods.[46]

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[44] *Id.* at 1375–1377.

[45] See Christopher M. Holman, *Patent Eligibility Post-Myriad: A Reinvigorated Judicial Wildcard of Uncertain Effect*, 82 Geo. Wash. L. Rev. 1796, 1799 (2014).

[46] *Bilski*, 561 U.S. at 604.

The patent in this case was directed to the concept of hedging to minimize risk.[47] The Supreme Court rejected the Federal Circuit's creation of the machine/transformation test—that patent-eligible processes must be "tied to a machine" or "transform something into a different state or article"—as the sole test for patent eligibility, and stated it may be a helpful inquiry.[48] Moreover, the Supreme Court noted that methods are patentable as provided by the statute which defines methods and does not include any such restrictions. "Section 100(b) provides that '[t]he term 'process' means process, art or method, and includes a new use of a known process, machine, manufacture, composition of matter, or material."[49] Additionally, the Congress passed a specific statutory section recognizing that business methods may be patentable.[50] Finally, the Court rejected the patentability of the concept of hedging to minimize risk as an abstract idea.[51] Hedging is a concept that has existed for many, many years and should not be patentable. Indeed, patenting it would result in preemption "in all fields and would effectively grant a monopoly over an abstract idea."[52] Justice Stevens, who authored an opinion concurring in the judgment, would have gone much farther than the majority opinion and, in part, denied patentability to business processes.[53]

Mayo Collaborative Services v. Prometheus Laboratories

In 2012, the US Supreme Court decided the *Mayo Collaborative Services v. Prometheus Laboratories* case. Importantly, that case sets forth the two prong test that dominates modern patent-eligible subject matter analysis. In that case, Justice Breyer, writing for a unanimous court, found that the claims at issue were directed to patent-ineligible subject matter and did not contain an inventive concept that added significantly more.[54] The main driving policy concern is to ensure that the patent laws promote innovation and do not act to impede it. At the heart of this concern is the danger of patenting basic principles or concepts that others may need to innovate. Thus, the Supreme Court is very concerned with whether a particular claim actually attempts to preempt all uses or applications of a particular natural law, phenomena of nature, or abstract idea.[55] This concern further includes not tying up future uses that may be developed, "such as refined treatment recommendations."[56] The approach in this case, which looks to inventive concept at the patent-eligible subject matter stage, is critiqued for several reasons. Some argue that Section 103 concerning obviousness embodies this analysis and that obviousness provides a bet-

[47] *Id.*

[48] *Id.*

[49] *Id.* at 603.

[50] *Id.* at 607.

[51] *Id.* at 611.

[52] *Id.* at 612.

[53] *Id.*

[54] *Mayo Collaborative Services v. Prometheus Labs, Inc.*, 566 U.S. 66, 73 (2012).

[55] *Id.*

[56] *Id.* at 87.

ter policy lever to delineate what should be protectable by patents than patent-eligible subject matter.[57] This is particularly true because most cutting-edge technology may not be understood well and an initial patent-eligible subject matter analysis may cut against new developments. At the same time, fundamental developments in new technologies may be tied up by early patenting, and prior art for new and certain technologies may be hard to come by to determine nonobviousness. The latter was a supposed problem with software.

The patent in *Mayo Collaborative Services* is directed to a method to detect the level of metabolites in a person's blood to inform the amount of thiopurine drugs to be administered to the patient.[58] The patented process essentially solved the problem of a proper dosage of thiopurine drugs because each person metabolizes the drug differently.[59] A dosage for one person is not sufficient to provide a therapeutic effect and for another person may cause harmful side effects.[60] The patent claim stated:

> 1. A method of optimizing therapeutic efficacy for treatment of an immune-mediated gastrointestinal disorder, comprising:
>
> (a) administering a drug providing 6-thioguanine to a subject having said immune-mediated gastrointestinal disorder; and
>
> (b) determining the level of 6-thioguanine in said subject having said immune-mediated gastrointestinal disorder,
>
> wherein the level of 6-thioguanine less than about 230 pmol per 8x10 red blood cells indicates a need to increase the amount of said drug subsequently administered to said subject and
>
> wherein the level of 6-thioguanine greater than about 400 pmol per 8x10 red blood cells indicates a need to decrease the amount of said drug subsequently administered to said subject.[61]

In analyzing if the patent covered patent-eligible subject matter, the US Supreme Court examined whether the claim "set forth" a law of nature.[62] The US Supreme Court first characterized the claim as using "relationships between concentrations of certain metabolites in the blood and [noting] the likelihood that a dosage of a thiopurine drug will prove ineffective or cause harm." The Court pointed to the specific "if then" nature of the claim and stated that this "relation" is a natural process when thiopurine is metabolized by a person.[63] This is true despite the fact that a human

[57] N. Scott Pierce provides a historical analysis concerning similar tests concerning preemption that he argues were legislatively disposed of by the passage of Section 103. See *Patent Eligibility As a Function of New Use, Aggregation, and Preemption Through Application of Principle*, 23 Rich. J.L. & Tech. 1, (2017).

[58] *Mayo*, 566 U.S. at 74–75.

[59] *Id*.

[60] *Id*.

[61] *Id*.

[62] *Id.* at 77.

[63] *Id.*

must administer the drug. This could "involve both natural laws and phenomena."[64] Notably, this has evolved into the first step of the so-called Mayo/Alice test. Numerous courts have applied the test as a so-called "gist" of the claim test. Basically, courts may attempt to abstract away from the claim language to derive the "gist" or basic idea behind the claim. Once that "gist" was obtained, the courts would move to the second prong of the analysis. However, as discussed infra, the US Court of Appeals for the Federal Circuit has modified and moved away from a "gist"-type analysis. This likely renders more claims patentable than with a "gist"-type test. Moreover, the scope of what is a natural law and phenomena are anything but clear.[65]

The US Supreme Court then moved to the second part of its analysis. It examined whether there are "additional steps" in the claims to make this a patent-eligible invention.[66] The additional steps include the administering, determining, and wherein step. The Supreme Court noted that these steps are not "themselves natural laws."[67] First, "the 'administering' step simply refers to the" doctors who provide this type of drug, which was well-known. Notably, the Supreme Court cited precedent for the principle that "the prohibition against patenting abstract ideas 'cannot be circumvented by attempting to limit the use of the formula to a particular technological environment." Second, wherein the clause directs doctors to apply the natural law. The Court provides the following example: "rather like Einstein telling linear accelerator operators about his basic law and then trusting them to use it where relevant."[68] Third, the determining step merely "tells doctors to engage in well-understood, routine, conventional activity previously engaged in by scientists who work in the field." Indeed, "methods for determining metabolite levels were well known in the art."[69] This was merely "conventional or obvious" "[pre]-solution activity." Finally, the Court followed precedent in analyzing the ordered combination as a whole and found that this merely "amounts to nothing significantly more than an instruction for doctors to apply the applicable laws when treating their patients."[70]

The Court distinguished *Diamond v. Diehr*, primarily by stating that the additional steps or combination of those steps in that case were not discussed as

[64] *See* Alan L. Durham, *Two Models of Unpatentable Subject Matter*, 31 Santa Clara Comp. & High Tech. L.J. 251, 284 (2014–2015).

[65] *See* Christopher M. Holman, *The Mayo Framework is Bad for Your Health*, 23 Geo. Mason L. Rev. 901, 919–922 (2016) ("[T]he interaction of the human body with a synthetic molecule, in particular a drug breakdown product, should not be considered a natural phenomenon because the interaction would never occur naturally, but instead only occurs as the result of active, purposeful human intervention").

[66] *Mayo*, 566 at 78.

[67] *Id.*

[68] *Id.*

[69] *Id.* at 79.

[70] *Id.*

"obvious," "already in use," or "purely conventional."[71] The Court further stated that the *Diehr* Court noted that the formula was not preempted by the patent claims.[72] The Supreme Court's analysis of the *Diehr* case is a slight stretch. First, the formula in *Diehr* apparently did not have many uses outside of the claimed use. Second, the steps claimed in *Diehr* seem to have been used before the patented invention. The facts of the two cases seem to be relatively close and the Supreme Court's attempt to distinguish the cases is not particularly helpful. However, the *Diehr* court in distinguishing *Parker v. Flook* noted that the "method for adjusting 'alarm limits' in the catalytic conversion of hydrocarbons" "were all 'well known,' to the point where, putting the formula to the side, there was no 'inventive concept' in the claimed application of the formula."[73] The *Diehr* court pointed to insignificant post-solution activity that fails to carry a claim. Ultimately, the Supreme Court in *Mayo* determined that the case was closer to *Flook* than *Diehr*.[74] Additionally, the Court stated that the claims at issue were not similar to "a typical patent on a new drug or a new way of using an existing drug," but "the claims do not confine their reach to particular applications of those [natural] laws."[75]

Importantly, the Supreme Court also addressed policy arguments that a restrictive test on patent eligibility, particularly for diagnostics, would "interfere with the ability of medical researchers to make valuable discoveries."[76] Notably, there were friend of the court briefs that made arguments that broad eligibility for patents was needed to encourage innovation and that narrow eligibility for patents were needed to encourage innovation as well as freedom "to provide sound medical care."[77] The Supreme Court recognized that:

> We do not find this kind of difference of opinion surprising. Patent protection is, after all, a two-edged sword. On the one hand, the promise of exclusive rights provides monetary incentives that lead to creation, invention, and discovery. On the other hand, that very exclusivity can impede the flow of information that might permit, indeed spur, invention, by, for example, raising the price of using the patented ideas once created, requiring potential users to conduct costly and time-consuming searchers of existing patents and pending patent applications, and requiring the negotiation of complex licensing arrangements.[78]

The Supreme Court avoided the issue by noting that patent-eligible standards apply across various and changing standards can have an "unforeseen" impact on different industries. However, that question is one for the Congress to consider.[79]

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[71] *Id.* at 81.

[72] *Id.*

[73] *Id.*

[74] *Id.*

[75] *Id.* at 87.

[76] *Id.*

[77] *Id.*

[78] *Id.* at 92.

[79] *Id.*

Professor Timothy R. Holbrook notes how courts and the Congress appear to treat methods differently based on industry.[80]

Professor Eisenberg criticizes the decision on several points, particularly for the lack of clarity in the first prong of the test.[81] She notes that the Supreme Court fails to explain, "why a method of treatment that makes use of patient's biological response to a drug is a patent-eligible application of natural law, while a diagnostic method that makes use of this same biological response is not."[82] Professor Jeffrey Lefstin is more direct: "[T]he notion of an 'inventive concept' was founded on a profound misreading of historical precedent."[83]

Alice Corp v. CLS Bank International

In *Alice Corp v. CLS Bank International*, the US Supreme Court applied the analysis set forth in *Mayo v. Prometheus* in determining whether computer-implemented claims involving mitigating settlement risk are patent eligible.[84] The Supreme Court characterized the *Mayo* approach as having two prongs: (1) "First, we determine whether the claims at issue are directed to one of those patent-ineligible concepts; [and (2) i[f] so, we then ask, '[w]hat else is there in the claims before us?"[85] The Supreme Court further explained that the second step involves an inquiry whether there is an inventive concept, "i.e., an element or combination of elements that is 'sufficient to ensure that the patent in practice amounts significantly more than a patent upon the [ineligible concept] itself'."[86] Moreover, the analysis is supposed to examine the claimed elements "individually" and as "an ordered combination."[87]

In applying the test, the Supreme Court determined that the claim is "directed to" an abstract idea—mitigating settlement risk with a third party or intermediated settlement.[88] This is a "fundamental economic practice long prevalent in our system of commerce."[89] Turning to the second step, the Supreme Court found that the method claims did not include an inventive concept and, that specifically, adding a "generic computer [for] implementation" of the method did not add significantly more.[90] The Court analyzed each step of the method claim as well as the combination of the steps and found that "each step [and together] does no more than require a generic

[80] Timothy R. Holbrook, *Method Patent Exceptionalism*, 102 Iowa L. Rev. 1001, 1006–1009 (2017).

[81] Rebecca S. Eisenberg, *Prometheus Rebound: Diagnostics, Nature, and Mathematical Algorithms*, 122 Yale L.J. Online 341, 343–44 (2013)

[82] *Id.* at 343.

[83] See Jeffrey A. Lefstin, *The Three Faces of Prometheus: A Post-Alice Jurisprudence of* Abstractions, 16 N.C. J.L. & Tech. 647, 656 (2015).

[84] *Alice Corp. v. CLS Bank International*, 134 S.Ct. 2347, 2352 (2014).

[85] *Id.* at 2355.

[86] *Id.*

[87] *Id.*

[88] *Id*.

[89] *Id.* at 2356.

[90] *Id.* at 2357.

computer to perform generic computer functions."[91] Professor Golden has suggested that based on language in *Alice* as well as the Supreme Court oral argument transcript in *Mayo* that, for diagnostics, "a post-diagnostic treatment step can provide a ready route to subject-matter eligibility."[92] Thus, "[i]f changing the course of patient therapy is understood to entail 'solving a technological problem,' one can then explain why Justice Kagan was apparently so confident that the addition of a detailed therapeutic step to Prometheus' claims would have rendered them patent eligible."[93]

Association for Molecular Pathology v. Myriad Genetics

In between issuance of *Mayo* and *Alice*, the Supreme Court decided *Association for Molecular Pathology v. Myriad Genetics*.[94] In that case, the US Supreme Court held that claims directed to naturally occurring isolated DNA were not patent eligible as products of nature.[95] However, the Supreme Court held that claims directed to complementary DNA, which are not naturally occurring, are patentable.[96] The claims were directed to the BRCA1 and BRCA2 genes, which can be studied to determine if a mutation is present that can raise a person's chance of developing breast cancer.[97] Claim one of the patent states: "[a]n isolated DNA coding for BRCA1 polypeptide,' which has 'the amino acid sequence set forth in SEQ ID NO:2.' SEQ ID NO:2 sets forth a list of 1,863 amino acids that the typical BRCA1 gene encodes."[98] In particular, claim one covers an isolated segment of the DNA. Moreover, the location of the DNA is the "principal contribution" by *Myriad*.

The Supreme Court, in distinguishing *Diamond v. Chakrabarty*, states that: "The location and order of the nucleotides existed in nature before Myriad found them [and] Myriad [did not] create or alter the genetic structure of DNA."[99] In *Chakrabarty*, the Supreme Court noted that human intervention created "markedly different characteristics from any found in nature"—the ability to the bacterium to consume oil.[100] In analogizing to *Funk Brothers Seed Co. v. Kalo Inoculant Co.*, the Supreme Court notes that, "[g]roundbreaking, innovative, or even brilliant discovery does not by itself satisfy the § 101 inquiry."[101] Funk Brothers patent arguably rested upon the discovery of strains of bacteria which did not mutually inhibit nitrogen fixation.[102]

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[91] *Id.* at 2359.

[92] *See* John M. Golden, *Flook Says One Thing, Diehr Says Another: An Need for Housecleaning in the Law of Patentable Subject Matter*, 82 Geo. Wash. L. Rev. 1765, 1792 (2014).

[93] *Id.* at 1792–1793.

[94] *Association of Molecular Pathology v. Myriad Genetics*, 133 S.Ct. 2107 (2013).

[95] *Id*.

[96] *Id*.

[97] *Id.* at 2112.

[98] *Id.* at 2113.

[99] *Id.* at 2116.

[100] *Id.* at 2117.

[101] *Id*.

[102] *Id*.

Those strains always were not mutually inhibiting and just discovering that they were not in combination is not patentable.[103] Similarly, simply discovering the location of the genes or gene fragments that indicate whether a person is predisposed to breast cancer existed in nature.[104] Moreover, mere isolation of the gene or fragment of a gene does not make it patentable subject matter.[105] The determination that mere isolation (and likely purification) is enough for patentability overturns the Judge Learned Hand US Court of Appeals for the Second Circuit decision in *Parke-Davis Co. v. H.K. Mulford Co.*[106]

The Supreme Court further determined that reliance on past Patent Office practices of allowing claims on isolated DNA were sufficient to make the DNA patentable.[107] The Supreme Court, however, did find that cDNA is generally "not naturally occurring" because it "results in an exon-only molecule that is not naturally occurring." Thus, "non-coding regions have been removed." The Supreme Court rejected the argument that "cDNA is not patent eligible because '[t]he nucleotide sequence of cDNA is dictated by nature, not by the lab technician."[108]

Importantly, the Supreme Court specified the situations that the decision does not cover:

> First, there are no method claims before this Court. Had Myriad created an innovative method of manipulating genes while searching for the BRCA1 and BRCA2 genes, it could possibly have sought a method patent. But the processes used by Myriad to isolate DNA were well understood by geneticists at the time of Myriad's patents "were well understood, widely used, and fairly uniform insofar as any scientist engaged in the search for a gene would likely have utilized a similar approach.
>
> Similarly, this case does not involve patents on new applications of knowledge about the BRCA1 and BRCA2 genes. Judge Bryson aptly noted that, "[a]s the first party with knowledge of the [BRCA1 and BRCA2] sequences, Myriad was in an excellent position to claim applications of that knowledge. Many of its unchallenged claims are limited to such applications.
>
> Nor do we consider the patentability of DNA in which the order of the naturally occurring nucleotides has been altered. Scientific alteration of the genetic code presents a different inquiry, and we express no opinion about the application of §101 to such endeavors. We merely hold that genes and the information they encode are not patent eligible under §101 simply because they have been isolated from the surrounding genetic material.[109]

The distinction made by the Supreme Court concerning the non-patentability of genomic DNA and cDNA has been roundly criticized by scholars.[110] Indeed, it is

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[103] *Id.* at 2117.

[104] *Id.* at 2119.

[105] *Id.*

[106] See Christopher Beauchamp, *Patenting Nature: A Problem of History*, 16 Stan. Tech. L. Rev. 257 (2013) (reviewing the "murky" history of the product of nature exception and Parke-Davis Co.).

[107] Id.

[108] *Myriad Genetics*, 133 S.Ct. at 2119.

[109] *Myriad Genetics*, 133 S.Ct. at 2119–2120.

[110] *See* Timothy R. Holbrook & Mark D. Janis, *Expressive Eligibility*, 5 U.C. Irvine L. Rev. 973,

difficult to understand this distinction, and clearly the difference cannot be an "inventive concept" passing the second prong of the *Mayo/Alice* test.[111] Indeed, Professor Burk insightfully noted, "the Supreme Court [in *Myriad*] said not a word explaining the relationship of the products of nature doctrine to the holding in [*Mayo*], decided only a year before."[112] However, the basic point from a practical perspective exists: cDNA is patentable. Thus, analogizing to cDNA lies a path to patentability.

1.2.2.2 The Federal Circuit Response

The Federal Circuit responded with several cases that attempt to explain, distinguish, and follow the *Mayo/Alice* test and the *Myriad* approach to natural products. This section will briefly review some cases concerning the *Mayo/Alice* test as applied to software for context. This section will also review and analyze in more detail cases applying *Mayo/Alice* and the *Myriad* approach in the biotechnology field.

The Federal Circuit has issued numerous opinions in the software/business methods space concerning the application of the *Mayo/Alice* test. Notably, the cases issued soon after the *Mayo/Alice* case all resulted in finding claimed inventions patent ineligible,[113] with the exception of *DDR Holdings v. Hotels.com*. Some believed that the Federal Circuit (and District Courts) was applying *Mayo/Alice* as something of a "gist" test. Basically, if you can generalize a claim to an idea, then it is relatively easy to state that it contains an abstract idea. The next inquiry is basically then whether there is an inventive concept, which is somewhat similar to an obviousness- or novelty-type analysis. There are many cases finding patent-eligible subject matter in the software space post-*Mayo/Alice*. All of those cases are not discussed in this paper. Two important Federal Circuit cases in the software context post-*Mayo/Alice* which likely include *Enfish v. Microsoft* and *Bascom Global Internet Services, Inc., v. AT&T Mobility LLC* are reviewed.

Enfish v. Microsoft

Enfish v. Microsoft is an important case because it redirects the district courts from applying the first prong of Mayo/Alice as something like a "gist" test. The Federal

981 (2015) ("The expressive perspective on eligibility might throw some light on Myriad's seemingly dubious distinction between gDNA and cDNA claims in eligibility analysis."); Dan L. Burk, the Curious Incident of the Supreme Court in Myriad Genetics, 90 Notre Dame L. Rev. 505, 507–510 (2014).

[111] *See* John M. Golden, *Flook Says One Thing, Diehr Says Another: An Need for Housecleaning in the Law of Patentable Subject Matter*, 82 Geo. Wash. L. Rev. 1765, 1767 (2014) (The Myriad court seems to indicate that, "the question of whether there is an 'inventive act' for purposes of subject matter eligibility seems largely to be code for the question of whether there is a 'marked difference' between the claimed invention and excluded subject matter, in this case a naturally occurring sequence of DNA").

[112] *See* Dan L. Burk, *The Curious Incident of the Supreme Court in Myriad Genetics*, 90 Notre Dame L. Rev. 505, 506 (2014).

[113] *See*, e.g., *Ultramercial v. Hulu*, 772 F.3d 709, 712 (2014).

Circuit specifies that the district courts must apply the first prong by examining what the claim, read in light of the specification, is directed to.[114] The Court cautions against overgeneralizing claims. This also means that just because a claim may be directed to software does not mean it is automatically patent ineligible. Specifically, the Court states: "we find it relevant to ask whether the claims are directed to an improvement in computer functionality versus being directed to an abstract idea, even at the first step of the Alice analysis."[115] The Court examines whether a computer-implemented invention improves the functioning of the computer itself.[116] This is done in the first step as opposed to later in the second step. Importantly, if the Court defines the first prong as not satisfied, then the invention is patentable.[117] Moreover, the Court rejects arguments that the claim is patent eligible because it uses a general purpose computer and does not include physical components. Importantly, the Federal Circuit noted that the invention claimed a self-referential database. Additionally, the specification included numerous examples of how the claimed invention actually improved the functioning of the computer itself.[118]

Bascom Global Internet Services, Inc., v. AT&T Mobility LLC

In *Bascom Global Internet Services v. AT&T Mobility*, the Federal Circuit focused on the second step of the Mayo/Alice test in determining that a computer-implemented invention may be patent eligible.[119] The claimed invention is designed to filter unwanted Internet content.[120] While the Federal Circuit determined that "filtering content is an abstract idea because it is a longstanding, well-known method of organizing human behavior, similar to concepts previously found in the abstract," the Court recognized that there was an inventive concept in the claims.[121] Notably, the Court recognized that the district court "looked at each limitation individually and noted that the limitations 'local client computer,' 'remote ISP server,' 'Internet computer network,' and 'controlled access network accounts' are described in the specification as well-known generic computer components" and that "as an ordered combination, are not more than routine additional steps involving generic computer components and the Internet, which interact in well-known ways to accomplish the abstract idea of filtering Internet content."[122] The Federal Circuit pointed out that "an inventive concept can be found in the nonconventional and nongeneric arrangement of known, conventional pieces." The Federal Circuit noted that the abstract idea is not preempted.[123] Further, the Court stated:

[114] *Enfish, LLC. v. Microsoft Corp.*, 822 F.3d 1327, 1335 (2016).

[115] *Id.*

[116] *Id.* at 1335–1336.

[117] *Id.* at 1336.

[118] *Id.* at 1338.

[119] *Bascom Global Internet Servs. v. AT&T Mobility LLC*, 8237 F.3d 1341 (2016).

[120] *Id.* at 1346.

[121] *Id.* at 1348.

[122] *Id.* at 1349.

[123] *Id.* at 1350.

> The inventive concept described and claimed in the '606 patent is the installation of a filtering tool at a specific location, remote from the end-users, with customizable filtering features specific to each end user. This design gives the filtering tool both the benefits of a filter on a local computer and the benefits of a filter on the ISP server. BASCOM explains that the inventive concept rests on taking advantage of the ability of at least some ISPs to identify individual accounts that communication with the ISP server, and to associate a request for Internet content with a specific individual account. … According to BASCOM, the inventive concept harnesses this technical feature of network technology in a filtering system by associating individual accounts with their own filtering scheme and elements while locating the filtering system on an ISP server. … On this limited record, this specific method of filtering Internet content cannot be said, as a matter of law, to have been conventional or generic.[124]

This case is important because it specifies how a computer-implemented invention is patentable under prong two of the Mayo/Alice test even if all additional limitations in the claims are well-known. Additionally, the case provides clues as to how to draft claims and the specification to overcome an attack on a patent at the motion to dismiss stage of a lawsuit—very early in the case.

This section reviews and analyzes several important Federal Circuit cases concerning biotechnology and patent-eligible subject matter. Notably, claims drawn to diagnostics have generally not done well since the issuance of the recent Supreme Court decisions concerning patent-eligible subject matter. However, the recent CellzDirect case provides an example of a patent-eligible method in the biotechnology space using the Mayo/Alice test.

In re BRCA1- and BRCA2-Based Hereditary Cancer Test Patent Litigation v. Ambry Genetics Corp

In *In re BRCA1- and BRCA2-Based Hereditary Cancer Test Patent Litigation v. Ambry Genetics Corp*, the Federal Circuit determined that all of the claims were patent ineligible.[125] This case is a follow-up case to the Supreme Court's Myriad decision involving claims that were not at issue in that particular case. The two sets of claims involve primers and method claims. First, Claim 16 is an example of a claim directed to a primer:

> A pair of single-stranded DNA primers for determination of a nucleotide sequence of a BRCA 1 gene by a polymerase chain reaction, the sequence of said primers being derived from human chromosome 17q, wherein the use of said primers in a polymerase chain reaction results in the synthesis of DNA having all or part of the sequence of the BRCA1 gene.[126]

The Court applied *Myriad* and determined that the claims directed to primers—strands of DNA—are "structurally identical" to those found in nature and thus are

[124] *Id.*

[125] *BRCA1-& BRCA2 – Based Hereditary Cancer Test Patient Litigation v. Ambry Genetics Corp.*, 774 F.3d 755 (2014).

[126] *Id.* at 759.

not patent-eligible subject matter.[127] Judge Dyk also rejected the argument that the primers should be patent eligible because they are synthetically created, they are not found in a person body as "single-stranded DNA," and as separated they have a different function.[128] First, Judge Dyk notes that they are "structurally identical," so that they were synthetically made does not matter under *Myriad*. Second, simply "separating [DNA] from its surrounding genetic material is not an act of invention."[129] Third, the function of the primer in the body and separated is to "form the first step in a chain reaction—a function that is performed because the primer maintains the exact same nucleotide sequence as the relevant portion of the naturally occurring sequence." Notably, Judge Dyk states: "Primers do not have such a different structure and are patent ineligible."[130]

Judge Dyk then analyzed the methods claims, which included claim 7:

> A method for screening germline of a human subject for an alteration of a BRCA1 gene which comprises comparing germline sequence of a BRCA1 gene or BRCA1 RNA from a tissue sample from said subject or a sequence of BRCA1 cDNA made from mRNA from said sample with germline sequences of wild-type BRCA1 gene, wild-type BRCA1 RNA or wild-type BRCA1 cDNA ,wherein a difference in the sequence of the BRCA1 gene, BRCA1 RNA or BRCA1 cDNA of the subject from wild-type indicates an alteration in the BRCA1 gene in said subject[,] wherein a germline nucleic acid sequence is compared by hybridizing a BRCA1 gene probe which specifically hybridizes to a BRCA1 allele to genomic DNA isolated from said sample and detecting the presence of a hybridization product wherein a presence of said product indicates the presence of said allele in the subject.[131]

Judge Dyk applied the *Mayo/Alice* test and relied on a prior decision concerning the same patents: "[The] claim thus recites nothing more than the abstract mental steps necessary to compare two different nucleotide sequences…."[132] Moreover, Judge Dyk noted that patenting such an abstract idea would potentially preempt other "basic building blocks of scientific research to be monopolized."[133] Under part two of the *Mayo/Alice* test, Judge Dyk referred to evidence that the additional steps of "1) hybridizing a BRCA gene probe and 2) detecting the presence of a hybridization product" were "well-understood, routine and conventional activity engaged in by scientists at the time of *Myriad*'s patent applications."[134] Additionally, Judge Dyk found that "claim 8 requires 1) amplification of the BRCA1 gene and 2) sequencing of the amplified nucleic acids," which were also well-known.[135]

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[127] *Id.* at 760.

[128] *Id.*

[129] *Id.*

[130] *Id.* at 761.

[131] *Id.*

[132] *Id.* at 763.

[133] *Id.* at 764.

[134] *BRCA1 & BRCA2*, 774 F.3d at 764.

[135] In another biotechnology case, *Genetic Technologies Ltd. v. Merial LLC*, the Judge Dyk determined that the diagnostic method claims at issue were patent ineligible using a relatively similar analysis. 818 F.3d 1369, 1371 (2016).

Ariosa Diagnostics, Inc., v. Sequenom, Inc.

In an important Federal Circuit decision concerning biotechnology that was closely watched by the patent bar and industry, *Ariosa Diagnostics, Inc.*, *v. Sequenom, Inc.*, the Federal Circuit decided not to rehear en banc the decision of a three-judge panel of the Federal Circuit that affirmed the district court that a patent directed to prenatal screening of "cffDNA in maternal plasma or serum."[136] An en banc decision is a review of a three-judge panel decision of the Federal Circuit by the full Federal Circuit. Researchers patented a test for determining fetal attributes.[137] The patented test used cffDNA in maternal plasma or serum.[138] That material was previously considered useless.[139] This test enabled discovering traits without "the risks of widely-used techniques that samples from the fetus or placenta."[140] The patents are methods for using the cffDNA in tests. As an example, claim 1 provides:

> 1. A method for detecting a paternally inherited nucleic acid of fetal origin performed on a maternal serum or plasma sample from a pregnant female, which method comprises amplifying a paternally inherited nucleic acid from the serum or plasma sample and detecting the presence of a paternally inherited nucleic acid of fetal origin in the sample.[141]

In applying *Alice/Mayo*, the district court determined that the claims were "directed to the natural phenomena of paternally inherited cffDNA" and that the remaining parts of the claim did not add an inventive concept.[142] In reviewing the district court's decision, the Federal Circuit three-judge panel found that cffDNA present in maternal biological material is a natural phenomenon. Moreover, the court noted that nothing was altered in the cffDNA itself.[143] This places the invention outside of the Supreme Court's *Myriad* upholding of non-naturally occurring cDNA as patent-eligible subject matter. The court further found that the method begins and ends with maternal cffDNA and paternal cffDNA, respectively, and is thus "directed to matter that is naturally occurring" under the first prong of Mayo/Alice. Importantly, the court pointed out that the disclosure in the patent supported this finding by referring to the "discovery" of cffDNA in maternal biological material as a "surprising and unexpected" finding.[144]

In examining the second part of the *Mayo/Alice* test, the Federal Circuit analogized to the *Mayo* case and found that the remaining steps, such as using PCR "to amplify and detect cffDNA [were] well-understood." Moreover, this case is similar

[136] *Ariosa Diagnostics, Inc. v. Sequenom, Inc.*, 788 F.3d 1371 (2015).
[137] *Id.*
[138] *Id.*
[139] *Id.*
[140] *Id.*
[141] *Id.* at 1373.
[142] *Id.* at 1375.
[143] *See Id.* at 1376.
[144] *Id.* at 1376.

to just stating "apply" the natural phenomena.[145] The court noted that the disclosure supports this finding because it referred to techniques used in the claims as "standard." This finding was supported by expert testimony.[146] Sequenom further argued that the natural phenomena were not preempted because there were other uses for it.[147] This argument was rejected by the Federal Circuit as not changing the analysis under *Mayo/Alice* even though the concern with preemption motivates the Supreme Court's *Mayo/Alice* test.[148]

Sequenom filed a petition for rehearing en banc at the Federal Circuit.[149] Moreover, at least 11 different organizations filed amicus curiae also known as friends of the court briefs, including the Pharmaceutical Research and Manufacturers of America, Biotechnology Industry Association, and the Intellectual Property Owners Association.[150] The Federal Circuit ultimately denied the petition for rehearing en banc.[151] There were two concurring opinions in support of the denial of the petition for rehearing en banc and one dissenting opinion. In a concurrence, Judge Dyk expressed some concern about the breadth of the Mayo/Alice test; however, he noted that any changes should come from the Supreme Court and not the Federal Circuit.[152] He also noted that his belief is that the test "is an essential ingredient of a healthy patent system allowing the invalidation of improperly issued and highly anticompetitive patents without the need for protracted and expensive litigation."[153] Importantly, he noted a concern for the life sciences industry and the application of the Mayo/Alice test:

> [T]here is a problem with *Mayo* insofar as it concludes that inventive concept cannot come from discovering something new in nature—e.g., identification of a previously unknown natural relationship or property. In my view, *Mayo* did not fully take into account the fact that an inventive concept can come not just from creative, unconventional application of a natural law, but also from the creativity and novelty of the discovery of the law itself. This is especially true in life sciences, where development of useful new diagnostic and therapeutic methods is driven by investigation of complex biological systems. I worry that method claims that apply newly discovered natural laws and phenomena in somewhat conventional ways are screened out of the *Mayo* test. In this regard I think Mayo may not be entirely consistent with the Supreme Court's decision in *Myriad*…. While the Court found ineligible *Myriad's* claims to naturally occurring gDNA sequences it suggested that "new applications of knowledge about the BRCA1 and BRCA2 genes" could generally be eligible…. *Myriad* thus appeared to recognize that an inventive concept can sometimes come

[145] *Id.* at 1377.

[146] *Ariosa Diagnostics, Inc.*, 788 F.3d at 1377.

[147] *Id.* at 1378.

[148] *Id.* at 1379.

[149] *Ariosa Diagnostics, Inc. v. Sequenom, Inc.*, 809 F.3d 1282, 1284 (2015).

[150] *Id.*

[151] *Id.*

[152] *Id.* at 1287.

[153] *Id.*

> from discovery of an unknown natural phenomenon, not just from unconventional application of a phenomenon.[154]

Judge Dyk further recognizes that a narrowly drafted claim covering an application of the law of nature without preempting the law should be patentable because the discovery is an inventive concept. Moreover, the claim would be limited by applications that were actually reduced to practice.[155] Sequenom appealed the Federal Circuit's decision to the US Supreme Court. However, the US Supreme Court denied the request to hear the appeal.

Rapid Litigation Management LTD v. CellzDirect, Inc.[156]

In one of the most important Federal Circuit cases concerning biotechnology, *Rapid Litigation Management LTD v. CellzDirect*, *Inc.*, the Federal Circuit upheld the claims covering a process for cryogenically freezing liver cells as patent eligible. In that case, the district court held that the claimed process was directed to a patent-ineligible process.[157]The process concerns a type of liver cells, hepatocytes, "useful for testing, diagnostic, and treatment purposes." Hepatocytes can be used to determine how a drug is metabolized by the liver.[158] Despite their utility, researchers are confronted with problems: useful hepatocytes "can only be obtained from liver resections or non-transplantable livers of organ donors, and their lifespan is short." One solution to the problem included cryogenically freezing liver cells.[159] However, this solution also included other problems: the process damaged cells and "the prior methods were unsuitable for preparing multi-donor hepatocyte pools." Thus, "the prevailing wisdom was that hepatocytes could be frozen only once and then had to be either used or discarded."[160]

The patentees discovered a method that allowed for freezing and thawing hepatocytes at least twice. The improved process claim includes: "(A) subjecting previously frozen and thawed cells to density gradient fractionation to separate viable cells from non-viable ones; (B) recovering the viable cells; and (C) refreezing the viable cells."[161]

The Federal Circuit emphasized the benefits provided by the invention:

> By separating out and refreezing only the viable cells, the preserved hepatocyte preparations can be thawed and used later without unacceptable loss of viability. Pooled hepatocyte preparations are also much more easily made: hepatocyte samples from single donors can

[154] *Id.* at 1289–1290.

[155] *Ariosa Diagnostics, Inc.*, 809 F.3d at 1291.

[156] *Rapid Litigation Management v. CellzDirect Inc.*, 827 F.3d 1042 (2016).

[157] *Id.* at 1044.

[158] *Id.* at 1045.

[159] *Id.*

[160] *Id.*

[161] *Id.*

> be pooled together to create a composition preparation that can be refrozen for later use. This was not possible with the prior art cryopreservation techniques.[162]

The Federal Circuit noted that the District Court determined that the claims were directed to a natural law: that hepatocytes can be frozen and reused several times. The Federal Circuit refused to discuss whether that finding was a natural law or not, but decided that an examination of the claimed invention revealed that it was "directed to a new and useful laboratory technique for preserving hepatocytes."[163] This was, according to the court, an "employ[ment of a] natural discovery to create a new and improved way of preserving hepatocyte cells for later use."[164] The Federal Circuit distinguished other cases that involved the claiming of a natural law that "amounted to nothing more than observing or identifying the ineligible concept itself."[165] Here, there was a method of achieving the result that was claimed. Importantly, the Federal Circuit stated: "That one way of describing the process is to describe the natural ability of the subject matter to undergo the process does not make the claim 'directed to' that natural ability. If that was the rule, the Federal Circuit stated that other clearly patentable claims would fail such as, 'methods of… producing a new compound,' 'treating cancer with chemotherapy,' or 'treating headaches with aspirin'."[166]

The Federal Circuit importantly distinguished *Funk Brothers*, *Myriad*, and *Ariosa*.[167] The Federal Circuit noted that *Funk Brothers* and *Myriad* involved product claims and not method claims that were held ineligible. Furthermore, *Ariosa* was distinguishable because the claims "were 'directed to' the patent-ineligible cffDNA itself."[168] Notably, the Federal Circuit is following an approach developed in the *Enfish* case that focuses on whether the claim is "directed to" an ineligible concept and not analyzing this case as one asking whether there is an inventive concept under the second prong. The Federal Circuit noted that under the second prong there must be an analysis of the claimed elements as a combination.[169] Here, even though the additional steps, freezing, thawing, and separating, were all known in the art, the combination of those steps in the context of the claims was an inventive concept. This is particularly true where the prior art taught away from freezing the cells twice.[170] Importantly, the Federal Circuit recognized that concerns with preemption drive patent eligibility analysis but that the district court noted that the "929

[162] *Id.* at 1045–1046.

[163] *Rapid Litigation Management v. CellzDirect, Inc.*, 827 F.3d at 1048.

[164] *Id.*

[165] *Id.*

[166] *Id.* at 1049.

[167] *Id.*

[168] *Id.*

[169] *Id.* at 1051.

[170] *Id.*

patent 'does not lock up the natural law in its entirety' and that 'LTC has already managed to engineer around the patent'."[171]

1.2.2.3 US Patent and Trademark Office Guidance

The USPTO has attempted to help parties seeking patents with counsel on the arguably conflicting and constantly evolving US Supreme Court and Federal Circuit case law on patent-eligible subject matter. The USPTO has authored numerous resources designed to help patentees understand and apply the new rules. The USPTO has also attempted to gather public comment on the success of the new rules as well as potential patent reform efforts. Indeed, numerous groups in the United States are proposing changes to patent-eligible subject matter that may change the path forward with respect to patenting generally as well as patenting microbiology.

The USPTO has issued documents discussing the main cases concerning patent-eligible subject matter, including graphs which attempt to explain and simplify the law. Moreover, the USPTO has several helpful videos available online concerning patent-eligible subject matter. Perhaps the most important contribution of the USPTO has been the issuance of the 2014 Interim Guidance on Patent Subject Matter Eligibility (2014 Guidance) along with updates in 2015[172] and 2016.

The 2014 Guidance document attempts to synthesize and break down the complicated patent eligibility analysis.[173] The 2014 Guidance document provides a flowchart for evaluating "subject matter eligibility test for products and processes."[174] The first step is to "establish the broadest reasonable interpretation of the claim" and "analyze the claim as a whole when evaluating for patentability."[175] The next step is to ask "is the claim to a process, machine, manufacture or composition of matter." If the answer is no, the "claim is not eligible subject matter."[176] If the answer is yes, the next step is to apply the first prong of the Mayo test: "is the law directed to a law of nature, a natural phenomenon, or an abstract idea." If the answer is no, then the "claim qualifies as eligible subject matter…."[177] If the answer is yes, the next step is to apply the second step of the *Mayo* test, "does the claim recite additional elements that amount to significantly more than the judicial exception." If the answer is yes, then the "claim qualifies as eligible subject matter…." If not then the claim is not

[171] *Id.* at 1052.

[172] USPTO, *The July 2015 Update: Subject Matter Eligibility*, addresses questions raised by applicants concerning, for example, an "explanation of the role of preemption in the eligibility analysis, including a discussion of the streamlined analysis." 1,https://www.uspto.gov/sites/default/files/documents/ieg-july-2015-update.pdf (accessed September 1, 2017).

[173] *2014 Interim Guidance on Patent Subject Matter Eligibility*, 79 FR 74618, 74620 (2014).

[174] *Id.*

[175] *Id.* at 74621.

[176] *Id.*

[177] *Id.*

eligible subject matter.[178] The 2014 Guidance document also suggests a "streamlined" analysis for cases that clearly do not involve preemption.

On May 4, 2016, the USPTO issued a memorandum entitled "Formulating a Subject Matter Eligibility Rejection and Evaluating the Applicant's Response to a Subject Matter Eligibility Rejection" [hereinafter, 2016 Formulation Memorandum].[179] That document explains that in crafting rejections, examiners must be relatively specific and provide an explanation. For example, the examiner must "identify the judicial exception by referring to what is recited… in the claim and explain why it is considered an exception."[180] As an example, the 2016 Formulation Memorandum states: "The claim recites the correlation of X, and X is a law of nature because it describes a consequence of natural processes in the human body, e.g., the naturally-occurring relationship between the presence of Y and the manifestation of Z."[181]

Importantly, the 2014 Guidance has specific instructions for analyzing part one of the *Mayo* test concerning "whether the claim is directed to … a 'product of nature' exception."[182] The guidance is to "compare the nature-based product in the claim to its naturally occurring counterpart to identify markedly different characteristics based on structure, function and/or properties."[183] The "markedly different" test is essentially based on the analysis from *Diamond v. Chakrabarty*. Notably, the 2014 Guidance provides that "care" should be exercised "not to overly extend the markedly different characteristics analysis to products that when viewed as a whole are not nature-based product limitation… but are directed to inventions that clearly do not seek to tie up any judicial exceptions…."[184] In those cases, the markedly different analysis is unnecessary, and the streamlined analysis may be used. In applying the markedly different analysis, the 2014 Guidance provides the following example:

> A nature-based product can be claimed by itself (e.g., "a Lactobacillus bacterium") or as one or more limitations of a claim (e.g., "a probiotic composition comprising a mixture of Lactobacillus and milk in a container"). The markedly different characteristics analysis should be applied only to the nature-based product limitations in the claim to determine whether the nature-based products are "product of nature" exceptions. When the nature-based product is produced by combining multiple components, the markedly different characteristics analysis should be applied to the resultant nature-based composition, rather than to its component parts. In the example above, the mixture of Lactobacillus and milk should be analyzed for markedly different characteristics, rather than Lactobacillus separately and the milk separately. The container would not be subject to the markedly different

[178] *Id.*

[179] Robert W. Bahr, *Formulating a Subject Eligibility Rejection and Evaluating the Applicant's Response to a Subject Matter Eligibility Rejection*, USPTO 1, https://www.uspto.gov/sites/default/files/documents/ieg-may-2016-memo.pdf (issued May 4, 2016).

[180] *Id.* at 2.

[181] *Id.* at 3.

[182] *2014 Interim Guidance*, 79 FR at 74622.

[183] *Id.* at 74623.

[184] *Id.*

> characteristics analysis as it is not a nature-based product, but would be evaluated [under the second step in the Mayo test] if it is determined that the mixture of Lactobacillus and milk does not have markedly different characteristics from any naturally occurring counterpart and thus is a "product of nature" exception.[185]

The 2014 Guidance document also addresses product-by-process claims and applying the markedly different analysis. It provides that the focus is "on whether the nature-based product in the claim has markedly different characteristics from its naturally occurring counterpart."[186] Moreover, if there is no meaningful distinction in a process claim and a product claim, then the markedly different analysis can be applied; otherwise this exception does not apply to process claims.[187]

The 2014 Guidance document further specifies that the markedly different analysis is applied by comparing "the nature-based product limitation to its naturally occurring counterpart in its natural state."[188] Notably, sometimes there is not a naturally occurring counterpart. The 2014 Guidance document recommends comparing with "the closest naturally occurring counterpart."[189] The document states that markedly differences can be even a "small change" in the "product's structure, function, and/or other properties."[190] Notably, the 2014 Guidance document provides "[n]on-limiting examples of the types of characteristics considered by courts when determining whether there is a marked difference."[191] The examples include: "Biological or pharmacological functions or activities; Chemical and physical properties; Phenotype, including functional and structural characteristics; and Structure and form, whether chemical, genetic or physical."[192] Importantly, the 2014 Guidance notes that, even in light of the Myriad decision, purification and isolation alone can result in a marked difference if "there is a resultant change in characteristics."[193]

The 2014 Guidance document provides additional substantial synthesized analysis concerning how to apply the Mayo test. On part two of the Mayo test, the 2014 Guidance provides examples to consider whether "the elements of the claim, considered both individually and as an ordered combination, are sufficient to ensure that the claim as a whole amounts to significantly more than the exception itself…."[194] Examples of "significantly more" include:

> Improvements to another technology or technical field; Improvements to the functioning of the computer itself; Applying the judicial exception with, or by use of, a particular machine; Effecting a transformation or reduction of a particular article to a different state or thing;

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[185] *Id.*

[186] *Id.*

[187] *Id.*

[188] *Id.*

[189] *Id.*

[190] *Id.*

[191] *Id.*

[192] *Id.*

[193] *Id.*

[194] *Id.* at 74624.

> Adding a specific limitation other than what is well-understood, routine and conventional in the field, or adding unconventional steps that confine the claim to a particular useful application; or Other meaningful limitations beyond generally linking the use of the judicial exception to a particular technological environment.[195]

The 2014 Guidance document also provides examples of what is not "significantly more":

> Adding the words "apply it" (or an equivalent) with the judicial exception, or mere instructions to implement an abstract idea on a computer; Simply appending well-understood, routine and conventional activities previously known to the industry specified at a high level of generality, to the judicial exception…; Adding insignificant extrasolution activity to the judicial exception, e.g., mere data gathering in conjunction with a law of nature or abstract idea; Generally linking the use of the judicial exception to a particular technological environment or field of use.[196]

The 2016 Formulation Memorandum provides the following additional guidance to examiners: "identify any additional elements (specifically point to claim features/limitations/steps) recited in the claim beyond the identified judicial exception; and explain the reason(s) that the additional elements taken individually, and also taken as a combination, do not result in the claim as a whole amounting to significantly more than the judicial exception."[197] The 2016 Formulation Memorandum specifies that the examiner must explain their "rationale" underlying a rejection.[198] For example, if the additional elements are "mere insignificant extrasolution activity," then the examiner must explain why.[199]

The 2014 Guidance document further includes information concerning how to deal with claims involving more than one exception. Moreover, the document provides examples of when a streamlined analysis is merited, for example, when a complex manufacturing process is claimed.[200] Additionally, there are numerous example analyses provided based on the facts of patent eligibility cases, such as *Diamond v. Chakrabarty*. Finally, there is a summary of several cases applying the exceptions to patentability.

There has been substantial disagreement as to whether the USPTO can enforce the "broadest reasonable interpretation" standard, which is different from the standard applied by the Federal Circuit and other courts. Arguably, the broadest reasonable interpretation standard will result in more claims found patent ineligible. However, the US Supreme Court has held that the USPTO has the authority to adopt and implement the broadest reasonable interpretation standard. Until the Congress or the USPTO overturns or revises that standard, it is here to stay.

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[195] *Id.*

[196] *Id.*

[197] Bahr, *supra*, at 2.

[198] *Id.* at 4.

[199] *Id.*

[200] *2014 Interim Guidance*, 79 FR at 74625.

Second, as discussed *supra*, there is a substantial additional analysis that must be applied to determine whether the Mayo test is satisfied or not. For example, numerous Federal Circuit cases analyze in relative detail and make fine distinctions concerning whether a claim is "directed to" patent-eligible subject matter. Moreover, the scope of the exceptions themselves is in doubt as previously discussed. There is also a question of what constitutes "significantly more" to the judicial exception.

In addition to discussions concerning recent cases addressing eligibility analysis, the USPTO has also released documents concerning examples of how the rules work as applied to specific exceptions. For example, the product of nature document contains ten examples, including claims drawn to gunpowder and fireworks; pomelo juice; amazonic acid, pharmaceutical compositions, and methods of treatment; purified proteins: genetically modified bacterium; bacterial mixtures; nucleic acids; antibodies; cells; and food.[201] The USPTO has also issued examples concerning the life sciences specifically. The examples include claims concerning vaccines, diagnosing and treating julitis, dietary sweeteners, screening for gene alterations, papermaking machine, and hydrolysis of fat.[202]

Life sciences example number 28 concerns vaccines. The example is too lengthy to quote for purposes of this chapter. However, the explanation of the example states:

> This example illustrates the application of the markedly different characteristics and significantly more analyses to claims reciting hypothetical nature-based products. It also illustrates the importance of applying the broadest reasonable interpretation in the eligibility analysis, and how that interpretation assists in the identification of appropriate naturally occurring counterparts of claimed nature-based products. Hypothetical claims 1,2 and 4–6 are eligible in Step 2A, because the claimed nature-based products have markedly different characteristics from what exists in nature. Hypothetical claim 3 is ineligible, because the claimed nature-based product lacks markedly different characteristics from what exists in nature, and the claim fails to amount to significantly more than the exceptions. Hypothetical claim 7 is eligible in Step 2B, because although the claim is directed to an exception, it recites a particular and unconventional device that amounts significantly more than the exception.[203]

The USPTO will likely continue to issue guidance for evolving patent-eligible subject matter doctrine as the courts issue more decisions.

[201] USPTO, *Nature-based Products*, 9–18, https://www.uspto.gov/sites/default/files/documents/mdc_examples_nature-based_products.pdf (issued December 16, 2014).

[202] USPTO, *Subject Matter Eligibility Examples*: *Life* Science, 28–33, https://www.uspto.gov/sites/default/files/documents/ieg-may-2016-ex.pdf (issued May 4, 2016).

[203] *Id.*

1.3 The Path Forward

There are several proposals before the US Congress to amend patent-eligible subject matter rules by broadening the scope of what can be patentable. Notably, the USPTO has held several roundtables to gather feedback from stakeholders concerning the future of patent-eligible subject matter.

1.3.1 Stakeholder Feedback Concerning Patent-Eligible Subject Matter

The USPTO prepared a report based on the feedback received from stakeholders concerning patent-eligible subject matter rules.[204] The report divides the feedback into two themes: first, views favorable to the current trend in patent-eligible subject matter and second, views against the trend in patent-eligible subject matter.[205] The specific views in favor of the current arc of patent-eligible decisions include "Common Law Process at Work," "Weeds Out Overly Broad Patents," "Requires Claiming a Specific Way," "Not Just a Result," "Litigation Tool Against Patent Assertion Entities," and "May Give US Entities an Advantage."[206] The viewpoints against the direction of case law in the US concerning patent eligibility decisions include "Decisions are Legally Flawed," "Judicial Exceptions are Overly Broad," "Two-Step Test is Unclear and Causes Unpredictability," "Preemption Conflates § 101 With Other Patentability Provisions," "Jurisprudence Stifles Innovation and Hurts Businesses," and "Consistency of US Law with International Norms."[207] Importantly, there is a relatively clear divide between industries.[208] The software and information technology industry is generally for the new narrowing of patent eligibility.[209] At the same time, the life sciences industry, including biotechnology and pharmaceuticals is for broadening patent eligibility.

In reviewing the arguments for the narrowing of patent eligibility, several stand out. For example, the Common Law Process at Work category notes that some participants viewed US Supreme Court decisions as evolving through the common law process.[210] However, at the same time, some participants also appeared to be in favor of Federal Circuit decisions pushing back against the US Supreme Court.[211] On weeding out overly broad patents, Google and other members of the software

[204] USPTO, *Patent Eligible Subject Matter: Report on Views and Recommendations from the Public* (July 2017), available at https://www.uspto.gov/sites/default/files/documents/101-Report_FINAL.pdf

[205] *Id.*

[206] *Id.*

[207] *Id.*

[208] *Id.*

[209] *Id.*

[210] *Id.*

[211] *Id.*

industry are in favor of the *Mayo/Alice* test for removing broad, low-quality patents.[212] Moreover, for Requires Claiming a Specific Way, commentators seem to dislike claiming results as opposed to the way of achieving those results.[213] Participants also pointed to the benefits of requiring claiming a specific way including increased disclosure.[214] On Litigation Tool Against Patent Assertion Entities, commentators favored Mayo/Alice as an easy way to dismiss claims brought by patent assertion entities against practicing software entities.[215] Notably, the Electronic Frontier Foundation stated: "R&D spending on software and the Internet was 16.5 percent during the 12 months prior to Alice, but over 27 percent in the 12 months after Alice."[216] Participants also noted that broader eligibility standards in other countries could result in higher prices for consumers located in those countries, while at the same time narrower eligibility standards in the United States may benefit US consumers with lower prices.[217] The report also notes that some considered the possibility of a research exception to balance calls for broader eligibility.[218]

1.3.2 Proposals to Amend Patent Act

There are three main proposals to amend the Patent Act on patent-eligible subject matter originate from the American Intellectual Property Lawyers Association (AIPLA), the American Bar Association Intellectual Property Section, and the Intellectual Property Owners Association (IPO). The proposals will radically change the patent-eligible subject matter inquiry in the United States.

The IPO is an association of prominent corporations that control intellectual property. The IPO's proposal to change Section 101 is basically identical to the AIPLA's proposal. That proposal states:

> 101(a) Eligible Subject Matter
>
> Whoever invents or discovers, and claims as an invention, any useful process, machine, manufacture, composition of matter, or any useful improvement thereto, shall be entitled to a patent for a claimed invention thereof, subject only to the exceptions, conditions and requirements set forth in this Title.
>
> 101(b) Sole Exception to Subject Matter Eligibility
>
> A claimed invention is ineligible under subsection (a) if and only if the claimed invention as a whole, as understood by a person having ordinary skill in the art to which the claimed invention pertains, exists in nature independently of and prior to any human activity, or exists solely in the human mind.
>
> 101(c) Sole Eligibility Standard

[212] *Id.*

[213] *Id.*

[214] *Id.*

[215] *Id.*

[216] *Id.*

[217] *Id.*

[218] *Id.*

> The eligibility of a claimed invention under subsections (a) and (b) shall be determined without regard as to the requirements or conditions of sections 102, 103, and 112 of this Title, the manner in which the claimed invention was made or discovered, or the claimed invention's inventive concept.[219]

The IPO proposal maintains the four main categories of patent-eligible subject matter, but expressly limits the exceptions to eligibility. This would essentially remove or limit the abstract idea exception and focus the product of nature/natural phenomena exception. The abstract idea exception is limited to an invention that essentially "exists solely in the human mind."[220] This would appear to allow claims that have some real world application, such as diagnostic processes that involve measuring or collecting information. Moreover, those claimed inventions would be patentable subject matter, particularly because Section 101(c) excludes examining inventive concept. The product of nature/natural phenomena exception may be narrower because, for example, isolated and purified genomic DNA does not exist in nature independently and there is some human intervention. Furthermore, the exceptions inquiry is expressly from the perspective of a person of ordinary skill in the art, and the claim must be analyzed as a whole. These changes all substantially broaden eligibility from the current state of affairs.

The ABA IP Section proposal is structured somewhat similarly, but differs in its use of exceptions. It appears more restrictive than the IPO/AIPLA proposal. The ABA IP Section proposal states:

> Section 101. Conditions for Patentability: eligible subject matter.
>
> (a) Eligible Subject Matter. – Whoever invents or discovers any useful process, machine, manufacture, or composition of matter, or any useful improvement thereof, shall be entitled to obtain a patent on such invention or discovery, absent a finding that one or more conditions or requirements under this title have not been met.
> (b) Exception – A claim for a useful process, machine, manufacture, or composition of matter, or any useful improvement thereof, may be denied eligibility under this section 101 on the ground that the scope of the exclusive rights under such a claim would preempt the use by others of all practical applications of a law of nature, natural phenomenon, or abstract idea. Patent eligibility under this section shall not be negated when a practical application of a law of nature, natural phenomenon, or abstract idea is the subject matter of the claims upon consideration of those claims as a whole, whereby each and every limitation of the claims shall be fully considered and none ignored. Eligibility under this section 101 shall not be negated

[219] Intellectual Property Owners Association ("IPO"), *Proposed Amendments to Patent Eligible Subject Matter under 35 U.S.C. § 101*, USPTO 1 http://www.ipo.org/wp-content/uploads/2017/02/20170207_IPO-101-TF-Proposed-Amendments-and-Report.pdf (accessed September 1, 2017); American Intellectual Property Law Association ("AIPLA"), *AIPLA Legislative Proposal and Report and Patent Eligible Subject Matter*, USPTO 4 https://www.aipla.org/resources2/reports/2017AIPLADirect/Documents/AIPLA%20Report%20on%20101%20Reform-5-19-17-Errata.pdf (accessed September 1, 2017).

[220] *Id.*

based on the considerations of patentability as defined in Sections 102 103 and 112, including whether the claims in whole or in part define an inventive concept.[221]

This proposal, unlike the IPO proposal, maintains the traditional exceptions to patentability. It does not mention the product of nature exception, but this is sometimes coextensive with a natural phenomenon. The proposal also focuses on preemption and specifies that preemption is of "all practical applications" of the exceptions.[222] This favors broad patent-eligible subject matter by ensuring that preemption applies to complete and total preemption. Practically, this means that addition of other limitations to the claim may carry the invention. Additionally, inventive concept is also excluded. Notably, the proposal does not state this is the "sole" exception, although exception is in the singular. A court may develop another exception. While favoring broader eligibility than the current standards, this proposal is not as broad as the IPO/AIPLA standard.

1.4 Conclusion

This paper provides an overview of patent eligibility trends in the United States with particular emphasis on biotechnology inventions. Notably, patent eligibility standards appear to be a work in progress. The Congress, the USPTO, and the courts continue to modify and change the standards. In counseling clients, attorneys should be aware of the potential for incremental and dramatic change.

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2 Challenges and Opportunities at the Interface of Synthetic Biology, Microbiology, and Intellectual Property Rights

Nicola Lucchi

Abstract

During the last decade, the genomics revolution has created powerful instruments for genetic manipulation of living organisms. In addition, new biotechnological tools allow modifying organisms in order to perform specific tasks. In particular, synthetic biology is a fast-developing and transdisciplinary field that uses engineering principles to design and assemble novel biological components. For example, within the area of industrial microbiology, synthetic biology has contributed to build from scratch or reengineer new microorganisms or chemical compounds. However, all these scientific and biotechnological innovations present a substantial challenge also for the law and especially for intellectual property rights. Considering this multifaceted scenario, this chapter discusses the current challenges and opportunities at the intersection of synthetic biology, microbiology, and intellectual property also reflecting on alternative forms of protection for genetically engineered works created by using synthetic biology.

Keywords

Synthetic biology · Genetic engineering · Biotechnology · Patents · IPR

2.1 Introduction

The exceptionally rapid technological progress in the field of biotechnology has resulted in more appropriate legislative and judicial responses to the evolving regulatory regime especially with regard to intellectual property rights, trying to balance

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H. B. Singh et al. (eds.), *Intellectual Property Issues in Microbiology*,
https://doi.org/10.1007/978-981-13-7466-1_2

the interests of both rights of holders and consumers (Lucchi 2016). The key to the success of the biotechnology industry was – in fact – the result of numerous supporting and "favourable government policies toward the sector in combination with a liberalized regime for the governance of biomedical research" (Vallas et al. 2011; Lucchi 2016). Debates and "concerns about the need to regulate the disruptive potential of biological manipulation were apparent almost from the moment when genetic engineering became feasible in the 1970s" (Jasanoff 2011). The emergence of all these issues and concerns set the basis for a new discussion on how to regulate "the use, access, distribution, and appropriation of essential public knowledge assets in the life sciences" (Lucchi 2016).

The purpose of this chapter is to consider whether genetically engineered works – artificially created by scientists – can be protected by developing alternative strategies, so not only through patents but also through other forms of intellectual property rights, namely, copyright. This idea is not really new but originated in the early 1980s at the time when the patentability of biotech inventions was still an open question. This approach has seen little development, at least until two recent US Supreme Court decisions (hereinafter Mayo[1] and Myriad[2]) have completely changed US patent eligibility criteria for biotechnology reversing more than 30 years of case law questioning the enforceability and validity of patents on naturally occurring genetic material (even if isolated). In particular, in Myriad, the Supreme Court held that naturally occurring DNA is not eligible for patenting just because it has been isolated from its natural state. Naturally occurring DNA remains a "product of nature" even after isolation and, therefore, falls under the "laws of nature" which is an exception to patent eligibility. In other words, isolation of naturally occurring DNA is not enough for the naturally occurring DNA to be considered man-made. At the same time in Mayo, the US Supreme Court held that certain diagnostic methods are not patentable because they involved standard conventional steps. In particular, the Court found that the procedure by which a drug is chemically converted in the body to a metabolite must be considered as a natural process, and so the relationship between the quantities of metabolites and the efficacy of drug dose is a law of nature. In other words, simply observing such a naturally occurring relationship – without adding anything else – cannot be considered enough to transform the concept of the claims into a patentable invention.

These two decisions narrowed patent-eligible protection over living organisms and created significant ambiguity among both patent applicants and patent examiners. In order to mitigate this confusion, the US Patent and Trademark Office (USPTO) arranged a series of guidance on subject matter eligibility. These new challenges faced by biotechnology innovators after Mayo and Myriad have also led to reconsider the idea of using the copyright system as a form of intellectual property protection for engineered nucleic acid sequences. Considering this more complex scenario, the chapter explores the possible legal arguments in support of,

[1] Mayo Collaborative Servs. v. Prometheus Labs., Inc., 132 S. Ct. 1289 (2012).

[2] Association for Molecular Pathology v. Myriad Genetics, Inc., 133 S. Ct. 2107 (2013).

or against, alternative legal forms of protection for genetically engineered works created using synthetic biology techniques.

2.2 Synthetic Biology and Microbiology

Synthetic biology is a fairly young research discipline that seeks to generate from scratch or reprogram existing cellular functions with other useful properties applying principles of mechanical engineering to biological design (Singh 2014; Boyle and Silver 2012; Davidson et al. 2012; Keasling 2012; Torrance 2010). Generally speaking, it can be explained as the application of engineering knowledge and principles to the essential components of biology (European Commission 2005; Royal Academy of Engineering 2009). All living organisms are – in fact – based on a set of instructions indicating how they look like and what they can do. These instructions are contained in the organism's DNA within every cell. The DNA is the molecule that "contains the genetic material and which then functions as information carrier" (Klug et al. 2012). The DNA is then composed of genes, which are – essentially – "traits or fragments of DNA containing the genetic information necessary to build a specific protein." The "totality of genetic information belonging to a cell or an organism and in particular the DNA that carries this information" is called "genome" (Alberts et al. 2014). For centuries, humans have been altering the genetic code of animals and plants in order to generate organisms with desired features. As scientists have gained more knowledge on how to decipher and artificially change the genetic code, they also developed the ability to transfer genetic information from one organism to an unrelated one. Recent developments in the emerging field of synthetic biology – particularly in the manipulation of organisms' genomes – have allowed biologists to build from scratch or reengineer the genomes of microorganisms (Perkel 2017). By combining these advances with engineering principles, synthetic biologists are now able to design cells and even organisms with completely new features involving the creation of novel DNA sequences "that may have never existed before in living organisms" (Mandel and Marchant 2014). Synthetic biology, therefore, stretches far beyond mere genetic engineering which is about the simple manipulation of a natural organism and tends to focus more heavily on the creation of entirely new synthetic life (Seitz 2016). In particular, this innovative research technology is built on the understanding that "DNA sequences can be assembled together like building blocks, producing a living entity with any desired combination of traits, much as one can assemble a car by putting together many individual pieces with different functions" (Mandel and Marchant 2014). This huge paradigm shift in the biological sciences gives rise to many new legal issues and rights, including the fact that – among other things – genetically engineered works, because of their very nature, seem to be inside the bounds of copyright protection.

2.3 Patent Protection for Genetically Engineered Works: Current Conditions and Requirements

The standard approach of the Trilateral Patent Offices [i.e., the US Patent and Trademark Office (USPTO), the Japan Patent Office (JPO), and the European Patent Office (EPO)] with respect to patents on biological subject matter is to grant ownership rights only for isolated and purified gene sequences with a demonstrated specific utility (Howlett and Christie 2003; Restaino et al. 2003; Reese and Opeskin 2006; Lucchi 2013). A clear dividing line between patentable subject matter and non-patentable products of nature was established for the first time by the US Supreme Court in Diamond v. Chakrabarty.[3] This historical court decision – in combination with the judgment in Moore v. Regent of University of California[4] – not only significantly impacted the US patent system, but it provided a new lens to look at how genetic resources can be used and privatized. A few years later, the USPTO, EPO, and JPO released a joint policy statement claiming that "purified natural products are not regarded as products of nature or discoveries because they do not, in fact, exist in nature in an isolated form. Rather, they are regarded for patent purposes as biologically active substances or chemical compounds and eligible for patenting on the same basis as other chemical compounds" (European Patent Office, Japanese Patent Office, and US Patent and Trademark Office 1998; Nuffield Council of Bioethics 2002).

The aim of this statement was to identify the relevant global planning policy regarding patentability of genetic material: in particular, it was specified that a purified natural substance was to be considered patentable if the "purification" results in "a compound with such distinct characteristics that it becomes a new product commercially or therapeutically valuable" (Lucchi 2013). In the process of isolation and purification of genetic materials, it is – in fact – possible to obtain the partition of different compounds from a biological cell. However, it should also be pointed out that various criticisms have been made related to the above interpretation. In particular, it has been stressed that even if genetic materials are purified and isolated, the core elements of such substances – which are the "useful" and exploitable information – "are naturally occurring, not created by the person who isolates and purifies the material" (Australian Law Reform Commission 2004). In addition, purified and isolated genetic sequences are "structurally similar or identical to the form that exists in nature" (Ibidem). The main point of this interpretation is that patents for biotech innovations are simply based and limited only on the ability of the individuals drafting the claim (Robinson and Medlock 2005).

[3] Diamond v. Chakrabarty, 447 US 303 (1980). In this landmark decision, the US Supreme Court held that a live and human-engineered microorganism can be considered a patentable subject matter under Section 1010 of the US Patent Act. According to the rule of this decision, patents can be issued on "anything under the sun that is made by man." For a review of the case, see Eisemberg 2006.

[4] Moore v. Regents of the University of California, 793 P.2d 479 (Cal. S. Ct) (1990).

In recent years, the patenting of genes and gene fragments has put under debate one of the fundamental principles of the patent law: the requirement of novelty (Doll 1998; Kevles and Berkowitz 2001; Larrimore Ouellette 2010). Consequently, the debate on the status as patentable subject matter has suddenly become topical again. Indeed, many questions surround this issue: "as DNA has existed well before the gene discoverer arrived, how can these molecules be novel?" (Liivak 2007). The answer, as it has been suggested, "is that the actual molecule produced and claimed by the gene discoverer is new in a strict sense of the word" (Liivak 2007). More specifically, "gene sequences exist naturally as part of a much bigger molecule" and "there is no doubt that this much bigger molecule would be unpatentable" (Ibidem). But, on the other hand, the gene discoverer's thesis is that "purified and isolated gene sequences are distinct from the overall DNA molecule" (Ibidem). This is also the thesis formulated by one of the first US patent infringement litigations involving a gene patent. In Amgen, Inc. v. Chugai Pharm. Co. Ltd., the district court ruled that the patent in suit was to be regarded as valid because the invention "is not as plaintiff argues the DNA sequence encoding human erythropoietin since that is a non-patentable natural phenomenon 'free to all men and reserved exclusively to none.' Rather, the invention as claimed in claim two of the patent is the 'purified and isolated' DNA sequence encoding erythropoietin."[5]

In order to be patentable under the US and European law, an invention must meet three basic requirements: (Mills 2010; Bently and Sherman 2009): (i) novelty, (ii) inventive step (nonobviousness in the USA), and (iii) industrial application (utility in the USA). These statutory limits provide the basic and general requirements that must be satisfied in order to obtain a patent. However, patents on DNA and human genes raise the question of where to draw the line between patentable and non-patentable inventions. In fact, the patenting of genes and gene fragments appears to challenge the novelty requirement. At the same time, there is a growing sensitivity to ethics in patent law.[6] This sensitivity is even more evident in the biotech sector where the structure of the patent system seems to require a more careful assessment of all the possible conflicting rights. As stated by the US Supreme Court Justice Stephen Breyer in the case of Laboratory Corp. v. Metabolite Industries, the justification for not allowing patents on natural laws is that "sometimes too much patent protection can impede rather than promote the Progress of Science and useful Arts."[7]

The patent dilemma in the biotech sector is also challenged by a regulatory framework built for a more conventional setting. For example, there are increasing policy and academic discussions about the ethical and social issues raised by owning, managing, and using essential public knowledge assets in the life sciences (Gitter 2001). From the mere legal perspective, Article 27 of TRIPs defines patentable subject matter expressly stating that patents must "be available for any

[5] See Amgen, Inc. v. Chugai Pharm. Co., 13 US P.Q.2d (BNA) 1737, 1759 (D. Mass. 1989).

[6] See, e.g., judgment of the Court of Justice of the European Union in Oliver Brüstle v Greenpeace eV (C-34/10) [2012] 1 C.M.L.R. 41.

[7] See Lab. Corp. of America Holdings v. Metabolite Labs., Inc., 548 US 124, 126, 79 US P.Q.2d (BNA) 1065, 1066 (2006) (per curiam) (Breyer, J., dissenting) (quoting US Const. art. I, § 8, cl. 8).

inventions, whether products or processes, in all fields of technology, provided that they are new, involve an inventive step and are capable of industrial application" (the so-called nondiscrimination principle).[8] It means that genes, gene fragments, and cell lines modified or altered by human effort can be patented if the inventor meets the general requirements of a patent (Bently and Sherman 2009; Andrews and Paradise 2005). Formally, states may refuse to recognize patents on their territory, but – up to now – very few countries have used this option. At the same time, the European Directive on the Legal Protection of Biotechnological Inventions stipulates that "elements isolated from the human body or otherwise produced by means of a technical process, including the sequence or partial sequence of a gene," may represent a patentable invention.[9] In particular, the Directive specifies that "biological material which is isolated from its natural environment or produced by means of a technical process is considered to be an invention even if this material previously occurred in nature."[10] In addition, the European Patent Convention (EPC) excludes the possibility to grant patents for "methods of treatment of the human or animal body by surgery or therapy and diagnostic methods practiced on the human body" (Reinisch 2010).[11] On this basis, the European Patent Office determined that "all methods practiced on the human or animal body which relate to the diagnosis or which are of value for the purposes of diagnosis" are precluded from being patented.[12] Nevertheless, biotech- and life science-related inventions are in principle considered patentable under both the EPC and the Biotechnology Directive (Spinello and Bottis 2009). Specifically, the European Patent Convention unequivocally recognizes the patentability of biotech inventions in Rule 26(1) EPC.[13] In addition, Rule 27(a) EPC offers complementary details about the "patentable subject matter" for life sciences inventions, specifying that "biotechnological inventions shall also be patentable if they concern biological material which is isolated from its natural

[8] See Agreement on Trade-Related Aspects of Intellectual Property Rights, Apr. 15, 1994, art. 27, Marrakesh Agreement Establishing the World Trade Organization, Annex 1C, 33 I.L.M. 1125 (1994) [hereinafter TRIPS]. On this point, see also Gibson 2008: 1,3.

[9] Council Directive 98/44/EC, art. 5(2), 1998 O.J. (L 213) 13 (EC).

[10] Id., at art. 3(2).

[11] Convention on the Grant of European Patents, art. 53(c), Oct. 5, 1973, 13 I.L.M. 270 [hereinafter EPC]. The EPC provides a uniform method and standard for examining a European patent application but reserves to members of the European Union the task of interpreting and enforcing a patent: "under the EPC, the EPO grants European patents for one or more of the contracting parties to the EPC. However, a European patent is not a uniform patent. Rather it consists of a bundle of parallel national patents granted as a result of a centralized grant by the EPO."

[12] See decision T 964/99 (OJ EPO 2002, 4), starting from the interpretation set out in decision T 385/86 and decision T 964/99.

[13] Rule 26(1) of October 5, 1973, as adopted by decision of the Administrative Council of the European Patent Organisation of December 7, 2006, and as last amended by decision of the Administrative Council of the European Patent Organisation of October 26, 2010 [hereinafter Implementing Regulations]. The rules cited are to the earlier version. On the point, see Macchia 2011: 37.

environment or produced by means of a technical process even if it previously occurred in nature."[14]

Privately funded research in the life sciences is normally profit-oriented, and patents are the primary strategy that firms use to protect their new ideas. In such specific circumstances, concerns arise because of the nature and extent of protection granted to patent holders. Patents – in fact – may play various roles in the knowledge-based economy. Under the current regulatory framework, patent holders have broad freedom in the exercise of their exclusive prerogatives[15] (Bently and Sherman 2009). Consequently, they are free to negotiate and set royalties, to accept, deny, or unreasonably limit licensing requests, or again they may select specific licensees imposing licensing terms freely, as long as the terms and agreements do not override relevant regulations, such as competition or antitrust law (Bently and Sherman 2009).[16] Unfortunately, this scheme – even though designed to support private research – could also bring undesirable results. When patents are licensed too restrictively or when patents are used excessively to protect information, "this could hamper research and development, clinical access, and availability of high-quality tests for patients" (Van Overwalle 2010). These considerations indicate that patents may have a chilling effect on research and innovation imposing a substantial barrier on other researchers' ability to undertake further investigations (Resnik 2004). Finally, licensing practices can generate the unintended consequence of restricting access to genetic information and to data necessary for other research purposes (Santosuosso et al. 2007).

2.4 Intellectual Assets in the Life Sciences Industry

Biotechnology and pharmaceutical corporations normally follow a conventional business model that is focused on a "closed innovation" scheme supporting a system that is completely enclosed by intellectual property rights. All ideas are internally generated and stay inside until the new product or innovation arrives on the market. In this context, it is relevant to consider how patent rights affect the process of "cumulative innovation" (Long 2000). Normally all inventions are based on previous knowledge and inventions: this means that innovation is cumulative because new innovations are grounded on previous innovations. The term "cumulative innovation" is commonly employed to describe a condition in which a second inventor uses previous knowledge protected by a granted patent in order to create a new innovation (Burk and Lemley 2009). In other words, the second innovation would not be achievable without the contribution of the previous scientific knowledge. As a consequence, the second innovator is necessitated to obtain a license from the first

[14] Implementing Regulations, Rule 27(a).

[15] See, e.g., Bement v. Nat'l Harrow Co., 186 US 70, 90–92 (1902) ("The general rule is absolute freedom in the use or sale of rights under the patent laws of the USA").

[16] In the USA, an intellectual property rights holder has no obligation to either use or license its property rights. On the point, see Hovenkamp et al. 2006: 13.

innovator in order to use and exploit the new invention. The cumulative effect of innovation necessarily prompts serious concerns regarding the significance of dissemination of and access to scientific information (Lessig 2001). An article published by Professor Jerome Reichman in the Vanderbilt Law Review in 2010 already noted that "how to enable entrepreneurs to appropriate the fruits of their investments in cumulative and sequential innovation without impeding follow-on innovation and without creating barriers to entry has become one of the great unsolved puzzles that the law and economics of intellectual property rights need to address as the new millennium gets under way" (Reichman 2000). Innovation is therefore a process performed so as to progress gradually and carefully from one stage to the next. But when one step is already protected with a patent by someone else, new developments could be impeded or compromised. The patent holder – in fact – might set excessively high royalties increasing research costs, thus discouraging companies to invest in that specific field of research. In the literature on cumulative innovation, it is generally assumed the presence of two additional elements with respect to property rights as patents for inventions: "patent thicket" and "anti-commons effects" (Burk and Lemley 2009; Heller 1998; Shapiro 2001). The term "anti-commons effect" is normally proposed to identify the phenomenon produced by "fragmented property rights that must be aggregated to make effective use of the property" (Burk and Lemley 2009). This particular condition is generated when the creation of a new invention involves the licensing of complementary patents from other patent holders. In this case the problem is that "too many owners can block each other" (Heller and Eisenberg 1998): these exclusive property rights can have the potentially negative effect of restricting access to knowledge and research information in the name of enforcing a nonfunctional setting of property rights. This situation could be particularly problematic when the process of developing of a new product requires licensing of multiple complementary patents owned by different patentees. As stressed in the Heller and Eisenberg's seminal article, "by conferring monopolies in discoveries, patents necessarily increase prices and restrict use" (Heller and Eisenberg 1998). Although numerous empirical studies on this phenomenon do not generally offer a definitive and unanimous evidence (Straus et al. 2004; Adelman 2005), it seems that the anti-commons effect could really have potentially negative consequences for scientific research as researchers are excluded from access to fundamental information. Another similar and interrelated effect is provided the phenomenon of the so-called patent thicket (Shapiro 2001; Bessen et al. 2003). This event is characterized by overlapping of patent claims involving the same process or technology (Shapiro 2001). Similar to the anti-commons situations, the patent thicket "has the potential to prevent all parties from making a final product that incorporates multiple inventions" (Burk and Lemley 2009). Both the phenomena of the "anti-commons" and "patent thickets" are supposed to hinder and limit innovation especially in the life sciences and biotech sectors because they may block the development of new products by restricting access to research materials. The increasing significance of molecular biology and microbiology within the life science – in particular for the prevention and diagnostics of human diseases (or for

protecting from diseases) – amplified the value of access to genomic information for the production of new drugs and therapies (Jackson 2003).

In order to enable the adjustment of patent law to an environment influenced and constrained by fast scientific advances, it is recognized as necessary to improve and flexibilize the overall operability of the patent system (Van Overwalle et al. 2006; Van Overwalle 2010; Moir 2013). Among the various suggested measures, it has been proposed to include the introduction or extension of restrictions and exceptions to property rights in the interest of other fundamental legal rights. For example, it was recommended to add a diagnostic-use exemption in order to protect diagnostic testing from patent infringement (Van Overwalle 2010). In addition, it has been recommended that patents should grant less protection: in particular, they should protect an innovation only in relation to a very specific application, specifically indicated in the patent application (Ibiden: 1631). Other suggested and considered measures of flexibilization include compulsory licenses (for public health) and patent pools (Van Overwalle et al. 2006). Generally speaking, intellectual property rights should be regarded not just as an absolute right but as a bundle of rights with some specific social limitations (Kohler 1880).

2.5 Copyright Protection for Genetically Engineered Works? Requirements, Theories and Applicability

The idea to use copyright protection for genetically engineered works is not new. A number of law scholars have already discussed the applicability of copyright law as an alternative to patent protection for nucleic acid sequences and biotechnology works in general (Kayton 1982; Davidson 1986; Smith 1988; Burk 1989; Hogle 1990; Goldstein 1984; Silva 2000; Scott McBride 2002; Coke 2002; Rimmer 2003; Wilson 2004; Karnell 2005; Chen 2007; Singh et al. 2016a, b). These proposals were mainly developed in the 1980s, but now – after the US Supreme Court addressed the issue of patent subject matter in the Mayo[17] and Myriad[18] cases – the concept is returned in the spotlight attracting again the attention of legal academics and practitioners (Burk 2018; Holman 2011, 2015, 2017; Walker 2016; Zhuang 2015; Roig 2016; Murray 2014; Torrance 2010, 2011; Michelotti 2007; Chen 2007). In particular, the idea of copyrighting genetically engineered works was first argued in 1982 in a law review article written by Professor Irving Kayton and published on the *George Washington Law Review* (Kayton 1982). The central thesis of his article was that a biotechnology work is automatically copyrighted when it is original and when the genetic information is fixed in a tangible medium because it satisfies exactly all the statutory and constitutional requirements for copyright protection. In reality, DNA sequences are normally considered non-original and non-protectable facts (Wilson 2004). However, redesigning and restructuring new biological entities (such as enzymes, genetic circuits, and cells) or the genomes of existing organisms

[17] Mayo Collaborative Servs. v. Prometheus Labs., Inc., 132 S. Ct. 1289 (2012).

[18] Association for Molecular Pathology v. Myriad Genetics, Inc., 133 S. Ct. 2107 (2013).

to make them more efficient or program new microorganisms in order to carry out new functions can really satisfy the originality requirement. This should be true because, presumably, the synthetic biologist would have to make a creative decision regarding which core components (parts of enzymes, genetic circuits, metabolic pathways, etc.) must be modeled, understood, redesigned, and modified in order to "meet specific performance criteria, and the assembly of these smaller parts and devices into larger integrated systems to solve specific problems" (Keasling 2005). Then, it has been argued that the written representation of an artificially engineered sequence of DNA or protein – fixed in a tangible form – may be protected as an original literary work (Coke 2002) because the statutory definition of "literary work" includes every production in the literary, scientific, and artistic domain, irrespective of the mode or form of its expression (so also any representation of words, figures, or symbols).[19] The written description of a genetic sequence – being a string of letters or an alphabet representing the four nucleotides, adenine, thymine, guanine, and cytosine (A, T, G, and C) – is likely to be a "literary work" within this meaning. At the same time, other scholars have questioned this approach, arguing that copyright may not actually be applied to a written description of a genetic sequence because there is only one established way to express or describe a certain sequence of nucleotides or amino acids (Karnell 2005; Resnik 2004). In this case, there is no distinction between idea and expression. According to the copyrightability argument, since DNA is made up of these four chemical nucleotides, engineered "DNA sequences should easily meet" also the fixation requirement (Torrance 2010). In particular – as studies of DNA have shown – it may meet all the fixation requirement because it "possesses definite sequences of nucleotides that can easily be determined; copies of DNA may be synthesized routinely and in effectively unlimited quantities; and molecular DNA has been known to last for at least many thousands of years with its nucleotide sequence intact" (Ibidem, 643). Concerning the authorship requirement, some elements of human creativity must have occurred in order for the DNA sequences to be copyrightable. This requirement can be met by products of synthetic biology because they involve "the design and construction of new, human-designed DNA sequences" (Ibidem). Specifically, synthetic biologists design and construct artificial biological systems that do not currently exist in nature, writing DNA sequences that instruct a cell or engineering organism to behave according to design specifications (Kuldell et al. 2015). Since here there is an author, such DNA sequences can be effectively qualified as "original works of authorship" (Torrance 2010).

Therefore – from a theoretical perspective – it would be a choice of the scientist to decide whether to enforce his copyright or not. In particular – according to this thesis – engineered genetic works can perfectly fall into the category of literary works. In fact, following the wording of the Berne Convention, the expression "literary and artistic works" includes every production in the literary, scientific, and

[19] See Article 2 (1) of the Berne Convention for the Protection of Literary and Artistic Works, Sept. 9, 1886, as revised at Paris on July 24, 1971, and amended in 1979, S. Treaty Doc. No. 99–27 (1986) ([hereinafter "Berne Convention").

artistic domain, whatever may be the mode or form of its expression. In other words – according to the US Copyright Act – "literary works are works expressed in words, numbers, or other verbal or numerical symbols or indicia, regardless of the nature of the material objects in which they are embodied."[20] A digital computer program is a literary work as it can be expressed in "indicia," such as magnetic impulses or other electronic signals, and it is also fixed in a tangible medium (Kayton 1982: 199). Analogously, "genetically engineered works are expressed in "indicia," namely, "the nucleotides that make up DNA" (Ibidem). All the genetic information in the DNA contains a set of instructions for producing something (typically a protein) just as a computer software contains a set of coded instruction designed to cause a computer to perform a specific task. There are therefore many similarities between genetic and computer code, and some companies have already tried – even if unsuccessfully – to register an engineered "biological artifact" with the US Copyright Office (Ledford 2013). In a very specific case (Samuelson 2016), some researchers in the field of synthetic biology have utilized novel techniques for creating completely new segments of DNA in order to get living organisms that behave differently from the way they would in the natural state (Torrance 2011). DNA, in fact, could be recombined into arrangements not found in existing genomes and, in addition, synthetic biology – designing and manipulating sophisticated synthetic cellular circuits – can create or reprogram new living organisms completely from scratch (Bhutkar 2005). These elements of scientific argumentation seem to support the analogy between synthetic biology artifacts and computer programs looking into alternative protection options such as copyrights, which are more straightforward than patents – as they have no substantive examination – and with the concrete possibility of fostering a feasible open-source regime for accessing and using essential public knowledge assets in the life sciences (Ledford 2013).

2.6 Challenges and Opportunities in Synthetic Biology

The challenges posed by scientific and biotech innovations present – from different perspectives – a substantial problem for the law. As mentioned in earlier pages, genetic information can have significant margins of "utility" and – at the same time – several aspects of vulnerability. This is a very sensitive subject where it does not only involve the freedom of scientific research or the right in one's scientific invention but also their effective and successful applications (King and Stabinsky 2005). It also involves factual consequences, which could theoretically give rise to a violation of rights and the challenge of striking a balance between contrasting interests. Here, the question is about to whom it belongs the right to determine the boundary lines between these two interacting domains. There is no doubt that the function to set the line between legal and illegal is up to the law, specifying the proper rules and provisions. It is a question of setting the correct approach in the field deciding and applying the proper legal instruments to regulate the actual use of

[20] 17 US C § 101.

these important knowledge assets. The current international legal framework for the protection of intellectual assets tries to maintain a flexible agreement capable of adjusting to the continuing and dramatic advances in scientific and technological innovation. So – for example – copyright protection was extended to cover computer software, and a sui generis system for the protection of semiconductor chips was created. Also, the patentability of biotechnological inventions has initially encountered several resistances: therefore, it seems plausible that any possible future and additional forms of protection for biotechnology works may not be easy to set up. The patentability of genetic information[21] was – in fact – gradually recognized only after a number of decisions of courts including the US Supreme Court in 1980[22] and by the board of appeal of the European Patent Office[23] in the 1990s (Guellec and van Pottelsberghe de la Potterie 2007). The question of whether copyright protection can be extended to genetically engineered works has not been judicially considered, and there are no statutory provisions dealing with this issue. Only the US Copyright Office has taken an express position. It has indeed clarified that it will not grant copyright registration to gene sequences or DNA molecules because they cannot be considered a copyrightable subject matter.[24] But this position – as it has been stressed by other legal scholars – does not preclude US courts "from declaring engineered DNA copyrightable" (Holman 2016; Holman et al. 2016). The only other official position on the subject has been made by the Australian Reform Commission in the report examining the laws and practices governing intellectual property rights over genetic materials and related technologies, with a particular focus on human health issues.[25] In particular, here the Australian Commission seemed more open regarding this question noting that "copyright could potentially subsist in the representation of a genetic sequence provided sufficient skill, labour and effort is involved in creating that expression."[26] Also, supporters of copyrightability for engineered biotechnology works agreed on the fact that copyright law may be broad enough to consider the engineered genetic code as copyrightable subject matter. Recent advances in genetic engineering allow – in fact – the creation of

[21] Here the term includes genetic materials and gene fragments, such as expressed sequence tags (ESTs) and single nucleotide polymorphisms (SNPs).

[22] Diamond v Chakrabarty 447 US 303 (1980).

[23] DecisionT19/90-3.3.2, 1990 O.J. Eur. Pat. Off. 476.

[24] See Office of Technology Assessment, US Congress, Publ'n No. OTA-BA-370, New Developments in Biotechnology: Patenting Life – Special Report 43 (1989) (reporting the Copyright Office's unofficial position that nucleic acid sequences are not copyrightable). More recently, the USPTO has explicitly rejected a copyright claim in a genetic engineering modified fish that an applicant had genetically altered so that the fish "fluoresces" when it is exposed to artificial light; see US Copyright Office, Re: GloFish Red Zebra Danio Glowing in Artificial Sunlight (5 September 2013) available at http://ipmall.law.unh.edu/sites/default/files/hosted_resources/CopyrightAppeals/2013/GloFishRedZebraDanioGlowing.pdf (cited in Samuelson, 2016).

[25] Austl. L. Reform Comm'n (ALRC), *Genes and Ingenuity: Gene Patenting, and Human Health*, ALRC Report 99 (Aug. 2004), § 28, available at https://www.alrc.gov.au/publications/report-99

[26] Id. at 28.21.

synthetic organisms that incorporate noncanonical or nonnatural amino acids into the complete set of proteins encoded by a genome (viz., the so-called proteome) (Lin et al. 2017; Holman 2015; Torrance 2011). It means that the current progress in genetic code engineering is characterized by entirely synthetic genes. Modern synthetic biology aspires to rewrite genomes encoding natural biological systems "producing engineered surrogates that might be usefully supplant some natural biological system" (Endy 2005). In particular, the recent advances in the development of engineered DNA are capable of reprogramming "biological machines" applying exactly "the same principles of engineering currently used in the development of the software used to program non-biological machines, i.e., computers" (Holman 2015).

Should copyright be recognized as subsistent in engineered biotechnology works, which rights would the owners be able to enforce? They would probably be able to prevent others from reproducing genetically engineered information fixed in an organism. In other words, they could preclude other scientists from using the genetically engineered work they have created and incorporating and fixing it into a "microorganism to make an identical or substantially similar copy" (Kayton 1982).

2.7 Conclusion

There is no doubt that genetic resources are playing a crucial and delicate role in shaping human society. For this very reason, genetic information should be considered as a public good, freely available to other researchers and investigators who want to use and test it in a similar process. Instead, it happened that biology and bioscience are being transformed into information sciences (Hess and Ostrom 2006), and those who want to do research are not always able to have unrestricted access to this information. In addition, the scope of the patent system has gradually stretched its boundaries to include subject matters whose protection is questionable. At the same time, biological discoveries have transformed from a "work of low inventorship" to a work of "mere cartography" (Liivak 2007).

As we have discussed in this chapter, there are many factors that determine whether there are alternative solutions to patent for protecting and using essential public knowledge assets. Here we are not talking about gene sequences obtained from nature, but we are talking about something that must have a real independent creation. Thus, the question is whether a gene can be simply considered a chemical compound or rather an information-carrying structure which – even if isolated and manipulated – is able to maintain the quality or state of being produced by nature. Currently, there are mainly two schools of thoughts on this subject (Resnik 2004; Guellec and van Pottelsberghe de la Potterie 2007). One holds the opinion that DNA or genetic material is simply an arrangement of various chemicals (Garforth 2008). Accepting this chemical approach, only patent protection can be allowed (Ibidem, 42). The other approach pursues the idea that all DNA is a non-patentable product of nature with no distinction between isolation and transformation in a laboratory or in the wild (Resnik 2004; Shiva 1997). In addition, opponents of gene patents also claim that patents for genetic inventions can violate the freedom of speech,

expressions, and communication – a well-accepted and long-established right in most Western liberal democracies – because of their potential to restrict the individual's freedom of expression and scientific research.[27] Looking over these opposing theories, it seems pretty clear that genes are different from other things that are normally patented, because they are not proper inventions and other researchers cannot invent alternative genes.

In the attempt to shed light upon this still confusing and uncertain scenario, some scholars and practitioners have recently started to suggest again a rather provocative alternative to gene patents. In particular, this school of thought proposes a sort of "genetic copyright regime" arguing that copyright seems to be flexible enough "to handle contemporary technologies that produce living organisms or organic components, but contemporary judges, practitioners, and scholars must reframe and, in some instances, reimaging the proper contours of copyrightability in order to bring living works under copyright protection" (Murray 2014). In addition – according to these scholars – copyright protection can be capable of producing the socially desirable balance of restricted and permissible uses of DNA sequences. Specifically, it would be able to achieve this balance by replacing the strict liability regime of patent law with the more flexible fair use defense and the fostering of a feasible open-source regime. Copyright protection of engineered DNA sequences could be also seen as a new way of framing discussions between genetic information and all attempts to abridge the full access to it. This result could be realized by applying to the genetic information a similar regulatory regime like the one used for the "free code": an intangible resource of public utility, which must be acknowledged paternity but not full ownership, whose exploitation is subject to transparency, not opposed to but distinct from the market (Madison et al. 2010; Contreras 2010).

Apart from this quite provoking approach, it is indisputable that scientific knowledge must be open and free in order to maximize public benefit. The current patent scheme seems incapable of serving this purpose because it is not able to deal with the potential abuse of genetic materials. Biotech inventions derived from genetic materials may be economically rewarding for investigators and patent holders but too often are not likely to benefit the community or individual from whom they are taken.

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[27] See complaint at 19, 22–25, Ass'n for Molecular Pathology v. US Patent & Trademark Office, 702 F. Supp. 2d 181 (S.D.N.Y. 2010) (No. 09 Civ. 4515).

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Microbiological Inventions and Intellectual Property Rights

3

Rajashree Sharma

Abstract

The function of the World Trade Organization (WTO) and the Trade-Related Aspects of Intellectual Property Rights (TRIPS) Agreement sets minimum standards for intellectual property protection. The objective of the above agreements is to ensure that each member state creates laws, regulatory mechanisms, and policies designed to protect IP rights, thus facilitating global trade. The agreements recognize the territorial nature of intellectual property rights. Article 27 of TRIPS states "that inventions are patentable provided that they are new, involve an inventive step and are capable of industrial application" without defining what is an invention. TRIPS allow patentability of microorganisms, and several landmark judicial decisions set the criteria of patentability of living forms including microbiological inventions. Microbiological inventions encompass new products, processes, uses, and compositions involving materials of biological origin. The ambit of these inventions includes innovation and methods to isolate and/or to create new organisms, modify characteristics, or find new and improved industrial application. The patent laws around the world were modified to now require the deposit of the microbiological material if the said microorganism is the focus of the patent application. As a result of intensive scientific research, biotechnology has emerged as one of the most innovative and promising technologies. New drug development based on microorganisms for cancer and HIV/AIDS is the new paradigm in science and technology. The Indian Patents Act, 1970, as currently in force, does not comprehensively define what is patentable in biotechnology and allied disciplines. Rather Section 3 specifies a list of biotechnological inventions that cannot be patented. Indian Patent laws and regulations require mandatory disclosure of biological material and specifies requirement for prior approval from the National Biodiversity Authority (NBA), and fair and equitable

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H. B. Singh et al. (eds.), *Intellectual Property Issues in Microbiology*,
https://doi.org/10.1007/978-981-13-7466-1_3

benefit sharing issues arising out of the use of bio-resources under the Indian Patent Regime exist, thus limiting access and benefit to inventors.

Keywords
WIPO · TRIPS · Indian Patents Act · TKDL

3.1 Introduction

Intellectual property rights (IPRs) provide certain exclusive rights to the inventors to reap commercial benefits from their invention. The importance of intellectual property rights was first recognized in 1883 in the Paris Convention for the Protection of Industrial Property and in 1886 in the Berne Convention for the Protection of Literary and Artistic Works. Both treaties are administered by the World Intellectual Property Organization (WIPO). As IPR has a vital role in the economy of a country, therefore, an efficient and equitable intellectual property system can help all countries to realize intellectual property's potential as a catalyst for economic development and social and cultural well-being. WTO and TRIPS recognized the territorial nature of intellectual property rights and drafted the agreement in very general terms maintaining appropriate local differences. The efficient and equitable intellectual property system helps strike a balance between the interests of innovators and the public interest, providing an environment in which creativity and invention can flourish, for the benefit of all. Therefore, TRIPS is the most important multilateral instrument for the globalization of intellectual property laws.

The Uruguay Round of TRIPS focused on patentable subject matter regarding biological materials. "(A) Plants, animals, essential biological process of production of plants and animals may be excluded from patenting. However, provides protection of plant variety by sui generis system under Protection of Plant Varieties & Farmers' Rights Act, 2001 (PPV&FRA); and (B) microorganisms per se and microbiological and non biological processes are patentable."

The intellectual property rights (IPRs) in India is more than 150 years old and provides statutory protection to most of the IPRs. There are several amendments to various IP legislations over the years as India is a signatory to a wide range of international treaties and conventions. The Patents Act was instituted in India in 1856, and since then it has been amended several times. After the President's assent in 1970, it came as a Statute "the Patents Act 1970." In 2005, the product patent regime was introduced with comprehensive and consolidated provisions related to patents. The Act was amended to make it TRIPS-compliant after completion of 10 years transition period (1995–2005). The amended Patents Act introduced product patents in foods, medicines, and chemical substances. India signed Patent Cooperation Treaty (PCT) in 1998, a single window mechanism for international patent filing that facilitates the streamlining of the filing procedure, and as an outcome, filing patent applications including PCT National Phase Applications has increased manifold in India. Considerable changes have been also made in the patenting procedure

through the introduction of Patents Rules, 2003, which were further amended from time to time since 2005, better outcome in efficiency in new practices and procedures with an evolving strategy for better focus for future. The Patents Act confer the rights of patentee as an exclusive right to prevent third parties "(a) where the subject matter of the patent is a product, the exclusive right to prevent third parties, who do not have his consent, from the act of making, using, offering for sale, selling or importing for those purposes that product in India; (b) where the subject matter of the patent is a process, the exclusive right to prevent third parties, who do not have his consent, from the act of using that process, and from the act of using, offering for sale, selling or importing for those purposes the product obtained directly by that process in India."

In this chapter we will discuss about microbiological inventions and how these inventions can be protected under the patent system. Indian patent practice and jurisprudence with respect to the patenting of biological/genetic materials are relatively new, and since 2013, guidelines to examine biotechnological inventions including microbiology made the practice and procedure settled and uniform. Biotech industry is one of the fastest-growing knowledge-based industries in India having a pivotal role in economic development by reaping benefits from its rich bioresources with enabling provisions for the protection of intellectual property in biotechnological inventions. Being one of the biodiversity-rich countries with four biodiversity hotspots, India has turned into a biotech hub and globally attracting collaborations, R&D and FDI, etc.

3.2 Trade-Related Aspects of Intellectual Property Rights (TRIPS) Agreement and the Intellectual Property Rights (IPRs)

TRIPS has set out a minimum standard in order to protect intellectual property rights, which include patent apart from copyright, trademark, geographical indications, etc. The TRIPS Agreement not only is aimed at the protection of IPR but also their due enforcement and made it mandatory globally for every member nation to make sure that the domestic laws are at par with TRIPS when they come to intellectual property rights. In Article 27(1), TRIPS mandates standards concerning the scope and use of patent, "patents shall be available for any inventions, whether products or processes, in all fields of technology, provided that they are new, involve an inventive step and are capable of industrial application. Patents shall be available and Patents rights enjoyable without discrimination as to the place of invention, the field of technology and whether products are imported or locally produced." Microorganisms were made patentable according to the TRIPS Agreement.

The TRIPS Agreement does not define "invention" per se; however, national laws defined this concept according to the standards set out as statutory rights enacted by the law-making authority of that country. But all these are subject to normal tests of novelty and inventiveness capable of industrial application. There is no uniform practice to distinguish between "invention" and "discovery." A

"discovery" is commonly considered to mean the mere recognition of what already exists and considered as "product of nature," and certain substances isolated or derived from naturally occurring substances by the way of human intervention are "inventions" and considered as "product of human ingenuity." As per the basic principles of patent law, the former is non-patentable, and the latter is patentable subject matter.

3.2.1 The Classic Case Law of "Discovery" v "Invention" Is the Myriad Case (No. 12-398) (569 U.S. June 13, 2013) on Patentability of Human Genes

This was a landmark case on the practice of gene patenting. In 2009, a group of plaintiffs led by the American Civil Liberties Union (ACLU) and the Public Patent Foundation (PUBPAT) filed a lawsuit against Myriad Genetics, the US Patent and Trademark Office (USPTO), and other defendants. The lawsuit – Association for Molecular Pathology, etc. v. US Patent and Trademark Office, etc. – alleges that patents on two human genes associated with breast and ovarian cancer (BRCA1 and BRCA2) are invalid and unconstitutional. The plaintiffs claimed that under Section 101 of Title 35 of the United States are non-patentable subject matter of nature and a mere isolation from nature, i.e., the human body. Myriad Genetics, a leading molecular diagnostic company based in the United States, obtained patents on two human genes as genetic base for breast and ovarian cancer that correlate to the risk of BRCA1 to the long arm of chromosomes known as BRCA1 and BRCA2. These patents claim every naturally occurring version of those genes, including mutations, on the theory that Myriad invented something patent eligible by isolating the genes from the body and sequenced, which place women at high risk for breast and ovarian cancer. Petitioners are primarily medical professionals who regularly use routine, conventional genetic testing methods to examine genes but are prevented by the plaintiffs from examining and taking a second opinion on predisposition of the human genes BRCA1 and BRCA2 that Myriad claims to own. However, the respondent argued that they received patents for isolated gene sequences as they render different characteristics in DNA sequences when isolated from human body and should be treated at par with other chemical compounds. Are human genes patentable? In this case "isolated" DNA does not have significantly different characteristics from the one found in nature. Both are DNA, and their structures are not notably different, the protein coded for by each is the same, and their use in storing and transmitting information in a sequence about a person's heredity is identical.

In the lower courts, the company's claims on BRCA1, BRCA2, and cDNA patents were decided as invalid as per35 USC Section 101 because the DNA segments were not separate from nature. The significance of Myriad's work on the BRCA1 and BRCA2 genes for breast and ovarian cancers is enormous "but mere separation of gene from its surrounding genetic material is not an act of invention" and "discovery, by itself, does not render the BRCA genes" eligible for patent; the mere changes made to the chemical structure of the genes or to the molecule would not

deem their work patentable. In 2013, the Supreme Court of the United States ruled in Myriad's patents that isolated genomic DNA (gDNA) is not patentable under Section 101 of the Patents Act, but complementary DNA (cDNA) is. The court held that the portion of DNA isolated from its natural state sought to be patented is identical to that portion of the DNA in its natural state; and that cDNA is a synthetic creation not normally present in nature. Therefore, Myriad Genetics did not create or alter the genetic information found within BRCA1 and BRCA2, what the company did was uncover the exact location and genetic sequences of the two genes within their respective chromosomes, the isolated portion of DNA from natural state and is in fact identical to that portion of DNA, which is in natural state (human body) and decided that such a mere could not be counted as patentable as a naturally occurring DNA segment is a product of nature and not patentable, merely because it has been isolated, but complementary DNA (cDNA) is patentable subject matter because it is not naturally occurring and a synthetic creation.

In the case of *Funk Brothers Seed Co. v. Kalo Inoculant Co.* 333 U.S. 127 (1948), the field of the invention of the impugned patent was a mixture of naturally occurring bacteria strains that helped plants extract nitrogen from the air and fix it in the soil, improving nitrogen levels, a discovery made by farmers. This mixture of the strains was not deemed as patentable by the court and held that the patent holder had not altered the bacteria by any intervention by way of technology in any way and thus the bacteria, whether on their own or mixed together, "fell precisely within the exception of law of nature" and an aggregation of select strains only. The majority of the Court opinion held that the properties of inhibition or non-inhibition in the bacteria were "the work of nature," and therefore not subject to being patented. "Patents cannot issue for the discovery of the phenomena of nature." The court further held that it was a mere state of the art to make the production of mixed inoculants a simple step; it may have been a product of skill, but it certainly was not the product of invention.

According to Article 27(1), each country should carefully consider the economic, legal, and ethical aspects involved in the patenting of living materials such as LMOs and GMOs, etc. The Agreement allows member countries to interpret "inventive step" as synonymous with "non-obviousness." One of the options to check and comply with the term invention relates to the concept of "prior art" to ascertain the novelty with reference to the prior arts, which may be defined more or less broadly about the processes that are not novel but the produce by that process is a novel product or both. To overcome the test of prior art, the invention should be sufficiently disclosed so that a person skilled in the art should be able to arrive at the invention without any undue burden of experiment.

Anticipation is another test to reject a patent – If an invention is disclosed in a patent application or in any publication before the date of priority of the application, then on the basis of anticipation the patent/patent application may be rejected, and if the inventor proves that the research paper was published without his/her consent, then it may not be considered anticipated.

- The test of prior publication was established in *Farbewerke Hoechst Aktiengesellschaft Vormals Meister Lucius v Unichem Laboratories*, wherein the court held as follows:
- "*to anticipate a patent, a prior publication or activity must contain the whole of the* test of anticipation and prior publication was established in *Farbewerke Hoechst Aktiengesellschaft Vormals Meister Lucius v Unichem Laboratories*, where the court held:
- "To anticipate a patent, a prior publication or activity must contain the whole of the invention impugned; i.e., all the features by which the particular claim attacked is limited. In other words, the anticipation must be such as to describe, or be an infringement of the claim attacked."

Similarly, in *Lallubhai Chakubhai Jariwala v Chimanlal Chunilal and Co*, the court observed that:

- "The two features necessary to the validity of a patent are novelty and utility, but the real test is the novelty of the invention. Novelty is essential, for otherwise there would be no benefit given to the public and consequently no consideration moving from the patentee [while interpreting the factor related to public knowledge and public use]."

Where the opponents fail to establish "prior publication" as well as "prior public knowledge" for an invention, however, the inventor has not been able to sufficiently describe the invention, which does not function in the way claimed by the applicants, and the application for grant of patent is liable to be rejected. The sufficiency of disclosure and enablement to describe the invention in a way is very important.

Exclusions covered by TRIPS Article 27(2): "Members may exclude from patentability inventions, the prevention within their territory of the commercial exploitation of which is necessary to protect ordre public or morality, including to protect human, animal or plant life or health or to avoid serious prejudice to the environment, provided that such exclusion is not made merely because the exploitation is prohibited by their law."

3.3 TRIPS and Microorganisms

Article 27(3)(b) TRIPs states "Members may also exclude from patentability plants and animals other than microorganisms, and essentially biological processes for the production of plants and animals other than non-biological and microbiological processes."

The language used in Article 27(3)(b) embodies a clear distinction between plants and animals and microorganisms. This, in turn, leads to a presumption that there is a common definition of the term "microorganism" which is acceptable to all signatories of the Agreement and that this definition is regarded as sufficient for the purposes of distinguishing between that which is patentable and that which is not.

As the microorganisms are excluded from non-patentability, a conjoined reading with Section 3 (c) of the Patents Act, 1970 implies that only those modified/purified microorganisms do not constitute discovery of living thing occurring in nature or mere isolation from nature are patentable subject matter under the Indian Patents Act.

Patenting of microorganism is permitted as applicable only to genetically modified microorganisms and not to those existing in nature. In accordance with the scientific concept the national legislation adopted, a "microorganism" is a member of any of the following categories: bacteria, fungi, algae, protozoa, or viruses. Section 3(b) of the Indian Patents Act excludes "inventions primary or intended use or commercial exploitation of which could be contrary to law or morality or which causes serious prejudice to human, animal or plant life or health or to environment." TRIPS Article 27 mandates that patents are granted on the utility function of the gene, i.e., the sequence or expressed sequence tag (EST) can be patented if it is useful and not merely isolated but has substantive human intervention. All patent offices in India have now included a new section in its Manual and Guidelines on examination of biotechnology inventions, whereby microorganisms need to qualify for patenting if modified through substantial human intervention.

3.3.1 Linkages Between the TRIPS and the Convention on Biological Diversity (CBD)

The growing importance of biotechnology worldwide and the increasing number of patents granted to biotechnology-based inventions highlight the potential value of genetic resources and associated TK as source material for biotechnology inventions. The concern with inventions based on biological resources is not only about the tangible physical resource but also about the intangible information associated with that resource, referred to commonly as traditional knowledge (TK). Individual countries' national laws on IPR particularly patent law need to be harmonized in the biodiversity-rich countries and amended in order to disclose the biological material, source of the biological resource, and/or the traditional knowledge used in the invention and evidence of prior informed consent through approval of authorities for a patent application relating to biological materials or to traditional knowledge. The CBD itself did not create any new intellectual property rights for indigenous peoples, and the WTO and the TRIPS will be the basis for any intellectual property rights.

Thus framework for linkages was essential for implementing the TRIPS Agreement and the CBD in a mutually supportive manner. The TRIPS Agreement was the first of its kind of an international agreement governing the protection of intellectual property and Article 27.3(b) of TRIPS Agreement which deals with patentability or non-patentability of plant and animal inventions and microorganisms and the protection of plant varieties. Patents are territorial in nature and had been governed solely by national law, while the World Intellectual Property Organization (WIPO) coordinated the different national legislations and mandated national

treatment, and the exact nature of the rights afforded under patent legislation, including patent requirements, restrictions, and rights, was left to national jurisdiction.

The CBD formally replaced the common heritage of mankind doctrine with national sovereignty as the guiding principle governing control over biodiversity. As per CBD the genetic material is any material of plant, animal, or other origins containing functional units of heredity and defines genetic resources as genetic material of actual or potential value. Aiming to preserve biological diversity and arrest environmental degradation, the Convention created a set of international legal guidelines governing biological resources worldwide. Article 27 of the TRIPS provides a broad scope for protection, allowing for the patenting of any inventions, whether products or processes, in all fields of technology, provided that they are new, involve an inventive step, and are capable of industrial application. These contradictions are more restrictive objectives of the CBD. Article 15.1 of the CBD recognizes the sovereignty of source nations and allows nations to determine access to their genetic resources.

The CBD recognizes the sovereign rights of the states over their natural resources while simultaneously mandating efforts toward sharing of genetic resources and the technologies and innovations resulting from their use (CBD Article 15). The CBD stipulates that states share genetic resources under their national sovereignty according to a general framework established by the agreement, subject to specific national legislation.

Article 2 states "Genetic material" means any material of plant, animal, microbial or other origin containing functional units of heredity. "Genetic resources" means genetic material of actual or potential value.

Article 2 of Nagoya Protocol on Access to Genetic Resources and the Fair and Equitable Sharing of Benefits arising from their *Utilization to the CBD states*:

- "'Utilization of genetic resources' means to conduct research and development on the genetic and/or biochemical composition of genetic resources, including through the application of biotechnology as defined in Article 2 of the Convention."

In India, patent office sets guidelines for prosecution of patent applications relating to traditional knowledge as part of the linkage between the TRIPS Agreement and the UN Convention on Biological Diversity (CBD) on the issue of Access to Genetic Resources and the Fair and Equitable Sharing of the Benefits Arising from their Utilization. India has also been able to sign Traditional Knowledge Digital Library (TKDL) Access (Non-Disclosure) Agreements with USPTO, EPO, JPO, etc. Consequently, many patent applications concerning India's traditional knowledge have either been canceled or withdrawn or claims have been amended in several international patent offices.

3.4 Protection to Microbiological Inventions

As there is no single scientific definition of a "microorganism" in the Patents Act anywhere, local patent purposes, it has to be carefully scrutinized to assess whether this is in compliance or a violation of the mandates set down in Article 27(3)(b). Conventionally a microorganism is considered as an organism that is microscopic. The microorganisms are of microscopic size, and the term "microorganism" includes organisms which differ widely from one another in form, life cycle, and mode of life. Under a microscope they are usually of the order of microns (millionths of a meter) or tens of microns in linear dimensions and include bacteria, mycoplasma, yeasts, single-celled algae, and protozoa. Multicellular organisms are normally not included, nor fungi apart from yeasts. Viruses are also not automatically included; many scientists do not classify them as organisms as they depend on cells to multiply. The term microorganism is derived from the minute size of the various organisms. Viruses are included though they are noncellular particles which are not capable of independent life and can proliferate only in living cells (microorganisms, function, form, and environment) (Hawker and Linton 1977). Many organisms have properties which mean that they cannot be readily characterized into a particular kingdom. There are many examples of which green algae are fairly typical. Green algae have many properties in common with members of the plant kingdom, e.g., they contain photosynthetic pigments and are autotrophic, and yet many are microscopic and unicellular and can thus be considered to be microorganisms. Furthermore, fungi are frequently included in the term microorganism, and yet many fungi are too large to be considered microscopic.

The genetic engineering of microbes involves practical applications in biomedical, chemical, food/agribusiness, as well as bioremediation and environmental restoration arenas. Biotechnology exploits biological materials, living or nonliving, and is broadly classified as classical and modern biotechnology. The age-old fermentation process for producing alcohol and isolation of antibiotics from molds or other microorganisms are only a few examples of classical biotechnology. Modern biotechnology started with the genetic engineering which developed in the late 1970s of the last century. Naturally occurring microorganisms, or, any form of natural microbes cannot be patented per se, without substantial human interventions through biotechnology (Singh et al. 2016a, b). Biotechnology is defined as "any technique that uses living organisms or substances from those organisms to make or modify a product, to improve plants or animals, or to develop microorganisms for specific uses." DNA is isolated, modified, and transformed into other organisms to carry out a desired function. This method has revolutionized ways to treat and study human diseases. Human insulin, for example, can be produced in bacteria *Escherichia coli* in large masses. In genetic engineering, an identified gene of other organisms that are responsible for a certain function is isolated, and it is introduced into another organism, letting the gene express and benefit from it. The introduction of foreign genes into an organism's genome is performed through the techniques of recombinant DNA technology (rDNA). The organism to which the gene has been introduced is called the genetically modified organism. When a certain food is

produced through a genetically modified organism, it will be a genetically modified food. Production of food and medicine has been the main practice performed through genetic engineering. In addition, the use of genetic engineering has been starting to benefit the agricultural crops so that there may be an increased immunity against insects or herbicides. Microbiological inventions can include new products, processes, uses, and compositions involving biological materials; inventions can also cover methods to isolate and obtain new organisms, improve their character, modify them, and find their new and improved uses, and new microorganisms isolated for the first time from the natural surrounding can only be patented if they differ in character from the known microorganisms and find a new or improved use or function. Synergistic compositions of new or known microorganisms can also be patentable, as can processes for isolating such substances. Patent claims to microorganisms have been allowed on the grounds that they are the products of microbiological processes.

An example of a granted claim in Indian Patent Office on novel modified microorganisms: "The present invention relates to a modified microorganism comprising a mutation that disrupts the expression of the nucleotide sequence defined herein as SEQ ID No. 15. It also relates to bacterial genes and proteins, and their uses. More particularly, it relates to their use in therapy, for immunization and in screening for drugs."

The patent laws around the world were modified in such a way that they now require the deposit of the microbiological material if the microorganism is the subject matter of the patent application. As a result of intensive scientific research, biotechnology has emerged as one of the most innovative and promising technologies and an important part of the modern economy. For this reason, the India has also developed new guidelines on examination of biotechnological inventions and traditional knowledge and biological material to harmonize the different legal protection systems of biotechnological inventions. The commercial application of microbiology in the agricultural industry has shown tremendous expansion in the last few years. Along with these developments, the ethical and legal issues have also arisen. As one more test has to be passed apart from the three tests such as novelty, non-obviousness, and capability of industrial application and unlike other countries, Indian Patents Act provides a fourth test, that is, Section 3(d), with regard to comparative and efficacy data to prove improvement and efficacy of the product.

US Patent Law in 1949 was modified in such a way that they now require the deposit of the microbiological material, if the microorganism is the subject matter of the patent application. The European Union has developed a new Directive to harmonize the different legal protection systems of biotechnological inventions. Some articles in this Directive, which has come in force recently, are related to microbiological inventions. The European legislation has been modified in relation to the terminology used in this kind of inventions: the term "microorganism" has been replaced by the term "biological material," to cover all entities which need to be deposited so as to cope with the requirement of sufficiency of disclosure. The EU Directive defines "biological material" as any material containing genetic information and capable of self-reproduction or of being reproduced in a biological system

and "microbiological process" as any process involving or performed upon or resulting in microbiological material.

The patenting of microorganisms requires that the invention is disclosed sufficiently keeping unity of invention clear so that a person skilled in the art can perform it to arrive at the invention, and in case of microbiological invention, it will not be able to disclose the invention unless the samples are publicly available. In order to meet this requirement, "Budapest Treaty on the International Recognition of the Deposit of Microorganisms for the Purposes of Patent Procedure" has established the system of deposition of microbial cultures and microorganisms. The Treaty is an international convention governing the recognition of microbial deposits and officially approved culture collections which was signed in Budapest in the year 1977 and later amended in 1980. Because of the difficulties and on occasion of virtual impossibility of reproducing a microorganism from description in the patent specification, it is essential to deposit a strain in a culture collection center for testing and examination by others. Under this Treaty, if a sample of the microorganism is deposited with one IDA, the enablement requirement is deemed to be satisfied in all of the countries that have signed the Treaty. It obviates the need of describing a microorganism in the patent application, and further samples of strains can be obtained from the depository for further working on the patent. The guidelines for examination in the European Patent Office specify that "…propagation of the microorganism itself is to be construed as a microbiological process…; consequently the microorganism can be protected *per se* as it is a product obtained by a microbiological process." The drafting of the claims will vary depending on their subject matter. Product claims whose object is a microorganism per se can be characterized in the following ways: microorganism characterized by the accession number, the name of the depositary authority, and the name of the genus and, if possible, of the species.

Examples:

- EP 0436508, see Claim 1 "A biologically pure culture of mutant *Bacillus sphaericus* strain ATCC No. 53969."
- The German Patent Office allows isolated DNA patent claims, without the specific need to mentioning the utility within the claim itself.
- DE-B-19983297 (Flament et al.; US 6511838 corresponds) granted on July 4, 2013 covering naturally occurring gene sequences from a marine bacterium coding for a β-agarase.

Under Article 35 of the US Code on Patents, Section 101 states that discovered microorganisms that "exist in nature and newly discovered plant species per se are discoveries" and *not* inventions and, thus, do not meet the requirements of utility. Inventing genes, vectors including recombinant vector, recombinant proteins, or say transformants and fused cells or monoclonal antibodies whose utility is not defined does not meet the requirement of utility. Under Article 35 of the US CODE, biological material are defined as those, which are of self-replication either directly or

indirectly Cell organelles, Viruses, vectors including other non-living material that exist in say a living cell may be deposited by submitting the host cell which can aid the non-living material to self-replicate. As a case in point, a certain strain of *Lactobacillus* was deposited under accession number NCIMB 41114," Claim 1 corresponding to US patent #7152708 was referenced to "a biologically pure culture" of the same strain. Patent EP-B-2154238 was granted to claims on a strain of *Lactobacillus pentosus* for use in the preparation of fermented food and drink.

3.4.1 Case Laws on Patenting Microorganisms in Different Countries

3.4.1.1 Diamond v. Chakrabarty, 447 U.S. 303 (1980)

This was a landmark case, where the US Supreme Court's historic judgment established that a living microorganism can indeed be patented under extant US law.

Large oil spills create serious environmental and ecological problems. A solution to dealing with oil spills is to introduce bacterial strains. At that time, there were four known strains of oil-metabolizing bacteria – but their efficacy was limited. In 1971, Dr. Ananda Mohan Chakrabarty, while working as a researcher in GE, had successfully genetically combined the oil-metabolizing genes from all the existing stains and successfully engineered a new species of oil-metabolizing bacteria *Pseudomonas putida*, which could degrade oil spills at rates of 10–100 times faster than before.

GE filed patent applications, listing Dr. Chakrabarty as the inventor. The application contained three claims: (1) the method of producing the bacteria, (2) the inoculum comprising the carrier material and the bacterium vector, and (3) the claim on the bacterial species itself. Two of the three above claims, excluding the claim on the bacterial species itself, were accepted, however the claim on patent for the bacteria was rejected.oil metabolizing. At that time the patent office stated that bacteria are naturally occurring and that living organisms cannot be patented within US Patent Law under Section 101 of Title 35 U.S.C.[3].

The Board of Patent Appeals and Interferences also took the same position. However, when the case was heard by the US Court of Customs and Patent Appeals (USCCPA), the board ruled in favor of Prof. Chakrabarty's favor, noting that "the fact that microorganisms are alive is without legal significance for purposes of the patent law."

The then Commissioner of Patents and Trademarks, Sidney A. Diamond, appealed to the US Supreme Court, and the case was argued and decided in Chakrabarty's on June 16, 1980. Subsequently the USPTO granted a patent on March 31, 1981.

US Supreme Court (SCOTUS) Decision[1]

The Supreme Court, in a 5–4 ruling, allowed for the patent cited the following (Judgment Excerpt)

> "A live, human-made microorganism is patentable subject matter under 35 U.S.C. § 101. Respondent's microorganism constitutes a 'manufacture' or 'composition of matter' within that statute. The claim was based on non-naturally occurring manufacture or composition of matter—a product of human ingenuity. Diamond v. Chakrabarty concerned the addition of four plasmids to a bacterium, enabling the bacterium to break down various components of crude oil. The court held that the modified bacterium was patentable because the addition of the plasmids rendered it new, 'with markedly different characteristics from any found in nature."

This *single most important landmark judgment* has helped accelerate the development of the US biotechnology industry by extending the umbrella of patent protection. The pace of innovation in biotechnology quickened and has brought to the market wide-ranging developments like regenerative medicines, genetically engineered microorganisms, custom-tailored antibodies, etc.

The British Patents Act of 1977 allows biological material, which is isolated or has been created using a new technical process to be considered as an invention, even though it may have earlier occurred in nature. Claims to microorganisms are allowed in cases where the said microorganisms produced or created using a microbiological process. Subsequently, the Patent Rules 2000 clarified that invention or creation of biological or biotech products, including gene sequences, can be the subject for patent applications.

In Brazil, as per Patent Law, living beings, in whole or in part, should not be patentable except for transgenic microorganisms. However the patent application must pass the three requirements – (1) patentability-novelty, (2) inventive step, and (3) industrial application. Transgenic microorganisms – excluding naturally occurring plants or animals – have been defined as organisms where human intervention is responsible in changing the genetic composition, so that these transgenic microorganisms express a desired altered characteristic, which for the said species in question is impossible under natural conditions. An example would be a transgenic bacterium that has been genetically modified to create human proteins for use in medicine, which the organism would otherwise not have produced without human intervention.

In China too patent claims on microorganisms are allowed. While claims to naturally occurring DNA sequences might be considered as products of nature, however, patent claims allow for "purified and isolated" DNA sequences to be considered if it is a result of human intervention. An excised gene can be patented as composition of matter or as an article of manufacture if the DNA sequence in question does not naturally occur in that isolated form without human intervention. Similarly, synthesized DNA preparations can also be patented if their purified state doesn't naturally occur.

[1] https://supreme.justia.com/cases/federal/us/447/303/

In Japan, microorganism includes protozoa, viruses, unicellular algae, actinomycetes bacteria, molds, yeast, mushrooms, etc. But the definition further allows inclusion of differentiated plant or animal cells or tissue cultures. In 1997, the Japanese Patent Office divided inventions in the biotechnology into four genres – microorganisms, genetic engineering, plants, and animals. Inventions in genetic engineering include vectors, genes, recombinant proteins, monoclonal antibodies, recombinant vector, transformants, and fused cells. Like in US law, Japan allows for microorganisms' patents for microorganism itself, as well as for the process and use/application of the microorganisms.

3.4.1.2 European Patent Office Decision: "Is the Claimed Microorganism Sufficiently Disclosed Without a Deposit?" This Is a Case of Biological Deposit Enabling Sufficient Disclosure to Grant a Patent on Microbiological Invention

An interesting European case that resulted from the patent application No. 06819369.7 which was refused by the patent examiners in Europe which ruled that the subject matter of 22 claims filed with letter on August 10, 2009, was "insufficiently disclosed," thus nonconforming with Article 83 EPC. In this patent application, Are Nylund was listed as the inventor and applicant at Intervet International B.V., Boxmeer, Netherlands. On rejection of the patent, applicant (appellant) filed an appeal against the decision of the patent examiners who had refused the patent application No. 06819369.7.

The claims don't mention the deposited strain per se. However, if the patent application describes and provides "sufficient guidance" on the method of re-isolating the claimed microorganism, then it should not be of consequence whether the deposit was in conformance of stipulated legal requirement. Claim 1 of the above examination appeal refers to a bacterium that causes Cod's syndrome in cod. Thus, the requirement of a deposit submitted to recognized depositary institution is required, only if the material is unavailable to the public and hence can't be described in the patent application in a manner that allows the invention to be replicated by those skilled in the art. This landmark judgment opens up new opportunities for obtaining patents related to live microorganisms subject to fulfilling basic criteria for patenting. In the above case, the inventor had deposited the strain well before the priority date. Additionally, in the priority document, the inventor who is different from the applicant had referred to the deposit. Unfortunately, the crux of the matter came to authorization – the depositor hadn't properly authorized the applicant to refer to the deposited material. Thus, the European Board of Appeal (Board) refused to allow the applicant to benefit from the deposit and to argue the enablement of the invention. (The decision was based on Rule 28(1) (d) EPC 1973, corresponding to Rule 31(1)(d) EPC2000.)

The subject matter of claims before the Board pertained to a rod-shaped bacterium that triggers Cod's syndrome in fish.

Neither the applicant of the priority application nor the applicant of the international application was properly authorized by the depositor of the microorganism to refer to the deposited material in accordance with Rule 28(1)(d) EPC 1973, since

the depositor's declaration of February 8, 2016, was submitted after 16 months from the priority and the international filing date, respectively, as requested by Rule 28(2)(a) EPC 1973. The declaration of January 24, 2007, is no authorization on behalf of either of the two applicants and postdates the priority and the filing date in any case. Furthermore, the declaration of January 24, 2007, reached the Office on September 17, 2009, which is again after 16 months of time limit set by Rule 28(2)(a) EPC 1973. Since the claimed microorganism cannot be re-isolated readily and since no documents were submitted to the European Patent Office within the time limits foreseen by Rule 28(2)(a) EPC 1973 that the applicants of the priority and of the patent application were authorized to refer to the microorganism deposited under accession number CNCM I-3511 at the CNCM (Institut Pasteur, Paris), the claimed invention was not disclosed in a manner sufficiently clear and complete for it to be carried out by a person skilled in the art (Article 83 EPC). Therefore, the Board concludes that the invention was not sufficiently disclosed under the legal provisions of the EPC, neither at the priority date (November 10, 2005) nor at the international filing date (November 6, 2006). This decision refers exclusively to the examination of the requirements of Article 83 EPC.

3.5 Microbial Drug Development

Drugs derived from microorganisms continue to make important contributions to drug development today, and bacterial-based therapies may represent a particularly promising new strategy in cancer treatment. In cancer therapy bacteria are used as sensitizing agents for chemotherapy. Further some bacteria are also used as vectors for drug delivery to affected organs in cancer patients. Gene therapy also utilizes transgenic bacteria as agents. There are emerging reports on the use of live and virulence-attenuated bacteria for the treatment of cancers. Few bacterial species such as *Salmonella*, *Clostridia*, and *Mycobacterium bovis*, when injected intravenously, intramuscularly, or other means, have the ability to enter into the human tumors and allow tumor regression. Also, the use of genetically modified bacteria where genes necessary for virulence factors production are removed or silenced has shown promising potential for selective destruction of tumors. Such bacteria can potentially find use in targeted cancer-destroying agents for tumors. They are also used for combinational bio-chemotherapy treatment of cancer.

There are many patent claims on bacterial proteins that display promise as anticancer agents. Some transgenic bacteria-produced proteins can potentially act as both anticancer and antiviral agents. They are also often antiparasitic. In addition to cancer treatment, many of the patent claims on newer synthesized bacterial proteins display promising potential uses in the treatment of diseases including malaria, parasitic diseases, and other viral diseases. Some synthesized biotech products show great promise in the treatment of HIV/AIDS.

"*P. aeruginosa* secretes a periplasmic protein azurin, as well as CpG-rich extrachromosomal, DNA, on exposure to cancer cells. Patents also covered the use of CpG-rich DNA,

including bacterial DNA and azurin-like protein Laz from gonococci/meningococci, as potential anticancer agents." (Dr. AM Chakrabarty 1996)

Patents have been granted for compositions containing broad spectrum anti-HIV/AIDS agent, a protein of microbial origin (Chakraborty 1996). In many of these cases, the required proteins are secreted by microorganisms. The use may be both in pathogenic and in nonpathogenic modes. Azurin has great potential in treatment of many diverse diseases. Azurin attacks the HIV-1 as well as the malarial agent *P. falciparum*. It also attacks the parasite *T. gondii* that causes toxoplasmosis.

Moreover, through microbial activity, hundreds of antibiotics such as streptomycin, penicillin, tetracyclines, erythromycin, polymyxin, bacitracin, etc. are derived. Modern vaccine development is undergoing a paradigm shift. Advances in many fields and computing have enabled the high-throughput technologies for leveraging functional and structural genomics. Reverse vaccinology leads the pan-genomic opportunity for the identification of novel vaccine candidates. More recent development in synthetic genomics shows promising opportunity to design custom tailored vaccines.

Tailored viruses are increasingly being used as targeted vectors or delivery mechanisms to carry drug and disease treatment material to target organs and cells. Cutting-edge current research shows potential of these vectors in the hereditary diseases, in genetic engineering, and in the treatment of cancer.

3.6 History of Microbial Patents

Though there is an ongoing debate on patenting living organism, patents on microorganisms are not a new phenomenon. The dairy, cheese, brewing, baking, wine, and tanning industries all have used yeast, renin, and a variety of other bioproducts. And many have obtained patents for their particular culture or strain of yeast and other biomaterials. For many new types of yeast, the patents have been granted in Belgium in 1833 and in Finland in 1843, and the patents are for the microbiological process. The United States had also granted a patent for a microorganism in 1873 (US 141072) to Louis Pasteur for the claim on "yeast free from organisms or germs of disease as an article of manufacture" (the microbiological process), and microorganisms are recognized as product of nature. Germany's Federal Supreme Court in 1975 ruled that microorganisms which are discovered can indeed be patented. Similarly, in the following year, the UK Court of Appeals allowed patent of mutant strains of bacteria. In the United States, patent office refused claims to grant patent to living organisms and rejected Anand Chakrabarty's patent application on modified bacteria that digests hydrocarbon. This trend was held up by the 1980 US Supreme Court decision on the Diamond v Chakrabarty case – which established in artificially produced strains of bacteria can be patented establishing for the first time that a live microorganism is patentable under US law. The patent was granted for the bacteria itself and the method of production as well as the vector. Thus, biological systems can have effective written description, principle of operability, and

reproducibility of written instructions. Indian Patents Act 1970 do not patent animals and plants per se. Moreover, specific industrial processes using microorganisms, etc. can be patented, as well as the process of producing the microorganism and how it is used can also be patented.

3.7 Microbiological Patent Jurisprudence in India

3.7.1 Provisions That Protect Microbes Under Patents Act, 1970

In conformance with countries, the Indian IPR law *states* "the subject matter claimed as the invention, must be new, non-obvious and industrially applicable." As, in other countries, in India too, the subject matter claimed as the invention must be new, non-obvious, and industrially applicable. What the above implies is that mere discovery of an existing compound or element which is present in nature is not patentable under Indian law for discovered component to be considered for patent patentable subject the component must have undergone sufficient transformation into a form that does not exist natively. For patentability claims to be tenable, transformation of microorganisms should come as a result of a distinctly defined process which results in technical advancement or increase in economic significance.

The Indian Patents Act does not comprehensively describe what is patentable. Rather, Section 3 of the Act specifies a list of items that cannot be patented or considered as a patent subject matter. This is of considerable significance for the biotech sector – Clauses 3(c), 3(d), 3(i), 3(j), and 3(p) are of particular importance for biotechnological inventions.

> Clause 3(c) states that "The mere discovery of a scientific principle or the formulation of an abstract theory or discovery of any living thing or nonliving substances occurring in nature." This means that products such as microorganisms, nucleic acid sequences, proteins, enzymes, compounds, etc., which are directly isolated from nature, are not patentable subject matter.

For instance, *Bacillus* sp. IN123 comprising rDNA (ribosomal DNA) sequence represented as SEQ ID No: 1 in the deposition is not patentable under the Patents Act, 1970 as it is merely isolated from nature *and characteristics are same from any found in nature*. Section 3(e) is another exception from patentability as it reads as "mere admixture resulting only in aggregation of the properties or a method of making such mere admixture."

For example, the following claim as constructed: "A composition of innovative combination of dormant spore of naturally occurring *Paecilomyces lilacinus* and *Arthrobotrys* sp. fungus with enzymes, fats and growth promoting molecules to control plant-parasitic nematodes"; here the two components do not show the advantages of their synergy composition over sum of their individual effects, and the synergistic effect is not shown.

The Clause 3(j) states that "Plants and animals in whole or any part thereof other than microorganisms including seeds, varieties and species and essential biological

processes for production or propagation of plants and animals as non-patentable invention."

This is an important feature of Indian patents with respect to microbiological inventions and differs from extant patent laws in Japan, Europe, the United States, and even China, where the patent regimes take a more liberal patent approach, in that patents are also granted to genetically modified organisms and plant varieties. However, this exception of non-patentability is in conformance with the TRIPS Agreement that specifies that for nonconforming exceptions member states need to provide an effective alternate legal protection of plant varieties (sui generis system).

Microbiological inventions encompass utility, uses, composition, processes, and products involving material biological origin. These include modes and means of isolating biological components and using genetic and other tools to modify them and tailor their characteristics and use them in new or specific application and use. Patenting new microorganisms depends on creating sufficient distinction, from other microorganisms extant previously – these new microorganisms for patent purposes should be sufficiently distinct in their form, function, and use differences. Genes and genetically engineered products are treated like chemical compositions. Patenting human or animal genes, like GMO foods and plants, raises some ethical, moral, and political issues. Even human genes are not included in the definition of biological materials.

In India, patent owners are afforded legal and commercial protection for their inventions, and patent ownership is granted for a period of 20 years. A patent provides patent owners with protection for their inventions, which is granted for a limited period; in India it is 20 years from the date of filing.

The Patents Act 2005 was enacted with the *objective of harmonizing* India's IPR regime in line with international treaties, especially with the Agreement on Trade-Related Aspects of Intellectual Property Rights (TRIPS). But, the TRIPS Agreement does not comprehensively or specifically define invention – the Indian Patents Act defined this concept as per the standards applied.

- *Invention* is defined in *Section 2(1)(j)* as a new product or process involving an inventive step and capable of industrial application.
- *Inventive step* of *Section 2(1)(j)* means a feature of an invention that involves technical advance as compared to the existing/"prior art"/knowledge or having economic significance or both and that makes the invention not obvious to a person skilled in the art.
- *Section 2(1) (ac)* defines "Capable of industrial application" that the invention is capable of being made or used in an industry.

The criteria for patentability of microbiological inventions specifies four basic requirements: three of which the invention itself must fulfill as per TRIPS compatibility, namely, (1) novelty, (2) inventiveness, and (3) industrial applicability, while the fourth one is the enhanced efficacy requirement test, i.e., which basically

translates the requirement of the amount of novel or difficulty or arriving at the invention.

Patents Act 1970 stipulates that "in order to acquire patent protection, the substance has to go beyond establishing the novelty, inventive steps, non-obviousness and industrial application test of enhancement of known efficacy of a known substance under section 3(d), which is not found in TRIPS. Section 3(d) specifically disallows patent protection for mere discovery of known substances unless such substance express substantial efficacy in the known substance. In effect of this provision it expressly excludes such substances having incremental innovations."

3.7.1.1 Technical Requirements for Microbiological Patent Applications in India

In court prosecution, arbitration and patent disputes involving microbiological invention investors need to establish the efficacy or novelty of the biological function of an invention beyond reasonable doubt; therefore, it is not only essential but vitally important to keep detailed experimental and efficacy data and process steps – both in vitro and in vivo. This helps to establish the effectiveness or advances generated by the claimed invention over prior art. The specific gene sequences and tags of the genetic material being claimed need to be described in sufficient detail in the accompanying description – the submission of SEQ ID in electronic form is mandatory. Insufficient disclosure and objections to the enablement of the claimed invention may be the reasons for refusal of a patent application. Additionally, if multiple rather than a single SEQ IDs is referred to, then it must be established beyond reasonable doubt that the multiple sequence of IDs is all so correlated that they are a single inventive step of the invention.

3.7.1.2 Disclosure and Enablement Requirements

In the Indian Patents Act, 1970, and as subsequently amended, genetic material or microorganism has not been specifically defined. Furthermore, for biological material from India, Form 1 of the Patents Act, 1970 (as amended), specifically requires declaration from the applicant in respect of biological material and necessary permission from the competent authority which is the National Biodiversity Authority (NBA) before the grant of patent.

The Biological Diversity Act, 2002 (BDA), on the other hand simply defines "biological resources." The said definition excludes human genetic material or value-added products derived from the biological material. Section 6(1) therein makes prior approval of NBA as a mandatory step for applying any patent or IPR for any research/information for biological resource obtained from India.

- Also, *Section 6(3) of BDA* exempts applicants seeking protection for using plant genetic resources under the Protection of Plant Varieties and Farmers' Rights Act, 2001 (PPV&FRA), and confers IPR to plant breeders who have bred or developed plant varieties. The Act has a provision of benefit sharing as well but requires notification to NBA.

- *Article 2(c) of BDA* "Biological Resources" means plants, animals, and microorganisms or parts thereof, their genetic material and by-products (excluding value-added products) with actual or potential use or value, but does not include human genetic material.
- *Article 2(p)* "Value-added products" means products which may contain portions or extracts of plants and animals in unrecognizable and physically inseparable form.

A patent application must disclose detailed information with regard to the invention that a person of ordinary skill in the field related to the invention is able to perform the invention. If the invention mentions a new biological material in the specification and such material is not available to the public, the applicant has to deposit the said biological material in the International Depositary Authority recognized under Budapest Treaty before filing of application. In India, Microbial Type Culture Collection and Gene Bank (MTCC) at the Institute of Microbial Technology (IMTECH), Chandigarh, and Microbial Culture Collection (MCC), Pune, are the recognized international depositories of microorganisms. A certificate of deposit and a certificate of viability of the biological material issued by the depository institution, depository number, sequence listing, functional aspects of biologics, etc. are required for completing a specification on microbiological invention for the grant of patent.

3.7.2 Patentability Criteria and the Judicial Intervention

3.7.2.1 Dimminaco AG vs. Controller of Patents and Designs

In the *Dimminaco AG* vs. *Controller of Patents*, the Calcutta High Court held in 2002 that a patent on a microorganism is valid. The court ruling interpreted that the Indian Patents Act does not exclude that a living end-product cannot be patented. This landmark court decision opened floodgates and started a scramble for patents and inventions where in many cases living microorganisms were the end-product of the claimed processes. Dimminaco AG filed a process patent application for a vaccine for infectious bursitis in poultry. It claimed a lyophilized microorganism. Application was rejected on the grounds that "the vaccine involved processing of certain microbial substances; this was only a natural process devoid of any manufacturing activities"; hence, therefore the application was turned down by the patent office on the grounds that the process was not an invention within the meaning of the Patents Act, 1970. On appeal, the Calcutta High Court considered the dictionary meaning of "manufacture" and "substance" and reversed the decision passed by the controller.

The Court held that "law does not bar processes where the end-product is a living organism. No statutory bar to accept a manner of manufacture as patentable even if the end product contains a living organism." One common legal test applied to patent claims is the *vendibility test*, which that product is capable of being sold and possesses commercial value, the patent manual and guidelines for biotechnology

inventions *states* that a "living entity of artificial origin such as microorganisms, or vaccines are considered patentable."

Until the defining Calcutta High Court judgment, under the, then, extant interpretation of Indian Patent Law, the legal position was that if a manufactured microorganism is physically indistinguishable from its naturally occurring counterpart, then such a microorganism cannot be the subject of a patent application. Alternatively, one may argue that the above is also non-patentable because it lacks novelty.

The landmark Calcutta HC judgment opens new opportunities for obtaining patents related to live microorganisms subject to fulfilling basic criteria for patenting. However, this raises a few issues vis-à-vis to existing Indian Patent Law. Neither the novelty of a process used to produce a product of nature nor the unprecedented status of its discovery can cure the inherent non-patentability of the product. The utility and consequent value of the product is irrelevant to its status as patentable subject matter. However, Section 3(c) of the Indian Patents Act provides that "The mere discovery of a scientific principle or the formulation of an abstract theory or discovery of any living thing or non-living substances occurring in nature." It is quite clear that it does not prohibit any invention which is result of human intervention, where living beings has been used initially for conducting experimentation.

3.7.2.2 The Monsanto Technology, LLC's Patents on Bt Technology and Debate with Regard to Section 3(j) of the Patents Act, 1970

Monsanto owns several patents for one particular *Bacillus thuringiensis* (Bt) gene sequence in a cotton genome. The technology involved over a certain gene sequence of the Bt bacteria as inserted into a cotton genome. Seed companies from the National Seed Association of India (NSAI), particularly Nuziveedu, provide their seeds to Monsanto, which then inserts its Bt genes in Nuziveedu's seeds. If Nuziveedu's seeds are of a new variety, the variety can be registered under the Protection of Plant Varieties Protection and Farmers' Rights Act (PPV&FRA), 2001, and Nuziveedu enjoys a monopoly protection of their seeds. Nuziveedu's seed products sold to the farmers are protected by two forms of IP Protection – (1) under the Patents Act belonging to Monsanto and (2) the other under the PPV&FRA belonging to seed companies like Nuziveedu. Both the IPRs are rightfully coexist. However, the argument of NSAI is that GM traits are patentable, but once they are introgressed into cotton genome, the resulting transgenic variety is not patentable because of Section 3(j) of the Patents Act, 1970. The following patents of Monsanto created a debate on patentability criteria under Section 3(j).

3.7.2.3 Monsanto's Patent No. 232681, Titled "Cotton Event MON 15985 and Compositions and Methods for Detection"

Claim No. 1 read as follows "An insect resistant cotton plant, or parts thereof, seed of said cotton plant having been deposited with the American Type Culture Collection under accession number PTA-2516."

Claim 2 is on similar lines "An insect resistant cotton plant, or parts thereof, wherein DNA having at least one nucleotide sequence selected from the group of

SEQ ID NO: 14, SEQ ID NO: 15, SEQ ID NO: 16, SEQ ID NO. 17 and SEQ ID NO.18 forms part of the plant's genome." The remaining claims are dependent on Claim 1 and Claim 2. These claims are allegedly contrary to Section 3(j) of the Patents Act.

The patent office in its examination report objected to these claims as objection No. 1 was "Claim 1 to 7 attracts 3(j) of the Patents Act, 1970." This provision of the Patents Act prohibits the patenting of plants, animals, seeds, etc. Monsanto then amended the claims. Wherein the *Claim 1* is "A synthetic DNA molecule, comprising at least fifteen nucleotides of SEQ ID No. 11 or SEQ ID No. 12, and overlapping the junctions of the Cry2Ab insertions in cotton event MON15985 or the junction of the Cry2Ab insertions and the genomic sequence in cotton event MON 15985, or the complement thereof, wherein said cotton event MON15985 occurs in the cotton seed having been deposited with the American Type Culture Collection under accession number PTA-2516." The amended claims claimed a synthetic DNA molecule having polynucleotide sequence inserted in cotton seed genome, which is patentable.

3.7.2.4 Monsanto's Patent No. 214436, Titled "Methods for Transforming Plants to Express *Bacillus thuringiensis* Delta Endotoxins" Claimed a Method of Introgression of Genomic Polynucleotide Sequence Encoding Bt δ-endotoxin Protein to a Cell

The claims have raised some debate as it is alleged that Monsanto instead of claiming nucleic acid sequence claimed the plant cell which is not patentable under Indian Patent law. The claim reads as follow:

- *Claim 1*: "A method for producing a transgenic plant comprising incorporating into its genome a nucleic acid sequence comprising a plant functional promoter sequence operably linked to a first polynucleotide sequence encoding a Cry2Ab Bacillus thuringiensis δ-endotoxin protein, wherein said plasmid transit peptide functions to localize said δ-endotoxin protein to a subcellular organelle or compartment."

A large of the Indian cotton seed industry's trade bodies and farmers' organizations have argued that Monsanto's patent rights should be invalidated as the patents contravene Section 3(j) of the Patents Act, 1970.Monsanto alleged against NSAI that they infringed their patents by violating by unauthorized sale of Bt cotton seeds.

The Major Debate Lies in the Following Claim:

- *Claim 25*: "A nucleic acid sequence comprising a promoter operably linked to a first polynucleotide sequence encoding a plastid transit peptide, which is linked in frame to a second polynucleotide sequence encoding a Cry2Ab *Bacillus thuringiensis* δ-endotoxin protein, wherein expression of said nucleic acid sequence by a plant cell produces a fusion protein comprising an amino-terminal plastid transit peptide covalently linked to said δ-endotoxin protein, and wherein

said fusion protein functions to localize said δ-endotoxin protein to a subcellular organelle or compartment."

Here the claim interpreted that "a nucleic acid sequence is to deliver its intended purpose" in subcellular organelle or compartment of a cell. The debate is also for the claim construction as term "wherein" is used and nucleic acid sequence having some effect in a plant cell. This violated Section 3(j) as plants, parts of plants, seeds, and plant varieties are non-patentable subject matter by virtue of Section 3(j) of the Indian Patents Act, 1970. The patent was granted on the basis that the claims are not directed to a plant per se but to a method of producing a transgenic plant. Moreover, the method claims are not related to essentially biological process, which are patentable as per Patents Act, 1970. The term "essentially biological process" has not been particularly defined either in the Act or through judicial decisions or the manual of the patent office. There is a need to define in the broadly for what constitute "essentially biological processes". Monsanto and Indian seed companies are involved in a series of lawsuits against each other including infringement suit on a variety of different issues such as infringement of patents, plant variety protection, trademark, and competition law.

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URUGUAY ROUND AGREEMENT: TRIPS, Part II—standards concerning the availability, scope and use of Intellectual Property Rights. Section 5

Intellectual Property Rights in Microbiology

4

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Abstract

Intellectual property basically takes into consideration any creation or innovation which could be seen as a sort of asset or a physical property related to individual's intellect. Intellectual property rights (IPRs) have been mainly categorized into four major areas including patents, copyrights, trademarks, and rights related to some unique design. IPR in the field of microbiology and more specifically for microorganisms is of paramount importance. Modern biotechnology includes microbiology and other allied fields including microbial biotechnology, industrial biotechnology, and food biotechnology. The advancements in life science disciplines with the evolution of microbial biotechnology, recombinant DNA (rDNA) technology, and genetic engineering have pressed policy makers to consider the engineered microorganisms and their products to be patentable. Any invention may lead to grant of a patent if the invention meets the standard criteria of being novel in itself or it has significant commercial applicability or industrial prospects. Whether microorganisms are patentable or not has still remained a question of debate, but the microbial products, metabolites, production processes, and techniques are very much patentable. In present scenario, native microorganisms are not patentable but genetically engineered ones, and having industrial importance can be considered to be patented subject to satisfying other regulations. Current chapter collectively describes various rights attributed to intellectual property in general and what are the prescribed guidelines related to microorganisms and their products for patent filing.

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H. B. Singh et al. (eds.), *Intellectual Property Issues in Microbiology*,
https://doi.org/10.1007/978-981-13-7466-1_4

Keywords
Intellectual property right · Patent · Microorganisms · Microbiological products · Microbiology · Budapest Treaty · TRIPS

4.1 Introduction

Intellectual property (IP) right includes legal property rights over particular creation or innovation. There are a variety of assets which are labeled as intangible ones including novel ideas, invention, discoveries, unique designs, and symbols for which the owners can be granted patents under the jurisdiction of intellectual property laws and regulations. These intellectual property rights (IPRs) given to the inventor further ensure protection to the author, ideas, designs, processes, products, devices, apparatus, etc. (Singh 2008).

A variety of intellectual efforts and creations have been covered under the ambit of IP protection (Saha and Bhattacharya 2011) which includes (i) any novel invention filed in the form of a patent; (ii) any unique design for an industrial setup in terms of configuration, designing pattern, shape, or any article having unique composition or applied a distinct color (Saha and Bhattacharya 2011; Universal Law Publishing Co. Ltd. 2004a, b); (iii) trademarks in relation to any name, marking, or logo which can be bought, sold, and licensed (Saha and Bhattacharya 2011; Commercial Law Publisher (India) Pvt. Ltd 2004, 2005); (iv) copyright in which any novel idea could be expressed in various forms like music, literary expression, art, drama, or in hardware or software forms (Saha and Bhattacharya 2011); and (v) geographical origin-related characteristics called as indicators reflecting a particular locality or specific region (Saha and Bhattacharya 2011; Universal Law Publishing Co. Ltd. 2004a, b). Therefore generally a patent could be granted for any invention which can satisfy the specified guidelines and criteria of being novel and nonobvious and has commercial or industrial significance (Saha and Bhattacharya 2011). Despite the above parameters, patents may also be granted for any bioactive product or process as well.

On the other hand, when we talk about microorganisms, they can be defined as "microscopic entities" (Raghuvanshi 2017). These include viruses, bacteria, yeasts, fungi, algae, etc. Microorganisms are very well-known to hold great economic value throughout the world. Despite some of the microbes cause diseases, even then many of them are beneficial for humans and associated animals. Microorganisms are currently being used in food, pharmaceutical, biofuel, and fermentation industries for the production of various valuable products including ethanol, antibiotics, enzymes, pigments, vaccines, and other food products (Garg et al. 2016). In the race for exploration of microbes for commercial purposes and other diverse applications, IPR has become very important particularly the patents application and filing. However existing natural microbes cannot be patented until unless some mutation or genetic modification has been involved leading to some better efficacy or active product, in which case it can be patented (Cameotra 2013; Singh et al. 2016a, b).

4.2 Intellectual Property Rights (IPRs)

Any creativity or invention which is considered as an individual physical property or asset has been covered under the jurisdiction of IPR. These are legal rights accorded to individuals for their creations of particular art or commercial product/process. Under IPR laws, owners or inventors have been granted exclusive rights pertaining to intangible assets (symbols, ideas, designs, discoveries, and inventions). IPR also provides economic incentives to the creators or inventors for their original work. Also this provides a platform to further develop and share ideas through the innovator by giving him or her temporary monopoly and rights (Sivakumaar et al. 2010).

The inventor or the innovator should be duly recognized and rewarded under the ambit of IP laws and regulations which in turn stimulates the overall techno-industrial growth and strengthen the socioeconomic fabric of the country (Nair and Ramachandranna 2010). The advancement and modernization of life sciences with evolution of microbial biotechnology and genetic engineering have pressed the policy makers to consider the engineered microorganisms and their products to be patentable. Novel technologies have led to the creation of forms in plants and animals which could be patented as well in the form of biopatents (Ammen and Swathi 2010; Nair and Ramachandranna 2010). Four major areas under the aegis of IPR have been identified as copyrights, trademarks, design, and patents.

4.3 Preview into Various Types of Intellectual Properties

Initially IP was known to cover patents, designs, and trademarks related to industry (also known as industrial property) only, but the coverage of IP for protection of the intellectual property has expanded exponentially in the past decade or so (Saha and Bhattacharya 2011). IP protection considers a variety of intellectual efforts (Saha and Bhattacharya 2011) including (i) patents, (ii) industrial designs, (iii) trademarks, (iv) copyright, and (v) geographical indications.

4.3.1 Patent

WIPO defines patent as a document which is issued upon once the application is filed by a regional office recognized by one or more than one country. The application is complete in a sense that it should be able to describe all about invention of a product or process. Filing a patent provides a legal protection to the invention, and only it can be exploited in the circumstances upon the approval or permission of the inventor or owner. This protection is given to the owner generally for 20 years. Different countries have their own rules and regulatory authorities, but in majority of them, inventions or creations could be protected either as short-term patent registration or in the form of a utility model. The requisite fee for such protections is also lesser than that of patents. However the duration period for such protections is

shorter than that for patents. Though in terms of rights, the utility model or short-term patents are quite comparable.

"Monopolies" is another term used for patents previously giving some sort of protection to the invention. On the positive side, the patented invention is allowed to be exploited by the owner of the invention only and is prohibited to be exploited by other persons without the permission of the owner. Therefore the owner though cannot practice his invention as his statutory right but has the right not to let others exploiting the invention commercially. In other words the inventor has the exclusive right to exclude others not to make, use, or sell the said invention. The inventor has the right to take action against if anyone steal or exploit the said invention without his prior permission or agreement. Since these exclusive rights give the inventor to derive material benefits as a reward for the novel work or the intellectual effort, in other words, these rights provide compensation to the inventor for the expenses incurred to the research and experimentation leading to the invention.

4.3.2 Trademarks

Any name, word, design, symbol, device, or slogan which makes a distinction of a product or organization has been termed as trademarks. The filing or the application process (registered at a national or regional level office) usually takes between 25 and 75 weeks (www.copyrightservice.co.uk). The trademarks registered in countries like the USA, UK, Japan, etc. are country specific and provide protection in that very country only apart from the Community Trade Mark (CTM) which is valid in all the European Union countries. Any registered trademark could be depicted as "TM" or the "®" symbol, while in the USA, there is a further differentiation between products and service marks, though protected under the trademark itself. National patent office in most of the countries has been assigned the job to administer trademarks. In simplified terms, WIPO defines a trademark as any sign that individualizes the goods of a given enterprise making them distinct from other goods in competition. For the individualization of a particular product for the consumer, TM must mention the source of that very product in order to distinguish the goods of a given enterprise from others.

4.3.3 Copyright and Related Rights

Copyright law (WIPO 2017) provides protection to certain creations of the innovators which covers primarily the mass communication, public communication, printed publications, sound and television broadcasting, films, music, poems, computerized systems, etc.

However, the copyright law tends to protect only the form of expression of ideas and not the ideas themselves. In terms of creativity, copyright law protects creativity in the choice and arrangement of words, musical notes, colors, shapes, etc. Therefore

the copyright law protects the owner of statutory rights in artistic works especially against those who copy the original work expressed by the actual author.

4.3.4 Trade Secret

Trade secret could be a process, formula, practice, design, instrument, pattern, or compiled information not generally known earlier. The trade secret tends to provide a business economic advantage over other competitors or customers (Sivakumaar et al. 2010).

4.4 Trade-Related Aspects of Intellectual Property Rights (TRIPS)

TRIPS is an international legal agreement between all the member countries of World Trade Organization (WTO) which was established in 1994 at the conclusion of the Uruguay Round of the General Agreement on Tariffs and Trade (GATT). WTO has set up certain guidelines and standards for regulation of intellectual property.

4.5 Microorganisms

If we go by the dictionary, one defines microorganisms as "microscopic organisms." These are minute or very small living microscopic entities (Raghuvanshi 2017) including viruses, bacteria, yeasts, fungi, algae, etc. Since long, microorganisms have been used as tools in food, pharmaceutical, and fermentation industries for the production of various valuable products including ethanol, antibiotics, enzymes, pigments, vaccines, and other food products (Garg et al. 2016). In recent years, microorganisms have been shown to produce colors, pigments, anticancer drugs, biofuel, and other metabolites (Garg et al. 2016; Yadav et al. 2016). The microorganisms and their products are in continuous demand which is further increasing continuously. In the race of exploration of microbes for commercial purpose, intellectual property rights have become immensely important particularly patents.

4.6 Microorganisms and Patent: Can Microbes Be Patented?

It is a well-known fact that microbes such as yeasts, bacteria, protozoa, unicellular algae, fungi, actinomycetes, and viruses, in their original form, do not qualify for the patent application but could be patented if they are genetically altered in which case the underlying process and the product generated do qualify for the patent (Cameotra 2013). Genetically modified microbes as a result of human intervention leading to improved efficacy in comparison to the ones already existing in the nature

were found to qualify for the patent (Raghuvanshi 2017). Written description about the invention has been a mandatory disclosure nowadays for the inventor especially after the establishment of the International Depository Authority under the purview of Budapest Treaty which was not the case in earlier times.

In earlier times microbial inventions were granted only product or process patents in India unlike the USA and other developed countries where these entities were allowed to be patented. India started granting patents on microorganisms since 2003 like other countries under the strict guidelines of the Budapest Treaty (Keswani et al. 2016). Currently India has two microbial repositories, i.e., Microbial Type Culture Collection (MTCC) and Microbial Culture Collection (MCC), both of them have acquired the status of International Depository Authority (IDA).

Some recent patents on microorganisms and their products have been summarized in Table 4.1. Patent applications related to living matter have increased rapidly due to the enormous developments in the field of biotechnology (Seriñá and Toledo 1999). However, over the last century, inventions which involved some kind of living matter were already protected by a patent. Initially, patent legislations were designed to protect inventions related to nonliving subject(s). But in recent, due to continuous developments in the technology, laws have been adapted to the peculiarities of each kind of matter including living organisms. For this reason, patent laws including the US Patent Law in 1949 were modified in such a way that they now require the deposit of the microbiological material, if the microorganism is the subject of the patent application. As a result of intensive scientific research, biotechnology has emerged as one of the most innovative and promising technologies. For this reason, the European Union has developed a new Directive (European Parliament and Council Directive on the legal protection of biotechnological inventions of July 6, 1998; Seriñá and Toledo 1999) to harmonize the different legal protection systems of biotechnological inventions. Some articles in this Directive, which has come in force recently, are related to microbiological inventions. The European legislation (European Patent Convention, EPC) has been modified in relation to the terminology used in this kind of inventions: the term "microorganism" has been replaced by the term "biological material," to cover all entities which need to be deposited so as to cope with the requirement of sufficiency of disclosure (Seriñá and Toledo 1999). The Directive in the Article 2 clearly defines the biological material which contains not only the genetic information but also is able to self-reproduce or which could be reproduced in any biological system, while microbiological process could be defined as any process which involves or results in the production of said biological material.

4.7 Requirements for Microbiological Patent Applications

Requirements for microbiological patent applications have been discussed in detail as reported earlier by Seriñá and Toledo (1999). In order to disclose his or her invention, the state in exchange for the same provides certain rights and monopoly to the inventor. It is anticipated that the disclosure of the invention by the inventor should

Table 4.1 Examples of recent patents on microorganisms and their products

Patent no.	Microorganism	Specific feature/function	Priority date	Publication date	Reference
US8969065B2	Recombinant *Saccharomyces cerevisiae*	Lead to enhanced pyruvate to acetolactate conversion	2008-06-05	2015-03-03	Anthony, L. C.; Maggio-Hall, L. A., Enhanced pyruvate to acetolactate conversion in yeast
WO2014122328A8	Recombinant *Saccharomycetes*	Enhanced secretion of steviol glycosides	2013-02-11	2015-09-17	Simon, E.; Andersen, I. N.; Mikkelsen, M. D.; Hansen, J.; Douchin, V., Efficient production of steviol glycosides in recombinant hosts
US20150197776A1	Modified microorganism of the family of *Enterobacteriaceae*, *Pasteurellaceae*, *Bacilli*, or *Actinobacteria*	Production and downstream processing of succinic acid	2009-02-16	2015-07-16	Schröder, H.; Haefner, S.; Abendroth, G. V.; Hollmann, R.; Raddatz, A.; Ernst, H.; Gurski, H., Novel microbial succinic acid producers and purification of succinic acid
WO2015100168A1	Genetically modified *S. Cerevisiae*, *E. coli*, *Methanosarcina mazei*	Production of industrial bio-products	2013-12-23	2015-07-02	Euler, L. J.; Muir, R. E.; Pollak, D. M. W.; Van, D. T. K., Composition and methods for control of industrial scale production of bio-products
WO2015011615A1	Mutant *Trichoderma harzianum* SK-55	Possesses pesticidal activity	2013-07-22	2015-01-29	Liebmann, B.; Jabs, T.; Berry, S. D., Mixtures comprising a *Trichoderma* strain and a pesticide
US20150118724A1	D-lactic acid-producing strain *Lactobacillus paracasei*, *Lactobacillus casei*, *Lactobacillus rhamnosus*	Produces D-lactic acid	2012-04-24	2015-04-30	Yang, E. B.; Lee, T. H.; Kim, S. H.; Yang, Y. L.; Li, H. X., Novel d-lactic acid-producing strain and use thereof

(continued)

Table 4.1 (continued)

Patent no.	Microorganism	Specific feature/function	Priority date	Publication date	Reference
US20150361436A1	Genetically modified *Propionibacterium acnes*	Express biomolecules that are beneficial to mammals and/or to reduce, or eliminate, expression of harmful virulence factors	2014-06-17	2015-12-17	Hitchcock, T.; Rhee, M. S., Genetically modified bacteria and methods for genetic modification of bacteria
US9506086B2	Recombinant *Cupriavidus necator* strain DSM 531	Converts producer gas to limonene	2013-08-22	2016-11-29	Jannson, C.; Carr, C. A. M.; Reed, J. S., Microorganisms for biosynthesis of limonene on gaseous substrates
US20160183535A1	*Bacillus pumilus* rti279	Exhibits plant growth-promoting activity	2014-12-29	2016-06-30	Taghavi, S.; Lelie, D. V. D.; Walmsley, M. R., *Bacillus pumilus* rti279 compositions and methods of use for benefiting plant growth
US20160186273A1	*Bacillus amyloliquefaciens* rti301	Beneficial for plant growth and treatment of plant disease	2014-12-29	2016-06-30	S.; Taghavi, D. V. D., Lelie, *Bacillus amyloliquefaciens* rti301 compositions and methods of use for benefiting plant growth and treating plant disease
US20160040118A1	Genetically modified methylotrophic bacteria	Optimized to reduce CO_2 waste	2013-03-14	2016-02-11	Marx, C. J.; Nayak, D. D., Genetically Modified bacteria
US20160145648A1	*Escherichia coli* containing mutated lpda gene	Production of chemical material such as ethanol, succinate, etc.	2013-05-24	2016-05-26	Zhang, X.; ZHU, X.; Chen, J., *Escherichia coli* containing mutated lpda gene and application thereof
US20160083755A1	Genetically modified *Clostridium cadaveris* ITRI04005	Production of butyric acid	2014-07-08	2016-03-24	Tong, C.; Chen, C.; Wu, S.; Tseng, S.; WANG, H.; Hsu, C., *Clostridium cadaveris* strain and uses of the same
US20160097064A1	Recombinant *Escherichia coli*	Production of succinic acid	2013-05-24	2016-04-07	Zhang, X.; Zhu, X.; Xu, H.; Tan, Z., Recombinant *Escherichia coli* for producing succinic acid and application thereof

US20160304917A1	Modified *Basfia succiniciproducens*	Improved production of alanine	2013-08-30	2016-10-20	Krawczyk, J. M.; Haefner, S.; Schröder, H.; Zelder, O.; Fabarius, J. T., Modified microorganism for improved production of alanine
WO2016164636A1	Engineered *Salmonella typhimurium*	For the production of therapeutic polypeptide kills tumor cells or inhibits the growth of tumor cells	2015-04-09	2016-10-13	Hasty, J.; Tsimring, L.; Din, M. O.; Prindle, A.; Bhatia, S.; Danino, T., Engineered bacteria for production and release of therapeutics
WO2016141108A1	Recombinant probiotic bacterial cell	Engineered to treat disease, disorders, and/or conditions associated with bile salts and bile salt metabolism	2015-03-02	2016-09-09	Falb, D.; Isablle, V. M.; Kotula, J. W.; Miller, P. F., Bacteria engineered to treat diseases that benefit from reduced gut inflammation and/or tightened gut mucosal barrier
WO2016012298A1	Modified *Geobacillus thermoglucosidans*	Production of enantiomeric pure (S)-lactic acid	2014-07-23	2016-01-28	Van, K. R.; Verhoef, A.; Machielsen, M. P., Genetic modification of (s)-lactic acid producing thermophilic bacteria
EP3141597A1	Recombinant *Corynebacterium glutamicum*	Improved l-lysine production	2014-05-08	2017-03-15	Lee, P.; Moon, J. O.; Kim, H. J.; Ryu, S. G., Microorganism having improved l-lysine productivity and method for producing l-lysine using same
WO2017044835A1	Genetically modified bacteria of the genus *Propionibacterium*	Expressing biomolecules that are beneficial to treat the skin or nail disorder	2015-09-10	2017-03-16	Hitchcock, T.; Rhee, M. S., Genetically modified bacteria, compositions and methods of making and using

(continued)

Table 4.1 (continued)

Patent no.	Microorganism	Specific feature/function	Priority date	Publication date	Reference
EP3141598A3	Modified *E.coli* and bacteria of genus *Corynebacterium*	Production of putrescine or ornithine	2015-07-20	2017-06-21	Park, S. J.; Yang, Y. L.; Um, H. W.; Li, H. X.; Lee, K. M.; Lee, B. S.; Lee, H. H.; Jung, H. K., Microorganisms for producing putrescine or ornithine and process for producing putrescine or ornithine using them
US20170232043A1	Genetically engineered probiotic bacterium	Engineered to treat disorders involving the catabolism of branched chain amino acids	2015-06-10	2017-08-17	Falb, D.; Miller, P. F.; Millet, Y.; Isabella, V. M.; Kotula, J. W.; Tucker, A., Bacteria engineered to treat disorders involving the catabolism of a branched chain amino acid
US20170145447A1	Genetically engineered *E. coli*	Production of muconic acid from a salicylic acid intermediate	2014-02-13	2017-05-25	Yan, Y.; Lin, Y., Microbial production of muconic acid and salicylic acid
US20170191088A1	Genetically modified strain of *S. cerevisiae*	Ferment xylose and arabinose to ethanol	2011-11-10	2017-07-06	Argyros, D. A.; Caiazza, N.; Barrett, T. F.; Warner, A. K., Genetically modified strain of s. cerevisiae engineered to ferment xylose and arabinose
EP3015547A4	Genetically engineered *E. coli*	Production of L-threonine	2013-06-24	2017-02-22	Lee, J. S.; Lee, K. H.; Koh, E. S.; Kim, H. J.; Lee, K. C.; Hwang, Y. B., L-threonine-producing microorganism and production method for l-threonine using same
US20170166937A1	Modified *Basfia succiniciproducens*	Involved in producing succinic acid	2014-02-07	2017-06-15	Krawczyk, J. M.; Haefner, S.; Schröder, H.; Costa, E. D.; Zelder, O.; Abendroth, G. V., Modified microorganism for improved production of fine chemicals on sucrose

be clearly stated in the patent application. In terms of specific requirements for patenting, the most essential part is the description of the invention which is expected to contain all the information about the properties and characteristics of the material which has been deposited and for which the patent has been applied. The date of deposition of the material to the Budapest Treaty recognized depository institution, and the date of patent application should also match. The name of the depository authority to which the inventor has deposited his/her material along with the accession number is also required to be mentioned in the description. Currently, there are 30 depository authorities all across the globe which have been duly recognized under the Budapest Treaty. The Spanish Type Culture Collection (Colección Española de Cultivos Tipo, CECT in Spain) located in the University of Valencia, at the Department of Microbiology of the Faculty of Biological Sciences, is one of the International Depository Authority under the Budapest Treaty (Seriñá and Toledo 1999).

4.8 Patentability of Microorganisms

Patentability of microorganisms has been discussed in detail by Nair and Ramachandranna (2010). Microbes such as bacterial, fungal, and viral entities are the major chunks of microbial kingdom that have been widely exploited by genetic engineers and biologists. The chromosomal material has been used as a raw material by these scientists, and through genetic manipulations, these microbial entities have been tailored through the use of enzymes such as restriction cutters, ligases, polymerases, etc. to generate a novel recombinant product. The recombinant DNA technology, transgenesis, and modern genetics have been known to have wide applications in many sectors of biotechnology including food biotechnology, environment biotechnology, agriculture biotechnology, and pharmaceutical biotechnology. Typical examples include use of many fungal products in bakery, wine, and antibiotic industry, bacteria/bacterial components for the manufacture of various vaccines, alteration of plants (transgenic plants) or insects' genome, etc. Living organisms were considered to be products of nature for the past 200 years or so; therefore they were not considered to be patentable. Moreover only patents were granted for the processes involved in obtaining the product majorly in the fields of chemical and mechanical engineering including some microbiological processes as well. Patenting of life forms got impetus after 1980 when it was included in ambit of patent laws. First patent which was based upon the microorganisms involved in the process of fermentation of beer was granted in the year 1873 to Louis Pasteur. Living matter is however still excluded from patentability in many countries across the globe considering them as products of nature. Under these products of nature doctrine, however, one could protect and secure his or her invention, for example, the process of microbial fermentation or the process of purification of naturally occurring compounds. More so, one could apply for a patent for microorganisms as a culture or in combination with a carrier or in the form of a consortium having synergistic effects. However the products made by the microorganisms naturally are not patentable because of the living matter. In the year 1980, however, the Supreme

Court in the USA in its landmark decision granted permission for the first genetically engineered bacterium to be granted as a patent to Professor A.M. Chakraborty.

4.9 Types of Patentable Microbiological Inventions

Most patent legislations distinguish among three types of findings or innovations relying upon the subject area to be protected: (a) inventions that protect a product, (b) process-based inventions which may lead to a product, and (c) applicability of the product-based inventions. However, one could claim for all of the above three types in the same invention. Typical example may include that one could stake claim for the product, process to obtain that very product and applicability of the product in one single application (Seriñá and Toledo 1999).

4.10 Budapest Treaty for Patents Involving Microorganisms

The patenting of microorganisms requires that the invention should be projected clearly with all its aspects covered under the ownership of the inventor or innovator. In case of microorganisms, it may not be possible to disclose the invention unless the samples are publically available (Gupta 1999). In order to meet this requirement, a system of depositing the microbial cultures has been established wherein microorganisms are deposited in centers meant for specific culture collection and made available on request to public. For this purpose, an international treaty named as "Budapest Treaty" was established in 1977, which was duly recognized for deposition of microorganisms. Under the treaty, the deposition of microbial strains with a single internationally recognized depository was identified.

According to WIPO (2017), the contracting state which permits or requires the depository of microbes for the patent protocols/procedures, the state must be duly recognized by "international Depository Authority," though it doesn't matter whether the said authority is present in or outside the state territory. For the grant or award of any patent, invention has to be disclosed as a prerequisite generally in the form of a written description. However in case of microbes or their applications, written description is not possible. In such cases, the microorganisms need to be deposited in specified collection centers duly recognized for the purpose. Therefore any biological material patent, the disclosure is best possible only through requisite depository of the said material.

As per the Budapest Treaty, any "International Depository Authority" could be a culture collection center which has the required capacity of storage of microorganisms. This is subject to assurances to the Director General of WIPO to the effect that the said institution complies and will continue to comply with certain requirements of the Treaty (WIPO 2017). As on January 16, 2017, there were 46 such authorities (WIPO 2017) including 7 in the UK; 4 in the Republic of Korea; 3 in China, Italy, and the USA; 2 each in Australia, India, Japan, Poland, the Russian Federation, and Spain; and 1 each in Belgium, Bulgaria, Canada, Chile, the Czech Republic, Finland,

France, Germany, Hungary, Latvia, Mexico, the Netherlands, Slovakia, and Switzerland (WIPO 2017).

4.11 IPR in Related Disciplines

Microbiology is considered as the base of biotechnology. All major disciplines of life, pharmaceutical, and medical sciences have many facts and principles in common. The major disciplines including microbiology, biochemistry, biotechnology, and pharmaceutical sciences are interrelated and support interfacial research. Various authors have discussed the intellectual property rights (IPRs) dimensions, facts, and issues with respect to different fields. Saha and Bhattacharya (2011) have discussed the IPR issues in pharmaceutical industry. Many investigators firmly believe that any novel idea, creation/creative expression, or discovery/invention should have the ownership to bestow the status of the property which has been well covered under the IP rights. More so the invention or creation could be better commercialized and best protected through IPR. These legal rights are exclusively granted to the inventor or the creator or his assignee for a certain period of time, and the said invention or creation is protected for that particular time period. New and novel technologies are being explored to handle these creations or inventions providing an impetus to research and development (R&D) activities (Saha and Bhattacharya 2011). IPR definitely has many pluses in terms of protecting ones physical property with nominal investments and simultaneously saving time, money, and effort of the inventor/creator. These exclusive rights covered under IPR certainly will uplift the economic growth and development of our country as one can speculate enhanced industrial growth, output, and competitiveness in various industrial segments. Montesinos (2003) further gave insights into the patenting process, registration protocol, and how one could protect microbial pesticides from exploitation by others. The author also chalked out a plan how to commercialize these microbial pesticides at a bigger platform/scale. There is a treaty named as Budapest Treaty which has been signed by all countries under the aegis of the World Intellectual Property Organization (WIPO). Under this treaty pure culture of the microbial strains has to be deposited in a Microbial Type Culture Collection center duly recognized by WIPO countries (Montesinos 2003). Countries like the USA, the UK, and Australia were the ones where majority of the patents on biopesticides were initially deposited. All patents related to microbial pesticides have been well regulated under the Budapest Treaty. There have been vast number of patents registered in the area of microbial pesticides; only few have materialized in terms of their agriculture applications and use thereof (Montesinos 2003).

For any invention or creation, therefore, the very first step was envisaged as to assure its protection which is feasible by filing a patent before looking into commercialization aspects. Any biotechnological invention which comprises of either a microbial product or a process thereof has been considered to be under the ambit of IPR, and patents, for example, on biopesticides could be applied. Many treaties at national and international level do exist in order to provide a strong regulatory

process for applying patents on microbial pesticides. Many patents related to living or attenuated bacteria or their products have been reviewed and discussed by Fialho et al. (2012) especially for their therapeutic potential having anticancer properties. When we talk about patenting of microbial products, one could apply for a patent on microbial toxins, enzymes/proteins or peptides, antimicrobial products like antibiotics, and small molecular weight proteins as well. Biffinger and Ringeisen (2008) emphasized upon the intricacies involved in the process of applying patents on microbial fuel cells (MFCs). MFCs have been widely recognized as potential alternatives to the existing standard commercial polymer electrolyte membrane (PEM) fuel cell technology. There are many potential merits associated with MFCs such as there is no need of the fuel supply to be purified. Moreover the ambient operating temperatures are usually maintained with biologically compatible materials. More so the biological catalyst has the potential of self-regenerating. With the vast developments in the IPR, there are many advanced technologies being employed in today's context providing impetus to industrial and microbial biotechnology. Seeing the vast exploration in microbial research, it is anticipated that the pool of patents on microorganisms and their by-products and secondary metabolites will significantly increase in the near future. One may envisage further modifications and amendments in microbial patenting process in the future to make it more client-friendly according to the need and requirements.

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Patenting Microorganisms: An Indian Perspective

5

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Abstract

The intellectual property rights (IPRs) aim to reward the innovator, so as to improve socio-economic progress. Patenting of microorganisms may have many dimensions that relate to the use of IPR concept in the agricultural sector and its appropriateness in the aspect of rights on knowledge, ownership, use, transfer and utilization of the patent. Defining the term microorganism precisely can itself solve many problems. IPRs for agricultural microbiological innovations pose complex problems relating to ethics, biosafety and biodiversity. The present chapter discusses the need of IPR in agriculture and patenting systems in relation to microorganisms with reference to India. The chapter explores the patent laws followed by India and the prospects to boost IPR framework and legislation in the global perspective.

Keywords

IPR · Microorganisms · Indian Patent Act · IDAs

5.1 Introduction

The past few years have shown tremendous growth in commercial application of microbiology in agricultural industry. Increase in the use of microorganisms in agriculture has also raised alarms regarding issues of intellectual property (IP) and ethical and legal issues concerned. Intellectual property rights (IPR) can be defined

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H. B. Singh et al. (eds.), *Intellectual Property Issues in Microbiology*,
https://doi.org/10.1007/978-981-13-7466-1_5

as ideas, inventions and/or original creation of the human intellect to confer the status of property. IPR provides certain legal rights to the inventors or creators of that property to protect the invention or creation for a certain period of time (Singh 2004). As such IPR gives exclusive rights to the inventor to commercialize their creation and get benefit from it. Thus, it becomes quite obvious that intellectual property has an important role in modern economic management. Protection of intellectual properties may be accomplished by patents, copyright, trademark, etc. IPR is a strong tool aiding in the economic development of countries worldwide by encouraging healthy competition among developers and promoting economic growth.

IPR regarding use of microorganism and microbiological research for commercial purpose is still in preliminary stage as compared to the other areas of IP. The multifaceted benefits of using microorganisms have rendered their commercial exploitation both in industrial and agricultural sectors. Thus, microorganisms and microbial products and processes have become a remunerative business worldwide. Patent is the strongest form of IPR, for an invention after satisfying the criteria of global novelty, nonobviousness and industrial application (Saha and Bhattacharya 2011). Agreement on Trade Related Aspects of Intellectual Property Rights (TRIPS) (1994) is the most important international agreement on IPR. According to Article 27(3)(b) of TRIPS Agreement, member states are allowed to exclude patents for 'plants and animals other than microorganisms, and essentially biological processes for the production of plants or animals other than non-biological and microbiological processes'. In compliance with TRIPS, the Patents Act, 1970 (amended in 2002), gives patent rights for new microorganisms. Naturally occurring microorganisms are not patentable in India, but genetically modified microorganisms or microbe-based products or processes can be protected by IPR. The present chapter furnishes a brief scenario of IPR in agriculture with special emphasis on patenting microbe based in India.

5.2 Criteria for Patenting

In 1873, Louis Pasteur was granted patent by the USA (US 141072) for his claim on yeast free from organisms as an article of manufacture and recognizing microorganisms. Indian patent Act, 1970, do not patent animals and plants. However, microorganisms and non-biological and microbiological processes of production of plants and animals and member will provide protection to plant varieties either by patents or by an effective sui generis system or any combination thereof (Art. 27, Para 3). In 1971, Dr. Ananda Mohan Chakrabarty was granted patent on genetically modified bacteria that digest oil spills. The patent was claimed on bacteria itself, method of modification and introduction of vector. According to TRIPS (Article 27, subsection 2), patents are granted on the utility function of the gene if it is useful. The US patent office has now included a new section in its Manual of Patent examining procedures, whereby microorganisms qualify for patenting if it is shown that they are man-made or its production involved the human brain.

IPR greatly depends upon the market needs and response and cost involved in commercialization. Different industries of IPR demand different treatment and different IPR policies and strategies with people involved from different domains such as engineering, pharma, law, finance, marketing and economics. IPR, antitrust law, need to be established to ensure that invalid rights are avoided to unlawfully assert and establish themselves. In 1949, the Patent and Trademark Organization (PTO) of USD has recommended deposit of microorganism with a culture collection, so that an accession number is provided to the culture. The World Intellectual Property Organization (WIPO) in 1973 worked on procedure of deposition which leads to signing of the Budapest Treaty. In 1977, the recognized depositaries have been ATCC and NRRL of the USA, FRI of Japan, CBS of the Netherlands, DSM of Germany and NCYC and NCIB of the UK. In India, national depositories for microorganisms, cells, tissue culture organism, etc. have been established at Delhi, Chandigarh and Pune.

5.3 IPR in Agriculture

Agriculture will be affected if our efforts to develop microorganism-based biofertilizers and biopesticides are hindered by foreign patents. The global market for biopesticides was valued at $2.78 billion in 2016 and is estimated to reach USD 6.55 billion by 2022. The member countries of TRIPS are obliged to make patents available for all inventions, whether products or processes in all the applied fields. While patenting microorganisms or microbial process or product, it is important to deposit the strain in one of the recognized depositories who would provide it with a registration number to be quoted in the patent specification. This obviates the need of describing a life form on paper. Further, patents involving genes and gene expression also need to be described in the patent specification. The alliances could be for many different objectives such as for sharing R&D facilities, improving product marketing and sharing production facilities (Keswani et al. 2016).

Several IPRs mainly patents, plant breeders' rights, trademarks, geographical indications and trade secrets are linked to agricultural sector. Patents are probably the most important IPR today in agriculture as they provide powerful protection for patentable microorganisms and microbiological processes for their production. Microbiology is the sector that holds the most potential for improving agriculture productivity. The US patent office has now included a new section in its Manual of Patent examining procedures, which states that microorganisms qualify for patenting if it is shown that the hand of man has been involved in their procurement. Another IPR mark more often used in agriculture are geographical indications, including appellations of origin. These are marks associated with products originating from a country, region or locality indicating the quality and characteristics of the products linked to that particular geographical origin. Examples are 'Darjeeling' for tea and 'feta' for cheese from Greece.

5.4 Impact of Microbiological Patents on Technology Development and Agricultural Biodiversity

Microbiology is the sector that holds the most potential for improving crop productivity and yield. A large number of patents are granted on microbial inoculants, but issues still pertain in patenting of microbiological innovations (Fig. 5.1). Filing the patent requires complete method of production, formulation and/or use of the product. Most of the patents were deposited in the USA and mainly consist of bacteria and fungi and very few of viruses. The current need in increase in food production and security requires microbiological innovations to enhance quality of food and fibre and provide easy and cost-effective processes for agricultural applications along with protecting the environment and improving health. The process of technology development and transfer would hugely impact farmers, researchers and industries (Kumar and Sinha 2015). Fears still pertain about adverse effects of applied microorganism or product on soil biodiversity, development of monopoly, restrictions on poor farmers and ethnic and social issues involved in their use.

5.5 International Depositary Authority (IDA)

The Budapest Treaty recognized certain culture collection centres as 'International Depositary Authorities' (IDAs). The deposition of patents of microorganisms in a culture collection recognized as an IDA will act as biological resource (Sekar and Kandavel 2004). IDAs accept deposits for biological materials, which do not fall within a literal interpretation of 'microorganism'. According to the Budapest Treaty, materials that can be deposited include bacteria, fungi, eukaryotic cell lines, spores,

Fig. 5.1 Issues involved in patenting of microbiological innovations

genetic vectors containing a gene or DNA fragments (Ames 2004) and organisms used for gene expression. It is a prerequisite that for obtaining microorganism's patent, a deposit has to be made to IDA (Table 5.1).

Table 5.1 International Depositary Authorities (IDAs)

Australia	The National Measurement Institute (NMI)
	Australian Government Analytical Laboratories (AGAL)
Belgium	Belgian Coordinated Collections of Microorganisms (BCCM ™)
Bulgaria	National Bank for Industrial Microorganisms and Cell Cultures (NBIMCC)
Canada	National Microbiology Laboratory, Health Canada (NMLHC)
China	China Centre for Type Culture Collection (CCTCC)
	China General Microbiological Culture Collection Center (CGMCC)
Czech Republic	Czech Collection of Microorganisms (CCM)
France	Collection Nationale de Cultures de Microorganismes (CNCM)
Germany	DSMZ, Deutsche Sammlung von Mikroorganismen und Zellkulturen GmbH (DSMZ)
Hungary	National Collection of Agricultural and Industrial Microorganisms (NCAIM)
India	Microbial Type Culture Collection and Gene Bank (MTCC)
	Microbial Culture Collection (MCC)
Italy	Advanced Biotechnology Centre (ABC); Industrial Yeasts Collection DBVPG
Japan	International Patent Organism Depositary (IPOD)
	Patent Microorganisms Depositary (NPMD)
Latvia	Microbial Strain Collection of Latvia (MSCL)
Netherlands	Centraalbureau voor Schimmelcultures (CBS)
Poland	IAFB Collection of Industrial Microorganisms; Polish Collection of Microorganisms (PCM)
Republic of Korea	Korean Cell Line Research Foundation (KCLRF)
	Korean Collection for Type Cultures (KCTC)
	Korean Culture Centre of Microorganisms (KCCM)
Russian Federation	National Research Centre of Antibiotics (NRCA)
	Russian Collection of Microorganisms (VKM)
	Russian National Collection of Industrial Microorganisms (VKPM)
Slovakia	Culture Collection of Yeasts (CCY)
Spain	Banco Nacional de Algas (BNA)
	Coleccion Espanola de Cultivos Tipo (CECT)
UK	CABI Bioscience, UK Centre (IMI)
	Culture Collection of Algae and Protozoa (CCAP)
	European Collection of Cell Cultures (ECACC)
	National Collection of Type Cultures (NCTC)
	National Collection of Yeast Cultures (NCYC)
	National Collections of Industrial, Food and Marine Bacteria (NCIMB)
	National Institute for Biological Standards and Control (NIBSC)
USA	Agricultural Research Service Culture Collection (NRRL); American Type Culture Collection (ATCC)

5.6 Patenting Microorganisms in India

The Patent Act of India (1970) Section 2(1)(j) 34 defines an invention as a new and useful *manner of manufacture or* a *substance produced by manufacture*. The Budapest Treaty on the International Recognition of the Deposit of Microorganisms for the Purposes of Patent Procedure allows 'deposits of microorganisms at an International Depositary Authority to be recognized for the purposes of patent procedure'. The grant of patent with respect to microorganisms in India is conditional to the deposition of microorganisms under the Budapest Treaty and accessibility of that microorganism from the depositories thereafter. Since 2001, India has become a member of Budapest Treaty on deposition of microorganisms, and consequently two microbial repositories in India, viz. Microbial Type Culture Collection (MTCC) and Microbial Culture Collection (MCC), have acquired the status of IDA on October 4, 2002, marking the amendment of existing systems in India. In 2002 the Government of India permitted patenting of microorganisms under the Patents (Second Amendment) Bill. Nevertheless, very small number of patents on microorganisms has been granted as of now. Still there exist a big debate regarding patenting of microorganisms in India. The Patents Act, 1970, was further amended in the year (The Patent Act 2005), to make the existing provisions in the patents bill permit as per TRIPS agreement. Unfortunately, controversy still pertains regarding the precise definition of the term 'microorganism' (Nair and Ramachandranna 2010). Bacteria, fungi and viruses have been extensively exploited by agricultural biotechnologists. Their genetic material provides us with large number of enzymes used as tools in molecular biology, viz. restriction endonucleases, DNA polymerases, ligases and vectors. Genetic engineering is broad and covers vast areas, especially for development of transgenic plants. A mixture of compatible microorganisms, which are either new or known, and/or a process using microorganisms to produce a substance, or lyophilized microorganisms are all patentable (Singh et al. 2016a, b). Also, biological synthesis of a new microorganism is patentable.

5.7 Conclusion

It is obvious that IPR management in agriculture is a multidimensional task and requires policies and strategies to be designed taking into account national laws and international treaties and practices. Patenting microorganisms employs a huge interest of agricultural sector for constant innovation and efforts, to increase inventions aiming for improved growth and yield of plants and thereby increasing food quality and quantity. Genetically modified microorganisms fall in the category of invention as they may perform any designed activity; hence, patenting of this genetically modified microorganism will restrict further research on that microorganism. Therefore, the rationale of patenting microorganisms must be advocated taking into account of its usefulness. TRIPS does not provide a definition of microorganism; hence, policy makers must also provide a complete definition of microorganism so that bacteria, virus, fungus and algae all are included. An efficient patent protection

system of the research concerning microorganisms is thus required to store and take care of this vast reservoir so that they may be brought into public domain.

Acknowledgements Akansha Jain is grateful to the Department of Science and Technology, Govt. of India, New Delhi, for financial assistance under Start-up Research Grant (Young Scientist) Scheme (YSS/2015/000773).

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Singh HB, Jha A, Keswani C (eds) (2016a) Intellectual property issues in biotechnology. CABI, Oxfordshire, p 304

Singh HB, Sarma BK, Keswani C (eds) (2016b) Agriculturally important microorganisms: commercialization and regulatory requirements in Asia. Springer, Singapore, p 336

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Bioinformatics: Nuances in Granting IP Protection

6

Abhijeet Kumar

Abstract

A society is built upon the information gathered by generations, left for advanced usage and analysis by the future generation. Besides books, scrolls and stone carvings, information have been carried around through genes, and its components, since always. Such information, commonly referred to as bioinformatics, requires preservation for continuous research. While the research upon bioinformatics have changed the dimensions of the inventions being carried out in this field, at the same time, it has also created a debate for protection of such information and means to extract and analyse them. This chapter explains the historical development of the term bioinformatics and explains its commercial and scientific value in the modern world. Furthermore, the chapter also deals with different types of IP protections available to bioinformatics, its researchers and benefactors.

Keywords

Bioinformatics · Genomic databases · IPR · Trade secrets

6.1 Introduction

Intellectual property rights (IPRs) are a set of rights which are granted to the creator or inventor for any kind of intellectual outgrowth in industrial, scientific, literary or artistic domain. Such rights are generally negative in nature, i.e. they enable the creator or inventor to prohibit any third party from utilising the fruits of the intellectual effort put in by them. Such protections of intellectual properties (IPs) have resulted

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H. B. Singh et al. (eds.), *Intellectual Property Issues in Microbiology*,
https://doi.org/10.1007/978-981-13-7466-1_6

in creation of wealth and economy for the researchers, giving an additional motivating factor, and have also helped the corporations in deciding to make more and more of investment for the purpose of invention/creation/product developments.

One of the most rapidly growing fields of technology has been bio related, i.e. biotechnology/bioinformatics, and its growth has ensured us that there no longer exists an arena of imagination and that is why it has also provoked the concerns of people around the globe. Some human/natural rights activists have raised serious concern towards the long-term effects of application of such advancement to human as well as animal health and environments. The constant increment witnessed in association with biotechnology, be it economic or technological, brought it in terms with the scope of protection which is being granted by the IP regime for invention/creation. For quite some time, the issues which have created hindrance for biotechnological invention from getting IP protection are being identified and taken care of, both by inventors and policymakers, which have and are still giving a boost to this technological field.

This advancement of technology, and enlargement of legal regime in order to encompass such advancement, has attracted new questions on the grounds of morality and ethics on the issue of creating monetary benefits through inventions which deals with genes and genetic alterations, of animals and plants, and therefore they require to be dealt with carefully and in a sensitive manner. While the inventions and methodology for extraction of information from microbial genes have not witnessed these hindrances till date, the fact remains the same that most of the inventions with respect to genetics that are being done on multicellular organisms nowadays are a direct result of the successful experiments conducted on the microbial genes, and therefore it cannot be ruled out from the debate. Therefore, the need of the hour is to have a balanced, and at the same time a sensitive and sensible, patenting approach towards conservation and preservation of global health such as biosafety, biological diversity, food security and sustainable development.

Before dwelling into the nuances of the same, the author would like to shed some light with regard to the understanding of bioinformatics, industrial development related thereto, recognition of bioinformatics as a viable information and the rationale for granting protection to bioinformatics, in order to have a premise of the subject matter.

6.1.1 What Is Bioinformatics?

In the last few decades, advancement in the field of biotechnology, viz. DNA, RNA and protein sequencing,[1] and the application of these technologies have led to the creation and building up of huge amount of information.[2] The amount of information so acquired has warranted the need for a digital database in order to secure,

[1] Bruce Birren et al. (eds) (1975) Genome Analysis: A Laboratory Manual, Vol 1, Cold Spring Harbour Laboratory, New York, p 1–36.

[2] Cynthia Gibas (2001) Developing Bioinformatics Computer Skills, O'Reilly, California, p 9–10.

index and systemise the data, so as to enable other tools developed to retrieve the information and analyse the same.[3]

Bioinformatics is nothing but the application of modern-day technology, computer-related inventions, in order to manage the genomic information. Such information is utilised by the researchers in creation of specific gene-oriented drugs. Human Genome Project has made such genetic information publicly available, and this in turn has precipitated the research and investment in this arena. The White House announced the completion of the working draft of the project, as early as in June 2000, and the same was made public through publication in February 2001.[4]

Bioinformatics, in other words, can be defined basically as the use of one technology, a computer or any other computer-based technology, which is used to manage the advancement of information gathered through another technology, i.e. biotechnology. The National Center for Biotechnological Information (NCBI), USA, published a paper in order to give a generic definition and understanding to bioinformatics, and it has defined it as:

> …. a field of study in which biology, information technology and computer science merge together to form a single discipline. Bioinformatics is conceptualizing biology in terms of macromolecules (in the sense of physical-chemistry) and then applying 'informatics' techniques (derived from disciplines such as applied maths, computer science, and statistics) to understand and organize the information associated with these molecules, on a large-scale.[5]

In short it can be stated that bioinformatics focuses on sequential isolation of definite genomic pattern and also matching of specific pattern.[6] This is such a discipline of science which has been brought into being through the emergence of various other fields, such as information technology, computer science and most importantly biology. Another attempt to define the field of bioinformatics was made by the National Human Genome Research Institute (NHGRI), wherein it stated that "while bioinformatics is the branch of biology that is concerned with the acquisition, storage, and analysis of the information found in nucleic acid and protein sequence data, computers and bioinformatics software are the tools of the trade of bioinformatics".[7]

Having dealt with the term bioinformatics, as it exists and is understood today, it is required to look into the historical development of bioinformatics, its industrial

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[3] See Andreas D. Baxevanis and B. F. Francis Ouellette (eds) (2004) Bioinformatics: A Practical Guide to the Analysis of Genes and Proteins, Wiley, New York.

[4] Working Draft of the Human Genome Project was published for public in February 2001. See generally National Human Genome Research Institute (2016) An Overview of the Human Genome Project. https://www.genome.gov/12011238/an-overview-of-the-human-genome-project/. Accessed on 12 Sep 2017.

[5] Luscombe NM et al. (2001) What is bioinformatics? A proposed definition and overview of the field. Methods of Information in Medicine 40(4):346–58.

[6] See Aris Persisis (2000) Data Mining in Biotechnology. Nature of Biotechnology 18:237.

[7] See generally National Human Genome Research Institute. https://www.genome.gov. Accessed on 12 Sep 2017.

application and also from its worth perspective, which has been dealt with in the following section. The chapter in its further section covers as to what is the information that is contained in the genomes and what are the technological means used to access and analyse such information. Then the discussion leads on to various kinds of IP protections that can be accorded for protection of bioinformatics. In the end the author will be concluding the paper with the analysis of bioinformatics as IP subject matter while taking into account the public policy and other arguments related thereto.

6.2 Bioinformatics: Evolution and Importance

The term was coined in 1970 by Paulien Hogeweg, while the reference was being made to the study being done over the "information processes" involved in biotic system. This brought the discipline of bioinformatics in line with the study of biophysics and biochemistry, which dealt with the aspects of physical and chemical processes involved in the biological systems.

However, efforts were being made in this regard even before this terminology came into existence. Fredrick Sanger, who found the insulin sequence, mentioned that composing those sequences manually was not only impractical but impossible.[8] Margaret Dayhoff, most popularly known as "mother and father of bioinformatics",[9] was the first one to successfully compile databases of protein sequence, and she also laid down the steps for aligning the sequences, which led to molecular evolution.[10] Elvin Kabat's contribution was that of the analysis of antibody sequences. All of this was done based on the foundation laid down by Sanger in the early 1950s, something which he thought was impossible to achieve, back then.

In 1982, Nucleic Acids Research brought a journal on the necessity and use of bioinformatics tools,[11] as the database was already available through GenBank and tools were required to conduct any kind of analysis over the same.[12] The Human Genome Organisation (HUGO), founded in 1988, published the first genome map of the bacteria named *Haemophilus influenzae*. Later on, the Human Genome Project (HGP) was initiated in 1990, and within a span of 2 years, they were successful in mapping 1879 gene sequences.[13] Such discoveries led to the establish-

[8] S. M. Thampi, Bioinformatics. https://arxiv.org/ftp/arxiv/papers/0911/0911.4230.pdf. Accessed on 12 Sep 2017.

[9] See generally Glyn Moody (2004) Digital Code of Life: How Bioinformatics is Revolutionizing Science, Medicine, and Business, Wiley Publications, New York.

[10] J Okpuzor, Introduction to Bioinformatics, National Open University of Nigeria. http://nouedu.net/sites/default/files/2017-03/BIO%20316_0.pdf. Accessed on 12 Sep 2017.

[11] T.C. Hodgman (2000) A Historical Perspective on Gene/Protein Functional Assignment. Bioinformatics, 16(1):10–15.

[12] See generally GenBank Overview: What is GenBank? https://www.ncbi.nlm.nih.gov/genbank/. Accessed on 15 Sep 2017.

[13] Cindy Pham Lorentz et al. (2002) Primer on Medical Genomics. Mayo Clin. Proc. 77: 773–782.

ment of databases to store the information, viz. GenBank, DNA Database of Japan EMBL, etc., and availability of the information acted as a fuel for the research and development in this field of science and innovation.

Bioinformatics is estimated to generate more than a billion dollars of revenue per year, worldwide.[14]The Strategic Direction International (SDI) also stated that, "Bioinformatics generated worldwide revenue (in 2000) of more than $700 million and total bioinformatics volume could exceed $2 billion (in 2001)".[15] There have been many deals which have found place in media and which suggest the fact that bioinformatics is very valuable for the companies,[16] because of the inherent information which can be utilised by the health and pharmaceutical sectors for monetary benefits. David Schook correctly pointed it out in his writing that "genomics information is nearly a commodity these days".[17] Examples can be seen from the factual scenarios when in 1993, in order to access the biological information kept with human Genome Sciences, SmithKline Beecham paid $125 million, and in 1999, Bayer and Millennium Pharmaceuticals signed a $465 million contract for validation and identification of drug targets.[18] Compaq, a company related with computer technology, while targeting innovations in the field of genomics, bioinformatics, and related areas, invested around $100 million in different companies working on life sciences.[19]

Not just the deals that have been made in this regard but the investment done in mapping has been enormous as well. HGP took 15 years to finish mapping every gene sequence in the human body, and it undertook a total cost of around $3 billion by the time it was finished in 2005. However, the positive aspect and the success story remained that as assumed in 2001, a working draft of human genome, the final outcome, came much sooner, thereby saving time and money. It came out with a total of 30,000 sequences of genes and approximately 18,000 megabases (a million of genetic base pairs).[20]

However, once the genomic sequences were made available to public in different repository, the economics involved saw a drastic fall in the sequencing pricing. While in 2001, megabase sequencing required an investment of $5000, it came

[14] John Thackray (2001) Bioinformatics Grows Legs.Elec. Business; as cited in M. Scott McBride (2002) Bioinformatics and Intellectual Property Protection. Berkeley Technology Law Journal 17:1331.

[15] Ibid.

[16] See G. Zweiger (2001) Transducing The Genome: Information, Anarchy and Revolution in the Biomedical Sciences. McGraw-Hill, New York, p 161.

[17] See M.J. Malinowski, Law, Policy, and Market Implications of Genetic Profiling in Drug Development. https://law.hofstra.edu/pdf/facwor_malinowski_paper.pdf. Accessed on 15 Sep 2017.

[18] Kenneth Offit (2011) Personalized Medicine: New Genomics, Old Lessons. Human Genetics 130 (1):3–14.

[19] See Compaq Computer (2002) Life Science Program. http://nuweb.neu.edu/bbarbiellini/CBIO3580/Overview_life.pdf. Accessed on 15 Sep 2017.

[20] Gareth Dickson (2013) Edwards Wildman Palmer LLP: Protecting Bioinformatics as Intellectual Property. IEEE Computer Society, 46(1):15–17.

down to a mere 9% of that value by early 2012.[21] Researchers, with the help of computers, have been using the sequences in order to establish a common pattern or for comparison of the same with another microbial or multicellular organism. With the help of in silico and in vitro research,[22] researchers have shown more efficiency in saving time and money and in analysing the data that have been sequenced before.

If we see it individually, different components of bioinformatics will be eligible to get protection under different IP regimes, but the best form of IP to protect biological information is to be critically analysed. Even when looking at it from a cost-benefit perspective, the regime which creates the possibility and opportunity of maximum returns from the investment is the most justifiable option. The issue of patentability of genes has also been a barrier in the protection being granted with respect to bioinformatics. However, all the countries have come to one conclusion in that regard, i.e. naturally occurring genes or mere isolation of genes are non-patentable subject matter, through various judicial pronouncements (such as *Myriad Genetics case*[23] decided by US Supreme Court) or through legal provisions (such as Section 3(j) of Indian Patent Act, 1970).

6.3 Genomic Information and Technological Interface

In order to understand as to whether bioinformatics should be given protection through IP, and if this is answered in the affirmative, the regime, which would be best suited for it, is important to understand the three different components that bioinformatics comprises of, i.e. genomic sequence, viz. nucleic acids and proteins, etc., databases used to organise these sequences and hardware and software used to generate, access, categorise and examine the databases, genomic sequences and information contained in it. The author will deal with all of these ingredients of bioinformatics one by one, in brief.

6.3.1 Sequences Explained

Biological molecules have been divided into four categories by the scientists, i.e. proteins, nucleic acids, carbohydrates and lipids, but the current studies, in regard to bioinformatics, have been limited to proteins and nucleic acids only.[24]

Nucleic acid consists of deoxyribonucleic acid, also known as DNA, and ribonucleic acid, also known as RNA. Herein DNA plays the role of the transmitter of

[21] DNA Sequencing Costs, Data from NHGRI Genome Sequencing Program (GSP). https://www.genome.gov/sequencingcostsdata/. Accessed on 15 Sep 2017.

[22] Valerie A. Walshe et al. (2009) Integrating In Silico and In Vitro Analysis of Peptide Binding Affinity to HLA-Cw*0102: A Bioinformatic Approach to the Prediction of New Epitopes. PLOS One 4(11): e8095 http://dx.doi.org/10.1371/journal.pone.0008095

[23] Association for Molecular Pathology v. Myriad Genetics, 569 U.S. 12–398 (2013).

[24] See Benjamin Lewin (1997) Genes VI, Oxford University Press, New York.

genetic traits from a former generation to a later one, and it is comprised in genes. Before bringing the traits into play, DNA leaves a copy of itself which then creates RNA. In the method of transfer of genetic traits, RNA plays a role of a mere intermediary only.[25] Later on the cellular machinery analyses and uses the information contained in the RNA in order to make a protein. This protein so formed becomes the point of reason for carrying the genetic traits.[26]

Furthermore, every gene, or DNA, is constituted of four basic nucleotides A (adenine), G (guanine), C (cytosine) and T (thymine), and these are present in various types of combinations.[27] These combinations form a unique chain creating a DNA sequence which in effect creates a particular RNA, thereby leading to creation of protein and then varied cellular structures. RNA also has a chain of its own nucleotides, wherein the only difference is that instead of T (thymine), which is present in DNA, RNA has U (uracil) as its fourth component.[28] Proteins on the other hand are comprised of 20 different kinds of amino acids, named A, C, D, E, F, G, H, I, K, L, M, N, P, Q, R, S, T, V, W and Y, and are a combination of any sequence thereof.[29]

Bioinformatics looks forward to study the genetic expression being performed by genes and proteins.[30] In the end, it can be understood that nucleic acids and proteins are the bigger molecules which contain within it nucleotides (depending on whether it is DNA nucleotides or RNA nucleotides) and amino acids. Functions of these nucleic acids and proteins are determined by the sequence that they follow, and therefore, every genomic sequence contains within it a particular kind of functional information.

6.3.2 Genomic Sequence Database

When the research in this regard started, it was very much required to create an organised and categorically created database for every new sequence which was found. Every time a researcher found any new thread or combination or sequence of nucleic acids or proteins, the information contained therein was very valuable to be stored for the reference of future researchers.

The value addition to these databases has been done by examining them and making them accessible for further examinations. So even though a particular sequence has been previously discovered, a new researcher might find an unknown biological characteristic being carried out by the specific genomic structure, which he/she can then assign to the respective genomic sequence in the database. If a

[25] B. Albert et al. (2002) Molecular Biology of the Cell, Garland Science, New York.

[26] See Benjamin Lewin (1997) Genes VI, Oxford University Press, New York.

[27] H Lodish et al. (2000) Molecular Cell Biology, W. H. Freeman, New York.

[28] Ibid.

[29] Ibid.

[30] Cynthia Gibas et al. (2001) Developing Bioinformatics Computer Skills, O'Reilly, California, p 9–10.

completely new sequence is spotted by the researcher, then the databases can be utilised to cross-examine and finalise the function being carried out by them.

There are many public databases, or in other words open source databases, wherein researchers from around the globe can submit a particular sequence and make it publicly and readily available. At the same time, there is no restriction on private researchers and corporations to carry out the research in this regard. One of the best examples of a privately kept genetic sequence is the latest case of *Myriad Genetics*[31] in relation to BRCA genes. Such cases (even after they have been decided) make room for debate as to whether any IP protection should be accorded to privately kept databases.[32]

6.3.3 Application of Computer Technology

The genomic information which are protected within the databases require specific software programmes in order to generate, access, categorise and examine the database and the genetic information inside it.[33] An example of such programmes can be understood in the form of "Basic Local Alignment Search Tool" (BLAST)[34] which "compares sequences for similarity by first aligning the two sequences at areas of local identity or similarity and then calculating a similarity score".[35] Following the structural and molecular biology of nucleic and amino acids, algorithms can be created and incorporated using defined and established scientific principles. There could be an algorithm which can compare the functioning aspect of two different amino acids or nucleotides, which are not same but are performing a similar function on the molecular level. Such algorithms are helpful in determining and assigning function to a previously unknown genetic sequence.[36]

Besides the development of software, much new hardware have also been created in order to facilitate the examination of a genetic sequence, and these help in acquiring and storing bioinformatics. "Thermocyclers", for example, amplify a small strand of nucleic acid molecule in order to provide the researcher with sequence in a workable amount.[37] "Sequencers" function on high speed for determining the sequence of the nucleic or amino acids presented with.[38]

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[31] Nayanah Siva (2009) Myriad Wins BRCA1 Row. Nature Biotechnology 27:8.

[32] Association for Molecular Pathology v. Myriad Genetics, 569 U.S. 12-398 (2013).

[33] H Liu & L, Wong (2003) Data Mining Tools For Biological Sequences. Journal of Bioinformatics and Computational Biology 1(1):139–67.

[34] See GeneBee, BLAST: Basic Overview. http://www.genebee.msu.su/blast/blast_overview.html. Accessed on 22 Sep 2017.

[35] Ibid.

[36] L. Feng et al. (2000) Aminotransferase Activity and Bioinformatic Analysis of 1-Aminocyclopropane-l-Carboxylate Synthase. Biochemistry 39(49):15242–49.

[37] James Tisdall (2003) Mastering Perl for Bioinformatics, O'Reilly, California.

[38] Ibid.

One of the best comparative hardware invented is called "gene chip", which allows researchers to cross-check and verify if the test sample can correlate to any of the existing genomic sequence that is available on the chip in microarray or grid,[39] and the method of conducting this test is popularly called as "hybridisation".[40] The advantage of gene chip is that it enables the researchers in obtaining huge quantity of information from a single trial, and therefore it is also functionally referred to as a "high-throughput device".[41]

Now, after understanding all the three components of the bioinformatics, i.e. genomic sequence, viz. nucleic acids and proteins, etc., databases used to organise these sequences and hardware and software used to generate, access, categorise and examine the databases, genomic sequences and information contained in it, the author will now examine the different IP regimes in order to establish the perfect protection which can be granted to these components.

6.4 Realising the IP Protections and Its Limitations

Bioinformatics primarily attracts three kinds of protections that can be accorded to it under the name of negative IP rights, for excluding various entities from reaping the fruit of someone else's effort, i.e. patent, copyright and trade secret.[42] However, the test doesn't stop here as there is a possibility that these protections can be accorded individually or can be made available in a group, with respect to the three components of bioinformatics, i.e. genomic sequence, viz. nucleic acids and proteins, etc., databases used to organise these sequences and hardware and software used to generate, access, categorise and examine the databases, genomic sequences and information contained in it.

Bioinformatics, as per its very own definition, is nothing but an application of computer-based technology used for the generation, accessibility, categorising and examination of data or information collected through biological materials available in the body.[43] Therefore isolation of gene and protection of isolated genes is not a part of the subject area covered by bioinformatics as this is a research based on molecular biological level which grants the researcher with raw data for which the tools are required, to decipher the information and make it usable. The scope of the paper is limited to bioinformatics protection, which would encompass within it the databases and other technological developments, and so, it does not include the

[39] F. Ferrari et al. (2007) Novel definition files for human GeneChips based on GeneAnnot. BMC Bioinformatics 8:446.

[40] Ibid.

[41] Ibid.

[42] D. Fernandez et al. (2003) IP strategy in Bioinformatics and Biochips. Journal of the Patent and Trademark Office Society 85:465–69.

[43] C.A. Ouzounis et al. (2003) Early Bioinformatics: the Birth of a Discipline. Bioinformatics Review 19(7):2176–2190.

computational biology, which in turn deals with the nuances of protecting isolated genes through IP regimes.[44]

6.4.1 Genomic Databases

In relation to bioinformatics, the database is a pool of collected data, which provides an opportunity to the researcher to utilise it and update it from any place for the purpose of genetic studies. The main purpose which can be accorded to the databases is that it serves as a platform for an easy access to data and genomic information and it allows examination and further comparison with other information for finding new results.

Being a mere compilation of data, the databases loose the patentability, as the information so available are abstract in nature and it contains only the detailed composition of nucleic and amino acids, which are naturally available as well. Therefore, a database, being a mere discovery and presentation of already known information, lacks innovation. However, it has been argued that if a database is doing more than being a mere catalogue of information, and if it is providing any tangible result by utilisation of raw data through any data processing system attached to it, then it can be patentable.[45] In the USA, such systems of data processing have been held to be patentable as they carry out functions in furtherance of the mathematical algorithm contained therein.[46]

Using this analogy, bioinformatics database which aren't a catalogue of information, but which are generated through computer, working on specific software and facilitating the functioning aspect of bioinformatics research, can be argued to do data processing and thus should be patentable.[47]

Such a mischievous interpretation can be followed in India, as well, where in computer programs are not patentable per se.[48] As a bioinformatics database is a combination of presented information, working in a particular manner on a specific computer programme can be claimed to be patentable, as it is not per se any of the non-patentable subject matter. However, such protection will not extend to the information contained in the database and will only be for the process on which it has been functioning, making the patent protection to database a mere token protection as an infringer is always allowed to utilise the information contained in the database through a non-patented process. Furthermore, considering the fact that

[44] For discussion on IP protection to isolated genes in India see generally Abhijeet Kumar et al. (2015) Gene Patenting vis-à-vis Notion of Patentability. Journal of Intellectual Property Rights 20(6):349–362.

[45] Raguvaran Gopalan (2009) Bioinformatics: Scope of Intellectual Property Protection. Journal of Intellectual Property Rights14 (1): 46–51.

[46] State Street Bank v. Signature Financial Group 149 F. 3d 1368.

[47] D. S. Chisum (2000) Chisum on Patents, Vol. 1, Lexis Publishing, New York, p 78.3.

[48] Section 3, Indian Patent Act, 1970.

sequencing has been happening for a very long time now, most of the claims will fall a prey to the nonobviousness test.[49]

IP regime of copyright comes as the most efficient mode of protection of databases. In the USA, the Supreme Court held that "even though facts are not copyrightable but compilations are, provided that there is a sufficient degree of originality in the compilation in terms of the selection and arrangement of term, in terms of indices employed etc.".[50] However, protection is accorded to the original part of the compilation only and not to the facts contained in it.

In EU, the Directive issued in this regard grants a "joint protection the content of the database and the originality part of the database through selection and arrangement of materials".[51] The rationale behind it is that a person who has invested time, money and intellect in collection and verification of the data should be granted exclusivity over such data. The protection granted through this Directive covers unauthorised access and use in whole or part, of a protected database.[52] Even though most of the compilation is done through computer does not make it non-copyrightable as it is the expression of the idea of the author which is made available in the end, regardless of the fact that the medium to obtain so was through the computer.[53]

The third kind of protection which can be accorded to databases is trade secrets. Trade secrets are information of economic value, which are not readily known or accessible apart from a group of people who use the same for the purpose of trade and business. Protection of such information is on the owner of the information who has to maintain circumstances of reasonable secrecy, in order to keep it protected. So, if a database is of economic value and if there has been reasonable amount of care taken by the owner to protect it, then it can be protected as a trade secret.

However, in regard to bioinformatics databases, where unlike the product component, the data in itself needs to be protected; trade secret would fail to provide any effective remedy. In order to have a better understanding, we need to analyse what is being protected and what is being commercialised. The database in bioinformatics is of valuable nature, and once the same is commercialised, the owner of such database runs a risk of losing the information to the public domain, and the secrecy aspect of such information is lost. Also, tortuous remedy in the form of damages can be prayed only for leaked information, but no injunction can be granted over leaked

[49] M. Scott McBride (2002) Bioinformatics and Intellectual Property Protection. Berkeley Tech. L.J. 17:1331.

[50] Feist Publication Inc v. Rural Telephone Service CO 499 US 340.

[51] M. J. Davision (2003) The Legal Protection of Databases, Cambridge University Press, Cambridge, p 11.

[52] Directive 96/09/EC of the European Parliament and of the Council on the Legal Protection of Databases.

[53] Section 2 (o), Indian Copyright Act, 1957.

trade secrets.[54] Moreover, while in the USA the trade secrets are protected through legislative provisions,[55] in India there is no law in that regard.[56]

6.4.2 Protecting Enabling Hardware and Software

As discussed above, looking at it, especially with regard to both the hardware and software aspects, there have been several inventions in the field of technology, considering it as an inherent field of interface for the protection and working of bioinformatics, in the software and hardware, both aspects. While protection of hardware is of no issue, with patent being the regime to grant protection and the criteria to fulfil the same being that of novelty, inventive step and industrial application, it is the protection of software running on such hardware or independently, on any hardware, that requires an overview to see the protection of IP.

Question that has been commonly raised through practice is that software has mostly been considered to be a subject matter of copyright, rather than patent, because of its inherent nature of constituting of merely mathematical formulas, accompanied by group of commands to be followed, in order to achieve the goal.[57] However, copyright is not a strong regime to grant protection to such vulnerable innovations, especially in the current global market of Internet, which has led to the bringing of the deterring dream of piracy of software-related invention alive.[58] Therefore, the developers are of the opinion, for which various demands have been constantly being made to ensure a patent protection to software industry.

The overlap, however, can be seen, as software fulfils the criteria of patentability, i.e. they are novel, contain an inventive step (also qualifies the test of nonobviousness) and are industrially applicable, but at the same time they are an original idea with an expression of the same.[59] As soon as the coder writes his/her code in a tangible form and stores in any kind of medium, the code becomes copyright protected, even without any requirement of specific registration. So, such kind of protection can be extended to three different aspects of a code, i.e. protecting the human readable form or the source code, protecting the machine readable form or the object

[54] M. Risch (2007) Why do we have trade secrets?. Marquette Intellectual Property Law Review 11:1–75.

[55] See Uniform Trade Secret Act, 1979 (USA).

[56] Abhijeet Kumar et al. (2015) Protecting Trade Secrets in India. Journal of World Intellectual Property 18(6):335–346.

[57] Abhijeet Kumar (2017) IP Protection to Software: Conflict between Indian Provisions and Practice. Journal of Intellectual Property Rights 22(5):247–256.

[58] Manuel Castells and Gustavo Cardoso (2005) The Network Society: From Knowledge to Policy, Center for Transatlantic Relations, Washington DC.

[59] Avinash Kumar (2000) According Legal Protection to Intellectual Property Rights in Softwares, Directorate of Extramural Research & Intellectual Property Rights, Defence Research & Development Organisations, p 4–43.

code and the related documentations.[60] Additional advantage for copyright protection is that it creates a better balance when it comes to fair and free circulation of protected material and it is economically more viable to obtain. However, the disadvantage is that the functional aspect of software is not protected through copyright, which is the primary difference between software and any other literary work. Software is a dynamic product which is not just for the purpose of reading and referencing. A learned developer can bypass the protection granted to the software through copyright very easily, by recreating new software without copying the code but while using the same functionality and idea behind the software.[61] The issue also arises in creating a differentiation between the idea and expression of the same.

If we take the case of bioinformatics, the protection that is granted and sorted through the copyright for software would fail in many ways. Copyright protects the expression and not the functionality, and most of the bioinformatics database software have inherent functionality through which the researchers have an ease of using the database for further research and examination of new and existing information. Such functionalities will remain unprotected through the copyright protection of such software.

In this case, trade secret protection can be invoked to protect bioinformatics software, provided the software is made available in machine readable language, which cannot be easily circumvented by any developer, regardless of whatever programming language is being used. Thus keeping the source code of the software as a trade secret, the modus operandi of the software is unknown to the public, and at the same time, the method of combination and achieving of the software is also kept a secret.[62] However, the disadvantage of trade secret protection of software is the same as any other subject matter, i.e. independent research can lead to losing the secret and thus the monopoly over the same. Reverse engineering or anti-circumvention, in case of trade secret protection, is not restricted, and thus the developer capable of deciphering the source code behind any software will always have an advantage.[63]

In contrast to both of these protections, where copyright is automatic in nature on the expression and trade secret is the protection through individual efforts, patent can be granted only if the software qualifies the patentability test of being novel, involving an inventive step, and if it is industrially applicable.[64] Therefore, when it

[60] Bronwyn H Hall (2002) On Copyright and Patent Protection for Software and Databases: A Tale of Two Worlds, Paper for Granstrand Volume. https://eml.berkeley.edu/~bhhall/papers/BHH%20OGvol02.pdf. Accessed on 22 Sep 2017.

[61] John Swinson (1991) Copyright or Patent or Both: An Algorithmic Approach to Computer Software Protection. Harv. Journ. of Law and Tech. 5:145.

[62] Abhijeet Kumar et al. (2015) Protecting Trade Secrets in India. Journal of World Intellectual Property 18(6):335–346.

[63] Ibid.

[64] Bronwyn H Hall (2002) On Copyright and Patent Protection for Software and Databases: A Tale of Two Worlds, Paper for Granstrand Volume. https://eml.berkeley.edu/~bhhall/papers/BHH%20OGvol02.pdf. Accessed on 22 Sep 2017.

comes to protect the functionality of bioinformatics software, the best possible protection regime is that of patent. Patent protection creates a limit on the rights of the software developer or patentee to the claims made in application, and at the same time it would also prohibit protection of software which is similar to already patented software.[65] Thus, this has led to an increase in demand for patent protection for bioinformatics software.

However, this overlap can be easily taken care of by granting part protection to the bioinformatics software. This solution, in fact, relies on the fact that while copyright protection is limited to the expression of the idea, the patent regime has no such limitation. Thus, while copyright can protect the written code of the software, the patent would grant a protection to the functional aspect of the same.[66] This solution is viable, because there is no other subject matter in which this overlap can be witnessed. Thus, this will be an exception, which would in turn be strengthening the general rule of not granting two different IPs to the same subject matter.

If we talk about trade secret protection for source code of the software, it has to be understood that the balance of the IP jurisprudence, which has to be maintained in between private and personal rights, will always be in favour of the developer and, in case of the secret being let out, it will be tilted against it.[67] However, there never will arise a scenario wherein the actual balance between private and public interest can be maintained and, thus, it is highly undesirable for the community. Yet, upon taking into account the economic aspect, it is reasonable to argue that a strong IP protection should be granted, with economic backing/sanctions in the case of infringement, for loss and/or damages, considering the amount of investment which is being done in R&D of software.

6.5 Way to the Future

Bioinformatics is the field that has brought revolution in the field of medicines and cures for diseases as it has led a pathway for innovations and discoveries in the study of genetic sciences and molecular biology, which has been motivated and triggered through the use of information technology and computer sciences.

A close study of this development does not only satisfy the great work that has been the interest of the pharmaceutical companies only (from an economic perspective), but also the opportunity of a situation wherein there is a possibility of creation of a magical medicine to cure a disease which was till now considered incurable cannot be ignored. However, at the same time, the heavy amount of investment

[65] Yogesh Suman & V K Gupta (2002) Patenting Issues in Software Industry. Journal of Intellectual Property Rights7(6):516–525.

[66] V K Gupta (2001) Managing Software Protection. Journal of Intellectual Property Rights 6(6):277–285.

[67] Abhijeet Kumar (2017) IP Protection to Software: Conflict between Indian Provisions and Practice. Journal of Intellectual Property Rights 22(5):247–256.

being made and underlying profit interest of various pharmaceutical companies has also fostered various ethical debates on this issue.

Corporations from different fields, such as pharmaceuticals, software industries, etc., which are owned privately or publicly or by not-for-profit organisations, all of them have been fuelling funds for research in this area with the expectation of returns or service.

The two aspects wherein the invention in this arena has been limited to have been creation of databases and development of better software for examination of such databases and information contained therein. Considering that there is no proper mechanism of protection which can be accorded to the database, a protection needs to be made available in a sui generis mechanism which would be in tandem with the protection which has been offered by EU, wherein while providing the traditional copyright rights, the additional right of prohibiting others from reutilisation and mere data extraction without authorisation could also be provided.

Bioinformatics software can be patented because of the presence of inherent transformation and the tangible result provided by it, and the jurisprudence of patent law in various jurisdictions would allow it as well, without any issues. This will obviously be available only if they are novel, contain an inventive step and are of industrial applicability.

The reason for granting protection to this aspect of innovations, viz. bioinformatics, is required for the same rationale that it required a lot of investment in R&D and the only way to keep up the wave of innovation is by providing incentives to the authors through IP or a sui generis protection.

But at the same time what should not be forgotten is that the main aim of this subject is to come up with treatments and medicines that in turn help masses to live a better, healthier and longer life. Therefore, the government is required to work wisely in creating such policies that bring both the investors, i.e. the pharmaceutical and software companies, and the citizens of a country in harmonised equilibrium. Compulsory licensing is an effective way of mitigating problems specially arising in fields relating to health, but unless a particular protection is being granted that exception can also not be utilised by the government. Therefore, a similar approach has to be adopted by the government if a *sui generis* protection is being made available as suggested, for protection of innovation in the field of bioinformatics.

Returning to the debate as to whether or not IP protection should be extended to this field, what should be remembered is that protection of database and software is not the same as creation of monopoly over surgical and diagnosis method. Moreover, no monopoly is created over the human genome sequence, and that has been established by the courts of different jurisdictions. The solution to this fear, however, can lie in the proper drafting of the legislation which would demand for a proper and complete disclosure of information, with all the exceptions required such as compulsory licensing, Bolar exception, academic and research use, fair use exception, provision for government use or acquisition, etc., thereby providing an extended IP protection to bioinformatics, but not an unequivocal protection.

Part II

Intellectual Property Issues in Food and Agricultural Microbiology

IPR Issues in Agricultural Microbiology

7

Irina Kireeva

Abstract

Intellectual property plays an important role in facilitating the process of taking innovative technology of microbiology to the marketplace and actual consumers. At the same time, protection of intellectual property contributes to enhancing competitiveness of technology-based enterprises, whether such enterprises are commercializing new or improved products or providing service on the basis of a new or improved microbiological knowledge. For most technology-based food enterprises, successful invention results of microbiology lead to a more efficient way of doing things or in a new commercially viable product; therefore protection and promotion of intellectual property rights is directly linked and contributes to success of microbiological research.

Keywords

Food security · GATT · TRIPS · GIs

7.1 Microbiology and Issues of Food Safety, Quality and Security

There are many definitions of food known, but one that is most appropriate for our purposes is referring to food as "any substance consumed to provide nutrition support to the human body, making it work, grow and repair itself".[1] In the contemporary

[1] See definitions in *Encyclopedia Britannica*, http://britannica.com, *The American Heritage Dictionary of the English Language*, 4th ed., 2009, Houghton Mifflin Company; World Food Programme, *Breaking out of the Poverty Trap: How We Use Food Aid*, electronically available at

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H. B. Singh et al. (eds.), *Intellectual Property Issues in Microbiology*,
https://doi.org/10.1007/978-981-13-7466-1_7

world, production of food is not simply known to be a result of numerous and different activities. However, all those activities could be linked to three important aspects, representing basic rights of every human being, namely, food safety, quality and security.[2]

Indeed, in the last few decades, mankind had several very important global problems, and among them, certainly, are all the three above-mentioned aspects – food crises and safety, shortage of food and famines, expectations of the consumers and issues of food fraud. Thinking about this it comes to mind that food microbiology – the study of the microorganisms that inhabit, create or contaminate food, including research on microorganisms causing food spoilage – is directly relevant to indicate above problems of food safety, quality and security.

Issues of quality and food security are also within the scope of agricultural microbiology, which concerns research of plant-associated microbes and aims to address problems in agricultural practices usually caused by a lack of biodiversity in microbial communities. An understanding of microbial strains relevant to agricultural applications is pertinent to food security addressing soil nutrients, plant-pathogen resistance, crop robustness, fertilization uptake efficiency and more. In addition, many symbiotic relationships between plants and microbes can ultimately be exploited for greater food production and better food quality necessary to feed the expanding human populace.

The importance of food and agricultural microbiology cannot be overestimated due to the link between food and health, since food-borne and waterborne diseases are the major cause of illness and death all around the world.[3] According to the World Health Organization, food-borne illnesses are the leading causes of health problems and deaths in developing countries, killing approximately more than three million people annually, most of whom are children.[4] Moreover, food safety problems and diseases are not only attributes of developing world, limited to some

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http://www.wfp.org/food_aid/introduction/index.asp?section=12&sub_section=1; P. Van den Bossche, *The Law and Policy of the World Trade Organization: Text, Cases and Materials*, UK: Cambridge University Press, 2005; A. Smith (ed.), "Food Marketing", in Oxford Encyclopedia of American Food and Drink, New York: Oxford University Press, 2007; J. Jango-Cohen, *The History Of Food*, Twenty-First Century Books, 2005; R.A. Carpenter, C.E. Finley, *Healthy Eating Every Day*, Human Kinetics, 2005.

[2] The significance of food and its central role in our health and pleasures as well as in our economy, politics and culture is excellently presented by P. Atkins and I. Bowler, in their book entitled *Food in Society: Economy, Culture, Geography*, Hodder Arnold, Great Britain, 2001.

[3] One of the most remarkable books on the link between food and health is *We Want Real Food* by Graham Harvey, published by Constable – London in 2006. Consider also P. Caplan (ed.), "Food, Health and Identity", London: Routledge, 1997; T. K. Marsden, "Food matters and the matter of food: towards a new food governance", *SociologiaRuralis*, 2000, Vol. 40, pp. 20–29.

[4] WHO estimates that world-wide almost two million children die every year from diarrhoea, most of this caused by microbiologically contaminated food and water (WHO, 1999a). See also WTO Agreements and Public Health, A Joint Study of the WHO and the WTO Secretariat, 2002 and J. Rocourt, *The present state of foodborne disease in OECD countries*, WHO 2003.

geographical regions, political regimes or social structures; they are present in different forms and shapes everywhere.[5]

Modern scientific research, new detection methods and consumer awareness have improved the understanding of food risks and their consequences.[6] However, there are many reasons for food-borne diseases remaining a global public health challenge. As some diseases are recognized and controlled, others emerge as new threats. Globalization of the food supply has led to the rapid and widespread international distribution of foods, and along with food, pathogens are also introduced into new geographical areas. So, with further globalization of food supply, the demand for food safety improvements is increasing, and investment into research on food and agricultural microbiology is not only well justified but absolutely essential. That is where legal dimension of intellectual property rights is coming into play.

7.2 Intellectual Property Rights: Relevance to Microbiology

In simple words, intellectual property rights are rights given by the State on the bases of legal acts to persons over the creation of their minds. One of the main distinctive features of intellectual property rights is that they give the owner exclusive right over the use of its creation or invention for a certain period of time. Requirements and particularities of protection granted would depend on the nature of the intellectual property type, as there are a number of them – patents, trademarks, copyright, etc. On the expiry of the relevant period of intellectual property protection, the earlier protected work is entering the "public domain", when can be used without particular restrictions applied earlier. The formal or official state registration is normally required for the recognition of most intellectual property rights, however, not for all and not in all countries, as relevant national law would explain what steps have to be taken to protect particular intellectual properties. Intellectual property rights can be divided into two major groups: copyright and rights related to copyright and industrial property rights.

[5] To prove that, see the WHO statistics (electronically available at http://www.who.int/topics/foodborne_diseases/en/): more than 9000 deaths in the USA, due to food- and waterborne diseases, are certainly a strong indicator that the food safety is an issue in developed part of the world, as well. Thus, it is not surprising that in highly industrialized countries, such as the USA, Australia and EU members, for example, percentage of people suffering from different issues of unsafe food has been reported to be up to 30%. The negative consequences of poor food safety are even more worrying in the developing world, where the WHO estimates that as much as 70 percent of the 1.8 million annual deaths from diarrhoea are linked to contaminated food. See also information on http://www.cdc.gov/foodborneburden/2011-foodborne-estimates.html, official web site of Centers for Disease Control and Prevention.

[6] Foodborne Disease Outbreaks Guidelines and Control, 2008, WHO Publication.

7.2.1 Original Expression of Ideas and Protection of Copyright with Related Rights

For protection of original literary, scientific, musical and artistic works, computer software and database copyright is used. The purpose and scope of protection is original expression of ideas fixed in a tangible medium or form, not the ideas themselves. For example, there is no infringement of the copyright of a book when a new technique is explained or used for other research or developments, but if that book is photocopied and distributed without the permission of the copyright owner (not necessarily the author of the book) – in such case – the copyright is infringed.

Copyright is relevant to food and agriculture microbiology as would be relevant to any field of study or research, since everything written down, painted, drawn, sculptured, filmed and performed for the purposes of that field would be automatically protected without registration in most parts of the world. The author (or "creator", or "owner of the right") can control the future of that work; such rights are usually protected for a minimum period of 50 years after the death of the author.

The legal protection provided by copyright in an original work usually so to say "embraces" two sets of rights: economic and moral rights. At the international level, the rights are conferred by the Berne Convention for the Protection of Literary and Artistic Works of 1886.[7] In the context of copyright protection, economic rights to control copying and dissemination of the work to the public, including broadcasting and recitation, public performance or display, adaptation, translation, distribution, etc. are relevant. Moral rights include the author's right to object to any distortion, mutilation or other modification of the work that might be prejudicial to the author's honour or reputation and the right to be identified as the creator of the work. Both economic and moral rights originally belong to the creator, who can exercise them and use the work himself or give the permission to any other party to use or prohibit someone else to use the work. Underlying all this is the general principle of the copyright protection that copyright protected rights cannot be used without the authorization of the owner of the rights. There are only a few limited exceptions to this principle that can be found in the national laws, such as the use of work under certain conditions for teaching purposes, for scientific research or for reporting current events. It is important to know that any new creation in the field of microbiology written down, painted or drawn, sculptured, filmed, performed, etc. is automatic and therefore does not require registration. "Related rights" to the copyright concern other categories of owners of rights – namely, performers (actors, singers, musicians, etc.), producers of phonograms (sound recording) and broadcasting organizations. In relation to microbiology, for example, it can be a new programme over food safety and microbiology to the general public with the information on how to preserve food from spoilage in the domestic household based on the published book. The rights of the performers are related to the original copyright of the book, as the owner of the "related rights" gives expression to the authors of the

[7] The text of the Berne Convention can be found at http://www.wipo.int/treaties/en/text.jsp?file_id=283698.

original works in their communication of the works to the public. At the international level, "related rights" are conferred by the 1961 International Convention for the Protection of Performers, Producers and Broadcasting Organizations, known as the Rome Convention.

7.2.2 Stimulation of Innovation and Protection of Distinctive Signs by Industrial Property Rights

Industrial property protection covers two main categories – first one designed to stimulate innovation and creation of technology, in particular inventions protected by patents, integrated circuit layouts, industrial designs and undisclosed information or trade secrets and second necessary to protect distinctive signs, such as trademarks, which distinguish the goods or services of one enterprise from those of other, and geographical indications, which identify goods as originating in a place where given characteristic of the goods is essentially attributable to its geographical origin. Protection for patents, designs and trademarks is usually limited in time, but for geographical indications, protection may last indefinitely, provided that the sign in question continues to be distinctive and goods possess the indicated qualities.

7.2.2.1 Patent Protection of Inventions

A patent refers to an exclusive right granted for an invention. It can be either a product or a process that provides a new way of doing something or offers a new technological solution to a problem. It is granted by the State to an inventor for the results of his or her invention for a certain period of time or to authorize another person to implement it.

To be protected by a patent, an invention must:

- Be of practical use and do what the application says it will do.
- Show an element of "novelty" – in other words, some new characteristic which is not known in the body of the existing knowledge ("prior art") in the technical field in question.
- Involve an "inventive step" – the invention must not be obvious to someone with knowledge and experience in the technological field of the invention.
- Be accepted as "patentable" under the law of the country where the patent is sought.[8]

A patent is normally granted by the patent office of a country or by a regional office that does the work for a number of countries – such as the European Patent

[8] In order to secure a patent, a formal application is required, containing the title of the invention, sufficiently clear description of the general nature of the invention and at least one "claim" of novelty, distinguishing the invention from what is already known. Patent rights are usually enforced in courts with possibilities to stop the infringements or declaring patents invalid upon successful challenge by a third party.

Office, based in Munich, Germany.[9] Under these regional systems, an applicant requests protection for the invention in one or more countries. Each country can decide whether to provide patent protection within its borders. The WIPO-administered Patent Cooperation Treaty (PCT) also provides for the filing of a single international patent application, allowing to seek protection in as many States Parties to the PCT as would be required.[10]

Microbiology is currently of considerable commercial importance. This can be explained due to the fact that microbiological processes afford quick, clean and relatively inexpensive methods of making a variety of useful chemicals, including antibiotic drugs and food additives. Among a few promising applications of microbiology, the following can be mentioned: commercial potential for the synthesis of human nutrients and a variety of other products in short supply; accomplishment by environmentally unobjectionable means many of the tasks now effected by chemical insecticides, fungicides, herbicides and other similar harmful substances; disposal of industrial and municipal wastes; and many others. Notwithstanding its ever-expanding importance, useful advances in microbiology appear to be treated less generously than similar discoveries in chemistry, physics, engineering disciplines and agriculture, with respect to availability of patent protection. This is because many questions have not been satisfactorily answered, neither judicially nor legislatively, as to whether microorganisms are patentable per se. According to the Trade-Related Aspects of Intellectual Property Rights (TRIPS) Agreement, legal protection of agricultural innovations as patents is currently extended to cover plants, animals and microorganisms, and this is of relevance to the microbiology research too.

7.2.2.2 Major Differences in Protection of Trademarks and Geographical Indications

Microbiology contributes to the development of food products, and their names and distinctive signs used to distinguish those goods are protected by trademarks and geographical indications.

A trademark is a distinguished and recognizable sign which is capable of identifying a product of a particular source from those of others. A trademark can be placed on a package, a label or on the products itself. Just for curiosity, the first legislative act concerning trademarks was passed in 1266 by King Henry III in Britain; it was in relation to the most consumed product – bread. The law required all bakers in London to use a distinctive mark for the bread they were selling (to trace the origin of the bread, for the purposes of detecting and preventing fraudulent activities). The first modern trademark laws were emerging in Europe in the late nineteenth century, for example, in France in 1857.

Geographical indications are also distinguishing signs used on goods produced in the places indicated, which have specific qualities and reputation that derive from

[9] For more information consult the official site of the EPO https://www.epo.org/index.html

[10] PCT has currently 152 contracting parties; for more information consult the official site of the WIPO.

their place of production and are influenced by specific local factors.[11] Historically, these signs used on goods were the earliest types of trademark.[12]

Over time, marks with geographical references evolved into ordinary type of trademarks, which identified a producer rather than the place of production. Trademarks, as a type of intellectual property, were traditionally maintained and protected under national and international law. However, the evolution of marks associated with a region into specific "trade" marks which apply to the products of individual manufacturers has not meant the disappearance of geographical marks.[13]

Among all types of intellectual property, geographical indications and trademarks are the closest legal concepts. This consideration follows from the definitions of these types of intellectual property rights provided by the TRIPS Agreement.

As protection of geographical indications has evolved in different ways under different national and international laws, there is no generally agreed terminology in the field. There are also no common legal definitions of what is the scope of application of a geographical indication. The first definition of geographical indications in international law was introduced within the framework of the World Trade Organization (hereinafter, the WTO) by the Agreement on Trade-Related Intellectual Property Rights (hereinafter, the TRIPS Agreement), which entered into force on 1 January 1995.[14]

The TRIPS Agreement defines geographical indications as "signs which identify a good as originating in the territory of a Member, or a region or locality in that territory, where a given quality, reputation or other characteristics of the good is essentially attributable to its geographical origin". This definition clearly states three conditions for recognition of a sign as a geographical indication: first of all, it must relate to a good; secondly, the goods must originate from a defined area; and finally, the goods must have qualities, reputation or other characteristics which are clearly linked to the geographical origin of goods. Without the fulfilment of these three conditions, any sign, even geographical, may not be considered as a geographical indication under the terms of the TRIPS Agreement.

Trademarks are defined by the TRIPS Agreement as "signs, or any combination of signs, capable of distinguishing the goods or services of one undertaking from those of another undertakings". It follows from this definition that only distinctive

[11] See I. Kireeva and P.R. Vergano, "Geographical Indications and the Interface between Trade Mark Protection and Sui Generis Protection: The Example of China, Thailand and Vietnam", International Trade Law and Regulation, Sweet & Maxwell, July 2006, Vol. 12, Issue 4, pp. 97–108.

[12] Often the products of specific places were more saleable than comparable products from other regions because of a particular quality trait associated to a given geographical area or site of production. This quality was a result of natural geographic advantages, such as climate, geology or food processing techniques peculiar to a region.

[13] This is particularly true in Europe, where substantial processed food markets and markets for alcoholic beverages are dependent upon the continued recognition of geographical indications.

[14] Before that date, several other international attempts of recognition and protection of appellations of origin had been made. Among them, one of the most relevant to the protection of geographical indications was the Lisbon Agreement of 1958, which, unfortunately, did not attract a lot of attention as only a few countries have ratified it.

signs can perform the function of trademarks. In addition, trademarks do not have to be necessarily linked to a geographical area.

Both geographical indications and trademarks are signs that are used to identify goods. These signs can acquire a high reputation and commercial value and, for these reasons, may be exposed to misappropriation, misuse and counterfeiting. At the same time, the main function of geographical indications is to identify the origin of goods. They point to a specific place or region of production that confers particular characteristics and qualities to the product. It is important to emphasize that the product derives its qualities and reputation from the place of origin.

Trademarks designate the source of products or services not in geographical terms but in relation to an enterprise or, in case of collective marks, an association of producers and its members. In other words, the main function of trademarks is to put emphasis on the producers of the goods and not on the place where the goods have been produced, since this place does not have any specific bearing on the quality and reputation of the goods. This is the main difference between geographical indications and trademarks.

It is a general rule that trademarks must not be of such a nature as to deceive the public in relation to, for instance, the nature, quality or, more specifically, the geographical origin of goods or services. Moreover, a trademark provides protection to the owner of the mark by ensuring the exclusive right to its use to identify goods or services. That may logically suggest that geographical terms should not be registered as trademarks. In fact, most countries have implemented provisions at the national level to the effect that it is generally not possible to register geographical terms as trademarks.

However, there are at least two situations when geographical terms could be registered as trademarks for goods, first, when the geographical word or symbol has acquired recognition or secondary meaning in favour of a particular enterprise (i.e. “Montblanc” for writing equipment and jewellery, “Budweiser” and “Malta Heineken” for beer, “London Dock” for tobacco, “Black Sea” for alcoholic drinks, etc.). It should be noted that only some of the registered trademarks that acquired recognition indicate the true origin of goods (among them, “Swiss Alps” for chocolate from Switzerland, “France-Caline” for perfumes from France, “Navarra” for liqueurs from Spain and “Schwartauer” for jams and jellies from a manufacturer located in the North German town of Bad Schwartau). Another situation when geographical words or symbols are accepted as parts of trademarks is when they are understood as fanciful words (i.e. “Antarctic” for orange juice, “North Pool” for footwear, “Vesuvius” for chimneys and heating equipment, etc.).

There are a number of differences between trademark protection and specific protection provided to geographical indications, for example, the conditions for protection and its duration and the costs involved in registration and protection. However, all these elements are provided in the national legislation and, therefore, vary from country to country. In some countries the registration of geographical indications is not compulsory for obtaining protection. One specific common feature, shared by many jurisdictions in the world, which distinguishes sui generis protection provided to geographical indications from trademark protection, is that

trademark regime protects a specific logo (i.e. the combination of signs, words, pictures and colours) while a sui generis system protects a geographical name as such and prevents any commercial use of the protected name. The trademark regime does not prevent other producers from registering similar signs, provided that they do not result in a likelihood of confusion. On the contrary, it is not possible to register similar geographical indications, since each of the registered names would already have established reputation and notoriety due to the quality or other characteristics; therefore, any attempt to register similar sign would be considered as free riding on the reputation of protected names and misleading for the consumers.

The TRIPS Agreement distinguishes geographical indications from trademarks and dedicates two separate sections to these types of intellectual property. The section on geographical indications of the TRIPS Agreement is necessarily brief; it contains only three articles. Article 22 establishes a minimum standard of protection for all geographical indications. Articles 23 and 24 are specific for the protection of geographical indications for wines and spirits. The TRIPS Agreement does not specify the legal means to protect geographical indications, as it does not require an introduction of a sui generis system of protection for geographical indications. Therefore, individual WTO member is free to decide the most appropriate method of protection. In other words, under the TRIPS Agreement, WTO members are not obliged to create a special system of protection of geographical indications as it is required, for example, by the TRIPS Agreement for trademarks or patents. At the same time, the TRIPS Agreement emphasizes that WTO members should not diminish the protection of geographical indications that existed in a particular WTO member immediately prior to the date of entry into force of the WTO Agreement.

Under the Agreement on Trade-Related Aspects of Intellectual Property Rights, geographical indications for all goods are protected against misuse,[15] but for wines and spirits, the level of protection is higher and is not conditional upon whether the public is misled or whether unfair competition occurs.[16] The differentiation in the level of protection afforded to geographical indications between wines and spirits and other goods is not justifiable on any grounds and could only be explained as a compromised solution of difficult negotiations on the protection of geographical indications.

When concluding the TRIPS Agreement, it was agreed that negotiations should be undertaken on the establishment of a multilateral system of notification and registration of geographical indications for wines eligible for protection in those WTO members participating in the system.[17] No timeframe for the completion of the negotiations was provided, and it was indicated that participation in the system may

[15] Article 22 of the TRIPS Agreement on the "Protection of geographical indications".

[16] Article 23 of the TRIPS Agreement on the "Additional protection for geographical indications for wines and spirits".

[17] Article 23.4 of the TRIPS Agreement provides that: "In order to facilitate the protection of geographical indications for wines, negotiations shall be undertaken in the Council for TRIPS concerning the establishment of a multilateral system of notification and registration of geographical indications for wines eligible for protection in those Members participating in the system".

be voluntary. Starting the negotiations on the multilateral register, some WTO members considered that the protection of other products was not adequately addressed during the Uruguay Round. Discussions on the scope of the protection of the TRIPS Agreement continued for some time, and soon it became clear that there is a division of the negotiating positions into counties in favour of extension of protection and countries opposing extension of protection.

The issue of protection of geographical indications and trademarks is often seen as a "fight" between the "Old World" (i.e. essentially the European countries) and the "New World" (i.e. to a large degree, the United States, Latin America and Australia). This conflict over geographical indications was once again confirmed by the recent WTO dispute on the European Community's system for the registration and protection of GIs.[18]

However, the commercial and regulatory landscape is not so well-defined and simple to draw. More and more countries are realizing the importance of geographical indications as valuable marketing tools and are becoming involved in the commercial and negotiating struggle to provide a better degree of international protection to their GIs.

7.2.2.3 Protection of Industrial Designs, Layout Designs of Integrated Circuits and Undisclosed Information

These intellectual property types could be considered of lesser relevance to microbiology but should be mentioned nevertheless for completeness of the overview of the IPRs.

An industrial design is the ornamental or aesthetic aspect of an article, which can be constituted by two-dimensional (such as lines, patterns or colours) or three-dimensional (such as shapes or various surface) elements, but cannot be dictated solely or essentially by technical or functional considerations. Industrial designs are meant to make goods more appealing to the consumer, thus increasingly marketable. Similarly to trademarks, when a design is registered, a registration certificate is issued. The person or entity who has registered the design is then assured an exclusive right against unauthorized copying or imitating of the design by third parties, thus ensuring honest trade practices and fair competition among the enterprises. It should be noted that an industrial design can be also protected as a work of art by the copyright or by special unfair competition laws; however, that would depend on the laws of the country concerned.

Industrial design protection is limited in time (usually not less than 5 years are granted) and to the country in which protection is granted. However, under the Hague Agreement Concerning the International Deposit of Industrial Designs – which is administered by WIPO – a procedure has been established to make an international registration. By submitting a single international deposit with WIPO,

[18] WT/DS 174, 290, *European Communities – Protection of Trademarks and Geographical Indications for Agricultural Products and Foodstuffs (EC – Trademarks/GIs)*.

the applicant can ensure that his design will be protected in many State Parties of the Hague Agreement as he wishes.[19]

In view of the importance of modern technology, as well as reliance upon computers, legislators in many countries have provided specific protection for design layouts of electronic circuits used in computers and many other electronic products such as radios and televisions. The Treaty on Intellectual Property in Respect of Integrated Circuits (IPIC) or Washington Treaty is currently not in force but has been incorporated by reference into the TRIPS Agreement of the World Trade Organization, seeking the term of protection as at least 10 years from the date of filing an application or of the first commercial exploitation in the world, but members may provide a term of protection of 15 years from the creation of the layout design; the exclusive right of the right holder extends also to articles incorporating integrated circuits in which a protected layout design is incorporated, in so far as it continues to contain an unlawfully reproduced layout design; the circumstances in which layout designs may be used without the consent of right holders are more restricted; certain acts engaged in unknowingly will not constitute infringement.

In many countries, national laws do not require registration of circuit layouts to be registered; this is also not required by the TRIPS Agreement.

Undisclosed information – trade secrets or know-how – covers confidential information of commercial value. Trade secrets are generally protected under the unfair competition rules, which under various legal systems provide a remedy against acts of competition contrary to honest business practices, such as confusing or misleading the customer and discrediting the competitor. In common law countries, the doctrine of "passing off" (misrepresenting one's business goods or services as another's, to the latter's detriment, using the same trademark without permission) may also be applied. The international minimum standards that WTO members are required to observe are set out in the TRIPS Agreement (Article 39).

7.3 The Role of Intellectual Property in Microbiological Research

It is generally accepted that in a knowledge-driven, competitive business environment, technological innovation is a principal determinant of successful performance. But differences of opinion persist among economists and policymakers about the exact role of intellectual property in relation to research and innovation. On the one hand, in theory, the IP system is considered to be absolutely necessary "to encourage creative intellectual endeavour in the public interest"[20], and on the

[19] There are 66 contracting parties at present to the Hague Agreement; for more information consult http://www.wipo.int/treaties/en/registration/hague/

[20] Ricketson, Sam., New Wine into Old Bottles: Technological Change and Intellectual Property Rights, ed. Drahos Peter "Intellectual Property", second series, p. 389.

other, some scholars believe that, in practice, the IP system hinders competition to the extent that it is often seen to be playing a negative role in innovation.[21]

Nowadays, consumers are taking unprecedented interest in the way food is produced, processed and marketed, considering aspects of quality and safety, and therefore the role of microbiology is vital.[22] Food businesses and the agro-processing sector use IP protection to strengthen their business potential accessing new trading markets.

As was noted, the protection of intellectual property is a matter of national law and the application of relevant international agreements to which a country is a party. Some of the international dimension is captured in WTO and WIPO membership. In the remaining cases, the relevance and application of intellectual property conventions is a matter of convention by convention ratification by a country and the subsequent implementation of the requirements of a particular convention.

Since nations are becoming to some extent dependent upon internationally traded agricultural products, international protection of IPRs is also critical in enabling countries to assure proper protection of their rights globally. As there are many stakeholders involved in facilitating the market success of an innovation, the effective use of the IP tools plays an important role in reducing risk for the parties concerned, who may then be able to reap acceptable returns for their participation in the process.

Intellectual property plays an important role in facilitating the process of taking innovative technology of microbiology to the marketplace and actual consumers. At the same time, protection of intellectual property contributes to enhancing competitiveness of technology-based enterprises, whether such enterprises are commercializing new or improved products or providing service on the basis of a new or improved microbiological knowledge. For most technology-based food enterprises, successful invention results of microbiology lead to a more efficient way of doing things or in a new commercially viable product; therefore protection and promotion of intellectual property rights is directly linked and contributes to success of microbiological research.

[21] Boldrin, M., and Levine, D.K., 2002, The Case Against Intellectual Property.

[22] L. J. Unnevehr, T. Roberts, and C. Custer, "New Pathogen Testing Technologies and the Market for Food Safety Information" *AgBioForum* Vol. 7, 2004, pp. 212–218; Reardon, T., C.P. Timmer, C.B. Barrett, J. Berdegue. 2003. "The Rise of Supermarkets in Africa, Asia, and Latin America," *American Journal of Agricultural Economics*, Vol. 85, 2005, pp. 1140–1146; K. Humphery, *Shelf Life: Supermarkets and the Changing Cultures of Consumption*, Cambridge University Press, 1998; A. Regmi (ed.), *Changing Structure of Global Food Consumption and Trade*, Market and Trade Economics Division, Economic Research Service, USDA, 30 May 2001.

Applications and Patents of *Bacillus* spp. in Agriculture

8

Estibaliz Sansinenea

Abstract

Biological control using biopesticides has been an environmentally friendly solution in recent years. *Bacillus* spp. was discovered as a soil bacterium, which has been used as a biopesticide in agriculture, forestry, and mosquito control. Specifically, *B. thuringiensis* has been widely applied in the control of crops insect pests due to insecticidal proteins produced by the bacterium during sporulation. To fight against the phytopathogens, *Bacillus* spp. bacteria produce secondary metabolites which have several biological activities that make it possible that bacterium can survive in the natural environment. These developments have amplified the target range of *Bacillus* spp. in special *B. thuringiensis*, for better understanding its role in soil ecosystem.

Keywords

Biological control · Biopesticides · *Bacillus* · Secondary metabolites · Cry(crystal) proteins

8.1 Introduction

Agriculture and forests are one of the most important resources to sustain global economy and environmental and social system; therefore their protection against pests is a priority. To fight against pest and diseases, the chemical pesticides have been the solution during years. However, the intensive use of these synthetic insecticides has caused a great damage to the ecology creating pest resistance and health problems, due to their persistence in the environment for a long time. In this context,

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H. B. Singh et al. (eds.), *Intellectual Property Issues in Microbiology*,
https://doi.org/10.1007/978-981-13-7466-1_8

integrated pest management is a program to reduce the risks caused by synthetic pesticides, and biopesticides play an important role to protect the crops controlling the pests and being environmentally safety biological pesticides. Typically, biopesticides have selective modes of action and are considered reduced risk pesticides because they were also more selective than chemical pesticides. Biopesticides were usually applied to control rather than to eradicate pests. Biopesticides can be microbials which consist of a microorganism as the active ingredient, biochemicals which are naturally occurring substances that control pests, and plant-incorporated protectants which are pesticidal substances that plants produce from genetic material that has been introduced to the plant. The microorganism is used as active ingredient. Spores or the organisms themselves can be either microbial ingredients. Microbial biopesticides include bio-fungicides and bioinsecticides. Development cost, time and ease of registration, and potential growing market in contrast to chemical pesticides make biopesticides interesting proponents to investigate. They can suppress pests by different mechanisms such as producing toxic metabolites specific to the pest, causing disease, preventing establishment of other microorganisms through competition, or various other modes of action (Singh et al. 2016a, b, 2017). In this sense, *Bacillus* genus has been the most used in agriculture. The members of the genus *Bacillus* are often considered as microbial factories that produce many biologically active molecules, some of which are potentially inhibitory for fungal growth. Specifically, *Bacillus thuringiensis*, which produces a crystal protein (δ-endotoxin) along with the spore in early stationary phase, has the capacity to cause lysis of the gut of insect larvae when ingested, leading to the host death within 48 h (George and Crickmore 2012). However, there are other several *Bacillus* species which are economically very important to produce several molecules and other products for food, pharmaceutical, environmental, and agricultural industries. In this context, there are many patents about the recent applications of both *Bacillus* spp. in general and *B. thuringiensis* in different fields such as food industry, chemical industry, cosmetic industry, and pharmaceutical industry. In this chapter I will give a brief overview about the last applications and findings of *Bacillus* spp. in agriculture considering different biotechnological uses of this interesting bacterium.

8.2 Biotechnological Applications of *Bacillus* spp.

8.2.1 *Bacillus thuringiensis*-Based Biopesticides

B. thuringiensis is one of the best-known and studied entomopathogenic bacteria that produces parasporal protein crystals, which are selectively toxic to different species of several invertebrate phyla, safe to people, and beneficial to organisms and the environment (Sansinenea and Ortiz 2011). Microbial Bt biopesticides contain a mix of spores and δ-endotoxin crystals produced by fermentation and formulated into solid powdery presentation or liquid sprays. Some inert substances can be added to the spore-crystal complex to protect it or to increase availability to insects.

Sprayable Bt formulations, which are used over small areas, have been applied and introduced to cotton, fruit and vegetable, aquatic, and other insecticide markets. However, the use of these Bt formulations has several disadvantages: (1) sometimes the formulations cannot cover all parts of the plant, (2) it cannot be reached to pests that are inside plant tissues, and (3) Bt is easily degraded by UV light and removed by water runoff (Federici and Siegel 2008). Therefore, to a better pest protection, some applications are required. To overcome the problem of sensitivity to UV irradiation of *B. thuringiensis*, some chemical screens have been found. But the chemical screens, due to the nature of the chemicals, have some negative impacts on the environment. Therefore, melanin has been used to protect Bt formulations from UV light since it is a natural pigment that is easily biodegradable in the nature and can absorb radiation (Sansinenea and Ortiz 2015; Sansinenea et al. 2015).

Presently, there are over 400 of Bt-based formulations that have been registered in the market (Abdullah 2012). Most of the Bt formulations are used to control many common leaf-feeding caterpillars. To control lepidopteran pests, there are many commercial products including Dipel®, Javelin®, Thuricide®, Worm Attack®, Caterpillar Killer®, and Bactospeine®, although many small companies sell similar products under a variety of trade names. *Bacillus thuringiensis* var. *israelensis* (Bti) has been widely used in the urban control of mosquitoes and the peridomestic and rural control of blackfly, since it is highly toxic to mosquito and blackfly larvae which are vectors of tropical diseases, such as malaria, dengue fever, Nile virus, Zika virus, and Chikungunya virus. Many commercial Bti products are also available, among them are VectoBac®, Teknar®, Bactimos®, and Skeetal®. Therefore, the market of Bt-based biopesticides has a lot of products, most of them still in use in agriculture. Six large companies such as Bayer, Syngenta, BASF, DuPont, Dow AgroSciences, and Monsanto account for 70% of the world pesticide sales market.

The formulations of Bt have some problems such as narrow host range, low persistence on plants, and inability of foliar application to reach the insects feeding inside the plants; therefore some formulations have a little effectiveness in field owing to variable environmental stress (Kaur 2007). Some improvements have been developed with the help of genetic engineering. Therefore, to encourage the commercial production of *B. thuringiensis* biopesticides, utilization of less expensive material is advisable, and several raw materials (industrial and agricultural by-products) have been tested as alternative culture media for entomotoxin production (Brar et al. 2006; Tirado-Montiel et al. 2001). One of the promising sources of cheap material is utilization of wastewater. The exploitation of sewage sludge for entomotoxin production by *B. thuringiensis* and application to agricultural crops and forests for pest control seem to be fully compatible with current sludge disposal practices (Tirado-Montiel et al. 2001).

As it has been mentioned, genetic engineering may play a complementary role in the development of more efficient formulations by increasing toxin production, broadening the host range, and enhancing germination and sporulation. The development of new methods, based on electroporation or particle bombardment, subsequently made it possible to transfer Bt *cry* genes into most plants, including

monocots such as maize (Sanchis and Bourguet 2008). These developments have resulted in increased yields and significant reductions of insecticide application (Shelton et al. 2008; Brookes and Barfoot 2008; Carpenter 2010). However, certain concerns have been raised about the environmental safety of Bt transgenic crops.

8.2.2 *Bacillus* spp. Controlling Plant Diseases

The major threats for crop and plant production are plant pathogenic fungi and oomycetes. Therefore, the control of fungal diseases by *Bacillus*-based biopesticides represents an interesting opportunity for agricultural biotechnology. Killing biodiversity is an important feature of patent activity. Many commercial products which have been marketed as bio-fungicides are based on various *Bacillus* species such as *B. amyloliquefaciens*, *B. licheniformis*, *B. pumilus*, and *B. subtilis* (Fravel 2005). Many antifungal compounds isolated from these bacteria have been identified such as mycobacillins, iturins, plistatins, bacillomycins, surfactins, mycosubtilins, fungistatins, and subsporins (Koumoutsi et al. 2004; Madonna et al. 2003; Nihorimbere et al. 2012; Nishikiori et al. 1986; Pathak et al. 2012; Pecci et al. 2010; Peypoux et al. 1999). Other metabolites, including chitinases and other cell wall-degrading enzymes and compounds, are also produced by *Bacillus* spp. (Chaaboni et al., 2012). A key issue arising from patent activity for biocides is the wider impact of compounds, including antibiotics, on biodiversity and human health (Gilbert and McBain 2003).

Surfactins are cyclic hepta depsipeptides with β-hydroxy fatty (β-OH FA) acid, while fengycin and plipastatins are cyclic decadepsipeptides with a lactone ring consisting of C-terminal eight amino acids and amino acid residue at N-terminal linked to β-OH FA of variable length. They exhibit a detergent-like action on biological membranes being powerful biosurfactants (Carrillo et al. 2003) and are distinguished by its exceptional emulsifying, foaming, antiviral, and antimycoplasma activities. To improve biosurfactant production, some strategies have been implemented, such as strain improvement, medium optimization, bioreactor design, or agro-industrial waste usage for fermentation to reduce the raw material cost among others. Their production is widely distributed among *B. subtilis*, *B. pumilus*, *B. licheniformis* (Tendulkar et al., 2007), and *B. amyloliquefaciens* strains (Wulff et al. 2002). The variations in their structure, which generate some isoforms of the same compound, are due to changes in the lipid portion and/or the amino acid composition. Surfactins are not toxic for fungal pathogens by themselves but sustain some synergistic effect on the antifungal activity of iturin A and fengycin.

The iturin family includes cyclic lipoheptapeptides mycosubtilin (Moyne et al. 2004), iturines, and the bacillomycins that contain one β-amino fatty acid and seven α-amino acids, exhibiting strong antifungal and hemolytic activities (Stein 2005) which are due to their capability of forming ion-conducting pores (Maget-Dana and Peypoux 1994). Iturin A contains the heptapeptide Asn1-Tyr2-Asn3-Gln4-Pro5-Asn6-Ser7 and is antagonistic to *Fusarium oxysporum*, which causes potato diseases (Han et al. 2005). Some *B. amyloliquefaciens* strains produce iturins (Yu et al.

2002; Kilian et al. 2000) inhibiting fungal plant pathogens and bacillomycin D which suppresses growth of *Fusarium oxysporum* (Ramarathnam et al., 2007; Koumoutsi et al., 2004).

The fengycin is a family of biologically active cyclic lipodepsipeptides produced by various species of Bacilli, such as *B. subtilis*, *B cereus*, *B. amyloliquefaciens*, and *B. globigii* (Romero et al., 2007; Hu et al., 2007; Bie et al., 2009; Pyoung et al., 2010), and are synthesized non-ribosomally by peptide synthetases. The members of fengycin family exhibit heterogeneity at sixth position in peptide moiety as well as in chain length of β-OH FA which varies from 14 to 18 carbons. Based on these variations, fengycins have been classified in two classes: fengycin A and fengycin B. Fengycin A contains Ala at position 6 which is replaced by Val in case of fengycin B. The two classes of fengycin and their fatty acid isomers have also been characterized by using tandem mass spectrometric techniques such as ESI-MS/MS, MALDI-PSD MS, atmospheric pressure MALDI (AP-MALDI), and GC-MS. The fengycins exhibit strong fungitoxic activity specifically against filamentous fungi such as *Ascodesmis sphaerospora*, *Botrytis cinerea*, *Colletotrichum acutatum*, *Monilinia fructicola*, *Mucor hientalis*, *M. hiemalis*, *Mycosphaerella pinodes*, *Paecilomyces variotii*, *Pleospora herbarum*, *Pyricularia oryzae*, *Rhizoctonia solani*, *Schizophyllum commune*, *Stemphylium* sp., *Thielaviopsis basicola*, *Fusarium moniliforme* Sheldon ATCC38932, *Colletotrichum gloeosporioides*, and *Podosphaera fusca* (Romero et al., 2007; Hu et al., 2007; Bie et al., 2009; Pyoung et al., 2010). The fengycins induce morphological changes in several fungi such as bulging, curling, or emptying of the hyphae. It also has been reported to form complex with sterols, which suggests the ability of fengycin to interact with membrane lipids. Bioactivity of fengycin seems to be driven by its amphiphilic character and affinity for lipid bilayers which facilitates its interaction with lipid bilayers in a dose-dependent manner, and to some extent it is known to alter cell membrane structure as well as permeability (Deleu et al. 2008). Fengycins due to their potential antifungal activity are promising biocontrol agents. The protective effect of fengycins against damping-off disease of bean seedlings caused by *Pythium ultimum* as well as against gray mold postharvest disease of apple has been demonstrated by Ongena et al. (2005). Thus, fengycins can be regarded as potential biocontrol agents and as direct fungal antagonists as well as elicitors for induced systemic resistance against plant pathogens.

Zwittermicin A is natural antibiotic, highly polar, water-soluble aminopolyol that was firstly isolated from the soil-borne bacterium *B. cereus*. The first signs that revised the biological effects on plant were discovered by the group of Handelsman (Handelsman et al. 1990, 1991a, b; Smith et al. 1993). They discovered that zwittermicin A has a potent antifungal activity protecting some crops such as alfalfa seedlings, tobacco seedlings cucumber fruits, and peanuts (Silo-Suh et al. 1994). Maximum accumulation of zwittermicin A antibiotic was detected in supernatants of trypticase soy broth cultures after sporulation (Milner et al. 1995). Zwittermicin A has a high activity against many plant pathogenic fungi such as *Alternaria* spp., *Fusarium* spp., *Helminthosporium* spp., and *Ustilago* spp. (Silo-Suh et al., 1998).

8.2.3 *Bacillus* spp. as Plant Growth-Promoting Bacteria

Several *Bacillus* species have been identified as plant growth-promoting bacteria since they produce antibiotics; they cause the inhibition of synthesis of ethylene, and they induce the plant systemic resistance (Lee et al. 2012).

The study of the processes that regulate the interaction between bacteria and plant is a recent and fundamental topic of biology since the bacteria can communicate by molecular signals through a process called quorum sensing (QS), and at the same time the plants have developed some mechanisms to receive these chemical signals.

Bacteria that inhabit the rhizosphere can influence on the plant growth producing phytohormones, such as indole-3-acetic acid (IAA), natural auxins, or other secondary metabolites. The application of these metabolites stimulates the formation of lateral roots which are involved in the uptake of water and nutrients, and this allows an increase in biomass production.

Plant-bacteria communication can take place through different compounds. Cyclic dipeptides and their derivatives, diketopiperazines, constitute a novel class of small molecules synthesized by microorganisms that have different biological functions such as antifungal, antibacterial, or plant growth promoters.

Although the diketopiperazines are notable bioactive molecules, there is little information concerning its biosynthesis in bacteria and their role in communication with plants. There is a study which reports that diketopiperazines have an important role in the communication between cells called quorum sensing (Ortiz-Castro et al. 2011), modulating the auxin signaling to promote plant growth. The diketopiperazines consist of a ring containing two peptide bonds, and this cyclic structure has a great stability and resistance to human digestion. This last property allows that these dipeptides are used as scaffolding for drugs, besides having a series of interesting biological properties, including antiviral and antibiotic properties and antitumor activity. Some of these compounds are extracted from many both marine and terrestrial organisms and have proved to be promising for several routes in the pharmaceutical industry and with multiple functions (Arachchilage et al. 2012).

Gibberellins (GAs) constitute a large family of tetracyclic diterpenoid carboxylic acids, and some members operate as in higher plant growth hormones. They have been identified for the first time in 1926 in Japan as by-products of the pathogenic fungus of rice *Fusarium fujikuroi* causing symptoms of overgrowth ("bakanae" disease) in rice seedlings. The compound GA3 was isolated for the first time by Japanese scientists, and this compound had the capacity to restore the normal growth of the dwarf mutant plants; besides the emergence of substances type GA3 in higher plants led to the suggestion that the GAs are natural plant hormones that regulate growth and development in higher plants (Tudzynski 2005).

Gibberellins are associated with several processes of plant development such as germination, elongation of stems, flowering, and fruit development (Gomi and Matsuoka 2003). They also promote the growth of roots, the abundance of root hairs, and delay on cellular aging of plants. The effects of exogenous and endogenous gibberellins in the breaking of dormancy of seeds have been recognized in

various species of plants; the application of gibberellins can replace the need for a specific temperature or light environmental stimulus. Two mechanisms of action of gibberellins in the germination process have been proposed: the first is its influence on the hydrolysis of food reserves and the second mechanism of action consists of a direct effect on the growth potential of the embryo (Debeaujon and Koornneef 2000).

8.3 Patents Focusing on the Uses of *Bacillus* spp. Strains in Agriculture

As already reviewed in the previous section, there are many compounds applied to agriculture, and many of them have been subjected to patents that will be reviewed in this section.

8.3.1 *B. thuringiensis*-Based Patents

Most of the patents are related to the improvement of strains of *B. thuringiensis* or production of their Cry proteins. There are many patents reporting novel crystal proteins exhibiting insecticidal activity against different insect orders. Baum et al. (2006) reported *B. thuringiensis* strains which have activity against lepidopterans that are producers of novel crystal proteins. For the control of diptera insects, it has been applicated *B. thuringiensis* strain LRC3 or its products (Lysyk et al. 2006). From *B. thuringiensis* isolates, new pesticidal proteins were developed and utilized for controlling corn rootworms (Narva et al. 2008). The discovery of novel *B. thuringiensis* strains extended the potential applications of this bacterium. The peptide sequences of these proteins were also patented (Riazuddin 2000); the amino acid sequences of the toxins and the encoding nucleotide sequences were determined (Narva et al. 2007). Aroian and Li (2007) reported the use of transgenic plants for expressing Cry5 proteins, as well as methods for using them.

As it has been revised before, *Bacillus thuringiensis*-based biopesticide production depends on high-quality and high-efficiency formulation processes. With this purpose, the formulations must include some components that can protect the spore-crystal complex. A starch graft copolymer, which combined with a *B. thuringiensis* strain among many other pesticides, constitutes a novel formulation that could be applied in an agricultural environment (Savich et al. 2009; Keswani et al. 2016a, b). *B. thuringiensis* subsp. *israelensis* suspended in ice granules was applied to control *Aedes vexans* larvae. The ice granules were prepared in a special ice machine and applied on the water surface where they melted and released the toxic crystals (Becker and Mercatoris 1999). A patent was reported by Suenaga et al. (2001) for improving the dispersion property and hydration tendency in an agrochemical preparation of a product derived from *B. thuringiensis* var. *aizawai*.

Many of the patents are related to the discovery of novel genes of Bt associated with toxicity or to the disclosure of new toxin families. A novel insecticidal crystal

protein gene *cry7Bal* from *B. thuringiensis* subsp. *huazhongensis* YBT-978 was patented, which has toxic activity against lepidopteran insects (Sun et al. 2008). Other nucleic acids, variants and fragments obtained from *B. thuringiensis* strains, have been patented (Abad et al. 2008a, b). The characterization of novel proteins with insecticidal activity toward different insect pests to protect plants has been patented (Baum et al. 2006; Soberon-Chavez and Bravo de la Parra 2007; Carozzi et al. 2008; Abad et al. 2008a, b). Carozzi et al. (2008) reported compositions and methods as well as a coding sequence for a delta-endotoxin to be used in DNA constructs or expression cassettes for transformation and expression in plants and bacteria and delta-endotoxin-associated polypeptides. Adams et al. (1995) patented another method for producing a larger quantity of a crystal delta-endotoxin with greater pesticidal activity.

The advances in genetic engineering and molecular engineering have allowed gene fusions and alteration of amino acid sequences creating recombinant proteins with commercial applications (Florez et al. 2012; Schnepf 2012). In this sense, the synergistic combination of a CryIF chimeric and CryIA(c) chimeric *B. thuringiensis* delta-endotoxins exhibited excellent toxic activity against lepidopteran pests (Bradfisch et al. 1992).

The modified Cry4Ba protein exhibits enhanced toxicity to *Culex* spp., as compared to Cry4Ba protein (Dean and Abdullah 2005). An interesting patent discloses new chimeric genes encoding a Cry1C, Cry1B, or Cry1D protein that are useful in the protection of plants from insect damage (van Rie et al. 2007).

8.3.2 *Bacillus* spp.-Based Patents

Several microorganisms are known for exhibiting biological activity and are useful in plant disease control. The biological activity of different microorganism types against plant pests and diseases has been described. Specifically, strains of *Bacillus* spp. (*Bacillus* spp. includes *B. subtilis*, *B. cereus*, and *B. thuringiensis*, among others) have been described to exhibit activity against various field pests. This activity may be due to different mechanisms of action, among which are the production of antibiotics that inhibit the development of fungi and bacteria or the production of toxins which act specifically and selectively against certain types of insects.

In this sense, Handelsman's group patented a pure preparation of *Bacillus cereus* antibiotic called zwittermicin for protecting alfalfa and soybeans crops (Handelsman et al. 1991a, b). Even the use of the antibiotic zwittermicin enhanced the biological activity of the biopesticide being a successful combination in pest control (Schnepf et al. 1994). Zwittermicin-producing *Bacillus thuringiensis* strain was reported to exhibit broad antifungal and antibacterial activity (Marrone et al. 1999).

Bacillus subtilis is an antagonistic bacterium that acts through production of antibiotics as well as by parasitism and competition for space and nutrients. Microorganisms acting through antibiotics generally have a broad spectrum of action, particularly fungal inhibition. This approach is more efficient than other antifungal mechanisms of action. It has been disclosed that the activity of the soil

fungus *Pythium aphanidermatum* that causes cottony cucumber leak can be suppressed using zwittermicin-producing *B. cereus* strain UW85. The production of anti-*Botrytis* and anti-*Alternaria* antibiotics by two *Bacillus* strains, *B. subtilis* CL27 and *B. pumilus* CL 45, has been reported. In vitro testing demonstrated that both the whole broth and cell-free filtrates were active against *Botrytis* and *Alternaria*. Leifert et al. (1997) patented that *B. subtilis*, *B. pumilus*, and *B. polymyxa* are effective at inhibiting postharvest disease causing fungi. Lehman et al. (2001) discloses a novel *Bacillus pumilus* strain which exhibits antifungal activity, but no antibacterial activity. More recently, an invention is related to the discovery of a new *Bacillus subtilis* strain (IAB/BS03), which can inhibit a wide range of fungal and bacterial diseases of plants. The invention also relates to fungicidal compositions comprising the said new strain of *Bacillus subtilis*, either alone, as part of a formulation, or in combination with other chemical and biological pesticides (Hinarejos et al. 2014).

Cyclic lipopeptides of the iturin class are other group of *Bacillus* metabolites, which are potent fungicidal agents. These compounds have interactions with fungal membranes, creating transmembrane channels that permit the release of vital ions. The novel microorganism *B. subtilis* AQ713 produces iturins, plipastatins, and surfactins. This combination of lipopeptides is the key to its usefulness as a biocontrol agent (Fernandez et al. 2015) to control the fungus *Sclerotinia sclerotiorum*. *S. sclerotiorum* is an important phytopathogenic soil fungus that causes economic losses in lettuce potatoes, cereals, and a wide number of other important crops. Signs and symptoms caused by *S. sclerotiorum* vary depending on the host. However, the most obvious sign is the appearance of white fluffy mycelia growth that will later produce sclerotia. There is an invention that relates a novel antibiotic-producing and metabolite-producing *Bacillus subtilis* strain exhibiting insecticidal, antifungal, and antibacterial activity. The invention also includes novel antifungal and antibacterial compounds designated agrastatins and a novel combination comprising an A type iturin, a plipastatin, a surfactin, and an agrastatin (Heins et al. 2000).

Plant growth-promoting bacteria (PGPB) are associated with many, if not all, plant species and are commonly present in many environments. There are some patents related with plant growth-promoting bacteria and methods of their use. There is an invention that is directed to a biologically pure bacterial culture wherein *Bacillus* is presented in the bacterial culture (Thompson et al. 2014). Another patent relates to a biocontrol composition comprising at least one isolated strain selected from the group consisting of *Bacillus megaterium* strain A-07, *Paenibacillus barcinonensis* strain A-10, *Pseudomonas fluoresceins* strain N-04, *Bacillus cereus* strain T-1 1, *Lysinibacillus sphaericus* strain T-19, *Paenibacillus alvei* strain T-22, and *Paenibacillus alvei* strain T29 which have been shown to be effective plant growth enhancers and biocontrol agents of plant disease in greenhouse and in field trials (Labuschagne et al. 2015). A recent patent relates the methods and compositions for increasing plant growth characteristics by growing the plant in the presence of plant growth-promoting microbial isolates (Hirsch and Kaplan 2016).

8.4 Conclusion

Crop pests produce the loss of millions of dollars to farmers per year; in addition, there is a growing demand for food worldwide. Therefore, it is essential to improve the quality and quantity of crops fighting the pests that threaten them. For years the chemical pesticides have solved that problem by increasing other problems related to pollution to the environment and human health. Biological control using biopesticides has been an environmentally friendly solution in recent years. A biopesticide should meet certain requirements to use it. It can be foreseen that biopesticides will make more contribution for humans to fight against diseases, insects, and other agricultural pests, and they will be the focus of pesticide industry in the future (Sansinenea 2016).

Bacillus spp. has been a very used bacterium as a biopesticide. It has been employed from different points of view. One of them is as a pesticide against insects that are pest of crops, another as antagonist of other microorganisms by antimicrobials (antifungals) secretion, thus avoiding damage to the plant, and finally as a promoter of plant growth that can even present the three possibilities together.

B. thuringiensis fits very well with the first point of action since it is a very effective pesticide against insects of different orders that affect cultures as varied as they are: rice, corn, soybean, tomato, potato, and cauliflower. Various patents have been based on the improvement of the strains producing the Cry(crystal) proteins, which are responsible for the toxicity to insects, improvement of formulations, to broaden the spectrum of activity of strains, and even the cloning of *cry* genes in transgenic plants.

To address the second and third point of action, there are different species of *Bacillus* spp., such as *B. subtilis*, *B. amyloliquefaciens*, *B. pumilus*, and *B. licheniformis*, among others, from which important antifungal metabolites have been extracted to combat phytopathogenic fungi that cause damage of the crops and other metabolites that help to promote plant growth. This chapter has sought to collect the more significant applications and patents in the *Bacillus* spp. genus in agriculture, which will continue to grow.

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Remedying the Misappropriation of Genetic Resources

9

Michael Blakeney

Abstract

In the absence of an effective international legal regime to regulate biopiracy, a second-best solution is for source countries to regulate access to their genetic resources. Among the pioneering legislation in this regard is the Indian Biodiversity Act of 2002. This legislation seems to accord with world's best practice of nesting bioprospecting within the broader environmental legal framework which will allow a greater degree of certainty. Similarly South Africa has enacted its National Environmental Management: Biodiversity Act, 2004, which regulates bioprospecting, within the framework of the National Environmental Management Act, 1998. The slow evolution of an international legal regime to deal with the biopiracy of genetic resources is now threatened with obsolescence as it now becomes possible to assemble DNA sequences in a laboratory. Those genes can be accessed in public databases without the necessity to access biological material from source countries. In 2016 the Conference of Parties of the Convention on Biological Diversity (CBD CoP) has begun meeting to consider how the Nagoya Protocol might be modified to deal with biopiracy and synthetic biology.

Keywords

Biopiracy · Traditional knowledge · WIPO · Genetic resources · Convention on biodiversity

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H. B. Singh et al. (eds.), *Intellectual Property Issues in Microbiology*,
https://doi.org/10.1007/978-981-13-7466-1_9

9.1 Biopiracy

Areas of biodiversity are valuable reservoirs of genetic material which can be used for both agricultural and medical innovations. For example, it is estimated that about 6.5% of all genetic research undertaken in agriculture is focussed upon germplasm derived from wild species and landraces (McNeely and Sherr 2002), and according to the World Health Organization's estimate, approximately 85% of the world's population depend upon plants for their primary health care (McGonigle 2016). Seventeen countries, including India, have been identified as "megadiverse" countries with significant proportions of the world's flora and fauna species (Mittermeier et al. 1989). Most of these countries are located in tropical and subtropical areas, and most of them, from an economic perspective, are developing or least developed countries (LDCs). In other words, their richness of genetic resources has not been translated into economic wealth. One of the reasons for this is the absence of a binding global legal regime which obliges the exploiters of genetic resources to seek the consent of source countries for access to those resources and to share the benefits resulting from their exploitation. The 1992 Convention on Biological Diversity (CBD) was an attempt to establish a global access and benefit-sharing (ABS) regime, but it failed to obtain the support of a number of exploiting countries, including the USA, which are located outside the areas of greatest biological diversity (Fowler and Hodgkin 2004).

This absence of a global legally binding ABS regime has permitted the unauthorised appropriation of a country's genetic resources. The typical method of appropriation is the securing of patent or plant variety rights over those resources in another country. This allows the proprietors of those intellectual property rights to prevent the utilisation in those other countries of the protected genetic resources. Thus, for example, the patenting of a gene in the USA of biological material obtained from an African country will have the effect of preventing that African country from exporting crops containing that gene to the USA. The privatisation of genetic material through intellectual property protection is of critical importance for food security as all countries are interdependent in their reliance upon genetic material from other countries. For example it is estimated that Bangladeshi rice contains 4 varieties from its own landraces and 229 borrowed landraces and USA rice comprises 219 native landraces and 106 borrowed landraces.

"Biopiracy" is the name given by some to the unauthorised appropriation of a country's biological resources (Blakeney 2004; Robinson 2010; Singh et al. 2016). An alternative characterisation of this practice is "bioprospecting", which was defined by the Secretariat of the CBD as "the exploration of biodiversity for commercially valuable genetic and biochemical resources" (UNEP 2000). Until there is a global legal regime which obliges all persons and enterprises to obtain permission for the exploitation of the biological resources of source countries, then bioprospecting can be undertaken with impunity.

The first notorious example of biopiracy concerned patents granted in 1994 by the US Patent and Trademarks Office (USPTO) and the European Patent Office (EPO) over Neem (*Azadirachta indica*) extracts by the US corporation W.R. Grace

& Company and the US Department of Agriculture. This patent concerned a method for extracting azadirachtin from neem tree seeds to be used as an insecticide.[1] A coalition of environmental NGOs challenged the patent on grounds that the patent lacked novelty and an inventive step because the fungicidal effect of hydrophobic extracts of neem seeds was known and used for centuries in India, both in Ayurvedic medicine to cure dermatological diseases and in traditional Indian agricultural practice to protect crops from being destroyed by fungal infections (Shiva and Holla-Bhar 1996). These arguments were accepted both by the US Patent and Trademarks Office (USPTO) and by the European Patent Office (EPO) in revoking the patent. This case generated a substantial campaign in India and other countries against perceived threats to the sovereignty of countries over their biological resources, and despite the revocation of the patent, it has come to be regarded as the quintessential example of biopiracy (Shiva 2013).

A second example of biopiracy involving the biological resources of India concerned a patent granted by the USPTO in September 1997 to RiceTec, an American company based in Texas, for "Basmati rice lines and grains".[2] Basmati rice has been cultivated in northern India, as well as in Pakistan for centuries. It is estimated that Basmati rice is India's primary rice export, being cultivated on between 10% and 15% of the total land area under rice cultivation (Shiva 2000). In April, 2000 the Indian Government challenged a number of the claims in this patent on the basis that the invention lacked novelty (Subbiah 2004). The USPTO ruled that most of the patent claims were invalid, but it upheld the patent in relation to three hybrid lines which RiceTec had developed from Basmati.[3] A separate complaint had been made to the US Federal Trade Commission (FTC) about RiceTec's description of its rice as "basmati", but the FTC took the view that this was a generic term and that consumers would not be deceived by the description "American basmati" (Subbiah 2004; Lightbourne 2003).

It should be noted that the acquisition of biological resources from one part of the world to establish valuable agricultural industries in other parts of the world has a long history, for example, the acquisition of tea and silk from China; potatoes, tomatoes and natural rubber from South America; oil palm from West Africa; and coffee from Ethiopia (Fowler and Mooney 1990).

Compounding the concerns about biopiratical exploitation of developing countries and LDCs is the perception that many instances of the appropriation of a country's biological resources is facilitated by reliance upon the traditional wisdom of indigenous and traditional peoples in identifying those resources. In almost all of the reported cases, those peoples did not share in the commercial benefits which resulted from the exploitation of those resources.

[1] US patent US5411736 A.

[2] US patent 5,663,484.

[3] US patent No. 5,663,484, Re-examination Certificate C1 (4525th) (reissued 29 January 2002).

9.2 Biological and Genetic Resources

"Biological resources" are defined in Article 2 of the Convention on Biological Diversity (CBD), 1992, as including "genetic resources, organisms or parts thereof, populations, or any other biotic component of ecosystems with actual or potential use or value for humanity". "Genetic resources" are defined as "genetic material of actual or potential value", and "genetic material" is defined as "any material of plant, animal, microbial or other origin containing functional units of heredity". Genetic resources are thus a subset of biological resources. It has been suggested that a resource is used as a biological resource if it is used in a way that its genetic characteristics are not central to its suitability for the respective use, such as "firewood, construction material, decoration, or for ecosystem services" (Rojahn 2010). On the other a biological resource whose specific utility is based on its heritable characteristics is a genetic resource. The following examples are given in a 2008 report commissioned for the CBD:

- Breeding new varieties and other genetic modification
- Further propagation and cultivation
- Identifying and extracting certain (novel) chemical compounds
- Taxonomic research and conservation
- Technical innovations based on that material (CBD 2008)

9.2.1 Sources of Genetic Resources

The CBD in Article 2 distinguishes between the country of origin of a genetic resource, such as a country which possesses this genetic resource in in situ conditions and a country providing a genetic resource from within its borders. Both countries may provide such resources from ex situ collections. Probably, the best-known ex situ collections are those administered by the Consultative Group for International Agricultural Research (CGIAR), which supports a collection of germplasm, which currently comprises over 710,000 accessions of cereals, legumes, roots and tubers, and trees and other essential staple crops are held at a number of international agricultural research centres, each focussing on crops and materials of interest to developing countries.[4] These centres include Africa Rice Center, International Center for Tropical Agriculture (Centro Internacional de Agricultura Tropical) (CIAT), International Maize and Wheat Improvement Centre (Centro Internacional de Mejoramiento de Maiz y Trigo) (CIMMYT), International Potato Centre (Centro Internacional de la Papa (CIP), International Center for Agricultural Research in the Dry Areas (ICARDA), International Crop Research Institute for the Semi-Arid Tropics (ICRISAT) and the International Rice Research Institute (IRRI).

[4] See http://www.cgiar.org/consortium-news/genebanks-investing-in-biodiversity-for-future-generations/, accessed 2 May 2017.

These CGIAR collections were established from the mid-1960s from deposits by source countries and by the collecting activities of CGIAR centre researchers, who were welcomed into source countries which were comfortable with the mission of the CGIAR to provide improved seed to farmers in developing countries (Blakeney 1998). With the development of recombinant DNA technology in the mid-1970s, it became possible for persons to identify and commodify, through patenting, the useful genes in germplasm in both in situ and ex situ collections.

An example of patenting from an ex situ collection maintained by a CGIAR institute involved the patenting of a gene from a strain of rice (*Oryza longistaminata*), originally from Mali. In the late 1970s, *O. longistaminata* was identified by a researcher working in Cuttack North India, as being resistant to bacterial blight. In 1978, this resistant sample was taken to IRRI in Los Baños, Philippines, for further investigation. Over a 15-year period, through conventional breeding, IRRI researchers developed a high-yielding, blight-resistant strain of rice. A postdoctoral research fellow from the University of California at Davis, working at IRRI, was permitted with co-workers at Stanford University to map, sequence and clone the gene Xa21, which was identified as the genetic locus which contributed the resistance to blight. On 7 June 1995, the Regents of the University of California filed a patent application for "Nucleic acids, from *Oryza sativa*, which encode leucine-rich repeat polypeptides and enhance *Xanthomonas* resistance in plants". The patent was granted by the US Patents and Trademark Office on 12 January 1999.[5] This patent generated some controversy because it was perceived to compromise IRRI's research efforts and those of its clients in the rice-producing regions of Asia. Bacterial blight is not a particular problem for US rice producers, and a primary effect of the patent was to prevent the export of bacterial blight-resistant rice, utilising the patent to the USA. This patent also raised the question of equitable compensation, at least for the traditional farmers of Mali who had conserved *O. longistaminata* (WIPO/UNEP, 2001).

Examples of the patenting of the genetic components of an in situ resource are the various patents obtained in relation to *Kava-kava* (*Piper methysticum* Forst. Piperaceae), which is native to a number of countries in the South Pacific. From this plant an intoxicating beverage had been made from its crushed roots to be used in ceremonies since ancient times. Patents have been obtained in the USA of genetic material from *Kava-kava* as an analgesic and anaesthetic and as a phytotranquiliser[6] and for the treatment of bladder and urinary tract cancers.[7] This patenting has been criticised as it has been undertaken without the informed consent of the source country and without any sharing of the benefits resulting from the patents (Forsyth 2003; Lindstrom 2009; Ji 2014).

Another example of "biopiracy" from in situ resources is the patenting of a gene isolated from *Streptomyces viridochromogenes* a micro-organism isolated from

[5] US patent 5,859,339.

[6] US patent 6,537,592, 25 March 2003; US Patent 7,105,185, 12 September 2006.

[7] US patent 7,326,734, 5 February 2008.

Cameroonian soil, which is responsible for the tolerance to glufosinate herbicides.[8] Despite the successful commercialisation of this chemical, no benefits have been shared with Cameroon (Mahop 2006).

9.2.2 The Role of Traditional Knowledge (TK) in Identifying Genetic Resources

In a number of cases involving appropriation of genetic resources conserved in situ, those resources have been identified with the assistance of traditional peoples. For example, in 1995, the South African Council for Scientific and Industrial Research (CSIR) obtained a patent on a compound found in the Hoodia cactus, used by the San People of the Kalahari Desert who had traditionally eaten the cactus to stave off hunger and thirst on long hunting trips. In 1997, it licensed this patent to the UK biotech company, Phytopharm, which in 1998, allocated its rights to the US pharmaceutical company Pfizer which marketed a Hoodia extract as a potential slimming drug and cure for obesity. Concern was expressed that the San, whose traditional knowledge (TK) had identified the utility of Hoodia, should have been consulted about the exploitation of their TK (Marcellin 2005) and their entitlement to a share of the benefits from its exploitation, estimated to be worth over US$3 billion per annum in the USA alone (Wynberg 2004).

An Australian example of the biopiracy of genetic resources identified with the use of traditional knowledge concerns the Kakadu plum (*Terminalia ferdinandiana*), a traditional food and medicine source for aboriginal Australian peoples in Northern Australia (Gorman et al. 2006). It is rich in vitamin C and contains gallic acids, which have antibacterial, antiviral and antifungal, anti-inflammatory, antitumour, anti-mutagenic and anti-bronchodilatory applications. US patents were granted in relation to the use of Kakadu plum in relation to skin care preparations and dietary supplements and for a food composition containing Kakadu plum[9] and

[8] US patent No. 5,276,268.

[9] Australian patent application 2007205838 by MARY KAY, INC. relates to a skin care product comprising Kakadu plum extract or acai berry extract. (Claim 1); Australian patent application 2004268233 by MANNATECH, INC. relates to a dietary supplement which may contain Australian bush plum (Claims 33–41); Australian patent application 2005328670 by MANNATECH, INC. relates to a modified release dietary supplement comprises polysaccharides which is compressed at a pressure of greater than 100 psi. (Claim 1); Australian patent application 2006237559 by MANNATECH INC. relates to a modified release dietary supplement which comprises polysaccharides which is compressed at a pressure of greater than 100 psi. (Claim 1); Australian patent application 2004203276 by CORADJI Pty Ltd relates to a method of removing the seed from the fruit of the *Terminalia ferdinandiana* (i.e. bush plum) (Claim 1); Australian patent application 2007231781 by EXIST MARKETING PTY LTD. to a method and compositions of treating bursitis which may contain Kakadu plum (page 14); Australian patent application 2007249801 by INTERLEUKIN GENETICS, INC. is to a food composition comprising rose hips and optionally Kakadu concentrate, from the Kakadu plum. (Claim 1); Australian innovation patent application 2008100919 by GREENTASTE Pty Ltd. is to a herbal composition which optionally may contain Kakadu plum (page 26).

a US patent granted for a method for preparing dried powder from the Kakadu plum and for anti-allergy compositions.[10] These US patents formed the basis of applications under the Patent Cooperation Treaty (PCT) designating more than 100 countries in which the patent would apply. When the skin care patent entered the national phase in Australia, a submission was made under section 27 of the Patents Act 1990 regarding the lack of novelty of many of the claims made in this application.[11] It was pointed out that the Kakadu plum had been used as a medicament by Aboriginal Peoples in Australia for over 40,000 years. This objection was communicated to the US applicant, which withdrew its Australian application (Robinson 2010), but the patent remains on foot in the other countries designated in the PCT application.

In 1995 and 2000, it was reported that University of Wisconsin scientists had patented and were exploiting patents[12] on "brazzein" a protein extracted from the berries of *Pentadiplandra brazzeana* from Gabon. This protein is apparently 2000 times sweeter than sugar, which makes it highly desirable as a natural, low calorie sweetener. Natur Research Ingredients, Inc., a US corporation, was reported in late 2008 to have acquired the sole rights to manufacture and distribute brazzein from the University of Wisconsin at Madison (Adams 2009). This exploitation of brazzein was reported as an early example of biopiracy in that there appeared to be no arrangements for the sharing of benefits with Gabon (RAFI 1995). It was cited as an instance of biopiracy to the UK Parliament's Select Committee on Environmental Audit in 1999 (UK Parliament 1999) and is referred to as the classic exemplar of biopiracy in analysing the concept of "justice" (Brody 2010).

In 2003, the Peruvian government identified several patents[13] and patent applications relating to "maca" (*Lepidium meyenii*), which had traditionally been cultivated in the Andes, including claims concerning therapeutic methods and uses of the plant (WIPO IGC 2003; NRC 1989). The Peruvian government expressed its concerns about the extent to which the patents and pending applications in the USA could prevent exports of maca extracts from Peru. Similarly, from 2001 the Japanese company Asahi Foods Co., Ltd., and an associated US company "Cupuacu International

[10] US patent 7175862 assigned to ACCESS BUSINESS GROUP INTERNATIONAL LLC is to a method of preparing dried powder from the Kakadu plum. US Patent 7384654 assigned to ACCESS BUSINESS GROUP INTERNATIONAL LLC is to an anti-allergy composition which may contain Kakadu concentrate. US patent 7384656 assigned to ACCESS BUSINESS GROUP INTERNATIONAL LLC is to a method of inhibiting an allergic response by administering a composition which may contain Kakadu concentrate.

[11] See D. F. Robinson: "The Biological Patent Predicament Traditional Knowledge and Biological Product Derivative Patents: Benefit-Sharing and Patent Issues Relating to Camu Camu, Kakadu Plum and Açaí Plant Extracts" Guest Article, United Nations University, Institute of Advanced studies, Traditional Knowledge Initiative, Published online 30 April 2010, accessed at http://www.unutki.org/news.php?doc_id=174.

[12] US patent No. 5,741,537, 21 April 1998; US Patent No. 5,527,555, 18 June 1996; US Patent No. 5,346,998, 13 September 1994.

[13] Granted patents include US 6552206 "Compositions and methods for preparation from Lepidium"; US 6428824 "Treatment of sexual dysfunction with an extract of *Lepidium meyenii* roots"; US 6267995 "Extract of *Lepidium meyenii* roots for pharmaceutical applications"; US 6878731 "Imidazole alkaloids from *Lepidium meyenii* and method of usage".

Inc." had obtained a number of patents on the extraction of lipids from the cupuaçu seeds.[14] The pulp of cupuaçu (*Theobroma grandiflorum*), which grows in the rainforests of Brazil, is used by traditional peoples to make fresh juice or as a sweetener for confectionary and as a medicament.

A final example of the patenting of genetic resources identified with the assistance of traditional peoples concerns camu camu (*Myrciaria dubia*), a plant with very high levels of ascorbic acid (vitamin C), used by traditional peoples in the Peruvian Amazon. In October 2005 Peru notified the World Trade Organization of "potential biopiracy" arising from a series of international patents and patent applications, principally published under the Patent Cooperation Treaty (PCT) and by Japanese Patent Office for skin preparations, cosmetics and food additives utilising camu camu (Peru 2005). This notification was also communicated to the World Intellectual Property Organization (Peru 2006).

In these various examples, the knowledge of traditional peoples is utilised to identify the biological resources which they use. In all of these patents were secured over genetic material which had different uses of that material to those of the traditional peoples. However, the important contribution of traditional peoples was in identifying those biological materials which might have promising active ingredients. The utilisation of this knowledge in identifying biologically active substances has saved bioprospectors the considerable amounts of money they would otherwise have expended in screening substances at random (Keswani et al. 2017). Discussed below are proposals for securing the consent of traditional peoples both to their knowledge and to the biological resources which they have identified as useful and the equitable sharing of commercial benefits with those peoples.

9.3 Remedying the Misappropriation of Biological Resources

9.3.1 Convention on Biological Diversity (CBD)

The Rio Earth Summit, which was convened in June 1992, promulgated the CBD which represented an attempt to establish an international programme for the conservation and utilisation of the world's biological resources (McConnell 1996). "The single most divisive issue in the negotiations was the relationship between intellectual property rights and access to genetic resources" (Chandler 1993), in particular the conditions for access and benefit sharing. Article 1 of the CBD declared the objectives of the Convention to be "the conservation of biological diversity, the sustainable use of its components and the fair and equitable sharing of the benefits arising out of the utilization of genetic resources". The Convention noted in Article 3 the sovereign right of nations "to exploit their own resources pursuant to their own environmental policies", but in Article 15 required contracting

[14] JP 2001299278, 30 October 2001, JP2001348593, 18 December 2001, EP 1219698A1, 03 July 2002, WO0125377, 03 July 2002, WO02081606, 17October 2002.

parties to "endeavour to create conditions to facilitate access to genetic resources for environmentally sound purposes" by other contracting parties on mutually agreed terms and conditions on the basis of "prior informed consent". Access to biological resources is required by Article 16 to be "provided on terms which recognize and are consistent with the adequate and effective protection of intellectual property rights". Article 19.2 provided for the grant of access on a fair and equitable basis and on mutually agreed terms, to contracting parties, "particularly developing countries, to the results and benefits arising from biotechnologies based upon genetic resources provided by those contracting parties".

Article 8(j) of the CBD had provided that TK holders should participate in the "the equitable sharing of the benefits arising from the utilization of such knowledge, innovations and practices".

The CBD did not set out how ABS would be implemented. At the conference of the parties (COP) of the CBD in October 2001, an ad hoc open-ended working group on ABS was established, and at its first meeting in Bonn, it developed the Bonn Guidelines on Access to Genetic Resources and Fair and Equitable Benefit Sharing which was adopted by the seventh COP on a non-binding, voluntary basis.[15] The contribution of traditional peoples referred to in Article 8(j) of the CBD was decision taken into account by further sessions of the working group, and in 2010 the COP adopted the Nagoya Protocol on Access to Genetic Resources and the Fair and Equitable Sharing of Benefits Arising from their Utilization to the Convention on Biological Diversity.[16] Article 6 of the Protocol reiterated the CBD's recognition of country's sovereign rights over natural resources and that access to genetic resources be subject to the prior informed consent (PIC) and on mutually agreed terms (MAT). Article 5 of the Protocol provided that the benefits arising from the utilisation of genetic resources "as well as subsequent applications and commercialisation" are to be shared with the provider of those resources in a fair and equitable way. Article 12 of the Protocol requires that signatories consider the customary laws, community protocols and procedures of indigenous and local communities (ILCs) with respect to traditional knowledge associated with genetic resources. The CBD and its Protocol are yet to secure acceptance or implementation by the principal bioprospecting nations.

9.3.2 International Treaty on Plant Genetic Resources for Food and Agriculture

The specific issue of the biopiracy of genetic resources from the international agricultural research centres of the CGIAR was sought to be dealt with by the 2001 International Treaty on Plant Genetic Resources for Food and Agriculture. Article

[15] 'Bonn Guidelines on Access to Genetic Resources and Fair and Equitable Sharing of the Benefits Arising out of their Utilization' in Report of the Sixth Meeting of the Conference of the Parties to the Convention on Biological Diversity, UN Doc. UNEP/CBD/COP/6/20 (2002).

[16] UNEP/CBD/COP/10/L.43/Rev.129 October 2010.

10.2 contains the agreement of the Contracting Parties to "establish a multilateral system, which is efficient, effective and transparent, both to facilitate access to Plant Genetic Resources for Food and Agriculture (PGRFA) and to share, in a fair and equitable way, the benefits arising from the utilisation of these resources, on a complementary and mutually reinforcing basis". The PGRFA to which the multilateral system applies are some 35 crops and 29 forages which are listed in Annexure I and other contributions by resource holders (Article 11(2)). The collections of the CGIAR are expressly included in the multilateral system (Article 11(5)). Access to PGRFA of such crops and forages is to be provided free or at a minimal cost. The treaty attempts to create an international genetic resources commons by seeking to limit the propertisation of the categories of crops and forages to which it applies (Halewood and Nnadozie 2008).

The International Treaty in Article 12.3 provides that facilitated access to PGFRA is to be provided under material transfer agreement on condition (d) that the recipients "shall not claim any intellectual property or other rights that limit the facilitated access" to PGFRA, or their "genetic parts or components", in the form received from the multilateral system. This, of course, does not prevent intellectual property rights being claimed in relation to germplasm which is modified by the recipient. A problematic issue is the extent of modification which must occur before it can be said that the form in which the germplasm was received has changed.

A standard material transfer agreement (SMTA) to be used for accessions of material falling within the International Treaty was finalised in 2006 (FAO 2006). The parties to the SMTA agree in Article 4.3 that the Governing Body of the Treaty and its Multilateral System (i.e. the Food and Agricultural Organization of the United Nations (FAO)) is identified as the third party beneficiary under the SMTA, including the FAO as the third party beneficiary puts it in a position to enforce the SMTA. The limited financial resources for legal enforcement actions of many of the institutes which will be supplying genetic resources under SMTAs means set up the FAO as a more likely litigant. However, Article 4.5 preserves the rights of the provider and the recipient from exercising their rights under the SMTA. Although the SMTA seeks to construct a legal basis for the enforcement of rights in relation to germplasm and other materials supplied under its terms, the greater likelihood is that the SMTA will be enforced as a moral obligation. Also recipients who do not abide by the terms of a SMTA are likely to be excluded from the receipt of any further material under the multilateral system.

Article 5 of the SMTA provides that in the case of transfers from CGIAR Centres, these will be subject to the Agreement between the FAO and the Centres under which trusteeship of their collections is conferred on the FAO. Article 5 (d) provides that access to PGRFA protected by intellectual and other property rights shall be consistent with relevant international agreements, and with relevant national laws, but under Article 6.2 the recipient agrees not to claim any intellectual property or other rights that limit the facilitated access to the material provided under the SMTA or its genetic parts or components, in the form received from the multilateral system. This terminology leaves it open for recipients to obtain intellectual property rights in modified derivatives.

Where a recipient obtains intellectual property rights on any products developed from the material supplied under a SMTA, or its components and assigns such intellectual property rights to a third party, Article 6.10 requires that the recipient shall transfer the benefit-sharing obligations of the SMTA, set out in Article 6.7 to that third party. Under Article 6.1 of the SMTA, the recipient undertakes that the material shall be used or conserved only for the purposes of research, breeding and training for food and agriculture. Such purposes shall not include chemical, pharmaceutical and/or other non-food/feed industrial uses.

Article 13.1 of the International Treaty recognises that benefits accruing from facilitated access to PGFRA shall be shared fairly and equitably under this Article. Article 13.2 envisages that this sharing of benefits include the exchange of technical information, access to technology, capacity building and the sharing of monetary benefits from commercialisation.

Article 7 of the SMTA provides that it shall be governed by "General Principles of Law", including the UNIDROIT Principles of International Commercial Contracts 2004, the objectives and the relevant provisions of the treaty and, when necessary for interpretation, the decisions of the Governing Body. Article 8 provides that disputes arising from the SMTA shall be by negotiation or third party mediation or where these are unsuccessful, "by arbitration under the Arbitration Rules of an international body as agreed by the parties to the dispute". Failing such agreement, the dispute shall be finally settled under the Rules of Arbitration of the International Chamber of Commerce. The result of such arbitration shall be binding.

9.3.3 World Trade Organization (WTO) Agreement on Trade-Related Aspects of Intellectual Property Rights (TRIPS)

Facilitating the biopiracy of genetic resources has been the establishment of a global patents regime pursuant to the TRIPS Agreement. Article 27 of TRIPS requires that patents be available in all fields of technology. This will include biotechnology and is obviously in tension with the objectives of the CBD and the International Treaty. It has been suggested that the TRIPS Agreement should be amended so as to require, or to enable, WTO members to require that patent applicants disclose, as a condition to patentability: (a) the source of any genetic material used in a claimed invention, (b) any related traditional knowledge used in the invention, (c) evidence of prior informed consent from the competent authority in the country of origin of the genetic material, and (d) evidence of fair and equitable benefit sharing[37] and that such provisions could be incorporated into the TRIPS Agreement by amendment.[17]

[17] WTO Doc. IP/C/W/228, IP/C/M/32, para. 128, IP/C/M/33, para. 121 (Brazil).

9.3.3.1 World Intellectual Property Organization (WIPO) and Genetic Resources

In September 1999, the delegation of Colombia proposed the introduction into the Patent Law Treaty, then under negotiation, that an article be inserted which provided that:

1. All industrial protection shall guarantee the protection of the country's biological and genetic heritage. Consequently, the grant of patents or registrations that relate to elements of that heritage shall be subject to their having been acquired made legally.
2. Every document shall specify the registration number of the contract affording access to genetic resources and a copy thereof whereby the products or processes for which protection is sought have been manufactured or developed from genetic resources, or products thereof, of which one of the member countries is the country of origin.

The Diplomatic Conference, which commenced on 11 May 2000, became bogged down on the question of obliging the identification of source countries in biotechnological patent applications. To facilitate progress on the procedural aspects, the source country question was referred to an expert group for further consideration. At the WIPO General Assembly in 2000, the member states agreed the establishment of an Intergovernmental Committee on Intellectual Property and Genetic Resources, Traditional Knowledge and Folklore (IGC). Three interrelated themes were identified to inform the deliberations of the Committee: intellectual property issues that arise in the context of (i) access to genetic resources and benefit sharing; (ii) protection of traditional knowledge, whether or not associated with those resources; and (iii) the protection of expressions of folklore (WIPO 2000).

The early sessions of the IGC were concerned with the formulation of model guidelines and intellectual property clauses for contractual agreements on access to genetic resources and benefit-sharing (e.g. WIPO, IGC 2001). At the same time the IGC has concerned itself with formulating treaties for the protection of traditional knowledge and traditional cultural expressions. This has been a long drawn-out process, largely attributable to conflicts between bioprospecting and source countries, as well as to tensions between traditional and dominant communities (Blakeney 2016). The draft text on the protection of genetic resources aims to prevent the misappropriation and patenting of these resources and of related traditional knowledge unauthorised third parties. This is sought to be achieved by requiring that a patent applicant disclose the country or source of origin of the subject matter (WIPO, IGC 2017). The negotiations have not yet settled an agreed definition of biotechnology, or whether the instrument will apply to derivatives. In any event, for a global regime based upon this text to be effective, national legislation will have to sanction the use of genetic resources obtained without informed consent or without benefit-sharing arrangements.

9.4 Conclusion

In the absence of an effective international legal regime to regulate biopiracy, a second-best solution is for source countries to regulate access to their genetic resources. Among the pioneering legislation in this regard is the Indian Biodiversity Act of 2002 which provides that "no person shall apply for any intellectual property right … in or outside India for any invention based on any research or information on a biological resource obtained from India without obtaining the previous approval of the National Biodiversity Authority before making such application, provided that if a person applies for a patent, permission of the National Biodiversity Authority may be obtained after the acceptance of the patent but before the sealing of the patent by the patent authority concerned".[18]

This legislation seems to accord with world's best practice of nesting bioprospecting within the broader environmental legal framework which will allow a greater degree of certainty "in the relationship between overlapping laws and policies" (Cabrera et al. 2012). Similarly South Africa has enacted its National Environmental Management: Biodiversity Act, 2004, which regulates bioprospecting, within the framework of the National Environmental Management Act, 1998.

The slow evolution of an international legal regime to deal with the biopiracy of genetic resources is now threatened with obsolescence as it now becomes possible to assemble DNA sequences in a laboratory. Those genes can be accessed in public databases without the necessity to access biological material from source countries. At a meeting next month in Cancun, Mexico, parties to an International Treaty governing the use of genetic resources, from medicinal plants to pest-killing microbes, plan to discuss whether and how the agreement should apply to digital DNA sequences. In late 2016 the CBD CoP has begun meeting to consider how the Nagoya Protocol might be modified to deal with biopiracy and synthetic biology (Manheim 2016).

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A Patent Survey of *Trichoderma* spp. (from 2007 to 2017)

10

Laith Khalil Tawfeeq Al-Ani

Abstract

The inventors produced the recent patents of *Trichoderma* in high numbers. The recent patents included many fields not focused on biocontrol only. Although *Trichoderma* can be alternative method of the chemical pesticides, but it can be also involved in industries and clean the environment. Therefore, the inventors are working on discovery the recent patents in many fields that contact with the importance of *Trichoderma*. The inventors detected the recent patents that are relevant in several fields: (1) discovering the new strains; (2) detecting the role of *Trichoderma* in biological control; (3) detecting the new antibiotics and importance in control of plant pathogens; (4) detecting the new methods for application in the fields; (5) detecting the role of Trichoderma in induction of systemic resistance; (6) special methods and best formulations for using *Trichoderma* in the manufacture of biofertilizers and biopesticides; (7) detecting the role of *Trichoderma* in biotechnology, nanoparticles, industrial, medical, and pharmacy; (8) eliminating the chemical and biological waste from the environment; and (9) controlling *Trichoderma* that causes high losses in the horticultural industry. The patents have shown many new strains of *Trichoderma*. Several new strains of *Trichoderma* are showed high activity in the confrontation of different plant pathogens and reduce of various the plant diseases, as well as, they have the ability for producing different enzymes and proteins useful for using as antifungal and antimicrobial. The patents are showed possible using *Trichoderma* in new production of biopesticides according to a new mixture and ability to mix with other microbes. Biotechnology and nanotechnology played a big role in improving the traits of some strains of *Trichoderma* as particular *T. reesei* and improved the utilization of them. *Trichoderma* is entered

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H. B. Singh et al. (eds.), *Intellectual Property Issues in Microbiology*,
https://doi.org/10.1007/978-981-13-7466-1_10

in several of important manufacture. *Trichoderma* has removed the different wastes from the environment. In Conclusion, some strains, and isolates can consider being a PGPF, due to have high efficacy in competition with other microbes that back to genome of *Trichoderma*.

Keywords
Trichoderma spp. · Antagonism · Biological control · Microbial formulations · PGPF · Systemic resistance

10.1 Introduction

Trichoderma is the most popular biocontrol agent used globally for management of seed and soilborne phytopathogens (Keswani 2015; Keswani et al. 2016). This ability may back to produce an augment of enzymes and compounds. These enzymes and compounds can be used (A) in direct control of plant diseases, (B) in indirect control of plant diseases and pests, (C) as plant growth-promoting fertilizer, (D) in biotechnology, and (E) in industry (Keswani et al. 2013, 2014; Al-Ani 2018a, b, 2019a, b). The usefulness of nonpathogenic fungi such as *Trichoderma* for the plants is by suppressing plant pathogens, inducing plant defenses, and enhancing the plant growth called PGPF (Dewan and Sivasithamparam 1989; Narita and Suzui 1991; Hyakumachi 1994; Meera et al. 1994; Masunaka et al. 2011). Therefore, these characterizes of *Trichoderma* spp. are useful for attractive the inventors to research about the utilize this genus in service our environment as alternative method from harmful that caused by using the chemical of pesticides for control of plant diseases and pests, as well as the chemical fertilizer in improvement the plant growth. Indeed, some strains of *Trichoderma* can cause the damage to the horticultural industry, due to attack the the edible mushroom.

For control of plant diseases and pests by *Trichoderma,* various mechanisms both direct and indirect have been used. There are many references mentioned regarding the ability of *Trichoderma* to attack the plant pathogens and pests by utilizing several mechanisms (Bisen et al. 2015; Singh et al. 2016). The several mechanisms are comprised of (1) mycoparasitism (Dumas and Boyonoski 1992; Cruz et al. 1995; Ojha and Chatterjee, 2011; Guzmán-Guzmán et al. 2017; Singh et al. 2017); (2) production of volatile (Al-Ani et al. 2013; Barakat et al. 2014; Zhang et al. 2014; Al-Ani and Albaayit 2018a, b; Al-Ani2017) and nonvolatile compounds (Barakat et al. 2014; Meena et al. 2017); (3) secretion of enzymes (Cruz et al. 1995; Ramada et al. 2010; Bisen et al. 2016); (4) proteins (Zhang et al. 2014); (5) induction of plant defenses of ISR and SAR; (6) competition for (A) space, (B) nutrients, and (C) on-site infection (Benítez et al. 2004; Arst and Penalva 2003); and (7) detoxification of the phytotoxin that is secreted by plant pathogens (Aggarwal et al. 2011). While, the role *Trichoderma* in the promoting of plant growth and be as biofertilizer, confirmed by secreting several of secondary metabolites, and siderophores (Al-Ani2017), phosphate solubilization, and production of ammonia (Rinuet et al.

2013) that reflect on the improvement such as increase in mass of plant, photosynthesis, and height of plant (Al-Ani2017). Therefore, *Trichoderma* has a role in producing biopesticides and biofertilizers.

On the other hand, *Trichoderma* has had the role in different fields. It ingress in biotechnology fields, by producing many enzymes such as hemicellulolytic, β-1,4-glucosidases, and carboxymethyl cellulose enzymes, as well as the recombinant proteins (Ahmad and Baker 1987; Harman and Kubicek1998; Kubicek et al. 2009; Druzhinina et al. 2010; Kubicek 2013). For the industry, *Trichoderma* secreted several enzymes that used very widely in manufactures (Saloheimo et al. 2004).

10.2 Recent Patents

The recent years between 2007 and 2017 appeared to have several patents about the characteristics and importance of *Trichoderma* such as (1) new strains, (2) biological control, (3) antibiotics, (4) new methods of application, (5) induction of systemic resistance, (6) biofertilizer, (7) in biotechnology, (8) nanoparticles, (9) new formulation, (10) production, (11) industry, (12) medical and pharmacy, (13) in environment field, and (14) horticulture industry. Therefore, many patents have shown in this chapter the importance of *Trichoderma* that may be covering 90% of their benefit as follows.

10.2.1 New Strains

This field is very interesting to detect several new strains and isolates or species of *Trichoderma* that is meaning novel compounds or other traits. *Trichoderma atroviride* MUCL 45632 is a new strain that has the ability to stimulate seed germination, plant growth, and natural defenses (Canaguier et al. 2008). *T. atroviride* AGR2 is a new strain used against plant fungal diseases, and Davet's medium is the special medium used for isolating it (Dhuicq 2008). *T. reesei* cip1 was having two genes encoding proteins that responsible on the cellulose-binding domain (Foreman et al. 2007a, b, 2011, 2017). A novel strain of *T. viride* NPI3a is very useful for producing cellulolytic enzyme complex (Anli and Jiang 2011). Also, the new strain of *T. atroviride* P1 enhanced the traits of biocontrol activity like antifungal properties and benefit it in biological control of plant diseases by expressing of the DPM gene that increases the efficacy of hydrolytic enzymes (Kruszewska et al. 2012). *T. atroviride* OB-1 is a novel strain that has high efficacy in controlling plant diseases and improving plant growth (Lee et al. 2012). Two novel strains of *Trichoderma*, such as *T. atroviride* and *T. harzianum*, are resistant to copper are used in protecting plants and as biofertilizers (Barroso et al. 2012). *Trichoderma harzianum* (NBRI 0815) and *T. viride* (NBRI 1218) are novel strains which are able to increase the chlorophyll content and yields, promote plant growth, and induce the content of trace elements and amino acids (Mishra and Nautiyal 2013a, b, 2015a, b).

Interestingly, *T. harzianum* Td50b was a new strain that has several characters comprising, (A) degraded the plant material and antagonism against plant pathogens of ornamental crops by producing the exohydrolases (B) produce the odorant volatile compounds having antifungal activity (Oancea et al. 2014). A new strain *T. atroviride* is coding ERG20 gene that enhances the antifungal activity in using biofungicides in agriculture, as well as, this strain contained a new composition of the antimicrobial and the plant growth (Kruszewska et al. 2014). A strain of *T. harzianum* ThLm1 which is deposited under patent number NRRL 50846 in the US Department of Agriculture culture collection is very beneficial for plants to increase growth and promote tolerance against stress (Rodriguez and Redman 2015a, b). A mutant strain of *T. harzianum* SK-55 was able to produce one or more pesticidal metabolites in the new mixtures (Liebmann et al. 2015). *T. reesei* strain QM6a is a new mutant strain that produces higher enzymes compared with the nonmutant strain (Poggi et al. 2015).

10.2.2 Biological Control

Trichoderma spp. are widely antagonistic against several plant pathogens. Some secondary metabolite of *T. viride* could use to a biodegradable of the mosquitoes eggs (Bette 2008). The isolate of *T. asperellum* T34 is able to suppress the growth of two plant pathogens such as *Fusarium oxysporum* f. sp. *lycopersici* and *Rhizoctonia solani* (Cotxarrera and Trillas 2009). The treatment of plants and plant seed with the transgenic strain of *Trichoderma* spp. is able to control plant disease (Lorito et al. 2009). *T. asperellum* T34 was a high active strain on the special substrate such as (A) CPV-type compost (compost + peat + vermiculite), (B) peat + compost (pine bark compost, hardwood compost, sludge compost from sewage treatment plants, cork compost, garden residues, etc.) for suppression of *R. solani* and *F. oxysporum* f. sp. *lycopersici* (Gay and Vilaplana 2009). Some strains of *T. atroviride* are able to biologically control soilborne plant pathogens such as *Rhizoctonia*, *Fusarium*, *Pythium*, and *Sclerotinia* (Stewart 2009, 2013).

The biological control agent of *T. atroviride* SC1 is specific for controlling some plant fungal pathogens that cause the diseases for woods, foliar, roots, fruits, and flowers of group plants like Liliaceae, Cucurbitaceae, Vitaceae, Cruciferae, Rosaceae, Ubelliferae, Solanaceae, and Compositae (Pertot et al. 2009, 2011, 2013, 2014). Two strains of *Trichoderma* spp. such as *T. harzianum* T22 and *T. virens* G41 are controlling many plant diseases that include species of fungi, such as *Pythium* (*P. aphanidermatum*, *P. irregulare*, and *P. ultimum*), *Fusarium* (*F. oxysporum*), *Phytophthora* (*P. cactorum*, *P. cinnamomi*, *P. citricola*, *P. citrophthora*, *P. cryptogea*, *P. drechsleri*, *P. infestans*, and *P. nicotianae*), *Rhizoctonia* (*R. solani*), *Sclerotium* (*S. rolfsii*), and *Thielaviopsis* (*T. basicola*) species, which infected several plants comprising bedding plants, ornamentals, flowers, hydroponic crops, fruiting vegetables, leafy vegetables and cole crops, deciduous trees, grapes, citrus, pine, stone fruit, pome fruit, grains, grasses, and tree nuts (Martin and Hayes 2010, 2011, 2014, 2016, 2017). While the special composition for biological control of plant fungal

diseases consists of two strains, *T. virens* and *T. harzianum*, with kaolin, vermiculite, and carboxylmethyl cellulose (Isyanti et al. 2010), a specific biofungicide comprises a new strain of *T. viride* with growth-promoting molecules, fats, and enzymes that are very efficient in controlling soilborne plant diseases such as root rot, set rot, wilt, damping off, club rot, stem rot, collar rot, rhizome rot, and red rot (Patel 2011).

Indeed, *T. viride* is a new strain that is used to control legume root rot (Dianlin et al. 2012). The new strains of *Trichoderma* spp. such as *T. erinaceum* and *T. spirale* used for controlling plant pathogens and improving the soil (Akiyama et al. 2013). A new strain of *T. asperellum* PD-19 is very efficient in suppressing *Phytophthora* of cucumber (Root et al. 2014). *T. asperellum* GY20 is a special strain which is used in controlling *F. oxysporum* f. sp. *fragariae* by preparing a specific paste (Li et al. 2014a, b). Strain SH2303 of *T. harzianum* is be able to control *Fusarium* wilt and soil restoration (New et al. 2015), while *T. asperellum* 04-22 is a new isolate and has mycoparasitic activity against *Phytophthora ramorum*—infested soil in the United States (Widmer and Samuels 2015, 2016). *T. brevicompactum* BF06 was a very interesting isolate for its ability to control of *F. oxysporum* f. sp. *cucumerinum* which is used here the mixture of conidia suspension mixing with garden soil as biocontrol matrix (Jin et al. 2017). The 4A-5 strain is *T. asperellum* as a biocontrol agent for antagonistic against *Fusarium* that caused an apple fruit replant disease (Kun et al. 2017). *T. atroviride* is a TF280 strain that is very efficient for protecting the wheat from infection of the plant diseases and confronting some plant pathogens such as *F. oxysporum* and *R. cerealis* (Jinfeng et al. 2017). Finally, the conidia of *T. virens* strain G1-3 is mixed with beneficial bacteria *B. myloliquefaciens* strain TJ1000 or 1BE to make a biofungicide composition that is antagonistic against several plant fungal pathogens such as *Pythium*, *Phytophthora*, *Penicillium*, and *Fusarium* in corn, tomatoes, turf grass, sunflower, wheat, peppers, and soybeans (Johnson 2017).

10.2.3 Antibiotics

Antibiotics are very efficient mechanisms that *Trichoderma* use in confronting the plant pathogens. *T. reesei* QM9414 is a new strain that produces peptides and has an antifungal activity used in different fields such as agrochemical (Liebmann et al. 2009). *T. longibrachiatum* produced polypeptides that have the antimicrobial activity (Van et al. 2009, 2013). A new strain of *T. longibrachiatum* MK1 produces a protein HYTLOl having the antifungal and antimicrobial activity against plant pathogens like *Alternaria* spp. and *Botrytis cinerea* (Lorito et al. 2015).

10.2.4 New Methods of Application

The inventors are working on detection of new methods in the application of *Trichoderma* in the fields to increase efficacy, to control plant pathogens and pests,

or to be used in other fields. Therefore, many methods were detected to improve the use of *Trichoderma*. The new method was to increase the activity of the cellulolytic enzymes that are produced by *T. reesei* (Mcfarland and Harris 2008, 2009). For controlling the wilt, sclerotia, and seedling blight of vegetables, fruit trees, flowers, and other crops, a hollow capsule is filled with solid particles of pure culture medium with the strain of *T. viride* (Haiying et al. 2012). The mixture of two strains of *T. harzianum* T-22 and *T. harzianum* T39 with some material comprises vermiculite, potato starch residue, and wheat bran to make a *Trichoderma* fungicide (Lijun et al. 2012). Encapsulation of conidia microparticles for *T. harzianum* is a new method, and microparticles are suspended in an aqueous solution with one type of sugar (Xixuan and Custis 2013). The cellulolytic enzymes that product from several strains of *T. reesei* are using a method depending on the special compositions and the producing method (Shasky et al. 2013).

Trichoderma as endophytic can enter to plant to flower, and then it is already transferred to seed of plant after produced them (Mitter et al. 2013). Mutagenesis was a perfect method for producing a new strain of *T. reesei* that creates very active enzymes for cellulose degradation (Bodie and Kim 2014). A novel method as antiproliferative for inhibiting growth of two genera such as *Rhizoctonia* and *Fusarium* is using a new HNT-01 strain of *Trichoderma* (Takashi et al. 2014). The new technology method via sexual crossing produced a new strain of *T. reesei*, enhancing the activities of carbohydrate enzymes (CAZymes) or gene expression (Wang 2015). The direct fermentation of some crop straw is a very effective method for preparing a special substrate which encourages *T. harzianum* SQR-T037 to rapid growth and reproduction (Rong et al. 2016). The preparation of microsclerotia propagules of mycoparasitic *Trichoderma* is including some species such as *T. asperellum*, *T. harzianum*, *T. lignorum*, *T. reesei*, *T. viride*, *T. pseudokoningii*, *T. hamatum*, *T. polysporum*, and *T. koningii* (Jackson et al. 2016a, b, 2017a, b).

Continuously, a method of improving the seedling growth of *Artemisia apiaceae* was by adding the strain of *T. atroviride* K fertilizer in cultivation (Xiaoli et al. 2017). Another method of using *Trichoderma* is spraying the place of grafting *Litchi* with suspension of some strains, protecting the wood wounds from bacterial infection; this treatment is more beneficial for the survival of grafted seedlings (Zhen et al. 2017). The method of soil treatment with *T. asperellum* train 4A-5 was very efficient to control the apple diseases (Kun et al. 2017). Also, the treatment of rice seedling with strain NECC20035 of *T. asperellum* is protecting them from rice seedling diseases (Zhihua et al. 2017).

10.2.5 Induction of Systemic Resistance

Induction of plant defenses is an indirect mechanism against phytopathogens and pests. The mechanism can be created according to two kinds, one as a direct way like colonizing the plant tissue and second as an indirect way as the biochemical secretes. The transgenic strain of *Trichoderma* spp. can confer the systemic resistance against plant disease (Lorito et al. 2009). Three strains of *Trichoderma*, one

strain of *T. atroviride* WW10TC4, and two strains of *T. harzianum*, such as RR17Bc and F11 Bab, are very active for inducing resistance (Harman 2010, 2011, 2014, 2015). *T. harzianum* strain MTCC5530 and *T. viride* strain MTCC5532 in the soil conditioner are able to induce the immunity against plant diseases and pests, which also enhance the content of organic matter of the soil (Paikray 2010). *T. atroviride* OB-1 is a novel strain having the ability to induce resistance against different plant pathogens (Lee et al. 2012). *T. reesei* FS10-C with a raw material, particularly orange peel, is prepared in a special fermentation process which is helpful to induce resistance against soilborne plant diseases (Ying et al. 2015). *T. longibrachiatum* strain MK1 can induce systemic resistance for producing the secondary metabolites and proteins (Lorito et al. 2015). The resistance in plant is stimulated by the novel strain of *T. atroviride* TF280 (Jinfeng et al. 2017).

10.2.6 Biofertilizer

Trichoderma has been able to promote plant growth by producing several secondary compounds, providing elements, and improving soil characteristics; therefore, it can be a biofertilizer, an alternative to chemical fertilizer. The chemical fertilizer has very negative effects and is dangerous to the environment. A composition of *T. harzianum* as plant growth-promoting fungi with some beneficial microbes is a biofertilizer and is very important for enhancing the shoot biomass, root biomass, plant height, and crown diameter (Jian et al. 2008). *T. atroviride* can increase the plant yield (Stewart 2009, 2013). *T. harzianum* T22 and *T. virens* G41 are improving the plant growth including many plants like ornamentals, fruiting vegetables, flowers, bedding plants, hydroponic crops, leafy vegetables and cole crops, pome fruit, citrus, pine, stone fruit, deciduous trees, grapes, tree nuts, grasses, and grains (Martin and Hayes 2010, 2011, 2014, 2016, 2017). A mixture of *T. harzianum* and *T. viride* with some beneficial microbes was very efficient for improving the soil characteristics and also providing the plant valuable nutrients and soluble minerals (Paikray and Malik 2010, 2012). *T. reesei* is beneficial for use as biofertilizer (Alam et al. 2012).

Indeed, *T. harzianum* TSTh20-1 is a novel strain which is able to increase the plant growth with water use efficiency of plants (Kaminskyj et al. 2011, 2012a, b, 2013, 2016a, b). *T. atroviride* OB-1 is a novel strain (Lee et al. 2012). A mixture of *T. viride* strain NRRL B-50520 with two strains of *Scopulariopsis brevicaulis* with substrate is a new composition of biofertilizer for enhancing the plant growth and release of nitrogen (Gary and Lei 2013). *T. atroviride* strain MUCL45632 is able to enhance plant growth (Cowper et al. 2013). A new method as protoplast fusion technique produces a new strain of *T. harzianum* MTCC 5659 that is very active in enhancing the plant growth, chlorophyll, yield, and the trace element and amino acid content (Mishra and Nautiyal 2013a, b, 2015a, b). *T. harzianum* (strain TRICHOSIL) with some microbes and soluble nitrogen is a good mixture for making a liquid biofertilizer (Lopez-Cervantes and Thorpe 2013). *T. atroviride* WW10TC4 with two strains of *T. harzianum*, RR17Bc and F11 Bab, is able to

improve the plant growth (Harman 2010, 2011, 2014, 2015). *T. longibrachiatum* strain MK1 was a good resource for HYTLOl protein and secondary metabolites such as harzianic acid and "6-pentyl-a-pyrone" that improve the plant growth comprised a weight of plant, dry and fresh, as well as evolve in root nodulation with percentage and speed of the root germination (Lorito et al. 2015). Mixing of *Bacillus subtilis* var. *amyloliquefaciens* strain FZB24 with *T. virens* Gl-3 was helpful to increase plant yield after being applied on the seed, leaf, and stalk (Fabbri et al. 2016). The combination of conidia *T. virens* strain G1-3 is blended with beneficial bacteria *B. amyloliquefaciens* strain TJ1000 or 1BE which increases plant yield and plant heights (Johnson 2017). The new strain of *T. atroviride* TF280 is promoting plant growth (Jinfeng et al. 2017). The special composition from two strains of *Trichoderma* such as *T. harzianum* and *T. reesei* with beneficial bacteria in the formula of the drying encapsulate was very efficient in improving the root system of the citrus tree by applying on rhizosphere (Maguire and Bruno 2017), while *T. viride* with *Azotobacter* and many nutrients for plant is used in plant growing (Possession and Su 2017).

10.2.7 In Biotechnology

Trichoderma secreted the different enzymes and secondary compounds in its ecological niche to get the nutrients for growth and also competition with other microbes. The role of biotechnology was exploitation the best isolates or mutants that produce more the important enzymes and secondary compounds to using in manufacture and removes the waste. A novel strain of *T. reesei* EGIII is producing cellulase enzyme in the tyrosine residue instead to modify stability (Day et al. 2007; Mitchinson et al. 2015). Two gene-encoding proteins of *T. reesei* cip1 are for cellulose-binding domain, one acetylxylan esterase and another one arabinofuranosidase (Foreman et al. 2007a, b, 2011, 2017). The production of endoglucanase enzymes that derived from *T. reesei* enhanced by the new method of the filterability and extract yield after filtration (Elvig and Festersen 2007). A glucoamylase enzyme is isolated from *T. reesei* strain 1A52 and tested for biological activity by hydrolyzing starch (Dunn-Coleman et al. 2007a, b, 2008, 2009, 2010, 2011a, b, 2013). A modified xylanase enzyme produced from *T. reesei* enhanced the alkalophilicity, thermostability, and thermophilicity (Sung 2007). Beister et al. (2008) estimated the proteolytic stability, thermostability, stability at low pH, a nucleic acid, and specific activity of the mannanase enzyme from *T. reesei*. *T. reesei* is producing the wild-type acetolactate protein that enhanced the resistance to ALS inhibitors, e.g., imidazolinone and sulfonylurea compounds (Bower et al. 2008, 2012).

Indeed, a novel glycosyltransferase protein is produced from *T. viride* (Ochiai et al. 2008). A strain TrAA of *T. reesei* is producing a maltogenic α-amylase that is beneficial for production of high-glucose syrups from corn liquefied starch (Duan et al. 2008a, b, c, 2010, 2011a, b). One or more cellulolytic enzymes such as (I) cellohydrobiolase and (II) endoglucanase from *T. reesei* strain RutC30 are mixed in cellulolytic composition for degrading the cellulose material (Merino et al. 2008).

The proteins are produced in a suitable promoter from *Trichoderma* spp. (Ward 2009, 2011). The yields of catalase are improved in *T. reesei* strain Morph through expression of the catR gene (Dodge et al. 2009). Genetically modified *T. reesei* through overexpressing produced a polypeptide with transcription-promoting protein methyltransferase activity that is used in industrial production (Kubicek et al. 2011a, b). The cloning of *T. reesei* QM6a produced a serine protease enzyme that is useful for removing the proteinaceous material (Valtakari et al. 2011), and same strain produced a glucoamylase enzyme that is helpful for processing the starch to produce alcohol (Chow et al. 2017). But another strain of M658 of *T. reesei* produced polypeptide (Linder et al. 2016, 2017). The mutants of a parent *Trichoderma* strain are for getting isolates that produce a polypeptide (Maiyuran et al. 2011, 2012). *T. reesei* produced the phytase enzyme after medium fermentation (Cervin et al. 2012; Dunn-Coleman et al. 2015). The starch substrates with the presence of a glucoamylase from *T. reesei* strain QM6a are utilizing saccharification with fermentation to get the end product (Bergsma et al. 2012; Ge et al. 2015) and modification on the strain QM6a to produce heterologous proteins (Landowski et al. 2017).

Interestingly, a mutant of *T. reesei* produced cellulase in high efficacy for degradation of plant biomass (Katsunori et al. 2012). The Malaysian strain of *T. asperellum* UPM1 produced the crude cellulase enzymes including pectinases, xylanases, and cellulases that are useful for degradation of lignocellulosic materials (Abd et al. 2012). The improvement of *T. reesei* RL-P37 leads to increased production of the protein amount (England et al. 2013; Arentshorst et al. 2016) and novel fungal enzyme proteins (Kruus et al. 2013). Two strains of *T. reesei* such as RUT-C30 and QM9414 are useful for overexpressing variant *bgl1* (Bott et al. 2011a, b, 2013a, b, 2016, 2017a, b, c, d, e, f). The thermophilic mutant of *T. reesei* EGI is beneficial for fermentation of biomass and conversion of sugars (Chokhawala et al. 2013). A modification of *T. reesei* enhanced the expression of this cellulose (Miasnikov et al. 2013) and the expression of polypeptide (Nicholas et al. 2013). *T. reesei* produced cellulolytic enzymes through a saccharification process that comprise conventional alpha-amylase and glucoamylase (Abbas and Bao 2013). *T. reesei* strain QM6a produced glucoamylase enzyme through expression of a polynucleotide (Dayton-Coleman et al. 2015). The new method is for enhancing the synthesis of hormone that is produced from strain 0248 of *T. brevicompactum* (Shen et al. 2015). The enzyme of beta-glucosidase through cellobiose is produced from *T. hamatum* strain YYH13 (Peng 2015). The novel strain of *T. reesei* endoglucanases can enhance the activity of two cellulolytic enzymes such as xylanase and cellulase in pH 6 and 30 °C (Blesa et al. 2015a, b, 2016). *T. reesei* strain QM9414 produced the N-acetylneuraminic acid (NeuNAc) (Mach-Aigner et al. 2016). *T. reesei* strain SCF41 produced the protein having an endoglucanase activity (Reisinger et al. 2016).

Continuously, the strain Morph 1.1 pyr+ of *T. reesei* was the increase in the gene expression to produce the proteins by method of insulator DNA sequences (Barends and Ward 2016). The recombinant strains Rut-C30 of *T. reesei* lead to produce the high enzymes of cellulase (Zhao et al. 2017; Fengming et al. 2017), and recombinant strain GF101 T. *hajji ahnyum* (*T. harzianum*) for gene encoding produced the new alpha-1,3-glucanase (Pan et al. 2017). The improved variants of

beta-slucosîdases are expressing some strain of *T. reesei* (Margeot et al. 2017). The mutant of *T. reesei* strain PCD-10 used for producing polysaccharide-degrading enzyme (Arai et al. 2017). The method for processing granular starch-converting glucoamylases is by using enzymes of glucoamylases and a-amylases enzymes from strain TrGA of *T. reesei* (Koops et al. 2017). The new method is used for improving the cellulase activity by interfering two genes into *T. reesei* (Liter and Hao 2017).

10.2.8 Nanoparticles

The nanoparticles are a biotechnological method that utilize the *Trichoderma* for operating parts at the nanoscale level. *T. reesei* used in synthesizing silver nanoparticles (SNPs) by exposing to special solution of silver nitrate under conditions that *T. reesei* cells produce at least metabolite or enzyme then reduces silver ions to silver nanoparticles (Mansoori 2010, 2013). Synthesizing silver nanoparticles of *T. reesei* is used as an antimicrobial and acceptable for use in the pharmaceutical field (Mansoori 2010). Mixture of *T. viride* with two species of *Bacillus* such as *B. thuringiensis* and *B. subtilis* with plant grams' antibiotic compound and natural organic macromolecules created a nanobiofertilizer to make a mixing of the fermentation in solid state with ammonium compounds (Hair 2011). A nanobiofertilizer of *T. viride* was useful for improving condition of soil environment and soil fertility, enhancing the quality product of crop and activity of the enzyme systems and the resistance of crop diseases, reducing pollution sources, reducing the cost, and playing a role in killing insect (Hair 2011). The preparing of nanosilver was of strain NYNJ03 of *T. hamatum* by restoring nanosilver hook (Jie et al. 2015).

10.2.9 New Formulations

The Inventors are trying to find new formulations to increase the efficacy of *Trichoderma* substrate; to support the conidia growth, sporulation, and secretion of enzymes and secondary metabolites; and to attack the plant pathogens and pests with mycoparasitism. The new formulation of *T. harzianum* with *Pseudomonas fluorescens* is producing a biopesticide composition in mother culture, liquid, and solid fermentation (Rao and Ramachandran 2007, 2008a, b, 2011). A new composition of many species of *Trichoderma* including *T. koningii*, *T. harzianum*, *T. viride*, *T. longibratum*, and *T. polysporum* was useful as fungicidal, bactericidal, and bacteriostatic which it can apply directly to plant, in seed impregnation, volley technique, incorporated to ferti-irrigation tanks, and different machines of back, pulverizing, and electrostatic machines (Salinas and Rencoret 2008). A synergistic composition of *T. harzianum* with some isolates is helpful for the bioinoculant (Singh et al. 2008). A new formulation of polymicrobial is comprised of several species of *Trichoderma* (many strains including *T. harzianum* G, *T. viride* LK, *T. viride* 3116, *T. harzianum* 3147, *T. harzianum* LK, *T. longibrachiatum* 3108, and *T. virens* 3107) that enhance

the plant growth, provide protection against plant pathogens, solubilize minerals, make nutrients available to the plant, lower the need for nitrogen-containing fertilizers, and are eco-friendly (Reddy and Janarthanam 2009). A new formulation of *T. harzianum* and *T. viride* with some beneficial microbe can be used against plant pathogens and as biofertilizer that enhance the plant growth, lower the need for nitrogen-containing fertilizers, make a nutrient and soluble minerals available for the plant, reduce pesticides, and are eco-friendly (Pakray and Owner 2010, 2012).

Indeed, a special formulation of *Trichoderma* as fermentation liquid from strain SH2303 of *T. harzianum* is useful against plant pathogens such as *Fusarium* wilt and soil restoration (New et al. 2015). A special formulation of viable microorganisms from *T. harzianum* strain T22 and bacteria of *Bradyrhizobium* is helpful for treating the plant seeds and plants (Harman and Custis 2015). The combination of the active compound phenylamidine formula (I) with biological control agent for some species of *Trichoderma* is beneficial against plant pathogens and is useful as plant growth regulators (Patent1 2015). The fermentation process of *T. harzianum* with a synergist X, a dispersant and a wettable agent, is by getting the wettable powder which is used for promoting seed germination and protection against the plant diseases and pests (Ao-Xue et al. 2016). The strain of *T. harzianum* is able to grow very quickly on the selective medium by adding bamboo powder and oxygen carrier powder into the medium (Zerong et al. 2016). Many species of mycoparasitic *Trichoderma* are producing microsclerotia and utilizing them for making a special formulation of biopesticides (Jackson et al. 2016a, b, 2017a, b).

Interestingly, a new composition in liquid formulation for plant protection is by mixing several species of *Trichoderma* (many strains of *T. atroviride*, *T. hamatum*, *T. harzianum*, *T. asperellum*, *T. virens*, *T. viride*, *T. gamsii*, *T. polysporum*, *T. stromaticum*, *T. koningii*, and *T. lignorum*) with two materials comprising a polyether-modified trisiloxane and precipitated or fumed silica (Eiben et al. 2016). The new formulation for three species of *Trichoderma* including *T. harzianum* GIM 3.442, *T. viride* CGMCC 3•2942, and *T. koningii* CGMCC 3•2942 blends with cyanobacteria in culture by using mud and adding protease enzymes that can be applied for agriculture directly (Xiaobei et al. 2017). The conidia and mycelia of *T. atroviride* and *T. harzianum* homogenized with the mass of food grade starch and brassinolide to be formulation the wettable powder for applying against tomato gray mold, and also this formulation is an eco-friendly due to the low toxicity (Di et al. 2017). Biocontrol agent of *Trichoderma* as solution of conidia suspension, water, and oil is coating the dry fertilizer granule for making the biological-laden dry fertilizer (Jacobson et al. 2017). Mixture of *T. harzianum* and carbendazim complex formulation as root pesticides is used for protecting the onion from root rot (Guojun et al. 2017).

10.2.10 Production

Trichoderma spp. produce many enzymes and secondary metabolites which can be useful for the different applications, as well as it can be used by involving it in the production of biopesticides and biofertilizer. For producing a glucose syrup was by

some enzymes that produced from *T. reesei* such as heterologous granular starch hydrolyzing enzymes (GSHE) (Baldwin et al. 2007a, b, 2008, 2011, 2012a, b, c, 2013, 2014, 2016a, b; Stom et al. 2011; Bao Dewen et al. 2016). The production of cellulase is very active from *T. reesei* strain SMA135-04 (Smith and Coward-Kelly 2007), strain Rut C-30 (Ju2008; Edwards et al. 2012), and strain P59G (Edwards et al. 2012). Rao and Ramachandran (2007, 2008a, b, 2011) produced a biopesticide of *T. harzianum* in the special composition of mother culture, and fermentation of liquid and solid. *T. reesei* (TrAA) is able to produce high-maltose syrups from liquefied starch (Duan et al. 2008a, b, c, 2010, 2011a, b). *T. reesei* is producing the cellulolytic enzymes in high efficacy (Mcfarland and Harris 2008, 2009). *T. reesei* ATCC-57560 is producing the cellulase enzymes useful for ethanol production (Bradley and Keams 2009a, b). The production of some enzymes is comprised of cellulose, hemicellulose, and β-glucosidase enzymes by a special process from *T. reesei* Rut C-30 (Da S. Bon et al. 2009). The polyunsaturated fatty acids are produced from *T. reesei* (Bauer and Beds 2009).

Amazingly, a commercial production of biopesticides in a special combination is from *T. harzianum* with some beneficial microbes such as *Pochonia chlamydosporia* and *Pseudomonas fluorescens* (Khan et al. 2010). This composition is by blending in the mixture of molasses, sawdust, and soil and then immobilizing the bioagents in a flyable-based carrier for controlling the wilt disease complex caused by *Fusarium* spp. + *Meloidogyne* spp. of legume crops (Khan et al. 2010). *T. reesei* produced the lipolytic enzyme (Madrid et al. 2010, 2016). *T. reesei* by fermentation produced a plurality of enzyme activities (Fish and Miller 2010, 2012). Some strains of *T. harzianum* and *T. fertile* produced the endoglucanase polypeptide (Puranen et al. 2010, 2011, 2013, 2017a, b; Erxi et al. 2014). The production of *Trichoderma* granules is from *T. harzianum* strain SK-5-5 and is applied on olive tree as a fertilizer and biocontrol agent against verticillium wilt (*Verticillium dahliae*) (Yonsel and Batumi 2009, 2010).

Indeed, the production of cellulolytic enzyme complex such as for degrading lignocellulosic materials is from *T. viride* NPI3a, and these enzymes included xylanase, endoglucanase, β-xylosidase, exoglucanase, cellulase, and β-glucosidase (Anli and Jiang 2011). The production of ethanol from cellulosic or lignocellulosic materials after pretreatment with enzymatic hydrolysis such as cellulolytic enzymes is from *T. reesei* strain CL847 (Warzywoda et al. 2011). Some mutant of *Trichoderma* spp. is producing a polypeptide (Maiyuran et al. 2011, 2012). The special capsule is produced from *T. viride* which is used for controlling the plant pathogens (Haiying et al. 2012). *T. reesei* produced one non-ribosomal peptide synthase (Peij et al. 2012), therapeutic proteins (Huaming and Ward 2013), and fucosylated glycoproteins (Natunen et al. 2013). The new method for using the conidia of *Trichoderma* is through packaging by reducing the water activity of the conidia and using humidity absorber agent (silica gel or calcium sulfate) with another agent of oxygen absorber (glass and laminate materials) (Faria 2013). Production of hydrophobin is from *T. reesei* (Ward 2013). Production of a new composition is by mixing some *Trichoderma* with beneficial microbes such as entomopathogenic PGPR which can be used for treating the seed to protect from plant pathogens and pests (Hellwege

and Hungenberg 2013, 2014, 2015). The production of the biocontrol agents of *T. citrinoviride* EGE-K-130 is using a new process in economical production (Eltem et al. 2014, 2015, 2017). *Trichoderma* produced cellulase in the special bio-fermentation technology (Shuzhi et al. 2014). Production of a protein HYTLOl is from a new strain of *T. longibrachiatum* MK1 beneficial in using it as antifungal and antimicrobial (Lorito et al. 2015). Production of a new sterilizing composition is mixed between *T. harzianum* with hymexazol which is used as pesticides and as the alternative to pesticide consumption (Round 2015). Extraction of specific metabolites from *T. harzianum* strain SK-55 is used for pesticide production (Liebmann et al. 2015).

Continuously, the improvement of cellulose production from *T. reesei* strain CstrxRl is by engineering method (Kun et al. 2016). The mixture of cellulase from *T. reesei* is mixed with flour of treated fibers and other baking ingredients to make a dough (Niemann 2017). Production the feed industry enzymes from *T. viride* was useful to produce the fermented feed that it is a rich of protein and the nutrition was fully meet for requirements of animals (Feng et al. 2017a, c). Production of cellulase enzyme in costs lower from some species of *Trichoderma* (*T. reesei*, *T. viride*, etc.) used a new method by inducing pulverized corncob corn/cob meal (Feng et al. 2017b).

10.2.11 Industry

Trichoderma is useful for producing many compounds and enzymes that involve in industry with low cost and more eco-friendly. For feed industry of chicken and cattle, *T. longibrachiatum* is utilized to supplement the animal nutrition (Altman 2007). Also, *T. viride* secreted many enzymes, fermenting the raw material to produce feed, and this feed is rich in protein and nutrition that fully meets the requirement of animals (Feng et al. 2017a, c). From feed industry to animal and avian, β-1,3(4)-endoglucanohydrolase enzyme of *T. longibrachiatum* is involved in the process of increasing the immune function against pathogens by adding feeds with other materials (Forsberg and Puntenney 2012).

For biodiesel industry, *T. viride* produced cellulase enzyme that is involved in the extraction of plant fat and then after esterification is converted to biodiesel (Wu2008). For textile industry, *T. reesei* is producing a mannanase that is used for bleaching and as a desizing agent (Beister et al. 2008). Then, the cellulase enzyme that producing by a novel strain of *T. reesei* is helpful for the industry in bio-processing of cotton-containing textiles (Goedegebuur et al. 2008). For sugar industry, *T. reesei* is helpful for degrading the plant biomass or lignocellulosic biomass to sugars through producing many enzymes such as glucoamylase, β-glucosidase, and α-arabinofuranosidase enzyme (Magnuson et al. 2008; Gang et al. 2011). For high-glucose syrups industry, it was a fermentation method by utilizing the enzymes from *T. reesei* (TrAA) (Duan et al. 2008a, b, c, 2010, 2011a, b). For biofuels industry, *T. reesei* is degrading the plant biomass material by producing one or more

enzymes that are used in converting the biomass into biofuels like ethanol (Daniell 2009; Koskinen and Tanner 2012). For ethanol industry, cellulase enzymes from *T. reesei* ATCC-57560 are used (Bradley and Keams 2009a, b) and form other strains (Lopes and Lfp 2010; Ferreira and Margéot 2013). For alcohol industry, the lignocellulosic biomass is processed with enzymatic hydrolysis such as cellulolytic and/or semicellulolytic enzymes produced from *T. reesei* (Margeot and Monot 2009).

For cleaning materials industry, *T. reesei* produced the lipase/acyltransferase enzymes that are useful for removing the lipid stain from hard surface, fabrics, and chemical synthesis reactions (Madrid 2010). Biofuels, biodiesel, and other valuable chemical industries were utilizing the enzymes of three species of *Trichoderma T. harzianum*, *T. lignorum*, and *T. reesei* (Eudes 2010). For enzyme industry, it can use a sophorolipid composition to induce producing proteins in *Trichoderma* that lead for increasing the production of enzymes such as cellulase (Huang 2013). For lipid and chitin industry, a novel strain of *T. harzianum* (TRICHOSIL) is degrading the marine animal such as fish and arthropods by secreting the chitinolytic enzymes (López-Cervantes et al. 2014).

For chemical material industry, the new variant of endoglucanases of *T. reesei* was beneficial in industrial processes by producing the ethanol that happen through decomposition in simultaneous of cellulosic biomass and converts to sugar monomers and then the fermentation of these sugars (Blesa et al. 2015a, b, 2016). For seed industry, mixing between *Trichoderma* and a vesicular-arbuscular mycorrhizal for coating the seed is stimulating the plant growth with protection from plant pathogens and pests (Marx and Lewis 2015).

10.2.12 Medical and Pharmacy

Trichoderma secreted different enzymes and also many secondary compounds that are involved in the manufacture of drugs and induced the immune functions in human and animals. *T. reesei* strain QM 9414 produced peptides as antimicrobial agents which are used in cosmetic compositions, finishing of medical care devices, pharmaceutical, agrochemical, and textile fibers and fabrics (Liebmann et al. 2009). The augmentation of immune function in mammalian and avian species is utilizing β-1,3(4)-endoglucanohydrolase enzyme derived from *T. longibrachiatum* strain and mixed with mineral clay, diatomaceous earth, β-1,3(4)glucan, and glucomanna and then admixed with feeds or foods, which are incorporated into pelleted feeds or foods or administered orally (Forsberg and Puntenney 2012). Strain IBPT-4 of *T. citrinoviride* produced the alkaloid compound that have the ability to inhibit the cell proliferation and useful in the antineoplastic drug (Li et al. 2014a, b). *T. longibrachiatum* strain MTCC 5721 produced brachiating D (a peptaibol) that is a pharmacologically active compound used as an anticancer agent and very efficient as immunosuppressants (Singh et al. 2015). A new strain DLEN2008005 of *T. harzianum* is helpful in manufacturing the specific drugs of anti-Alzheimer's (Yi et al. 2016). The kudzu isoprene production is a synthesis of *T. reesei* (Serban et al. 2017).

10.2.13 In Environment Field

In environment, several wastes and residues were coming from factories, the industrial shops, and the residue of the marine animals and have a major effect on the environment. Some strains of *Trichoderma* are able to secrete degrading enzymes for removing the residues and wastes, but also they can convert them to benefit materials and utilize these materials in industrial, drugs, pharmaceutical, and chemical material industry. A mannanase from *T. reesei* is used for the removal of biofilm and the processing of coffee waste (Beister et al. 2008). *T. reesei* is helpful for environmental biorefinery (Margeot and Monot 2009). *T. harzianum* strain TRICHOSIL is removing the residue in the environment of marine arthropods and fish, such as crab, crayfish, and shrimp (López-Cervantes et al. 2011, 2012, 2014). Utilizing sewage sludge in culture medium of *T. reesei* is beneficial to reduce the environmental pollution resulting from wastewater and produce the cellulase enzymes (Alam et al. 2012).

To remove the wastewater from the environment, degradation of chemical and biological residues in industrial wastewater is possible by treating with *T. harzianum* strain 1228 which produces a p-toluenesulfonic acid (Jia-you et al. 2015). For removing the white phosphorus from contaminated soil, treating this soil with a novel strain of *T. asperellum* VKPM F-1087 leads to detoxification of waste (Mindubaev et al. 2016). For disposal of the chemical fertilizer or any residue, used *T. atroviride* strain K as biofertilizer to be as the natural alternative of the fertilizer synthetic, greener, and eco-friendly (Xiaoli et al. 2017). For bioremediation of contaminated soils, the removal of Suaeda-contaminated soil with heavy metal is possible by colonizing with *T. virens* strain F7-Suaeda, improving the soil microbial biomass and microenvironment of the rhizosphere for plants (Ningning et al. 2017). Removing the residue of monosodium glutamate (MSG) in the wastewater and converting it to be an organic fertilizer for the plant are based on MSG fermentation with three strains of *Trichoderma* such as *T. harzianum*, *T. viride*, and another one which enhanced the plant growth through fertilizer and cleaned the environment from the residue of MSG in shortened time (Fuli et al. 2017). Eliminating nitrogen pollution from sewage water is prepared by mixing *T. viride* with *Paracoccus* (denitrifying bacteria) to treat the sewage and to reduce pollution of the environment (Ge et al. 2017).

10.2.14 Horticulture Industry

Trichoderma is causing economic losses for the horticulture industry through attacking and affecting the cultivation of mushrooms. Therefore, some of the inventors focused on detecting a new antifungal agent against some species of fungi but must not have an effect on the mushroom. The new formulas (I) and (IV) of antimicrobial are used against *T. virens* ATCC 9645 (De et al. 2008). A product including mixture of 2-n-N-butyl-1,2-benzisothiazolin-3-one (“BBIT) and 3-iodpropynyl-N-n-butylcarbamate (“IPBC”) is antifungal against *T. virens* ATCC 9645 (Smith and Gaglani 2011). A novel agent of *Bacillus subtilis* strain P13 is useful against *T.*

harzianum strain biotype 4 and reduces the mold that appears in the process of mushroom production (Gheshlaghi and Verdellen 2012a, b). The compounds I and II are fungicidal potential against many species of *Trichoderma* spp. (Gewehr et al. 2012, 2013). A new composition of two antifungals, such as natamycin and thiabendazole, is used to apply with substrate of the mushroom growth to control *T. harzianum* (Stark 2014). The special method of activation for *T. viride* strain on culture medium is by preparing a solid fermentation that is used in the conventional technology to produce edible fungus like mushroom (Chuanlun et al. 2017).

10.3 Conclusion

Trichoderma is a very widespread genus and interestingly plays a big role in secreting many enzymes and secondary compounds that contribute in the control of plant pathogens with pests and in other fields. These traits of *Trichoderma* spp. are helpful to compete with the wide range of microbes and adapt in plants, soil, and rhizosphere. The high diversity of *Trichoderma* in soil, plant, and rhizosphere is allowing the inventors to research more about this genus for detecting the new isolates, new strains, new enzymes, and new compounds. Possible utilizing of the new isolates or strains of *Trichoderma* are getting it from the research in the centers and universities, because the new isolates have a repository of many enzymes and compounds that waiting for discovery.

The inventors discoveried many patents that introduced more services for our life including environmental without the residue of the chemical pesticides, degradation the waste such biological and chemical, and don't residue for the chemical fertilizer. *Trichoderma* have the ability to be an alternative to the pesticides and fertilizer chemical, as well as it can produce many enzymes on raw materials for converting to benefit materials. They discovered many strains comprising *T. harzianum*, *T. reesei*, *T. atroviride*, and *T. viride*. Several novel strains and isolates could be used including *T. asperellum*, *T. brevicompactum*, *T. erinaceum*, *T. spirale*, *T. asperellum*, and *T. virens* against many plant pathogens such as *Rhizoctonia*, *Phytophthora*, *Fusarium*, *Pythium*, and *Sclerotinia*, which also can control plant diseases comprising root rot, wilt, set rot, damping off, club rot, rhizome rot, stem rot, collar rot, and red rot. *T. reesei* and *T. longibrachiatum* were the new strains producing some antifungal and antimicrobial agents such as peptides, polypeptides, and proteins like HYTLOl.

Many methods are used for utilizing *Trichoderma* through making (A) a capsule, (B) encapsulation of conidia microparticles, (C) preparation of microsclerotia propagules, (D) spraying the conidial suspension on the grafting site, and treating the rice seedling for protection from infection. Five species of *Trichoderma* include *T. reesei*, *T. viride*, *T. harzianum*, *T. atroviride*, and *T. longibrachiatum* that have a high efficiency in the biofertilizer production. These species were useful as biofertilizer to be an alternative of chemical fertilizer that is able to (A) increase the plant growth with water use efficiency of plants, (B) plant valuable nutrients, and (C) soluble

minerals, (D) release nitrogen, (E) enhance the root system with chlorophyll and yield, and (F) increase trace element and amino acid contents.

T. reesei was a very active species in producing several enzymes comprising cellulase, cellohydrobiolase, phytase, endoglucanases, glucoamylase, xylanase, and mannanase enzymes, as well as acetolactate protein. Industrial applications of nanotechnology in utilizing of *Trichoderma*, such as *T. reesei*, *T. viride*, and *T. hamatum*, are for manufacturing SNPs, nanobiofertilizer, and nanosilver hook. The patents have shown *T. harzianum* is very beneficial in the production of biopesticides and biofertilizers. Many new formulations and products are used for utilizing *Trichoderma* in plant protection and the provision of nutrients for reducing the chemicals that are used in the manufacture of pesticides and biofertilizer. Therefore, the inventors found the best idea for producing a mixture of *Trichoderma* in special production which is low cost and eco-friendly. *Trichoderma* appeared to have a huge role in several industries where it have been already involved. They are useful for industries including feed for chicken, cattle, and avian, biodiesel, textile, sugars, biofuels, ethanol, alcohol, and cleaning materials. Many products of drugs were relevant with *Trichoderma* comprising anti-Alzheimer's by inhibiting the cell proliferation and in antineoplastic, enhancing the immune function, and anticancer. *Trichoderma* is a very important genus for saving the environment from waste. *Trichoderma* could remove the biofilm, the coffee waste, residue of marine waste, the white phosphorus in soil, heavy metal, and MSG in wastewater. On the other hand, control on *Trichoderma* by antifungal was mentioned in few patents due to its role in affecting mushroom cultivation.

Finally, the genus *Trichoderma* has been shown to be very efficient and helpful for our life according to discoveries by the recent patents. Many species of *Trichoderma* are PGPF (plant growth-promoting fungi) comprising *T. asperellum*, *T. reesei*, *T. viride*, *T. harzianum*, *T. atroviride*, *T. longibrachiatum*, *T. virens*, *T. brevicompactum*, *T. erinaceum*, *T. spirale*, and *T. asperellum*. Therefore, *Trichoderma* can be as PGPF for introducing it high benefits to plants including as agent in biopesticides to control of plant pathogens and pests, as well as, as agent in biofertilizer for the ability to produce several enzymes and secondary metabolites useful to promote growth of the plants. Some species of *Trichoderma* are able to highly colonize, grow, and produce several active enzymes and secondary compounds in habitat. These traits almost are back to the high expression of genome that confers a high ability in competition with other microbes. The present patents are showing here the important role by exploiting it in different fields comprising (1) Method to get new strains and isolates (2) New methods for making the formulations and production of biopesticides and biofertilizers more friendly for environmental and in lower cost. (3) A contribution of Trichoderma in different industries also more saves for environmental with low cost. and (4) Shown the big role of Trichoderma in removing and degrading the different waste, and also detoxification some metal in the contaminated soils that lead to clean the environment at low costs.

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Zhao X, Fengwu B, Fei Z (2017) A high cellulase enzymes of *Trichoderma reesei* recombinant strains and Applications. CN Patent, CN106978360A
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Zhihua L, Shu ZR, Jinjie W, Huifang Z, Cedel S, Yucheng W, Haijuan F (2017) Spores of *Trichoderma* and its application a ratchet. CN Patent, CN107058126A

Intellectual Property: Data Mapping in the Area of Biofertilizers

11

Shivani Srivastava and Alok Adholeya

Abstract

Global patent landscape analysis in the current study aims to present patent activity, geographical, technical and innovation trends in the field of biofertilizers from 2007 to 2017. Analysis of the developed patent dataset has uncovered several interesting facets in the field of biofertilizers. The patent activity trend of biofertilizers has revealed that innovation in this field grew in two distinct phases in the last 11 years. 2010 and 2016 were recognized as the best years of innovation. Geographical analysis showed Asian countries to be main players of biofertilizer related innovations. China (642) followed by USA (192) and India (140) holds top-most position in terms of dominance of patent families. Similar to patent family trend, China was also recognized as top-most country to hold highest number of granted patents (86) followed by USA (42). Data on applicants revealed individuals (39%) followed by industries (35%) and universities (11%) to be the most active participants. Interestingly, in terms of assignees, industries hold topmost position in comparison to individuals and universities indicating growing participation of industries in the field of biofertilizers. Technical analysis of the developed patent dataset revealed that inventions in this filed are focused on product development or on strategies/methodologies that can lead to the development of biofertilizers with improved efficacy, storage, production or application as well as on devices/equipment that can ease/improve their production at large scale. Through this report we predict that next generation of innovations in the field of biofertilizer industry will focus on the development of efficient products and robust technologies that can mitigate the impact of climate change and support sustainable agriculture practices.

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H. B. Singh et al. (eds.), *Intellectual Property Issues in Microbiology*,
https://doi.org/10.1007/978-981-13-7466-1_11

Keywords
Biofertilizers · Bioinoculants · Agriculturally important microorganisms · Patents · WIPO

11.1 Introduction

Biofertilizers are fertilizers derived from microbiological sources that promote plant growth, productivity and tolerance to biotic and abiotic stress (Bhardwaj et al. 2014). Also known as soil conditioners or organic fertilizers, they maintain and multiply soil fertility by various mechanisms that includes fixation/solubilisation/mineralization of macronutrients (nitrogen, phosphate and potassium), release of plant growth regulating substances, production of antibiotics and biodegradation of organic material (Sinha et al. 2014). Generally, microorganism's such as bacteria, cyanobacteria, fungi, algae, their products and organic residues that promote plant growth and improve their productivity are grouped as biofertilizers. Owing to their properties of environmental safety, maintenance of soil health and multiplication of soil biodiversity, biofertilizers are recognized as an efficient alternative to chemical fertilizers playing a paramount role in sustainable agricultural practice (Mahanty et al. 2017; Malusa et al. 2016).

Worth of global biofertilizer industry was found to be USD 1.07 Billion (2016) and it is projected to grow further to USD 4.03 Billion by the end of 2026 (https://www.techsciresearch.com/report/global-biofertilizers-market/1301.html). Such a prodigious growth of this industry indicates growing awareness and utilization of biofertilizers towards sustainable agriculture. Furthermore, indirectly it also hints towards need of continuous development of innovations in the sector of biofertilizers. To identify the questions for research and development activities pertaining to the field of biofertilizers, it is essential to identify the current innovation status and landscaping of patents can be performed to obtain such a information.

Patents hold important position in the field of agricultural biotechnology (Keswani et al. 2016; Singh et al. 2016a, b, 2017). According to World Intellectual Property Organization (WIPO), "a patent is an exclusive right granted for an invention, which is a product or a process that provides, in general, a new way of doing something, or offers a new technical solution to a problem." In general terms, patents are thus an indicator of innovations and development that act as an incentive for the inventor safeguarding his and investors interest (Hing and Back 2009; Chandler 2016).

Patent landscaping is a process whereby larger, specifically selected collections of patent documents (published applications or granted patents) are studied in detail to derive important technical, legal and business information (Patent Landscape Report: Microalgae-Related Technologies WIPO 2016). Recently, landscaping of Indian patents relevant to the field of biofertilizers/bioinoculants/biopesticides was reported by Srivastava et al. (2016) that supports continuous need of development of innovative strategies in the field of agriculture.

The objective of the present study was to develop a global patent landscape report on biofertilizers from 2007 to 2017. Biofertilizers patent landscape development in the present study involved collection of published applications and granted patents globally from 2007 to 2017 through online resources, their classification and screening followed by step-wise analysis to conclude information on patent activity trends at geographical, technical and commercial scale.

11.2 Search Methodology and Development of Patent Dataset for Data Mining Studies

The aim of the present study was to develop a global patent dataset on biofertilizers from 2007 to 2017 followed by data mining of collected patent families (refers to published application/granted patent or utility models). In detail steps involved in generation of present report involved the following:

11.2.1 Data Collection for the Development of Patent Dataset

A rigorous online search was performed for data collection and dataset development in the present study. Broadly, search involved data collection using search engines, patent databases and country specific patent websites. The term "biofertilizers" and time period 2007–2017 were used in the keyword and time period sections during data collection. Data collection was performed in three stages. Firstly, information on published applications and granted patents was collected through Google patents (https://patents.google.com/). Secondly, similar information available on the databases that allow free access such as PATENTSCOPE-WIPO (http://www.wipo.int/patentscope/en/), ESPACENET (European Patent Office; https://worldwide.espacenet.com/), AUSPAT (Australia; https://www.ipaustralia.gov.au/patents), SIPO (China; http://english.sipo.gov.cn/), DPMA (Germany; https://www.dpma.de/english/), ROSPATENT (Russia; https://www.eapo.org/en/ru.html), Japanese patent office (Japan; https://www.jpo.go.jp/), CIPO (Canada; http://www.ic.gc.ca/eic/site/cipointernet-internetopic.nsf/eng/Home) and USPTO (Unites States of America; https://www.uspto.gov/patents-application-process/search-patents) was collected. Thirdly, to gain access to published and granted patent applications, other than specified above, a patent database "PatSeer" was also screened. It is a web-based patent search and collaboration platform (https://patseer.com/).

11.2.2 Screening, Classification and Development of Patent Dataset

The collected patent families were screened for their relevance to the field of biofertilizers. Published applications and granted patents that were related to development of composite and compound biofertilizers, plant growth promotion and stress

tolerance, enhanced nutrient solubilisation and mobilization, bioherbicides and biopesticides, isolation of novel microorganisms, formulations, large scale production, green house based production, plantation and spraying technologies and devices related to biofertilizer production were selected.

To perform in-depth and cross analysis, the selected information was then tabulated under the categories of record number, record type; application/grant, publication/grant date, application date, priority country, title, abstract, applicants, applicant category; University/industries/individuals/reserach and development (R & D) institutes/collaborations/colleges, inventor/inventors, international classification, original assignee, current assignee and product/process type of patent family. The prepared dataset was further analysed for records that were directly related to integration of biofertilizer technology. This included analysis of type of raw material, compound/composite biofertilizer, biological organism, formulation, specific biological activity, production technologies, novel microorganisms and application. On the other hand, records that were not directly related to integration of biofertilizer technology (for example: biogas, ethanol and secondary metabolite production and bioreactors) were categorized as indirect. For quality check, the prepared patent dataset was cross-checked thrice to remove any duplicated record number and its details.

11.2.3 Data Mining Studies

The developed patent dataset was used to identify patterns and establish relationships in the field of biofertilizers in the past 11 years on the following:

- Patent activity: granted and published application trend, granted patent trends, international classification analysis
- Geographical analysis: country-/region-wise patent filing record, country and year-wise publication trend
- Key players: key applicants and their share percentage, key inventors and key assignees and their share
- Technological areas: classification of concepts: product and process patents, current technical scenario of patents granted from 2007 to 2017
- Innovation trends in the past 11 years

11.3 Overall Trends and Patent Family Analysis

11.3.1 Patent Activity

In total 2047 patent families were collected in the field of biofertilizers from 2007 to 2017. Patent families related to biofertilizers preparation, production, formulation, micro-organism and novel processes/devices were screened out and 1288 patents were further used for in-depth and cross analysis studies.

11.3.1.1 Granted and Published Application Trend

The timeline activity showed that interest in the field of biofertilizers has been continuously growing (Fig. 11.1a) with two distinct phases of growth from 2007 to 2010 (24% Compound annual growth rate percentage; CAGR) and 2011–2016 (31% CAGR). The number of granted patents from 2007 to 2017 was found to be 247 while number of published application was 1047. CAGR for published application was 39.53% while for granted application it was found to be 54.82% from 2007 to 2017 (Fig. 11.1b).

11.3.1.2 Granted Patent Trends

Out of 247 granted patents 237 were granted by patent offices of 27 different countries while 10 were granted by European Patent Office (EPO) and World Intellectual Property Organization (WIPO). Among the countries China tops the list by 86 patents followed by USA (42), Korea (18), Russia (32), Australia (10) and Ukraine (6). Countries such as Japan, India, and Canada hold four patents each. Singapore, Germany, Denmark, Egypt, Austria, Argentina, Denmark, Cyprus, Croatia, Poland and Netherland have one patent each to their credit.

11.3.1.3 International Classification Analysis

The collected patent families' dataset was analysed for areas of technology to which they pertain by collecting, identifying and analysing International Patent Classification (IPC) codes. As per WIPO, IPC is a hierarchical system of language independent symbols for the classification of patents and utility models (http://www.wipo.int/classifications/ipc/en/). Seven different classes were found in the collected dataset from A to G and Y (A; human necessities; 819, B; performing operation and transporting; 78, C; Chemistry and metallurgy; 2113, D; textiles and papers; 4, E; fixed constructions; 8; F; mechanical engineering; 8, G; physics; 4, Y; Technologies or applications for mitigation or adaptation against climate change; 69). Class C was identified as the dominant category and was further classified (Fig. 11.2). C05F and C05G were identified as major subclasses related to organic fertilizers and mixture of fertilizers followed by microorganisms, phosphatic and nitrogenous fertilizers classes. IPC classification and its statistics aligns with classification of concepts.

11.3.2 Geographical Analysis

Here, we have considered priority countries where patent protection was first sought for a given invention in the field of biofertilizers from 2007 to 2017.

11.3.2.1 Country/Region-Wise Patent Filing Record

Analysis of patent dataset developed in the present study revealed that 39 countries have filed or have been granted with patents from 2007 to 2017 in the field of biofertilizers (Fig. 11.3a). Innovation trend at regional level in biofertilizers shows that majority of activity is Asian, followed by North American, European and South

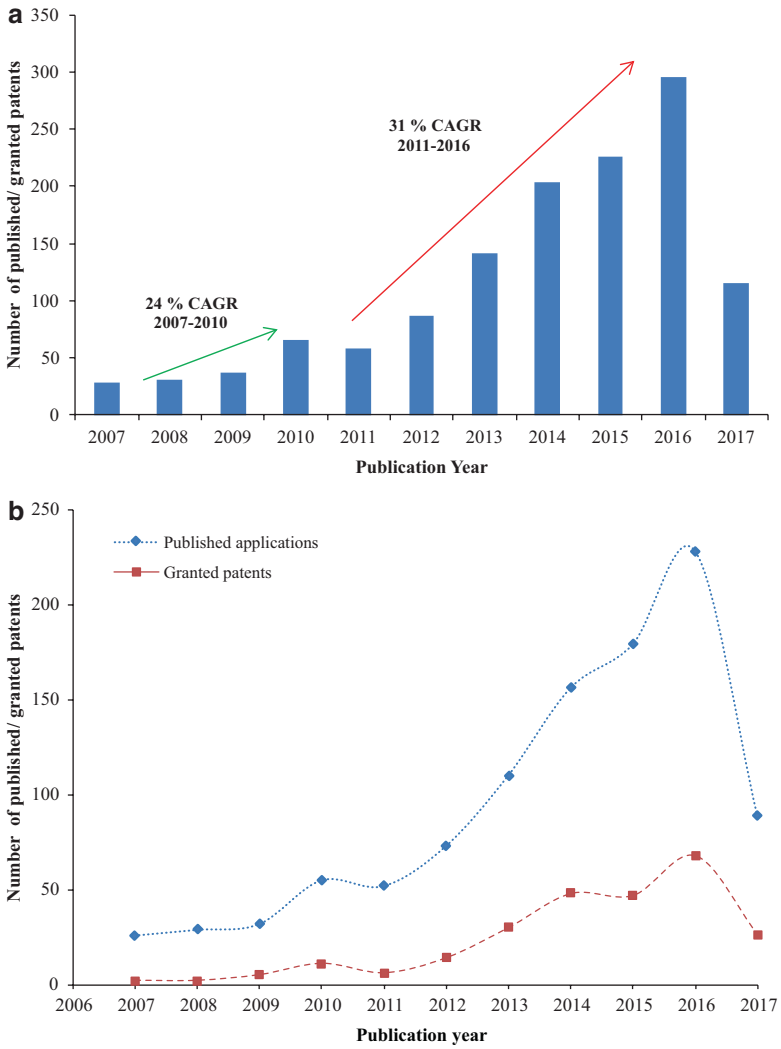

Fig. 11.1 Patent activity trend from 2007 to 2017 in the field of biofertilizers (**a**) Total granted patent and published application trend and (**b**) Separated published application and granted patent trends. The timeline trends in both sub-figures clearly show the continuous growing interest in the field of biofertilizer. Two phases of growth were observed in (**a**) with CAGR (24%; 2007–2010 and 31%; 2011–2016). Subfigure (**b**) show fourfold higher published application than granted patents in the last 11 years and 2010 and 2016 as the year of innovation in the two recognised phases

Class type	Sub-Class	Tn	Class details
C: Chemistry and Metallurgy (Tn=2113)	C05F	788	Organic fertilisers
	C05G	703	Mixtures of fertilisers belonging individually to different sub-class of class C05
	C12N	280	Micro-organisms or enzymes
	C05B	69	Phosphatic fertilisers
	C02F	60	Treatment of water, waste water, sewage, or sludge
	C10G	46	Cracking hydrocarbon oils; production of liquid hydrocarbon mixtures from materials other than hydrocarbons recovery of hydrocarbon oils from oil-shale, oil-sand, or gases; refining mixtures mainly consisting of hydrocarbons; reforming of naphtha; mineral waxes
	C05D	44	Inorganic fertilisers not covered by sub-classes C05B, C05C; fertilisers producing carbon dioxide
	C09K	40	Compositions not provided for elsewhere; miscellaneous applications of materials
	C12M	31	Apparatus for enzymology or microbiology; unicellular algae, plant or animal cell, tissue, or virus-culture apparatus
	C05C	29	Nitrogenous fertilisers
	C10L	9	Fuels not otherwise
	C10B	5	Destructive distillation of carbonaceous materials
	C11B	5	Producing, refining or preserving fats, fatty substances, fatty oils or waxes, including extraction from waste materials; essential oils; perfumes
	C08K	3	Use of inorganic or non-macromolecular organic substances as compounding ingredients
	C08L	1	Compositions of macromolecular compounds

Fig. 11.2 Block diagram of chemistry and metallurgy patent classification for biofertilizers from 2007 to 2017. The figure shows major subclasses of family chemistry and metallurgy under which patent applications are filed or granted in the field of biofertilizers from 2007 to 2017. *Tn* stands for total number of patents. The codes and details of the codes are defined in the figure

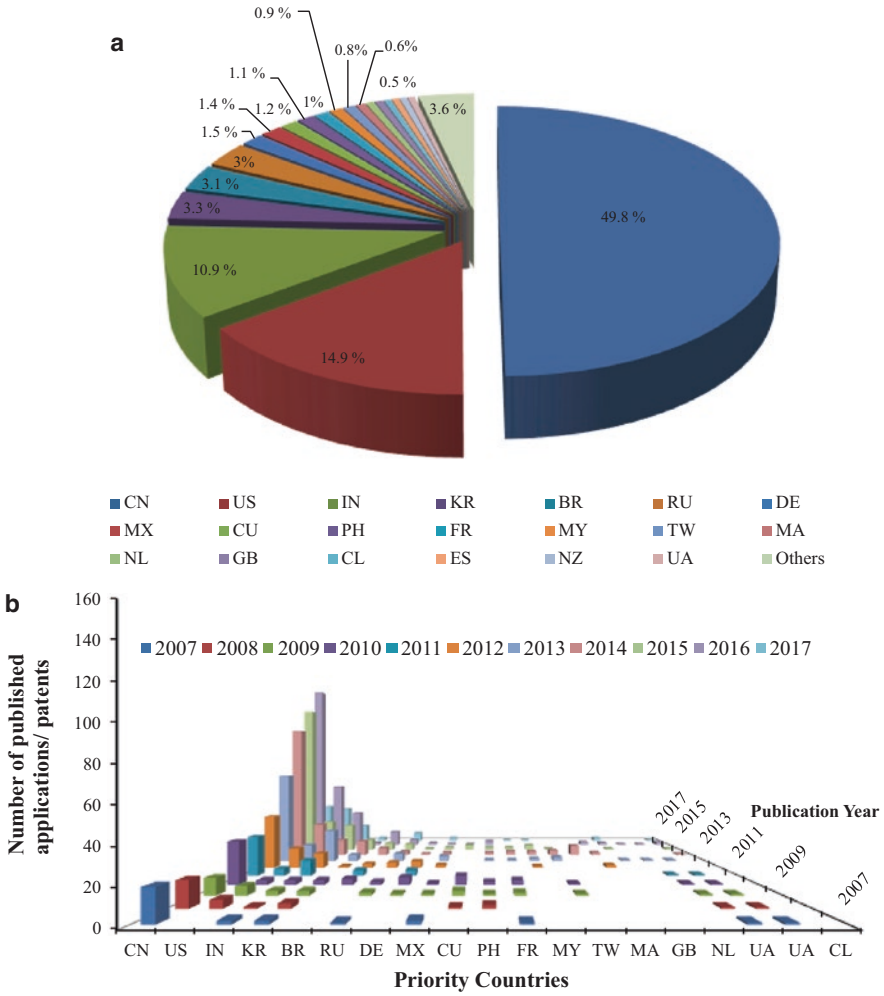

Fig. 11.3 Geographical trend of patent families from 2007 to 2017 in the field of biofertilizers. (**a**) Trend on country-wise patent filing record**.** Pie-chart shows share percentage of priority countries. (**b**) Country and year-wise publication trend. *CN* China, *US* United States of America, *IN* India, *KR* Korea, *BR* Brazil, *RU* Russia, *DE* Denmark, *MX* Mexico, *CU* Cuba, *PH* Philippines, *FR* France, *MY* Malaysia, *TW* Taiwan, *MA* Moldova, *NL* Netherlands, *GB* Great Britain, *CL* Chile, *ES* Spain, *NZ* New Zealand, *UA* Ukraine. Others denotes countries having five or less than five patent families

American activity. Among the 39 countries, China (642), USA (192), India (140), Korea (43), Brazil (40) Russia (38) top the list. Countries such as Denmark (19), Mexico (18), Cuba (15), Philippines (14), France (13) and Malaysia (11) follow the top-most countries in number of patent applications/grant. Countries that had less or equal to 5 patents were categorized as others in the present study for analysis purpose and 46 patent families were accounted under the same.

11.3.2.2 Country and Year-Wise Publication Trend

Data on countries which had higher than five patents to their account was segregated to identify the country and year-wise patent trend (Fig. 11.3b). In the first phase (2007–2011) of patent families' growth, 2010 showed highest numbers of patent families while 2016 was recognised to be highest in the second phase (2012–2016). Thus, 2010 and 2016 can be considered as innovation year in the field of biofertilizers in the past 11 years. Among the 39 countries, following trend in compound growth rate was found: China (38% CAGR, 2007–2017), USA (39% CAGR, 2008–2017), India (47% CAGR, 2007–2017), Korea (32% CAGR, 2007–2017) and Brazil (35% CAGR, 2010–2016). India showed emerging growth from 2007 to 2017 among the five most active countries.

11.3.3 Key Players

This section analyses ownership status in the filed biofertilizers related to patent activity in the past 11 years.

11.3.3.1 Key Applicants and Their Share Percentage

Based on the patenting activity (both application and grant), six major categories of applicants such as Universities, industries/individuals, R&D, institutes, collaborations and colleges were recognized. The category of active applicants was decided by number of the patent families filed by the above categories. Activity trend was individual (39%)> industries (35%)> Universities (11%)> R&D institutes (9%)> collaborations (4%)> colleges (2%) (Fig. 11.4a). Further analysis of year and application number revealed 2016 as the most active year (Fig. 11.4b). Industrial (43%) applicant showed highest share percentage followed by individuals (32%) and Universities (10%). Similar to 2016, industrial applicant were recognized as most active applicant (43%) in 2017 also. Thus last 2 years data indicate that interest of industries is growing in the field of biofertilizers.

In detail, information on top ten applicants is provided in Table 11.1. Jawaharlal Nehru University; India (5), Anhui Xintiandi Biological Fertilizer Co., Ltd.; China (33), Council of Scientific Industrial Research; New Delhi, India (21), Accelergy Corporation; United States of America), Shanghai Advanced Research Institute of the Chinese Academy of Science; China (3) were identified as top applicants under category of universities, industries, institutes and collaborations.

11.3.3.2 Key Inventors

All inventors who had five or higher than five published application/granted patent were screened and identified. Table 11.2 list the top inventors in the field of biofertilizers from 2007 to 2017. Zhou Guoli is the top inventor. In view of dominance, topmost inventors are from China followed by USA, Denmark, Cuba and India.

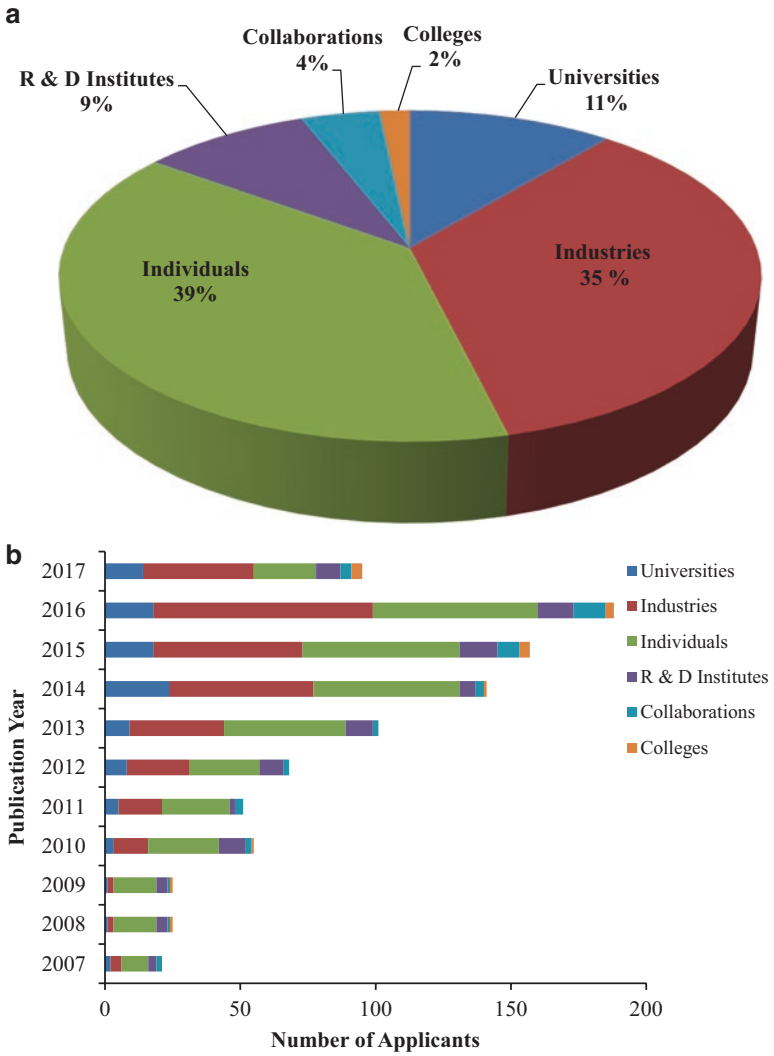

Fig. 11.4 Key applicants from 2007 to 2017 in the field of biofertilizers (**a**) Share percentage of key applicants and (**b**) Trend on year-wise applicant trend

11.3.3.3 Key Assignees and Their Share

According to the norms of USA patent activity "assignee of patent" is defined "as a person who holds, by a valid assignment in writing, the whole interest of a patent, or any undivided part of such whole interest". Among the granted patents, assignees data was also analysed which revealed that in the past 11 years industries holds highest number of granted patents followed by individuals, universities and collaborations. Top 11 assignees data is presented in Fig. 11.5 and it clearly indicate industries to be topmost key assignee. On the basis of dominance Council of Scientific

Table 11.1 Global top ten key applicants for grant of patents from 2007 to 2017 in the field of biofertilizers

S. No	Applicant type	Number of patents
	Universities	
1	Jawaharlal Nehru University, India	5
2	Nanjing Agricultural University, China	5
3	Michigan state university, United States of America	4
4	Kuban State Agrarian, Russia	3
5	Hebei Agricultural University, China	2
6	Hohai University, China	2
7	Guangxi University, China	3
8	Universidade Federal Rural De Pernambuco, Brazil	3
9	Chungbuk National University, South Korea	3
10	University of Guelph, Canada	3
	Industries	
1	Anhui Xintiandi Biological Fertilizer Co., Ltd., China	33
2	FMC corporation, Philadelphia, United States of America	31
3	Qingdao Tashi Biological Technology Co., Ltd., China	29
4	Chongqing Yifeng Biological Fertilizer Co., Ltd., China	12
5	Qingdao Hai-Cheng Management Technology Co., Ltd, China	9
6	Suzhou Rencheng Biological Technology Co., Ltd, China	9
7	Jinan Shun Cheung Pharmaceutical Technology Co., Ltd., China	6
8	Dragon in the organic fertilizer company limited	6
9	CAL SAFE SOIL, United States of America	9
10	Georg fritzmeier GMBH CO., Germany	5
	R & D Institutes/Organizations	
1	Council of Scientific Industrial Research, New Delhi, India	21
2	Centro De Ingenieria Geneticay Biotecnologia, Cuba	5
3	Institute of Geochemistry, Chinese Academy of Sciences, China	2
4	South China Sea Institute of Oceanology, Chinese Academy of Sciences, China	2
5	Empresa Brasileira De Pesquisa Agropecuaria, Brazil	2
6	Institute of Agricultural Resources and Regional Planning, Chinese Academy of Agricultural Sciences, China	2
7	The Energy and Resources Institute (TERI), India	4
8	Hunan Institute of Soil and Fertilizer, China	3
9	Hunan Institute of Microbiology, China	2
10	Federal State Budget Scientific Institution "All-Russian Scientific Research Institute Of Meliored Land", Russia	3
	Collaborations	
1	Accelergy Corporation (United States of America), Shanghai Advanced Research Institute of the Chinese Academy of Science (China)	3
2	Abitep GMBH (Germany), Profert Technology Gmbh (Germany)	3
3	Chungbuk National University Industry-University Collaboration Foundation (South Korea)	3

(continued)

Table 11.1 (continued)

S. No	Applicant type	Number of patents
4	Department of Biotechnology, Ministry of Science Technology (India), Jawaharlal Nehru University (India)	4
5	Universidad De Concepcion (Chile), Universidad De Talca (Chile)	3
6	Jiangsu New Ground BioFertilizer Engineering Center Co., Ltd. (China), Nanjing Agricultural University (China)	3
7	Biochemical Co., Ltd. (China), Xinjiang Tianfu Sunshine Biotechnology Co., Ltd (China)	2
8	Republic Korea of Rural Development (South Korea], Chungbuk National University (South Korea)	2
9	Organic Biofertilizer Co., Ltd. (China), Liaoning Fangxing Green Industry Group (China)	1
10	Korea Research Institute of Bioscience and Biotechnology (South Korea), Ultimate Biotech Sdn. Bhd. (Malaysia)	1

and Industrial Research (11), Chongqing Yifeng Biofertilizer Co. Ltd. (9) and Anhui Xintiandi Biofertilizer Co. Ltd. (7) tops the list however, they show indirect relation to biofertilizers. Under direct relationship category Barrientos Leticia, Berrios Graciela, Cabrera Gustavo, Gidekel Manuel, Gutierrez Ana and Mihovilovic Ivan (individual; 6), Ct Ingenieria Genetica Biotech (institute; 6) and Biodiscovery Inc., Fritzmeier Georg Gmbh Co Kg and Valorhyze (industries; 4) are the key assignees.

11.4 Technical Analysis of Biofertilizer Patent Dataset

11.4.1 Classification of Concepts: Product and Process Patents

To develop concept on the key areas of patent filing and grant in the field of biofertilizers from 2007 to 2017, the developed dataset was classified under two categories of product and process patents (Fig. 11.6). Under product patent category classification was made on the basis of strategies where biofertilizer/biological organism/formulations/devices were developed as a product for agricultural application. For process patent category, patents families that disclosed methodologies/novel process related to development and application of biological fertilizers were selected. Broadly, product patents consisted of seven different groups while process patent category had nine subgroups. Raw material, composition, biological organisms, formulations, specific activity, bioreactors and devices were found to be major subgroups under product patent categories. However, technologies/methodologies such as large scale production, preparation of biofertilizers and their formulation for better shelf-life; release and activity, isolation, planting, spraying, heavy metal resistance and technologies that were indirectly related to biofertilizers were included under process patent category.

Table 11.2 Global top key inventors for grant of patents from 2007 to 2017 in the field of biofertilizers

S. No	Inventor's name	Number of published applications/ granted patents
1	Zhou Guoli	33
2	Xue Jing	29
3	Wang Juan	17
4	Wang Yan Li, Li Yang	14
5	Wu Zhigang	12
6	Zhang Xudong	12
7	Zhou Lidong, Zhou Guoli, Zhu Shunshan	10
8	Zimmermann Jennifer, Dott Wolfgang	10
9	Qin Qian	12
10	Morash Daniel M, Lejeune Mark	11
11	Mena Campos Jesus, Pimentel Vazquez Eulogio, Marin Bruzos Marieta, Hernandez Garcia Armando Tomas, Sanchez Ortiz Ileana, Ramirez Nunez Yamilka, Gonzalez Blanco Sonia, Garcia Siverio Marianela, Borroto Nordelo Carlos Guillermo	11
12	Ghosh Pushpito Kumar, Mishra Sandhya Chandrika Prasad, Gandhi Mahesh Ramniklal, Upadhyay Sumesh Chandra, Mishra Sanjiv Kumar, Pancha Imran, Shrivastav Anupama Vijaykumar, Jain Deepti, Shethia Bhumi, Maiti Subama, Zala Krushnadevsinh Sukhdev Singh	14
13	Gidekel Manuel, Cabrera Gustavo, Barrientos Leticia, Mihovilovic Ivan, Berrios Graciela, Gutierrez Ana	11
14	Reddy C A, Janarthannam Lalithakumari	9
15	Halos Saturnina, Halos Ponciano	9
16	Banerjee Manas Ranjan	9
17	Chen Siyu	9
18	Fiato Rocco A, Sun Yuhan, Allen Mark, Zhao Quanyu	9
19	Lee Jong Tae, Lee Ki Sung , Lee Kwang Su, Lee Kyung Mok	8
20	Taghavi Safiyh, Van Der Lelie Daniel	7
21	Ning Yiwei	7
22	Finlayson Wayne, Jury Karen	7
23	Adholeya Alok	7
24	Bullis David T, Grandlic Christopher J, Mccann Ryan, Kerovuo Janne S	7
25	Dodd John, Marsalek Blahsolov, Vosatka Miroslav, Bashir Nazir	6
26	Fiato Rocco A, Bauman Richard F, Zaczepinski Sioma, Bisio Attilio	6
27	Martin Timothy M	6
28	Raizada Manish, Tessaro Michael, Shehata Hanan Reda Hassan Elsayed	6
29	Taghavi Safiyh, Van Der Lelie Daniel, Silinski Melanie Ann Rehder , Lee Jaeheon	6
30	Wang Yajun	6

(continued)

Table 11.2 (continued)

S. No	Inventor's name	Number of published applications/ granted patents
31	Yang Jin, Yang Zhixian	6
32	Mazeaud Isabelle, Tse Kathryn, Obert Jeanphilippe, Berger Claudette, Babin Geoffrey, Chaigneau Patrick, Jensen Hans Hedegaard, Henri Erwan	5
33	Mody Kalpana Haresh, Ghosh Pushpito Kumar (In), Sana Barindra, Gnanasekaran G, Shukla Atindra Dinkerray, Eswaran K, Brahmbhatt Harshad Ramanbhai, Shah Bharatiben Gunavantray, Thampy Sreekumaran, Jha Bhavanath	5
34	Salvador Pascal	5
35	Taghavi Safiyh, Van Der Lelie Daniel, Mcleod Roderick, Brost Kevin Ronald John, Kibbee John Edward	5
36	Tariq Nadeem, Arshad Muhammed, Jamshed Hamad Raza, Ahmed Nasim	5
37	Wigley Peter, George Caroline, Turner Susan	5

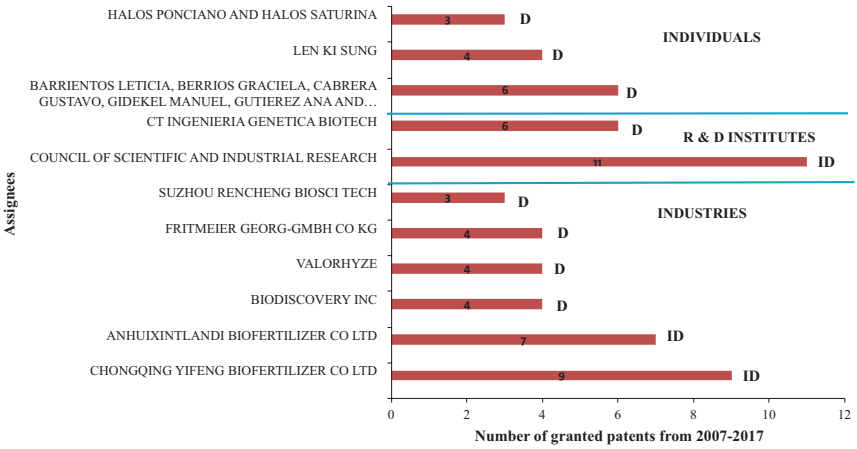

Fig. 11.5 Top patent assignees in the field of biofertilizers from 2007 to 2017. Industries, Individual and R & D Institutes were identified as the main assignees. In terms of dominance Industries was found to be the top assignee among the three. *D* stands for direct integration of biofertilizer technology while *ID* stands for indirect integration of biofertilizer technology

11.4.2 Current Technical Scenario of Patents Granted from 2007 to 2017

Out of 247 granted patents, 191 patents were found to be directly related to integration of biofertilizer technology while 56 showed indirect relationship. A detailed overview is provided in Table 11.3 where classification was performed on the basis of relationship to biofertilizers, biofertilizer type (composite/compound), novel

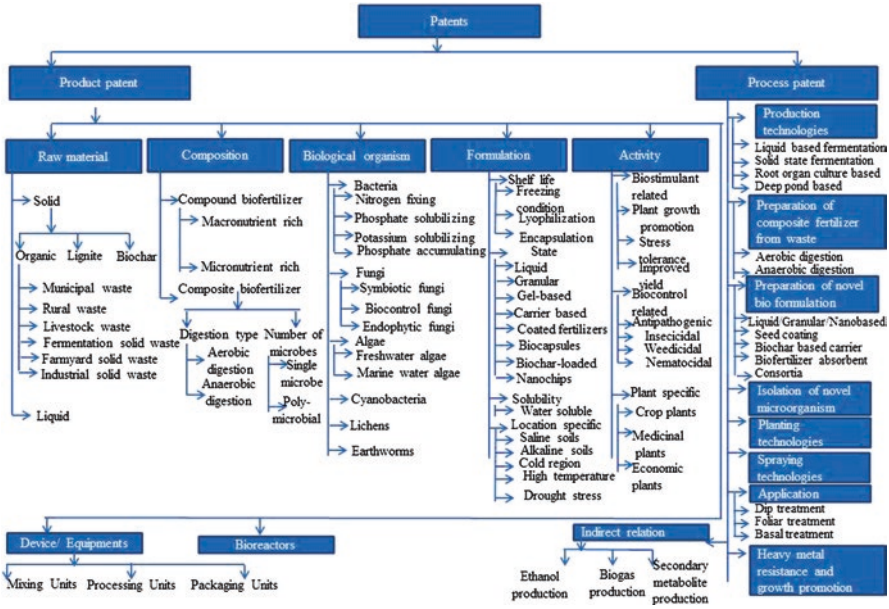

Fig. 11.6 Technical classification of key concepts. Patent families of biofertilizers from 2007 to 2017 were classified into two categories of product and process patent. Seven subclasses were found in product patents while process patent showed nine subclasses. Directly related concepts revolve around product or process that lead to development/isolation of biofertilizers, their bioformulations for better shelf life, activity and release or sites/plants specific activity. Indirectly linked concepts involved ethanol/secondary metabolite/biogas production

production technology, raw material used, microorganism and formulation development. Formulation development (38), novel production technologies (36) and utilization of organic waste (36) were recognized as the major technical categories among the granted patents. Other than, technical categories mentioned in the table patents have been also granted for isolation and development of novel species as in CN103275895B, RU2551968C2, KR101475260B1, and US9101144B2. Under indirect category, granted patents mainly focus on ethanol or oil production (for example, US8741628B2/EP2475776B1). Country-wise, China shares the highest percentage of granted patent and majority of its patents revolve around utilization of organic waste for development of biofertilizers. *Azospirillum brasilense*, *Bacillus amyloliquefaciens*, *Bacillus licheniformis*, *Bacillus subtilis*, *Pseudomonas fluorescens* and *Tsukamurella paurometabola* were found as dominant bacterial isolates in the granted patents.

Table 11.3 Technical classification of granted patents from 2007 to 2017 in the field of biofertilizers[a]

S. No	Record Number	Granted patent from 2007-2017	Technical category							
			Direct relation	Indirect relation	Composite fertilizer	Compound fertilizer	Production method/ technique	Organic waste	Microorganisms	Formulation
1	CN100349831 C	Green organic agricultural fertilizer and preparation method thereof	■			■				
2	UA27093U	Process for preparation of biofertilizer	■				■			
3	UA29997U	Process for preparation of biogas and biofertilizers from organic wastes	■					■		
4	KR100842449B1	*Pseudomonas sp.* CL-1 and method of solubilizing insoluble-phosphate by using the same	■						*Pseudomonas sp* CL -1	
5	CN100575315C	Active molecular composite biological fertilizer and production method	■			■				
6	UA46323U	Process for the preparation of biogas and biofertilizers from organic wastes	■					■		
7	RU88665U1	Technological line for producing biofertilizers based bird droppings		■						
8	AR066364A1	Biofertiliser composition	■						*Tsukamurella paurometabola*	
9	KR100908412B1	*Acinetobacter calcoaceticus* strains and microbial agent for the treatment of soil having the same	■						*Acinetobacter calcoaceticus* BYS-2	
10	CN1896036	Nutrient activated soil and its production	■			■	■			
11	UA54210U	Process for the preparation of biofertilizer	■							■
12	IN243311A1	A novel granular nutrient coated nitrogenous fertilizer and a method to produce the same	■							
13	CN101254999B	Preparation of belt seeding carrier by steam explosive-crushing straw solid-state fermentation		■			■			
14	CN101302124B	Multi-element biofertilizer	■		■			■		
15	CN101066899B	Organic biofertilizer prepared through closed anaerobic fermentation	■				■	■		
16	KR100938490B1	Method for preparing biofertilizer using palm oil mill wastage	■					■		
17	CN100579940C	Method for preparing biologic organic fertilizer for preventing and curing eelworm harm and use thereof	■							

18	US8029593B2	Biofertilizer for treatment to improve growth of turf grass and method of developing the biofertilizer	■					■	*Azospirillum brasilense*		
19	MA32636B1	Method for selectively extracting phosphorous from solids	■								
20	UA94301C2	Organic granulated complex biofertilizer	■								■
21	RU2415558C1	Method to increase reproduction factor of potato tubers	■								
22	RU2408563C1	Method of producing biohumus	■					■			
23	CN101372424 B	Method for preparing humic acid biofertilizer from lignite	■				■	■	*Phanerochaete chrysosporium CICC40719*		
24	KR101212047B1	Bacterial strain *Lactobacillus parakefiri* NAAS-1 promoting plant growth	■						*Lactobacillus parakefiri*		
25	RU2467989C2	Method of treating organic wastes	■					■			
26	RU2458894C2	Method of producing biofertiliser	■			■					
27	CN101100401B	Organic composite potassium fertilizer and its producing method	■				■				
28	CN101955903B	*Bacillus licheniformis* bacterial strain and application thereof	■						*Bacillus licheniformis*		
29	CN101691556B	Deep sea *Thalassospira* and application thereof	■						*Thalassospira* Q25-2		
30	CN101712933B	*Curvularia* bacterial strain and application thereof in preventing and weeding weeds		■					*Curvularia affinis* Boedijn		
31	CN101704688B	Method for producing solid biofertilizer from potato fermentation residue		■				■			
32	RU2445295C1	Method for biological processing of poultry droppings	■				■	■			
33	AT543908T	Method for selectively extracting phosphorous from solids	■				■				
34	EP2324118B1	Process for the isolation of phosphorus from solid material employing leaching and phosphate-accumulating microorganisms	■				■				
35	CN101704688B	Method for producing solid biofertilizer from potato fermentation residue		■				■			
36	HRP20130850T1	Biofertilizer formulation	■						*Pseudomonas antarctica* DaBact TI-9, *Pseudomonas trivialis* DaBact 2H and *Arthrobacter spp*. DaBact MII-9		■
37	CN102757277B	Paddy biofertilizer, preparation method thereof and *Bacillus subtilis*	■			■			*Bacillus subtilis*		
38	ES2427595T3	Biofertilizer formulation	■								
39	CN101973803B	High-efficiency multi-bacterial activity biogas residue biofertilizer and preparation method thereof	■			■					
40	DK2150610T3	Biofertilizer formulation	■								
41	UA83688U	Process for the preparation of biofertilizer "Vermimah"	■			■					
42	TWI409242B	Thermo-tolerant multiple-functional phosphate-solubilizing microbes and its biofertilizer preparation	■					■	C45 BCRC 910392 and *Bacillus smithii* F18 BCRC 910393		
43	RU2491264C2	Method for biological treatment of animal wastes	■					■	*Bacillus cereus* 10.09.63 DEP strain		■
44	RU2488997C1	Method of disposing cellulose-containing wastes	■					■			

(continued)

Table 11.3 (continued)

45	CN102079675B	Magnetic biofertilizer and preparation method	■	■						
46	CN102276304B	Biofertilizer for plantation of medicinal materials in Shaolin pharmacy and preparation process thereof	■	■						
47	EP2150610B1	Biofertilizer formulation	■	■				*Pseudomonas antarctica* DaBact TI-9, *Pseudomonas trivialis* DaBact 2H and *Arthrobacter* spp. DaBact MII-9	■	
48	US8455461B2	Compositions containing a synergic mixture of polyols and xyloglucanes as phytosanitary and biofertilising products	■	■						
49	PL213953B1	New strain of *Rhizobium leguminosarum* bv. *Viciae* GR09 used in production of a biofertilizer for papilionaceous plants and method for producing the biofertilizer	■	■				*Rhizobium leguminosarum* bv. Viciae GR09		
50	RU2481760C2	Method of plant cultivation	■	■				*Bacillus subtilis* of RNCIM B-10641, *Bacillus amyloliquefaciens* RNCIM B-10642 and *Bacillus amyloliquefaciens* RNCIM B-10643	■	
51	MY148649A	Fybosoil novel biofertilizers through the bioconversion of rice bran and palm oil trunk	■	■						
52	CN102344326B	Organic biofertilizer capable of inhibiting continuous cropping obstacle of flue-cured tobaccos	■	■			■			
53	NL2007663C	Method for recycling horticultural waste.	■	■			■			
54	SG188540A1	Integrated process for the production of oil bearing *Chlorella variabilis* for lipid extraction utilizing by-products of Jatropha methyl ester (jme) production								
55	RU2480438C2	Manufacturing line for processing of poultry manure	■				■			
56	US8415271B2	Biofertilizer formulation	■	■					■	
57	CN102173924B	Preparation method of special biofertilizer for tobaccos	■	■						
58	RU2477596C2	Method to stimulate growth and protect small-fruit crops against diseases caused by fungic pathogens	■	■				*Bacillus subtilis* VKPM B-10641, *Bacillus amyloliquefaciens* VLPM B-10642, *Bacillus licheniformis* VKPM B-10561 and *Bacillus licheniformis* VKPM B-10562		
59	RU125995U1	Technological line for obtaining different forms of biofertilizers from bird dung					■			
60	CN101880183B	Toosedarin biological fertilizer and preparation method thereof	■	■						
61	CN102391965B	Preparation method of biological agent for preventing and treating ginseng diseases	■	■						
62	CN101993305B	Composite microbial agent and production method thereof	■	■						

63	EP2225932B1	Method for enhancing market garden plant growth					
64	CN102295494 B	Melon-bean fermentation broth, fermentation fertilizer and its preparation method					
65	KR101475260B1	*Bacillus subtilis* JS strain promoting plant growth isolated from rhizosphere soil of Miscanthus and uses thereof				*Bacillus subtilis*	
66	TWI464260B	Novel isolated purple non-sulfur photosynthetic bacteria and use and screen method thereof					
67	CN103184184B	*Streptomyces albidoflavus* and applications thereof				*Streptomyces albidoflavus* 144	
68	CN103184162B	*Trichoderma asperellum* and applications thereof				Trichoderma asperellum	
69	MA35584B1	Liquid formulation of two *Azotobacter* strains which can be use as biofertilizer product				*Azotobacter*	
70	MA35583B1	Liquid formulation comprising two phosphorus-solubilizing *Pseudomonas fluorescens* lrl for use in agricultural fertilization				*Pseudomonas fluorescens*	
71	MA35582B1	Biofertilizer product based on *Bacillus megaterium* LR2 and *Bacillus mucilaginosus* LR5 which can be used for agricultural fertilization				*Bacillus megaterium* and *Bacillus mucilaginosus*	
72	MA35581B1	Method for the stable formulation of a biofertilizer product based on an atmospheric nitrogen fixative strain, *Azospirillum brasilense* LR11				Azospirillum brasilense LR11	
73	KR101456171B1	Plant growth promotion by using bacterial strains isolated from roots of *Miscanthus sacchariflorus*				*Tome Bacillus, Bacillus, Agrobacterium and La shinny Bacillus*	
74	AU2007355202B2	Stable organic-carrier-based microbial inoculants and method for producing the same				*Azospirillum spp*	
75	CN103275895B	A strain resistance and saline tolerance production of indole of acetic acid by *Bacillus laterosporus* and *Bacillus subtilis* and its application				*Bacillus laterosporus* and *Bacillus subtilis*	
76	US8852312B2	System and method for biological treatment of biodegradable waste including biodegradable municipal solid waste					
77	RU2529174C1	Method of composting post-harvest crop residues					
78	US8834853B2	Coated dehydrated microorganisms with enhanced stability and viability					
79	CN102775233B	Novel insecticidal and antibacterial biofertilizer and preparation method thereof					
80	US8822190B2	Polymicrobial formulations for enhancing plant productivity					
81	CN103361277B	*Galactomyces geotrichum* P14, application method thereof, and microbial inoculum prepared from same					
82	EP2618664B1	Use of single amino acids at low concentrations for influencing the life processes of crops					
83	CA2684617C	Biofertilizer formulation					
84	AU2009281133B2	Method for extracting phosphorous from solids using active leaching and phosphate-accumulating microorganisms					
85	CN102633565B	Method for producing tobacco biofertilizer by utilizing rape seed					

(continued)

Table 11.3 (continued)

		cake										
86	CN102633544B	Method for taking farmyard manure as raw material to produce tobacco biofertilizer										
87	US8741628B2	Integrated process for the production of oil bearing *Chlorella variabilis* for lipid extraction utilizing by-products of Jatropha methyl ester (JME) production										
88	CN102701828B	Chelated trace element organic fertilizer and production method thereof										
89	KR101394668B1	Bacteria strain having arsenic-resistance and promoting plant growth isolated from heavy metal-contaminated soil and uses thereof									*Pseudomonas JS128* strain *Pseudomonas draw* Monti and *Terry's borane*	
90	CN103073361B	Special controlled-release fertilizer for field crops, and its preparation method										
91	CN102311925B	Endophytic fungi *Chaetomium globosum* strain, microbial agent and application thereof									*Chaetomium globosum*	
92	RU2512277C1	Method of obtaining biomineral fertilisers and meliorants										
93	RU2511299C2	Method of improvement of symbiotic activity of leguminose grasses										
94	US8691551B1	Method for recovering phosphorus from organic materials										
95	KR101377874B1	Novel *Bacillus aryabhattai* LKS28 comprising solubility upon insoluble salts.									*Bacillus aryabhattai* LKS28	
96	KR101377852B1	Novel *Weissella koreensis* LKS42 comprising solubility upon insoluble salts and antifungal activity.									*Weissella koreensis* LKS42	
97	KR101377800B1	Novel *Lactococcus lactis* subsp. Lactis LKS49 comprising solubility upon insoluble salts and antifungal activity.									*Lactococcus lactis* subsp. lactis LKS49	
98	KR101377781B1	Novel *Weissella kimchii* LKS2 comprising solubility upon insoluble salts and antifungal activity.									*Weissella kimchii* LKS2	
99	AU2008242441B2	Biofertilizer formulation										
100	CN103131657B	*Bacillus subtilis*, biological prevention and control preparation thereof and application of biological prevention and control preparation									*Bacillus subtilis*	
101	CN102875203B	Biofertilizer with function of protection and use method of biofertilizer										
102	CN102701842B	Biofertilizer capable of decomposing insoluble phosphorus and preparation method										
103	CN102674913B	Organic fluid fertilizer and preparation method										
104	MY150765A	Method for preparing biofertilizer using palm oil mill wastage										
105	CN102701869B	Crop straw leach liquor for improving fertilizer efficiency of mycorrhizal fungi fertilizer and preparation method of crop straw leach liquor										
106	AU2008306812B2	Compositions containing a synergic mixture of polyols and xyloglucanes as phytosanitary and biofertilising products										

107	US8642325B1	Advanced photobioreactor deep pond system		■			■		
108	TWI424979B	Thermo-tolerant multi-functional phosphate- and potassium-solubilizing microbes and its biofertilizer preparations	■					*Bacillus licheniformis* A3 BCRC 910522 and *Bacillus subtilis* H8 BCRC 910523	
109	CN102597251B	A process for integrated production of ethanol and seaweed sap from *Kappaphycus alvarezii*		■					
110	AU2013101180A4	Carbon Smart BioFertiliser	■						
111	KR1020140028777	*Bacillus subtilis* js strain promoting plant growth isolated from rhizosphere soil of *Miscanthus* and use thereof	■					*Bacillus subtilis* JS	
112	KR1020150021672	Composition for improving antioxidant activity or growth of plant comprising lacquer tree extract as effective component	■						
113	CN103483073A	Special compound microorganism bacterial fertilizer for peanuts and production method thereof	■		■				
114	CN103695321	Microbe, application of microbe in biofertilizer preparation, biofertilizer and application of biofertilizer	■			■			■
115	CN103951522 B	The method of preparation of special fertilizer Tian Qing	■		■	■			
116	CN102531761B	Humic acid biofertilizer and its preparation method	■			■			
117	US8932383B2	Compositions and methods of making and using the compositions for improving soil and/or plant growth and improved soil, improved plants, and/or improved seeds	■						■
118	US8932382B2	Process of producing bioorgano-phosphate (BOP) fertilizer through continuous solubilization of rock phosphate by a composting bioprocess and bioaugmentation with phosphorus solubilizing microorganisms	■						
119	RU2539781C1	Method of production of biofertiliser	■						
120	CA2685100C	Use of *Tsukamurella paurometabola* to stimulate plant growth	■			■		*Tsukamurella paurometabola*	
121	CN101720312B	Biofertiliser composition	■						
122	RU2542115C1	Method of production of biofertiliser	■			■			
123	US8969056B2	Process for integrated production of ethanol and seaweed sap from *Kappaphycus alverezii*		■					
124	US8993482B2	Process to make pelletized granules based on endomycorrhizal fungi covered with minerals clays and their composition	■						■
125	CA2845408C	Phosphate solubilizing rhizobacteria *Bacillus firmus* as biofertilizer to increase canola yield	■					*Bacillus firmus*	
126	CN103282483B	Integrated process for the production of oil bearing chlorella variabilis for lipid extraction utilizing by-products of jatropha methyl ester (jme) production		■					
127	CN103387427B	Method for manufacture of biofertilizer by pleuromutilin bacterial residue harmless treatment	■			■			
128	RU2551968C2	*Bacillus pumilus* A 1.5 bacteria strain as agent for increasing plant productivity and plant protection from diseases caused by	■			■		*Bacillus pumilus* A 1.5	

(continued)

Table 11.3 (continued)

		phytopathogenic microorganisms									
129	CN103058772B	Preparation method for high-activity humic acid biofertilizer									
130	JP5746029B2	Method for selectively recovering phosphorus from solid									
131	EG27124A	Minimizing consumption of mineral nitrogen and phosphate fertilizers through applying boron, non-symiotic nitrogen and phosphate solublizing biofertilizers to organic substance and rock phosphate									
132	MD4359B1	Nutrient medium for cultivation of alga *Anabaenopsis* sp.									
133	KR101537806B1	Composition for controlling pathogen or improving resistance to pathogen in plant comprising Lacquer tree extract as effective component									
134	EP2154121B1	Biofertiliser composition								*Tsukamurella paurometabola*	
135	US9096836B2	Liquid microorganism consortia formulation									
136	US9101144B2	Plant growth promoting rhizobacterium								*Pseudomonas fluorescens* strain GM30	
137	CN103301199B	Chinese toon tender leaf comprehensive utilization method of									
138	CN103204717B	Using fungus xing bao the leftovers of producing organic fertilizer method of									
139	IN267958A1	A nanomaterial based culture medium for microbial growth enhancement									
140	US9113605B2	Methods and compositions to aggregate algae									
141	KR101546757B1	Composition for improving antioxidant activity or growth of plant comprising Lacquer tree extract as effective component									
142	JP5769715B2	*Kappaphycus alvarezii* (carrageenan original algae) ethanol and seaweed sap of integrated production process that was extracted from									
143	RU2562526C2	Method of biotechnological processing solid wastes of pulp and paper industry for obtaining biohumus, comprising step of processing with fungi and step of vermi-processing									
144	IN268863A1	A method for treatment of biodegradable municipal solid waste									
145	CN103011965B	This utility model claims a *Polygonum multiflorum* biological fertilizer and its preparation method and application									
146	US9150851B2	Accelerated directed evolution of microbial consortia for the development of desirable plant phenotypic traits									
147	US9150461B2	Bioorganic agent for treating plants (variants)									
148	EP2464721B1	Coated dehydrated microorganisms with enhanced stability and viability									
149	CN104016787B	Flower nutritive soil									
150	KR101563349B1	Microorganism mixture of arbuscular mycorrhizal fungi and *Massilia* sp. Rk4 promoting plant growth under salt stress condition and uses thereof									
151	EP2475776B1	A process for integrated production of ethanol and seawood sap from *Kappaphycus alvarezii*									

152	PT2154121E	Biofertiliser composition	
153	US9187381B1	Composition and method for formulating a biofertilizer and biopesticide	
154	MD4385B1	Nutrient medium for cultivation of *Nostoc flagelliforme* alga	
155	CN103626578B	With corn straw fermentation producing poly-basic microbe fertilizer and preparation method thereof	
156	KR101575666B1	*Pseudomonas vancouverensis* ob155 strain promoting plant growth at low temperature and uses thereof	*Pseudomonas vancouverensis* OB155
157	CN104003817B	A corn special antivirus compound microbial fertilizer and preparation method thereof	
158	US9809503B1	Method for formulating a biofertilizer and biopesticide	*Paenibacillus polymyxa M10, Azospirillum canadense B2, and Bacillus pumilus L13*
159	RU2629776C1	Method for obtaining compost suppressive with respect to *Fusarium oxysporum* pathogene of plant fusarium wilt	
160	EP2479253B1	Antagonistic bacteria for preventing and treating panama wilt disease of continuously planted banana and microorganism organic fertilizer thereof	
161	RU2628411C2	Microbial inoculants and fertilisers composition containing them	*Lactobacillus parafarraginis*, *Lactobacillus buchneri*, *Lactobacillus rapi* and *Lactobacillus zeae*
162	US9732336B2	Accelerated directed evolution of microbial consortia for the development of desirable plant phenotypic traits	
163	US9713333B2	Product and method for managing Ganoderma disease in oil palm	
164	RU2625977C1	*Bacillus amyloliquefaciens* ops-32 bacteria stain for the production of complete biopreparate for protection of agricultural plants from phytopathogenic mushrooms, stimulation of their growth and increase in yield	*Bacillus amyloliquefaciens* OPS-32
165	KR101756682B1	*Cedecea lapagei* strain having nitrogen fixation activity microbial agent containing the same and biofertilizer containing the same	
166	CN104204211B	Nitrogen fixation recombinant microorganisms and use thereof	
167	RO129229B1	Process for preparing an organic biofertilizer and product prepared thereby	
168	US9687000B2	Plant growth-promoting microbes and uses therefor	
169	US9681667B2	Process to make pelletized granules based on endomycorrhizal fungi covered with minerals clays and their composition	
170	JP6139544B2	Microbial inoculant and fertilizer composition containing it	
171	RU2620298C1	Method of obtaining biodegritation from bird litter	
172	AU2013346743B2	Composition for dip treatment of plant roots	
173	US9643895B2	Nutrient rich compositions	
174	RU2617693C1	Method for product manufacture from production and consumption waste, and product made from production and consumption waste	

(continued)

Table 11.3 (continued)

		(versions)								
175	RU2617345C1	Complex fertiliser							*Bacillus megaterium* VKM B-396, *Bacillus subtilis* VKPM B-5328, *Bacillus amyloliquefaciens*	
176	US9622484B2	Microbial compositions and methods of use for benefiting plant growth and treating plant disease							*Bacillus amyloliquefaciens* RTI301 and *Bacillus subtilis* RTI477	
177	US9617190B2	Bioactive nutrient fortified fertilizers and related methods								
178	US9615584B2	Polymicrobial formulations for enhancing plant productivity								
179	CY1116864T1	Biofertiliser composition							*Tsukamurella paurometabola*	
180	WO2017042833A1	Biofertilizer composition							*Tsukamurella paurometabola*	
181	US9565859B2	Compositions and methods for use of insecticide with *Bacillus* sp. D747							*Bacillus* sp. D747	
182	RU2610309C2	Method for extending shelf life of biofertilizer based on nodule bacteria								
183	RU2606912C2	Method of producing granular bioorganomineral fertilisers								
184	CN205761577U	Screening equipment is smashed to fertilizer								
185	RU2603748C2	Method for production of fatty acids methyl ester suitable for use in engine								
186	RU2603584C2	Method of protecting a root system of woody plants for biological reclamation								
187	RU2603281C1	Phosphate-dissolving strain *Pseudomonas chlororaphis* ssp *chlororaphis* Vsk-26a3, with fungicidal and bactericidal activity							*Pseudomonas chlororaphis* ssp *chlororaphis* Vsk-26a3	
188	US9499784B2	Process for production of microalgae, cyanobacteria and metabolites thereof including lipids and carbohydrates								
189	US9499447B2	Stable organic-carrier-based microbial inoculants and cultures							*Azospirillum* spp	
190	CN205603216U	Be used for vitriolic dilutent equipment								
191	US9439440B2	Biofertilizers and bioherbicides								
192	CN205561470U	Novel bio -feritlizer is dried device								
193	CN205556495U	Bioferitlizer granulator								
194	CN205550217U	Spiral granular fertilizer make -up machine								
195	BRPI0901482B1	Of biofertilizers fertilizer production process with a high concentration of carbon using physical and biological processes								
196	US9428425B2	Methods and compositions for treating soil and plants								
197	AU2012210354B2	Process for production of microalgae, cyanobacteria and metabolites thereof								
198	CN103936516B	Is used for preparing biological foliage fertilizer and preparation method thereof								
199	CN103951475B	Rich in selenium to resist disease and insect compound fertilizer								
200	US9416062B2	Nutrient rich compositions								
201	US9402378B2	Mini space farm-A food regenerative system in the long-term space mission								

202	CN205398492U	Little bioorganic fertilizer dewatering equipment						
203	CN205392654U	Dead fertilizer rubbing crusher of anti -sticking						
204	CN205392344U	Bio -fertilizer processing equipment						
205	CN205392229U	High -speed agitating unit of bio -fertilizer						
206	DE102009051901B4	Use of a mixture of substances as biofertilizers and for soil improvement, a method for the production of the mixture of						
207	CN205383876U	Biofertilizer stoving control structure						
208	CN205380801U	A device for retrieving plastics in fertilizer raw material						
209	CN205379824U	Granular fertilizer mixing arrangement						
210	CN205366126U	Biofertilizer automatic title material packaging machine construct						
211	CN205366125U	Bio -fertilizer ration packing plant						
212	CN205366117U	Sealed bio -fertilizer packaging structure						
213	CN205357521U	The roots of plants fertilizer liquid fertilizer applicator						
214	CN205357520U	The roots of plants solid fertilizer fertilizer applicator						
215	CN205357097U	Fertilizer liquid fertilizer applicator						
216	CN103992159B	An all-membered complex microbial fertilizer and preparation method and application						*Bacillus amyloliquefaciens* *Bacillus amyloliquefaciens* SQR-9
217	CN103910570B	A vegetable by using biologic fertilizer and preparation method thereof						
218	MD4385C1	Nutrient medium for cultivation of *Nostoc flagelliforme* alga						
219	JP5940540B2	Jatropha (jatropha) using methyl ester (JME) Preparation of by-products, for lipid extraction, integrated process for the production of *Chlorella variabilis* containing oil (*Chlorellavariabilis*)						
220	US9365847B2	Accelerated directed evolution of microbial consortia for the development of desirable plant phenotypic traits						
221	US9365461B2	Integrated processes for producing fuels and biofertilizers from biomass and products produced						
222	AU2012352161B2	Plant growth-promoting microbes and uses therefor						
223	CN103626543B	Compound micro-organism fertilizer and preparation method thereof						
224	AU2011306356B2	Integrated process for the production of oil bearing *Chlorella variabilis* for lipid extraction utilizing by-products of Jatropha methyl ester (JME) production						
225	US9321697B2	Recombinant nitrogen fixing microorganism and uses thereof						
226	EP2619303B1	Integrated process for the production of oil-bearing *Chlorella variabilis* for lipid extraction utilizing by-products of jatropha methyl ester (jme) production						
227	CN103880482B	A crop organic fertilizer preparation method of						
228	RU2580365C1	Method of producing biological fertiliser						
229	RU2579254C1	Method of producing biological fertiliser						
230	CN104130076B	A pest-proof leaf vegetables special biologic fertilizer and preparation method thereof						

(continued)

Table 11.3 (continued)

231	IN272255A1	Stable organic-carrier-based microbial inoculants and method for producing the same	■									■
232	CN103848651B	A bonding rhodotorula of the biological fertilizer and its preparation method and application	■				■					
233	CN103920706B	An immobilized mixed microbes repairing agent rare earth polluted soil the invention claims a method for	■									■
234	CN103739323B	Method for preparing a compound biological fertilizer	■		■					*Aspergillus niger, Bacillus megaterium, Bacillus subtilis*		
235	US9279139B2	Media comprising a glutamine biosensor and methods of use thereof		■								
236	MD4359C1	Nutrient medium for cultivation of alga *Anabaenopsis* sp.	■				■					
237	RO128587B1	Mulberry tree - morus spp. Vitro plantules inoculated with endomycorrhizae of the vesicular-arbuscular type intended for cultivating lead-contaminated soils and process for obtaining the same	■									
238	CN103553814B	A method for using multiple fermentation preparing nanometer controlled release fertilizer and preparation method thereof	■				■					■
239	US9260713B2	Accelerated directed evolution of microbial consortia for the development of desirable plant phenotypic traits	■									
240	CN103449917B	Mycorrhizal this utility model claims a biological fertilizer and preparation method thereof	■									
241	BRMU8703068Y1	Provision introduced device for capturing gases from treatment of various effluents		■								
242	ES2557317T3	A process for integrated production of ethanol and seaweed sap from *Kappaphycus alvarezii*		■								
243	CN103773716B	A high-efficient compound biological fertilizer				■						
244	CA2764253C	Bioorganic preparation for processing plants (variants)	■		■							
245	AU2012321092B2	Microbial inoculants and fertilizer compositions comprising the same	■		■							
246	US9234139B2	Diesel fuel production process employing direct and indirect coal liquefaction		■								
247	US09403729	Composition and method for pelletized compost	■									

[a]Grey colour in a box of each category denotes its presence for a particular record

11.5 Innovation Trends in the Past 11 Years

In general, it can be concluded that innovation trend in the field of biofertilizers from 2007 to 2017 includes:

- Prospection of novel/better bioresources for utilization in biofertilizer industry
- Conversion of organic waste to biofertilizers
- Technologies/products that have better shelf life or controlled release
- Development/application of biological resources for location-/ plant-/stress-specific fertilization activities
- Application methodologies for improved activity of biofertilizers
- On devices/equipments that can ease/improve their production at large scale.

11.6 Conclusion and Future Perspective

Patent dataset developed and analysed in the present study have revealed that biofertilizer industry is in its booming state and this state will continue to multiply in the years to come to support sustainable agriculture. Future leads for innovations in biofertilizer industry are:

- Bioprospection of
  - Novel microbial isolates for nutrient fixation, solubilisation or mobilization properties
  - Isolates that can convert non-arable land to arable land
  - Algal resources for production of compounds having fertilization properties.
- Development of next generation biofertilizers
  - Formulations that have better shelf life
  - Formulations for slow and controlled release of biofertilizers
  - Nano-based formulations.
- Efficient delivery technologies for biofertilizers application.
- Development of valuable bye-products in addition to biofertilizer production.
- Utilization and conversion of inorganic waste material to biofertilizer.
- Technologies that can reduce cost of biofertilizer production at large scale.

Acknowledgements We sincerely thank Director General, The Energy and Resources Institute (TERI), New Delhi, India, for the infrastructure and financial support. We also thank GridLogics Technologies Pvt. Ltd., Pune, India for providing free online access of Pat-Seer for 10 days. We also thank Dr. Reena Singh for helpful discussions on former versions and the structure of the manuscript.

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Entomopathogenic Fungi in IP Landscape

12

Laith Khalil Tawfeeq Al-Ani

Abstract

Entomopathogenic fungi are very effective, ecofriendly alternative to the chemical pesticides for the biocontrol of pests and pathogens. Therefore, the focus on entomopathogenic fungi is back for having the high potential in control of insects. Entomopathogenic fungi are exposed to the loss in capabilities or trait in attacking and killing the host insects. This is relevant to several factors that lead changes to occur in the ability to control the insects. This chapter explores the recent research trends of entomopathogenic fungi in intellectual property landscape. The inventors worked on recent patents as follows: (1) finding a new strain, or isolate, or new species, (2) enhancement of the sporulation, (3) improvement of the formulation, (4) new productions, and (5) new methods using the entomopathogenic fungi against insects, as well as using them in the biotechnology by utilizing the secondary compounds and enzymes. The patents were detected in many new strains of *Beauveria* spp. and *Metarhizium* spp., with some new species such as *Isaria javanica*, *I. fumosorosea*, and *Nomuraea rileyi*. Chitosan can increase the sporulation of *B. bassiana* and find a special media that enhance the sporulation. Also, new formulations and products have been detected by inventors. Additionally, the patents have shown many new methods which are very efficient in controlling insects and have potential use in biotechnology. The patents in the field of entomopathogenic fungi are very important to save the dynamics of biopesticides in reducing or killing the insects to be near the level of controlling the insects by using chemical pesticides. In conclusion, the increase in efficacy of entomopathogenic fungi and production of biopesticides at low cost through the inventors leads to the reduction in using the chemical pesticides.

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H. B. Singh et al. (eds.), *Intellectual Property Issues in Microbiology*,
https://doi.org/10.1007/978-981-13-7466-1_12

Keywords
Entomopathogenic fungi · Microbial formulations · Bioinsecticides · Biological control

12.1 Introduction

In recent years, there is a rising interest in the reduction of using chemical pesticides. The chemical pesticides are very dangerous on the ecosystem, but it is very efficient in controlling pests. This calls to find the alternative methods and arrive to the level of the chemical method or near it. There are some alternative methods, but the best method is biological control agents. Biological control utilizes the microbes (entomopathogen) that attack the insect and cause several diseases to insect. Many entomopathogens can infect the insect including viruses, bacteria, fungi, and nematode. Entomopathogenic fungi are very great pathogen to use for plant protection instead of insecticides to save the ecosystem.

Entomopathogenic fungi are comprised of several fungi that attack insects, but most of these fungi are *Zygomycota* and *Ascomycota*. Most of the fungi are used in the biocontrol of insects including many species and order such as *Hirsutella thompsonii*, *Beauveria* spp., *Verticillium lecanii* (Hasan et al. 2013), *Metarhizium*, and the *Entomophthorales*. Also, some species of *Fusarium*, *Penicillium*, and *Alternaria* are pathogenic for insects. *Fusarium proliferatum* m2 are isolated (Malaysian isolates, GenBank: KP057226.1) from mosquitoes in Malaysia and can be entomopathogenic for insects (the result not publish yet). *F. oxysporum* attacks the larvae of the mosquito *Aedes detritus* and causes 80% of mortality in the laboratory (Hasan and Vago 1972). *F. solani* and *Penicillium* that produced some secondary metabolites are insecticidal (Claydon 1978; Paterson et al.1987). *Fusarium solani* and *Trichoderma harzianum* are entomopathogenic fungi and cause higher mortality for cockroaches (Abdul-Wahid and Elbanna 2012). *F. proliferatum* and *B. bassiana* used to control the adult of wheat flour insect *Tribolium confusum* (Al-Ani et al. 2018). *Trichoderma* spp. and *B. bassiana* can enhance the crop protection against insect and diseases (Pus 2017). *Aspergillus* sp. is a pathogen for *Scolytus amygdali* Geurin-Meneville (almond bark beetle) and causes 100% mortality in 24 h for larvae (Zeiri et al. 2014). The spores of entomopathogenic fungi attacks the insects starting with the adhesion of the conidia, followed by conidial germination, creation of the appressorium, cuticular penetration, hyphal growth with invasion of the tissue of the host, secretion of various hydrolytic enzymes and secondary metabolites, and finally death.

12.2 Recent Patents

For the recent patent, the inventors are working on the discovery of entomopathogenic fungi that have higher effect on insect and using the biotechnology to prepare very effective bioinsecticides as an alternative to chemical insecticides. The patents include the discovery of (A) finding a new strain, or isolate, or new species, (B) enhancement of the sporulation, (C) improvement of the formulation, (D) new products, and finally (E) new method to use the entomopathogenic fungi against insects as follows:

(A) **New species or isolates or strains**

Hard conditions like drought and rise of the temperature degree, host, competition on place, etc. are leading to create a new isolate or strain of entomopathogenic fungi that may possibly differ in pathogenicity. The inventors try to find a new isolate or strain and new entomopathogenic fungi that are more aggressive against insects. Cao et al. (2009) detected *Metarhizium anisopliae* var. *dcjhyium* Lj01 (CCTCC No. M206077, GenBank accession number: DQ288247). The inventors identified a new variant depending on some characteristics such as the morphologic, molecular biologic, physiologic, and biochemical analysis. The isolate is very efficient to be used in biopesticide product. *M. anisopliae* var. *dcjhyium* Lj01 has high toxicity that affects termite *Odontotermes formesanus* Shiraki and has the ability to cause 100% mortality after 3 days (Cao et al. 2009). *Nomuraea rileyi* is a species of entomopathogenic fungi that can enter into the composition of insecticides (Ford 2010, 2011). A new agent of entomopathogenic fungi *Nomuraea rileyi* is isolated from larvae of *Spodoptera exigua* (beet armyworm) (Sub et al. 2011). A new strain of *Beauveria bassiana* is an aggressive strain against larvae of *Iraella luteipes* and protects the poppy plant (*Papaver somniferum*) systemically (Ledesma et al. 2012). A novel strain of *Beauveria bassiana* M130 (KCTC12104BP) is detected and able to be a biological control agent against the whitefly insect (Gi et al. 2013, 2016, 2017). A new entomopathogenic fungi is *Isaria javanica* Pf04(Joon et al. 2013), and new strain of *B. bassiana*m130 (Gi et al. 2013) that isolated from the *Bemisia tabaci* and used to control it (Joon et al. 2013; Gi et al. 2013).The entomopathogenic fungus *Isaria fumosorosea* CCM 8367 is a new strain that is used against pupae of *Cameraria ohridella* (Prenerova et al. 2013). *Metarhizium* sp. (accession number V15/001452.) is an isolate that can be used as insecticide to control the cotton pests (Mensah 2017). Amazingly, they have isolated two strains of entomopathogenic fungi *B. bassiana* and *B. brongniartii* from diseased insects and use it against the house dust mites in various concentrations (Harper 2017).

(B) **Enhancement of the sporulation**

Entomopathogenic fungi as natural organism are used to control the pests in the environment. Entomopathogenic fungi as biocontrol agent must use a special medium that increases the sporulation (Keswani et al. 2013; Singh et al. 2014). The

natural enemies of entomopathogenic fungi *Nomuraea rileyi* can enhance the germination through an active ingredient D-erythro-C14-sphingosine and help to control several insects that consist of Coleoptera, Lepidoptera, Hemiptera, and Orthoptera (Onoet al. 2013). Therefore, Agullo et al. (2009) and Palma et al. (2016) added 1 mg/ml of the chitosan concentration to the Corn Meal Agar (CMA) for entomopathogenic fungi *Beauveria bassiana* that caused the increase in production of conidia. Conversely, the preconidial or mycelium of *Metarhizium* and *Beauveria* is very efficient for attracting and killing the insects and arthropods that carry contagions and disease (Stamets 2012, 2016a). The wood, grain, agricultural wastes, or other cellulosic material and extracts were used to cultivate the entomopathogenic fungi and enhance the preconidial growth (Keswani et al. 2016; Stamets 2009, 2011, 2013a, b, 2016a). The conidia, mycelium, and microsclerotia affiliated two strains of entomopathogenic fungi that are selected from *Metarhizium robertsii* and *M. anisopliae*, and this composition reduced overall damage to insects (Bruck et al. 2017a,b). The increase in sporulation of entomopathogenic fungi is useful to enhance the virulence against pests that augment the insect mortality and efficiency of biopesticides.

(C) **Improvement of the formulation**

Entomopathogenic fungi are needed to the special formulation that enhances the biocontrol efficacy and increases the proportion of death in the pests. The formulation of entomopathogenic fungi must be suitable to use in tropical and subtropical environment. The formulation suspended for *Metarhizium anisopliae* in oil in water emulsions (containing the fatty acid salts, polyhydric alcohols, and additional emulsifiers) was used to control tick on cows (Maor et al. 2008, 2010). Another formulation consists of one or more entomopathogenic fungi (genera *Beauveria*, *Metarhizium*, *Paecilomyces*, *Verticillium*, and *Nomuraea*) by making a mixture of the culture mass according to biphasic solid-state fermentation; finally, it get on a dry powder as tablet form that contains about 20% conidia (Divi et al. 2009). The special formulation was prepared as natural pesticide that consists of two mixtures, (1) entomopathogenic fungi blend of *Beauveria bassiana* strains and (2) botanical products (two oil mixes of garlic and chili) (Benavides and Góngora 2014). The blended formulation of (1) and (2) has high efficacy in killing several insects such as coffee berry borer (*Hypothenemus hampei*) in coffee plants and other insects in fields of corn plants (Benavides and Góngora 2014). The enaminocarbonyl compound (Formula I) is commingled with one entomopathogenic fungus *Metarhizium anisopliae* (or other entomopathogenic) beneficial to boost the efficacy of biopesticides and control pests and plant pathogens (Jeschke and Hungenberg 2014). While the selection of one from the groups consisted of entomopathogenic fungi (*Metarhizium anisopliae* FI-1045, *M. anisopliae* var. *acridum* IMI 330189, *M. anisopliae* var. *acridum* FI-985, and *Beauveria bassiana* PPRI 5339), with one pesticide (as active components) of insecticide or compound of plant growth regulating or fungicide, this creates the special pesticide for making a synergistic mixtures to improve the procedure to control the pests and plant pathogens and in addition to

enhance plant growth (Brahm et al. 2014). Some patent is mixed between two biological agents (A) and (B) to prepare a mixture of pesticides that help for the biocontrol of pests and phytopathogens; they consist of biological control agents (A), one of the group that includes *Paecilomyces lilacinus* strain 251 and *Coniothyrium minitans* CON/M/91-08 and/or a mutant of these strains, and (B), one of the groups that is comprised of viruses, entomopathogenic nematodes, and protozoans (Andersch et al. 2014).

On the other hand, the conidia of entomopathogenic fungi such as *B. bassiana* can be mixed with carriers like starch and xanthan gum to get solid wettable formulations through dry compaction (Miron and Ivanova 2015). The mixture of 1% entomopathogenic fungi (*M. anisopliae* with *B. bassiana*) was mixed with two surfactant materials such as 10% cellulase and adds 89% surfactant of anionic organophosphate that is making a synergetic pesticide for control of different pests (Pascual 2015a). Prolonging the viability of spores from *Purpureocillium lilacinum* is in liquid formulations to reduce the exposure to oxygen (Wiese et al.2016). *B. bassiana* (JEF007) is succeeded in protecting the rice crops from the vermin (Soo et al. 2016; Gimjaesu et al. 2016). The spray formulations can be prepared from the oilseed rapes, then mixed with *B. bassiana*, and used against the pests and plant pathogens of crop plants (Patel et al. 2016). By mixing neem oil and *B. bassiana*, its biocontrol efficacy against insects like whiteflies increases, thereby preventing the eggs from hatching (eclosion), and ultimately protecting the plants from insect feeding (Mazariegos 2016a).

(D) **New productions**

Entomopathogenic fungi need to be prepared as biopesticides, which survive for a long time and attack pests. This leads us to protect the plants from pests for the existence of the biological control agents in the active state. On the other hand, reducing the use of synthetic chemicals in pesticide composition leads to the increase in insect resistance for chemical pesticides. The natural compounds can be used in the production of pesticides.

A composition of insecticide is in the effective state against a wide range of insects, specially soil-dwelling insects that produce the amount of dried microsclerotia of *B. bassiana*, *Metarhizium* spp. (such as *Metarhizium flavoviride*, *M. anisopliae*), and *Lecanicillium* species (Jackson and Jaronski 2009a,b, 2010, 2011, 2014, 2016).The capability to enhance the efficacy of biopesticide production may be through doing formulation from the oil- and carnauba wax-based spore of *B. bassiana* isolate (IMI 398548) which caused high mortality after 28 days after tests on three species of pests (Storm et al. 2011a, 2015). A combination of entomopathogenic fungus *Nomuraea rileyi* and a chitin synthesis inhibitor (CSI) is a product of pesticides used in a method of protecting or treating pest infestation in plant or environment around plant (Applebaum et al. 2011). Some products of biopesticides focus to genetically modify some strains of entomopathogenic fungi *B. bassiana* and *M. anisopliae* to improve the virulence through expression chitinase gene signal peptide (Keyhani and Fan 2013). The crashes of palm seeds (species *Phoenix*

dactylifera) and blend with *B. bassiana* produced biopesticides as phytosanitary composition, and this product can reduce the populations of the red palm weevil (*Rhynchophorus ferrugineus*), both adults and caterpillars (Asensio et al. 2008, 2014; Berbecal et al. 2010). For controlling the water insects, we used strain of *M. anisopliae* CQMa421 to manufacture a new product of biopesticides in the wettable powder formulation for controlling the rice water weevil (*Lissorhoptrus oryzophilus* Kuschel) in China (Toes and Pengokuo 2015). This product has many advantages such as very efficacy against *Lissorhoptrus oryzophilus*, and very good for wettability, UV resistant, and storage (Toes and Pengokuo 2015). Interestingly, some species of entomopathogenic fungi as *B. bassiana* was extracted as lipids and used as insecticidal agents (Ford and Glare 2014; Ford et al. 2014, 2015). While the botanical pyrethrum extract is to use in mixing with *B. bassiana* BbGA strain 1991 and add the adjuvants to manufacture a special product of pesticide (Mazariegos 2016b). Amazingly, the spore, preconidial, and hyphae, as well as extract of mycelium for entomopathogenic fungi (*M. anisopliae*, *Aspergillus flavus*, and *B. bassiana*), can be used as natural miticides through blending them with some natural chemicals comprising neem extracts, oxalic acid, formic acid, and lactic acid for controlling the *Varroa* mites of bees (Stamets 2016b). The preparation of blastospores of two entomopathogenic fungi as *Isaria fumosorosea* (formerly *Paecilomyces fumosoroseus*) and *B. bassiana* was culturing it in a liquid medium (containing a carbon and a nitrogen source) to increase the tolerance for desiccation and enhance the control on the soft-bodied insect (Jackson and Gabriel 2016a, b). The changes in environmental conditions such as the rising of temperatures and humidity may affect the efficacy of biopesticides against pests.

The special mixture of a spore powder of novel strain for entomopathogenic fungi *Beauveria* sp. (DBB2507) and olive oils is enhancing the efficacy of biopesticides in biocontrol of the pests and increasing the thermal tolerance in both the spores and enzymes that are produced by a novel strain (Kim et al. 2008). The mixture of *B. bassiana* and endogenous *Bacillus* is able to enhance the plant resistance against stem eelworm, rotting resistance, lodging resistance, yellowing resistance, and integrates of insect (Huailiang et al. 2013). The new bioinsecticide product of entomopathogenic fungus *Metarhizium anisopliae* CQMa421 strain is very effective against striped flea beetle (*Phyllotreta striolata*) or diamondback moth (*Plutella xylostella*), and this new bioinsecticide is consisting of dry conidial powder of *M. anisopliae*, nano-aluminum trihydrate, Tween80, OP10, kieselguhr, and sodium carboxymethylcellulose (Tamasaki and Pengokuo 2015).

(E) **New method to use the entomopathogenic fungi**

Entomopathogenic fungi can be used against pests through different methods. In technical field, two strains of entomopathogenic fungi *B. bassiana* Bb 147 and GHA can be used to control both larvae and eggs of *Paysandisia archon* (moth pest of palm trees), and strain GHA is more pathogenic for eggs (Besse 2009; Besse and Bonhomme 2016). To control the vine plant pest like *Planococcus ficus* is by using a new method in preparing a particular mixture of entomopathogenic fungi group of

the genus *Beauveria*, *Paecilomyces*, and *Metarhizium* (Mayra and Assaf 2010). Amazingly, a special method for using the conidia of entomopathogenic fungi *B. bassiana* is doing an admixture between carnauba wax and conidia to be the particle composite (Storm et al. 2011b). This method is beneficial to enhance adherences of conidia on the insect cuticle that increase the efficacy of biopesticides in control of grain insects in stores such as grain storage beetles (Storm et al. 2011b).

Indeed, a new method that treated the plants, parts of plants, and the surrounding of plants with biopesticide is consisting of *Beauveria bassiana* strain ATP02 and DSM 24665 (Vidal and Tefera 2011). For a new method to control cockroaches or other soft-bodied insects, we used the drain method enclosing organic matter that inoculated with *Metarhizium* and could introduce the fungus into the drain as liquid, foam, spray, and powder (Scuilla et al. 2011). The genetic engineering or mutation can use it here for evolving the entomopathogenic fungi artificially into a particular strain with the special desired traits in improving the efficiency of biopesticides that service in removing or reducing the pests without using the chemical pesticides. The improvement for entomopathogenic fungi in the attack and infection comprises (A) secretions of enzymes such as chitinase, protease, and lipases, (B) passing the enzymes or toxins through the layers, (C) conidia growth on the cuticle of insect and penetration by germ tube, (D) growth and expansion inside the body, (E) sporulation, (F) dispersal, and (T) infection of a new host. The two isolates of entomopathogenic fungi *B. bassiana* and *M. anisopliae* are selective after the mutation by culture method; show several characteristics like tolerance for the UV Thermo; increase the growth rate on a carbon source, chemical material, and growth on the specific host; and are modified in sporulation characteristics (De 2011). In special method of a bioinsecticide prepare, is production that consists of dormant spores of entomopathogenic fungi *M. anisopliae*, *B. bassiana*, and *Verticillium lecanii* with group of material such as molecules in growth promoting, enzymes, and fats (Patel 2011). This method is very efficient in controlling the soilborne insects (such as termite and white grub) and other insects such as jassids, whitefly, aphids, thrips, mealybug, caterpillar, and mite (Patel 2011). While, a method for protecting the woody plants against egg and larvae of *Euzophera pinguis* Haw was by using a strain of entomopathogenic fungi *B. bassiana* (Moraga 2012). Strikingly, for the superior control of *Spodoptera exigua*, an insecticide composition of *B. bassiana* ($1.0 \times 10^{\wedge 5}$–$1.0 \times 10^{\wedge 6}$ cfu/mL) and benzylidene acetone (0.5–5 mg) was used by Kyun and Jung-Ah (2012). In control of *Varroa* mites in honey beehives used a particular method in evolving a mixture a strain of entomopathogenic fungi *B. bassiana* as form of spores (effect on mites but not honey bees) and a wax group that consist of jojoba wax powder, candelilla wax powder, and carnauba wax powder (Meikle and Nansen 2012). But a combination of viable cells of some entomopathogenic fungi (*Metarhizium* sp., *Verticillium* sp., *Paecilomyces* sp., and *Beauveria* sp.) with keratin hydrolysate in forming a foam is very efficient against subterranean or soil-dwelling insects such as termites, especially the family Rhinotermitidae (Dunlap et al. 2012). While controlling the pests in motels, residential housing, commercial hotels, and restaurants, like different species of cockroaches (consist of a smoky-brown cockroach *Periplaneta fuliginosa*, a brown-banded cockroach *Supella*

longipalpa, a field cockroach *Blattella vaga*, an Oriental cockroach *Blatta orientalis*, a Turkestan cockroach *Blatta lateralis*, an American cockroach *Periplaneta americana*, and German cockroach *Blattella germanica*), utilized the decaying arthropod cadavers that infect with one or group of entomopathogenic fungi as *Paecilomyces* spp., *Beauveria* spp., *Lecanicillium* spp., *Hirsutella* spp., and *Metarhizium* spp., this method transmitted the conidia of entomopathogenic fungi horizontally among the cockroaches (Leland 2012). The control method of *Aethina tumida* (small hive beetle) is preparing a mixture of entomopathogenic fungi as *B. bassiana* and *M. anisopliae* in the bait and soil drench (Kanga 2012). While a dry solid of culture solids for group of entomopathogenic fungi *Metarhizium* spp., *Beauveria* spp., *Verticillium helium*, and *Nomuraea* spp. is very efficient in the control of insects (that infect the crops and grain of wheat, millet, and barley) (Nakajima and Yamanaka 2013). Anyway, the inoculation of parts of plants, all plants, or the surrounding around plants with two strains of *B. bassiana* ATP02 and DSM 24665 is a very effective method in the control of herbivorous insect (in particular *Helicoverpa armigera*, *Spodoptera* spp., *Trialeurodes vaporariorum*, *Plutella xylostella*) and plant pathogens (Nairobi and Goettingen 2013).

Of another methods, the mixing one or combination of enzyme that the cuticle degrading like protease, cutinase, chitinase, chitosanase, peptidase, and lipase with one entomopathogenic fungi are enhancing of the biopesticides efficacy in control of pests (Leland 2013). Also, the new method in controlling bed bugs (*Cimex lectularius* and *C. adjunctus*) between 24 h and 10 days using entomopathogenic fungi is called prophylactic (barrier treatment) by transferring conidia and blend with a specific oil formulation (the oil is odorless and clear) (Jenkins et al. 2013). Another method for the control of bed bugs and invasion of the parasitic pests is horizontally through preparing a composition of entomopathogenic fungi targeting insects at different life stages (Leland et al. 2014; Jenkins et al. 2015). For controlling the leaf-cutting ants, used an entomopathogenic fungus *Escovopsis* and a special method for increasing the conidia production (Folgarait et al. 2014). For the control of mosquito, there is a float provided with a powder coating that comprises pyriproxyfen (a juvenile hormone) and two entomopathogenic fungi *B. bassiana* and *M. anisopliae* and adds intensifying agent (like diatomaceous earth or synthetic or non-synthetic silica) which is making a chance to contact the conidia of fungi on cuticle of an insect than penetration and infection (Osinga et al. 2012).

For protection of wood and plant against infection with pests such as insect and mite, it treated the infested plant with conidia of the entomopathogenic fungus *Isaria fumosorosea* CCM 8367 strain (Prenerova et al. 2015). To further control the pests of insect and mite by biopesticides, made a composition of one or more of entomopathogenic fungi with one surfactant or combinations such as sorbitan fatty esters, alcohol ethoxylates, polyoxyethylene, and sorbitol ethoxylated esters (Kellar et al. 2015). For the control of arthropods in storage areas in both grain silos and grain bins by a special method, used a dry powder that includes dry conidia of entomopathogenic fungus *B. bassiana* strain IMI 398548, with other dry particles (Wakefield 2016). For controlling the pests of plant crops, evolved a new biocontrol method called the dissemination system (spread). This method is prepared from a mixing between one insect population of predator (as wasp) or parasitoid (as *Cotesia*

flavipes) with one entomopathogenic fungus as *Metarhizium* spp. or *Beauveria* spp. (Giglioti et al. 2016). Continuously, to control the pests and insects in different crops in a very stable composition of pesticide, we include some entomopathogenic fungi with adjuvant microorganism and added the suitable carrier (Villamizar et al. 2016). Increasing the shelf life of conidia is an invention and a method for packing entomopathogenic fungal conidia (Faria 2017). Finally, a method for protection against various horticultural pests by application of microcapsules comprising of a bioinsecticide consisting of a conidial suspension of entomopathogenic fungus *Metarhizium anisopliae* var. *acridum*, and in a solid phase microcontainers, was found to be very efficient (Fokin and Seregin 2017).

12.3 The Use of Entomopathogenic Fungi in Biotechnology

Entomopathogenic fungi have other traits through using them in biotechnology fields such as producing the secondary compounds or metabolites and fertilizer industry. Entomopathogenic fungi produce a diversity of toxins, proteins, enzymes, and secondary metabolites such as other microbes. Entomopathogenic fungi are using some compounds with plant fungal pathogens in the environment for the competition on nutrition and place. The productions are including antifungal, antimicrobial, nonvolatile, and volatile compounds. Also, we are using the toxins for killing the pests as feature prominent for strain or isolates of entomopathogenic fungi. This encourages many inventors to detect the novel compounds. For controlling different plant insects, applied an entomopathogenic fungus *B. bassiana* strain K4B3 in two tests, first the conidia powder and second one or more metabolites (toxins or other compounds), on the plant or surrounding it (Ford 2015). Therefore, two strains of *M. anisopliae* (SD4-2) and *B. bassiana* (SD15) are used as insecticides to control the two-spotted spider mite (*Tetranychus urticae*) and the peach aphid (*Myzus persicae*); at the same time, they are able to control plant pathogens by producing the antimicrobial (antifungal and antibacterial) (Woorami et al. 2016). Conversely, strain Pf212 of *Isaria fumosorosea* as entomopathogenic fungi can be pathogenic for peach aphid (*Myzus persicae*) and cotton aphid (*Aphis gossypii*), as well as using it to restrict growth of *Pythium ultimum* and biocontrol of the plant pathogens *Colletotrichum acutatum* (caused the red pepper anthracnose) (Gimjeongjun et al. 2017). Some secondary metabolites and enzymes can use them in another field.

Entomopathogenic fungi are able to secrete different compounds and enzymes that can be used in other fields far from biocontrol. The entomopathogenic fungi *B. bassiana* and *M. anisopliae* are used in the production of the enzymatic catalyst for decreasing the viscosity of oils both of extra-heavy crude and heavy (Pascual 2015b). Wonderful, entomopathogenic fungi *B. bassiana* can be used to produce the bioethanol from a chitosan source by degradation of the shellfish waste (López et al. 2016).

Indeed, the isolate or strain of entomopathogenic fungi has the ability to be used in dual action in environment through control of pests and plant pathogens in one spray. One spray doesn't mean just one exactly, but it means to reduce the use of different types of pesticides. As fungicides, bactericides, nematicides, insecticides,

etc. are used to control the pests and plant pathogens, not generally, everyone targets a specific pests or pathogens.

For biotechnology of fertilizer, *B. bassiana* as endophyte is able to provide several benefits such as improvement of the crop growth, plant reinforcement, root system, fertility increase, and the quality of agricultural products (Huailiang et al. 2013). A strain of *B. bassiana* could use it in manufacturing microbial fertilizer; this strain is able to colonize maize and wheat that leads to the growth promotion which causes toxicity to corn borer larvae (Xiaolin et al. 2015). Indeed, *B. bassiana* is used in seed biotechnology through preparing the imidacloprid seed dressing by the fermentation of conidial powder which has many advantages as it improves the seed germination, saves the seeds from being damaged, and protects it from underground pests (Menget al. 2014).

12.4 Conclusion

The chemical insecticides are very destructive as direct or indirect for the ecosystem. Entomopathogenic fungi played an important role in eliminating the pests and limiting the use of pesticides. The different inventions in this field provided a high service for community worldwide through saving our environment from the residue of the chemical pesticides. The recent patent in this field started through getting on a new isolate or strain to a new species that is very aggressive against pests. These comprised many strains, but most of these strains from two species of entomopathogenic fungi are *Metarhizium* spp. and *Beauveria* spp. with three new species *Isaria javanica*, *I. fumosorosea*, and *Nomuraea rileyi*. These species are already known as very effective in the control of insects as well as other pests such as mites and nematodes. But why the inventions focus on this species? It is because we are looking for strains or isolates more virulent against the pests. Also, we cannot use the same isolates or strains for a long time. The biopesticide production is costly, and the time is lost with the effort in treating the field or another place in any way. The microenvironment factor has a big impact on efficacy of the strains to attack and cause the diseases for pests and killing them. There are several factors that are thought to have impact on traits of the strains or isolates. These include some factors such as (A) higher temperatures or extremely low, (B) UV light, (C) residue of chemical pesticides, (D) the differences in the host of insects, (H) competition with other strains or isolates or species, (G) humidity or degrees of moisture, (J) drought, (K) metabolites, (N) occurrence in the genetic variations in sexual reproduction of fungi, and (R) the immune system of insects against diseases.

On the other hand, the inventors are working to improve the sporulation of entomopathogenic fungi. The sporulation is very important in the procedure of killing the pests and dispersal from infected insect to free insects or uninfected. This is a very important point; therefore, we are looking for the best media that enhance sporulation like conidia, mycelium, and sclerotia. The secondary metabolite is very interesting due to fungi secreting so many compounds, some antifungal, antimicrobial, antibacterial, bioinsecticide, fungicide, nematicide, acaricide, etc. The

inventions on these compounds may be using them in biotechnology and biomanufacture of the drugs. Interestingly, the patents of entomopathogenic fungi connected with different fields like formulations, products, and different methods in control of pests. All these are also very interesting because we can't treat all insect or pests in the same way. The habitat of pests is different according to the insect kind, some of the inside or outside the plants, under or up of water or in grain stores, and medical insects. Also, the differences among treatments are depended on the type of life stages such as egg, larva, pupa, and adult. We need a special formulation such as dry powder, liquid, gas, and granules that can control the wide insect in the different environments. While new particular products are very attractive for the factories that work in the field of the biopesticides manufacture very useful to control of pests and plant pathogens in the fields. Why? The inventors take a long time in determining the appropriate composition to control the insects dependent on life stage or the habit of life.

Therefore, the biopesticide industry according to these studies by inventors is playing an important role in increasing the efficiency in reducing the spread of insects. In the same time, the biopesticide production is linked with the methods in controlling the pests or insects. The methods of using the biopesticides are by determining the suitable concentrations in control or protection of plants of insects. Also, the preparation methods are important in mixing the composition between natural compounds and entomopathogenic fungi. On the other hand, the patents do not focus on the use of insect pathogenic fungi to fight insects, but it can be used in other areas, such as control of plant pathogens, seed enhancement and plant growth, improved oil quality, and removing the waste. Finally, the patents must take into consideration to increase the efficacy of control on insects. The enhancement of the efficacy entomopathogenic fungi in control is to reach the efficiency of chemical pesticides. In this status, we encourage the consumers or farmers to use the biopesticides that are more safe for the ecosystem. Indeed, we need to increase the efficacy of biopesticide and its use in biotechnology; therefore, they must work on finding new strains by making a mutation or isolate from the insects and increase the sporulation with high secrete of the secondary metabolites. Additionally, we are looking for enhancing the formulation and production appropriate, with the best methods that ensure the production of a biopesticide at the level required for high quality in biocontrol of pests and less costly as well as, more save for ecosystem and appearance the resistance strains or isolates of pests and phytopathogens from residues of chemical pesticides.

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An Innovative Method Through Fungal Engineering for Recycling of CO_2 into Biomass

13

Rafia Azmat and Sumeira Moin

Abstract

The current novel method uses vesicular-arbuscular mycorrhiza (VAM) fungi as green technology for controlling global warming. This method relates the usual dual symbiosis in favor of extracting more biomass via putting back CO_2 into its original form, i.e., fuel. A trait is provided where a fungus is applied to the soil of plants to activate the process of reduction reaction of CO_2 into starch followed by biomass to biofuel. The trait is comprised of fungi *Glomus fasciculatum* and plant *Conocarpus erectus* L. under seasonal variation with excessive pressure of CO_2. The process narrates the highest photosynthetic activity, consequently creating biomass, which is assimilated into the plant tissues through polymerization of glucose into starch and cellulose. The present investigation revealed that VAM symbiosis induced modification in plants' structure which results in deep root growth, high stomatal conductance, and high nutrient uptake including P, rapid C, and N metabolism. It was suggested that these modifications in various environmental conditions provide help in plants' survival, with efficient recycling of CO_2 into biomass production.

Keywords

VAM · *Glomus* spp. · *Conocarpus* spp. · Carbon assembling · Green technology

13.1 Claims

1. The method of concentrating atmospheric CO_2 through activation of photosynthesis in plants required the two following natural biological materials:

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H. B. Singh et al. (eds.), *Intellectual Property Issues in Microbiology*,
https://doi.org/10.1007/978-981-13-7466-1_13

i. VAM (*Glomus fasciculatum)* as a natural activator resource
ii. *Conocarpus erectus* L. as carbon-concentrating plant

2. The method illustrates increase in biomass to biofuel production in plants through C assembling coupled with rapid oxygen production.

13.2 Description of Methodology

Biomass production linked with C assembling through activated plant photosynthesis in several usually existing conditions such as CO_2-enriched condition, various seasonal temperature zones, and drought conditions, proved as a best fungal engineering program for bio-sequestration of CO_2 where plants were cultivated in randomized design in three replicas and titled as Pot 1, control plants (CP); Pot 2, normal VAM fungal inoculated plant (MP); Pot 3, CO_2-enriched atmospheric VAM fungal inoculated plant (EMP); and Pot 4, VAM plants grown in drought condition (DMP). The biomass to biofuel production is restricted to the leaves section of the bioengineered MP system for continuous sinking of CO_2 into starch to cellulose followed by biomass to biofuel (Azmat et al. 2016).

As used herein, nursery soil was dried, crushed and sieved, steamed, autoclaved, and sterilized. In one trait, prepared soil provided MP system to ensure the role of fungi in activating the biosynthetic reduction of atmospheric carbon dioxide into its original state: biomass to biofuel at various temperature for 1 year. In another trait, an isolated VAM *Glomus fasciculatum* species is provided which is characterized as (i) an activator of biological reactions in plants and (ii) provides high temperature tolerance to plant as growth regulator in the temperature range 25–40°C, (iii) has the ability to enable the plant to assimilate the excess nutrient from the soil, and (iv) has an ability to solubilize insoluble P into soluble one at various temperature (Azmat et al. 2015a, b).

Also, in another trait, *Conocarpus erectus* L. plant species is provided which is characterized by the (i) ability to grow in existing ecological conditions, (ii) ability to concentrate carbon, (iii) ability to accumulate more pigments, and (iv) ability to grow in various temperatures or posterity thereof.

As used herein, the proverb "ability to grow" means that the VAM fungi are capable of inducing growth in plants in the various environmental conditions. In addition, the proverb "ability to accumulate high quantities" means the following: for starch and high-value pigments like chlorophyll and carotenoids, high quantities mean, for example, 1–7% of cell dry weight and fresh weight 4–10%.

The MP of the present invention can effectively remove CO_2 from the atmosphere through strong branching structure of the plant (19 to 21 %) consequently capturing more light for biomass construction.

In one aspect, MP system of the present disclosure can effectively remove CO_2 from the atmosphere coupled with large size of stomata to greater assemblage of CO_2 and higher K contents to regulate stomatal opening to other value-added biomass (Azmat et al. 2016).

13.3 Description

13.3.1 FIELD: Fungal Engineering (Biotechnology)

This innovation narrates the usual dual symbiosis for concentrating atmospheric CO_2 into biomass to bioenergy and biofuel using plants and VAM fungi under various climatic conditions. The association of VAM fungi in dual symbiosis resulted in elevated height of plant, biomass, strong root and leaves branched system of the host plant. A method describes the activation of plant metabolism under VAM inoculation through large surface area of leaves and deep root system of plant with adequate nutrients supply especially P (Azmat et al. 2016; Barea and Richardson 2015; Willmann et al. 2013). The discovery describes an innovative method for relocating and integrating atmospheric carbon dioxide into host plants as heritable components starch to biomass to bioenergy to bio young fuel (Azmat et al. 2016; Schrama et al. 2016).

13.3.2 Background of Invention

Advancement in the current era is based on the consumption of oxygen. Oxygen is a vital component of sustainable life. Its only natural resource is plants. Oxygen consumers and CO_2 producers on earth are increasing day by day. There are two main oxygen consumers: (i) animals including human and (ii) fossil fuel burners that include automobile and fuel-based industry. These two oxygen consumers are the counterpart of world advancement, urbanization, and luxurious lives as well as both are the main contributors of CO_2 which is an important part of global warming. Today's global warming is at its highest level due to greenhouse effect as well as fossil fuel burning. There is a mutual relation between living beings (plants and animal) in terms of two gases, i.e., oxygen and carbon dioxide, on earth which are the important constituents of atmospheric gases (0.032%). Greenhouse gases and its effects play significant role in earth climate for sustainable environment. The ability of CO_2 for absorption and re-emission of infrared energy makes it effective as heating trapper of greenhouse gases which is contrary to all other gases.

Carbon dioxide is now 30% higher than it was 150 years ago. It is the highest level of carbon dioxide for the last 800,000 years. The excessive level of carbon dioxide is related to the burning of fossil fuel where it is released as a by-product. Contaminants are precarious composites for living beings. CO_2 is not a pollutant or contaminant, but its high concentration in the atmosphere is playing significant part in global warming (Azmat 2013b).

Moreover, advancement of the twenty-first century is linked with the practices which involve massive amount of oil, natural gas, coal, and nuclear energy, to achieve world energy requirement for industry and agriculture and energy ingestion of daily life. That put burden on the natural energy reserves of these non renewable fossil fuels which now shrink drastically. For example, with the existing rate of depletion, now-recognized oil assets will roughly reduce for 50 years or less (Heijden et al. 2015). Production of fossil fuel requires a long period of time. Therefore, progress and

execution of various renewable ecological energy sources become progressively imperative for biomass production from reverse reaction of CO_2. There are various methods available nowadays which are applicable for biomass production leading to biofuel (Azcón-Aguilar et al. 2009; Bago et al. 2002a; Gavito et al. 2000; Ravikumar et al. 1997). Shinjoh (2007) disclosed in their invention that genetically engineered microorganisms are used for biomass production from carbon source including glucose. The invention also relates to polynucleotide sequences comprising genes that encode proteins that are involved in the bioconversion of a carbon source such as glucose into biomass. This invention also provides processes for generating such microorganism. The invention also features polynucleotides comprising full-length polynucleotide sequences of novel genes and fragments thereof, the novel polypeptides encoded by the polynucleotides and fragments thereof, as well as their functional equivalents. Also included are processes using polynucleotides and modified polynucleotide sequences to transform host microorganisms into a microorganism with reduced carbon source, i.e., higher yield and/or efficiency of biomass production from a carbon source such as glucose. Bagasra et al. (2014) in their invention disclosed that biofuel production was achieved efficiently by biomass digestion and fermentation through a new thermophilic microorganism which was generated after fusion of two different bacteria, namely, *Clostridium thermocellum* and *C. acetobutylicum*. The bacterial colonies were effective in the production of biofuel from lignocellulosic-derived renewable biomass. Bokinsky and Keasling (2012) in their patent provide consolidated bioprocessing methods and host cells. The host cells are capable of directly converting biomass polymers or sunlight into alcohols or branched-chain hydrocarbons. Karamanev and Globin (2007) in their invention disclose a new type of biofuel cell, based on the microbial regeneration of the oxidant, ferric ions. The biofuel cell is based on the cathodic reduction of ferric to ferrous ions, coupled with the microbial regeneration of ferric ions by the oxidation of ferrous ions, with fuel (such as hydrogen) oxidation on the anode. The microbial regeneration of ferric ions is achieved by metal-oxidizing *chemolithotrophic* microorganisms from the *Leptospirillum* genus (excluding *Leptospirillum ferrooxidans*), members of the *Ferroplasma* genus, and members of the *Acidithiobacillus* genus (excluding *Acidithiobacillus ferrooxidans*). Electrical generation is coupled with the consumption of carbon dioxide from the atmosphere and its transformation into microbial cells, which can be used as a single-cell protein. Vujanovic and Germida (2013) in their patent disclose method of improving seed vitality, biotic and abiotic stress resistance, plant health, and yield under both stressed and unstressed environmental conditions, comprising inoculating a seed with the novel endophyte strains and cultivating a plant therefrom. It was established that the modification in lipid content of soybean seeds was observed in the presence of AM fungi which was related with the phosphorus availability, as this content can be increased (Richardson 2007; Benedetto et al. 2005; Schachtman 1998). It is interesting to note that the fungal species play a significant role such as when plants were cultivated with *Gigasporaceae* fungi, an increase in lipid content was observed in comparison with *Glomus* species (Olsson et al. 1995; Cooper and Losel 1978). Triacylglycerols are the main type of neutral lipids found in large amounts in AM fungal spores and vesicles which were certainly part of active

photosystems of plant metabolism during symbiosis (Abdel-Razzak et al. 2013; Azmat 2013a, b; Stumpe et al. 2005; Van Aarle and Olsson 2003; Bago et al. 2002b; Sancholle et al. 2001). Literature revealed that arbuscular mycorrhiza induced alterations in metabolism of plants which resulted in strong branching pattern in root and shoot with expended leaf area and put impact on nutrient uptake and C assembling (Schweiger and Müller 2015; Peterson et al. 1984). The C cycling in mycorrhiza plants reflects in relation with nutrient uptake (Smith and Smith 2011), water absorption (Tauschke et al. 2008; Newman and Ritz 1986), and high photosynthetic rates which are all C-dependent processes. Approaches using chemicals may efficiently eliminate nutrients from wastewater or soil, but their side effects sometimes yield toxic or non-useful compounds. Micro-propagation is the best technique for large-scale biofuel production where *Arundo donax* has become one of the most promising species for cellulose paste, biomass, and second-generation biofuel production (Tauler and Baraza 2015; Koçar and Civaş 2013). Several studies showed that mycorrhizal plant displayed large number of leaves and greater number of stems, pigment contents, and nutrient in comparison with non-mycorrhizal plant (Azmat et al. 2016; Azmat et al. 2015a, b; Ferrol and Pérez-Tienda 2009).

The use of natural resources to eliminate the toxicants and convert it into beneficiary products is the art of bioengineering which can add value-added biomass in plants coupled with simultaneous production of oxygen with sinking of CO_2. A bioengineered MP system may be designed for removal of soil nutrients and atmospheric CO_2 for renovating the fossil fuel after using energy for requirements via advancement in photosynthetic machinery of plants. VAM/plant system showed enforcement to convert the oxidation of fossil fuel into its reduction to biomass to young fuel (Gupta et al. 2002).

13.4 Objective

The scientist community nowadays has engaged into putting back CO_2 into its original form, i.e., fuel, to control global warming. For this purpose, various techniques are currently applied to capture carbon dioxide in those industrial regions where fossil fuels are used to run the plant. These C-capturing plants used microalgae which have the ability to grow rapidly in carbon dioxide-rich environment, thereby playing a significant role in reducing the CO_2 from the atmosphere and producing biofuel, while some plants used lime container for trapping it. All these new innovations are based on renovation of CO_2 into respective compounds, but nothing is mentioned in any experiment about the simultaneous production of oxygen.

The fungal inoculation in host plant tested as a best redox balancer of two gases coupled with biofuel production. The experiment provides evidence that fungal inoculated plants possess large leaf surface area which plays effective role in intercepting photon of light and capturing CO_2 coupled with release of oxygen and biomass production. The experiment is well suited for control of emission of CO_2 in high traffic density and industrial zone based on coal burning. These fungal-engineered plants are found effective in drought condition as well as in temperature variations.

13.5 Detailed Results Description of Innovation

As used herein, the proverb "ability to grow" means that the VAM fungi are capable of inducing growth activation in plants in the related conditions as reported earlier (Kucey and Janzen 1987; Caglar and Akgun 2006) (Fig. 13.1).

As used herein, the proverb "ability to accumulate high quantities" means the following: for starch and high-value pigments like chlorophyll and carotenoids, high quantities mean, for example, from 1 to 7% of cell dry weight and fresh weight 4 to 10% similar to that of work of Tauschke et al. (2008) (Figs. 13.2 and 13.3).

As used herein, MP of the present disclosure can effectively remove CO_2 from the atmosphere coupled with strong branching pattern of the plant simultaneously capturing more light for value-added biomass and increasing branching pattern from 19 to 21% (Maldonado-Mendoza et al. 2001; Hall 1998) (Figs. 13.4 and 13.5).

In all aspect, MP system of the present disclosure can effectively remove CO_2 from the atmosphere coupled with large size of stomata to greater assemblage of CO_2 and higher K contents (Kadian et al. 2013) to regulate stomatal opening to other value-added biomass (Figs. 13.6, 13.7, 13.8, and 13.9).

In all aspect, MP system of the present disclosure can effectively remove CO_2 from the atmosphere coupled with high pigments like chlorophyll a and b, carotenoids, mesophyll, and xanthophyll (Azmat 2013a) to store more light energy for other value-added biomass increasing chlorophyll a from 5 to 8%, chlorophyll b 4 to 6%, and carotenoids 3 to 7% (Fig. 13.10).

In all aspect, MP system of the present disclosure can effectively remove CO_2 from the atmosphere coupled with producing high starch contents (Helber et al. 2011) and other value-added biomass (Figs. 13.11, 13.12, 13.13, and 13.14).

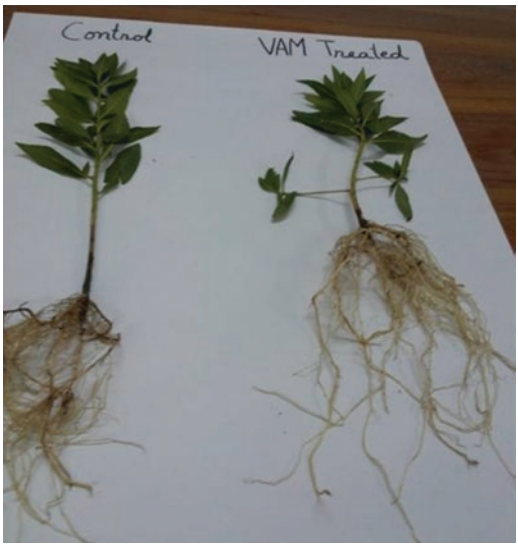

Fig. 13.1 Initial growth regulation of 1-month-older plants *Conocarpus erectus* L. of VAM-treated and control plants

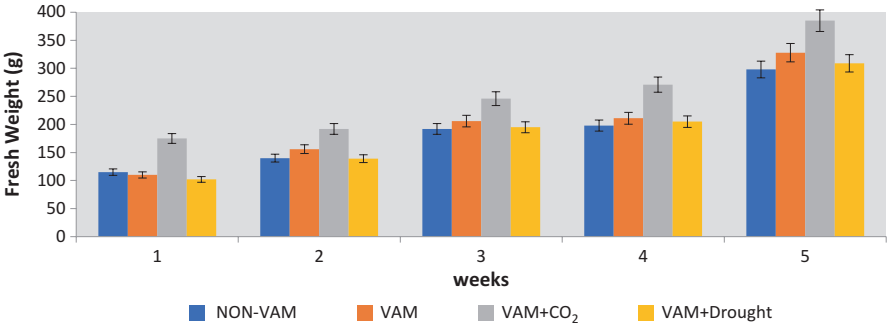

Fig. 13.2 Weekly monitoring of fresh weight of VAM, VAM+ CO2, VAM+ drought inoculated and non-inoculated *Conocarpus erectus* L.

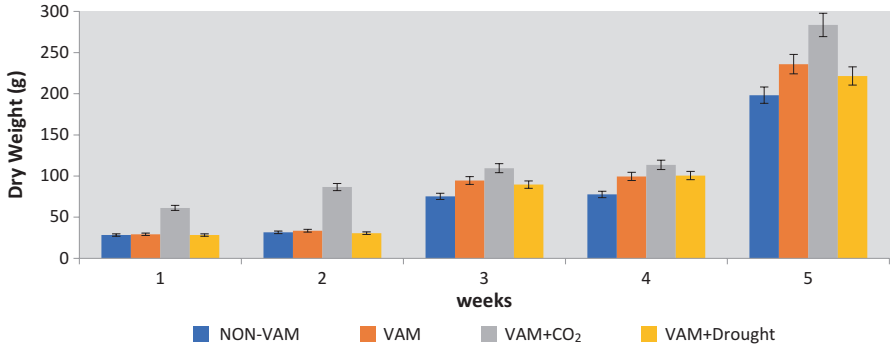

Fig. 13.3 Weekly monitoring of dry weight of VAM, VAM+ CO2, VAM+ drought inoculated and non-inoculated *Conocarpus erectus* L.

Fig. 13.4 A well-developed aerial branching pattern of 90-day-older control and VAM-treated *Conocarpus erectus* L. plants

Fig. 13.5 Aerial branching pattern of 90-day-older VAM+ CO_2- and VAM+ drought-treated *Conocarpus erectus* L. plants

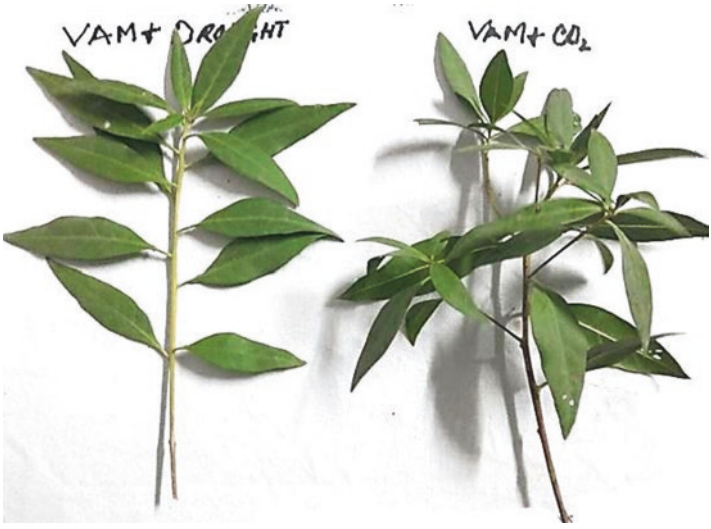

Fig. 13.6 SEM showing the width of stomatal opening size of *Conocarpus erectus* L. plants

In all aspect, MP system of the present disclosure can effectively remove CO_2 from the atmosphere coupled with activating ATP system of the plant for conversion of solar energy to chemical energy to other value-added biomass to provide as a sink of CO_2 thereof (Fig. 13.15).

In all aspects, MP system of the present disclosure can effectively remove CO_2 from the atmosphere coupled with activating proline in leaf/root system of the plant that provided internal rehydration, whereas increase in proline content (Figs. 13.16

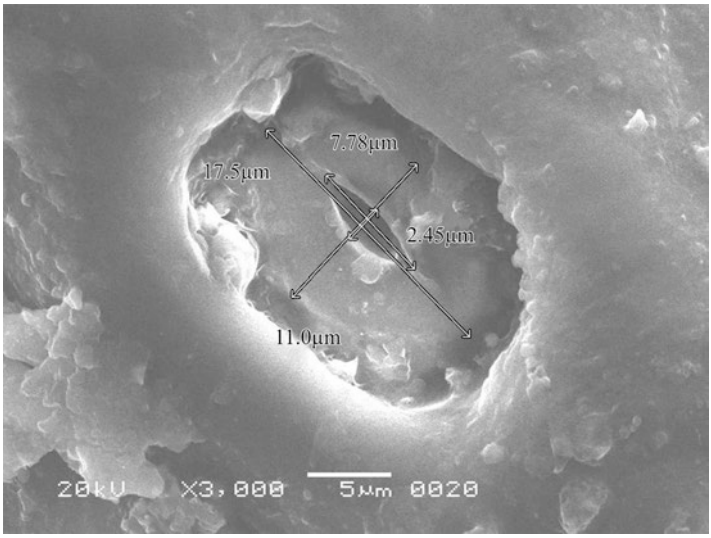

Fig. 13.7 SEM showing the width of stomatal opening size of VAM *Conocarpus erectus* L. plants

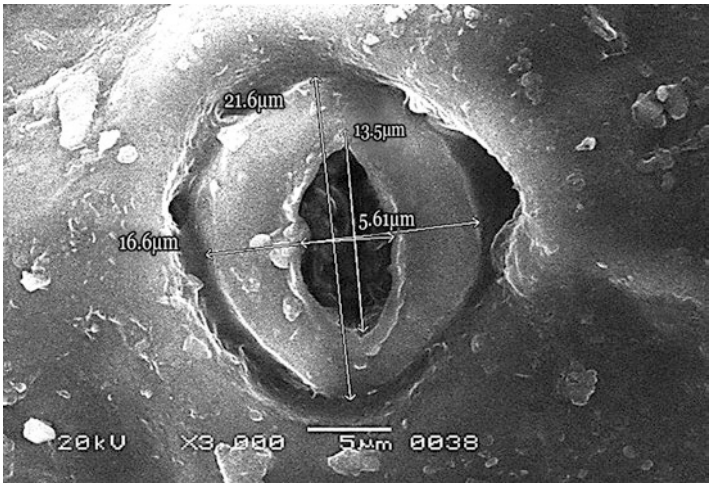

Fig. 13.8 SEM showing the width of stomatal opening size of VAM+ CO_2 *Conocarpus erectus* L. plants

and 13.17) in leaves was from 6 to 24% and in roots 15 to 28% to other value-added biomass (Harrison and van Buuren 1995; Kadian et al. 2013; Masuta et al. 1999).

As used herein, MP system of the present disclosure can effectively remove CO_2 from the atmosphere coupled with activating phenol (Kikuchi et al. 2014; Martins et al. 1997) in leaf/root system of the plant for defense to other value-added biomass increasing from 25 to 37% in leaves and 16 to 33% in roots (Figs. 13.18 and 13.19).

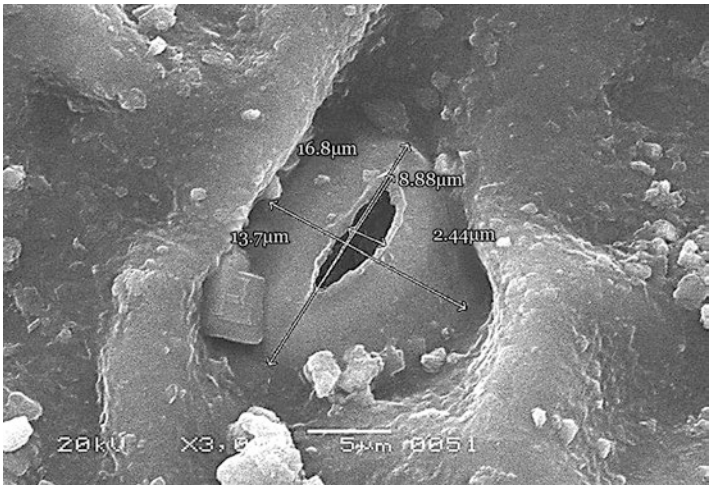

Fig. 13.9 SEM showing the width of stomatal opening size of VAM+ drought *Conocarpus erectus* L. plants

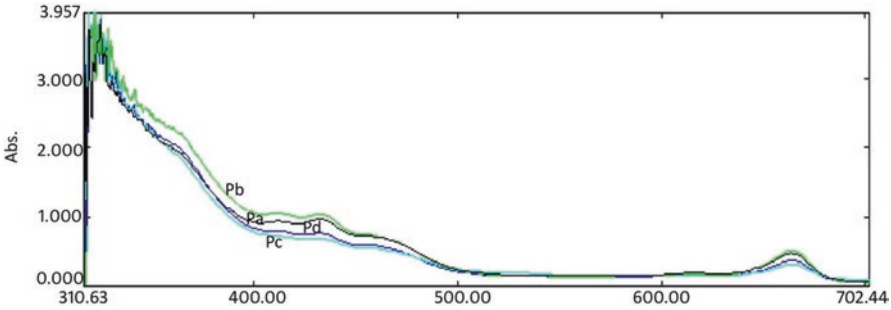

Fig. 13.10 Spectral analysis of high pigments of plants (**a**–**d**)

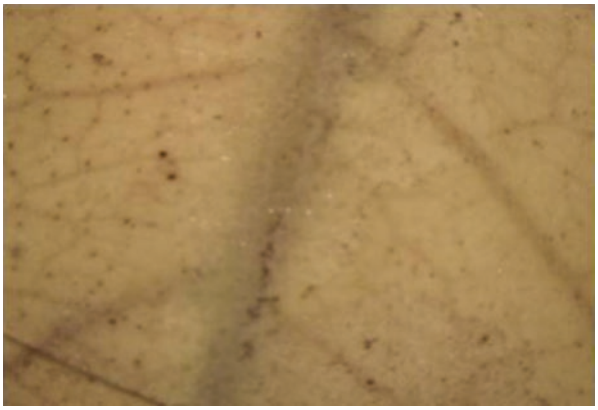

Fig. 13.11 Accumulation of sugar contents in control *Conocarpus erectus* L.

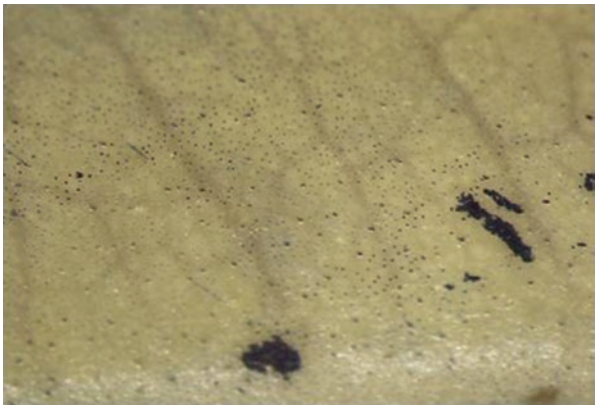

Fig. 13.12 Accumulation of starch granules (brownish white) in VAM *Conocarpus erectus* L.

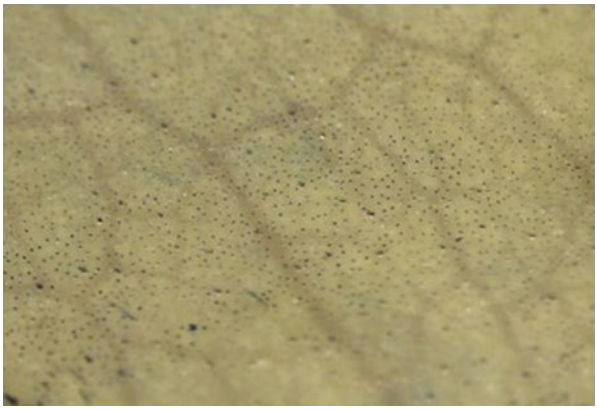

Fig. 13.13 Accumulation of starch granules (blue) in VAM+ CO_2 *Conocarpus erectus* L.

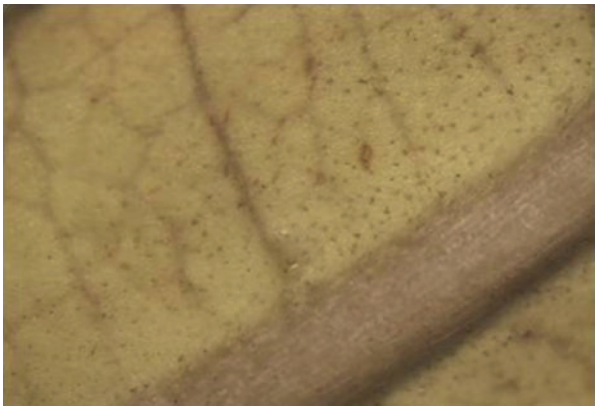

Fig. 13.14 Accumulation of glucose/sucrose granules (brownish) in VAM+ drought *Conocarpus erectus* L.

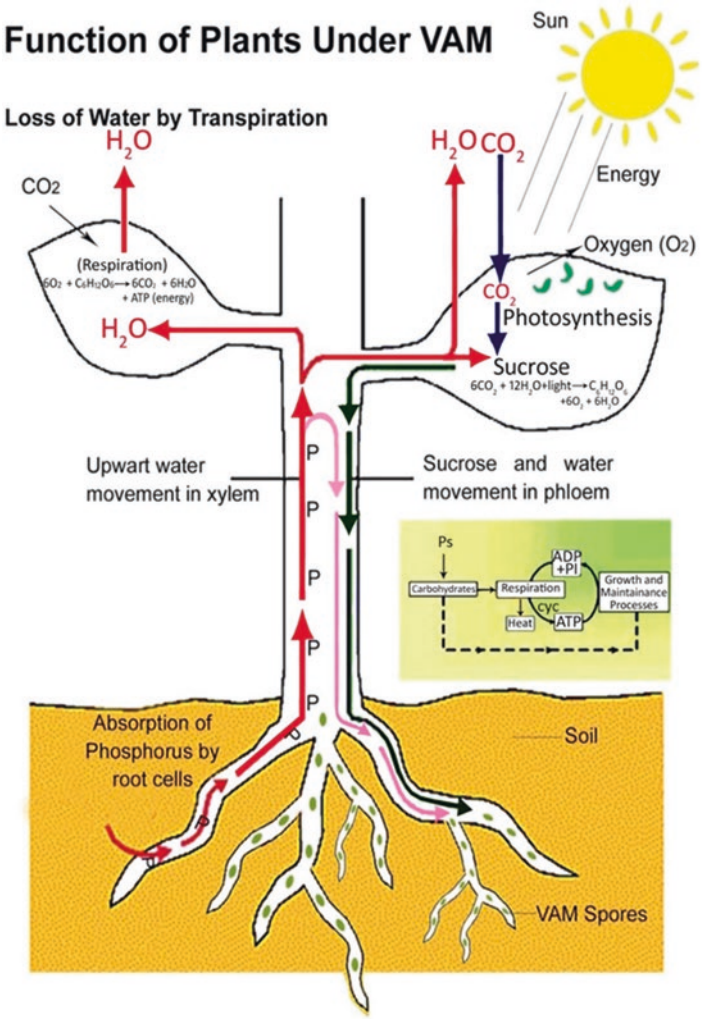

Fig. 13.15 An activated system of plant under VAM inoculation

In some embodiments, MP system of the present disclosure can effectively remove CO_2 from the atmosphere coupled with activating starch in leaf/root system of the plant for carbohydrate to other value-added biomass increasing from 8 to 20% in leaves and 7 to 18% in roots (Figs. 13.20, and 13.21).

As used herein, MP system of the present disclosure can effectively remove CO_2 from the atmosphere coupled with activating reducing sugar (Figs. 13.22 and 13.23) in leaf/root system of the plant in excessive concentration of CO_2 to other value-added biomass increasing from 22 to 27% in leaves and 21 to 31% in roots (Jorquera et al. 2008; Martins et al. 1997).

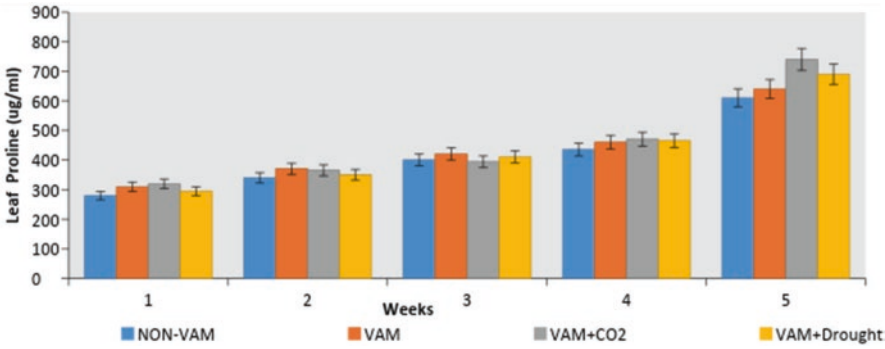

Fig. 13.16 Comparison between leaf proline content of VAM, VAM+CO_2, and VAM+ drought inoculated and non-inoculated *Conocarpus erectus* L.

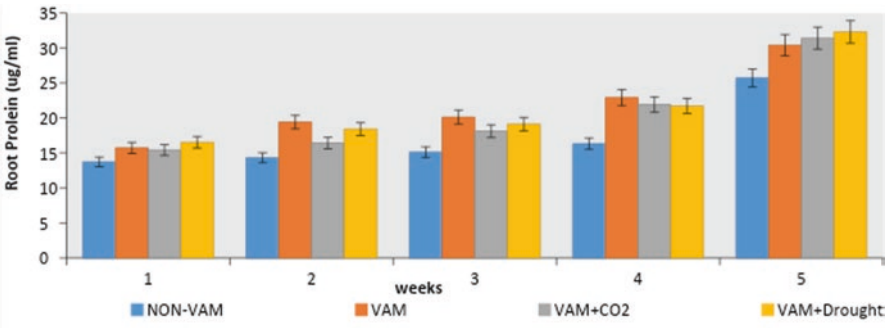

Fig. 13.17 Comparison between root proline content of VAM, VAM+CO_2, and VAM+ drought inoculated and non-inoculated *Conocarpus erectus* L.

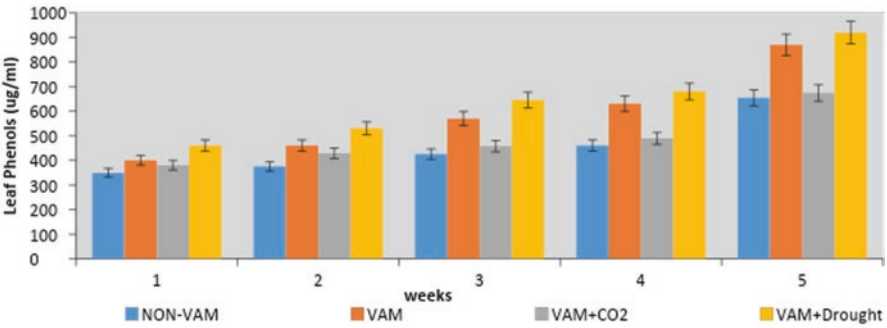

Fig. 13.18 Comparison between leaf phenol content of VAM, VAM+CO_2, and VAM+ drought inoculated and non-inoculated *Conocarpus erectus* L.

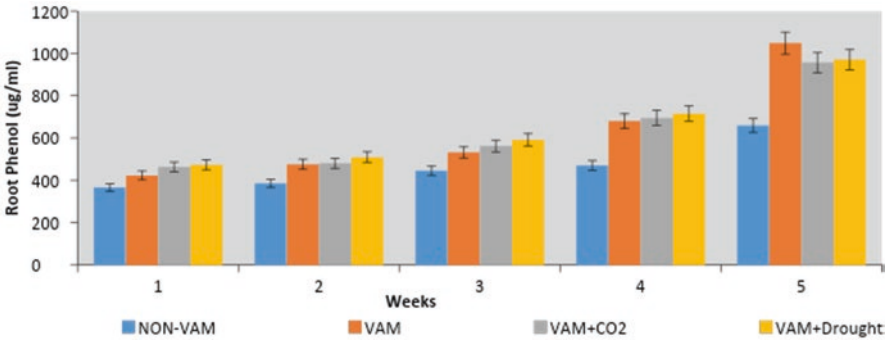

Fig. 13.19 Comparison between root phenol content of VAM, VAM+CO_2, and VAM+ drought inoculated and non-inoculated *Conocarpus erectus* L.

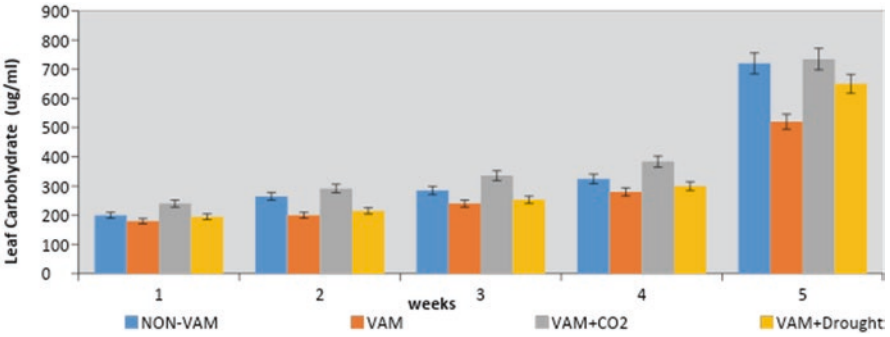

Fig. 13.20 Comparison between leaf carbohydrate content of VAM, VAM+CO_2, and VAM+ drought inoculated and non-inoculated *Conocarpus erectus* L.

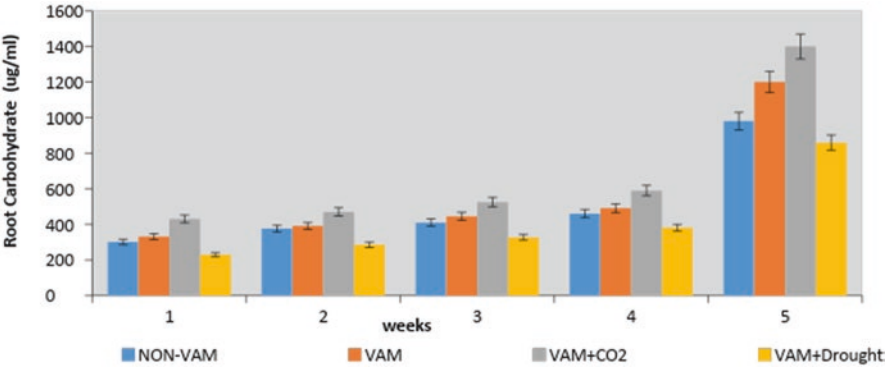

Fig. 13.21 Comparison between root carbohydrate content of VAM, VAM+CO_2, and VAM+ drought inoculated and non-inoculated *Conocarpus erectus* L.

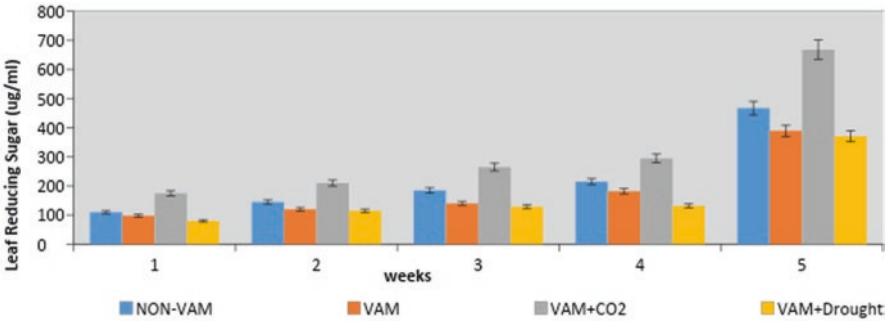

Fig. 13.22 Comparison between leaf reducing sugar content of VAM, VAM+CO_2, and VAM+drought inoculated and non-inoculated *Conocarpus erectus* L.

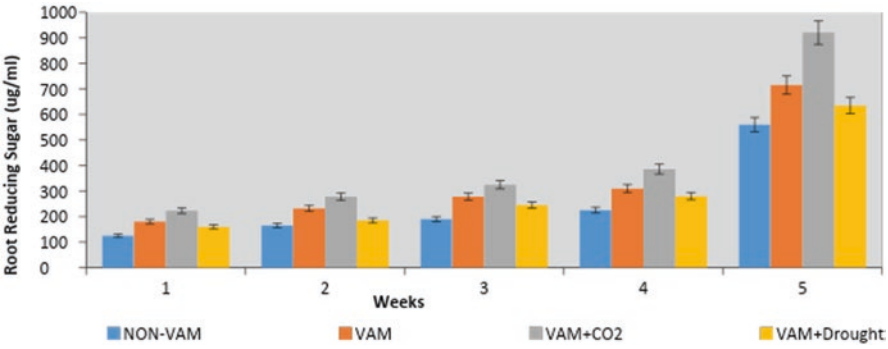

Fig. 13.23 Comparison between root reducing sugar content of VAM, VAM+CO_2, and VAM+drought inoculated and non-inoculated *Conocarpus erectus* L.

As used herein, MP system of the present disclosure can effectively remove CO_2 from the atmosphere coupled with activating protein in leaf/root (Kiers et al. 2011 Masuta et al. 1999) system of the plant to work at high temperature 40 °C to other value-added biomass increasing from 12 to 17% in leaves and 4 to 5% in roots (Figs. 13.24 and 13.25).

In some embodiments, MP system of the present disclosure can effectively remove CO_2 from the atmosphere coupled with activating strong root system of the plant to assimilate large amount of nutrients (Govindarajulu et al. 2005; Cox et al. 1980; Karandashov and Bucher 2005) from soil to other value-added biomass thereof (Figs. 13.26, 13.27, 13.28, and 13.29).

As used herein, MP system of the present disclosure can effectively remove CO_2 from the atmosphere coupled with an ability to assimilate large quantities of nutrients selected from the assembly comprising of nitrogen, phosphorous, Ca, K, and inorganic carbon (Figs. 13.30, 13.31, 13.32, and 13.33), as well as an ability to accumulate large quantities of protein mass to other value-added biomass thereof (Mali et al. 2009; Bagayoko et al. 2000).

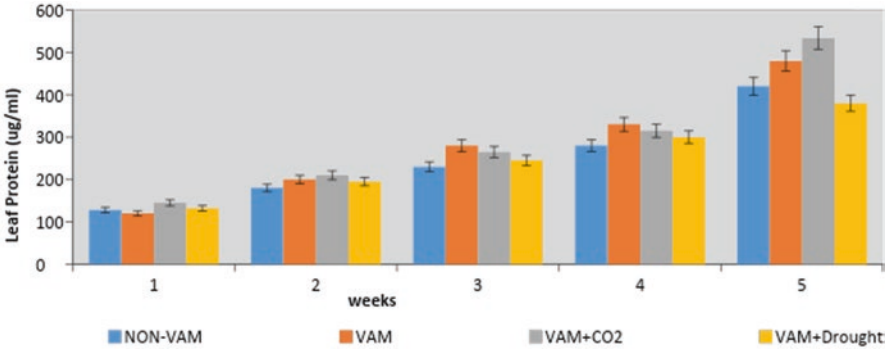

Fig. 13.24 Comparison between leaf protein content of VAM, VAM+CO_2, and VAM+ drought inoculated and non-inoculated *Conocarpus erectus* L.

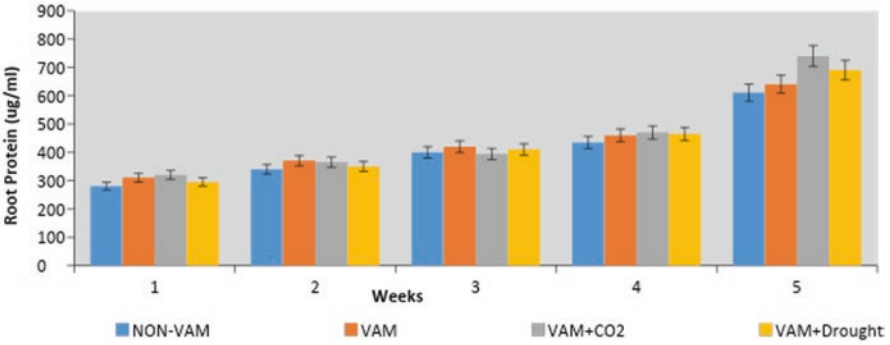

Fig. 13.25 Comparison between root protein content of VAM, VAM+CO_2, and VAM+ drought inoculated and non-inoculated *Conocarpus erectus* L.

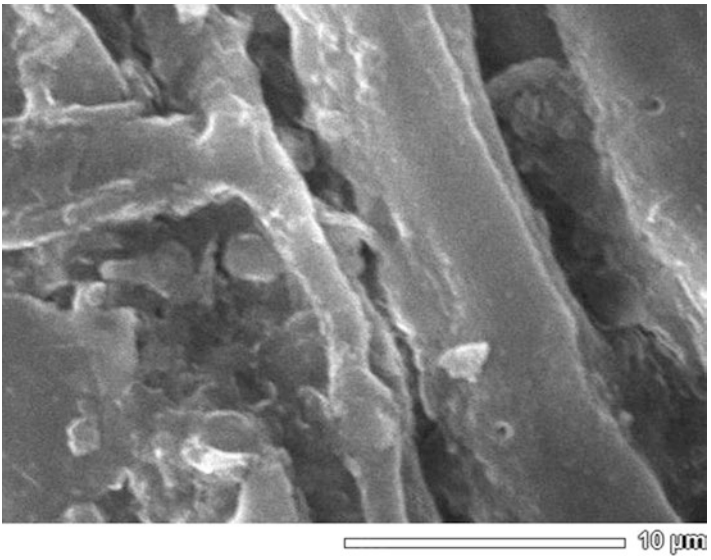

Fig. 13.26 The scan electron microscopy of surface structure of control roots in *Conocarpus erectus* L. plants

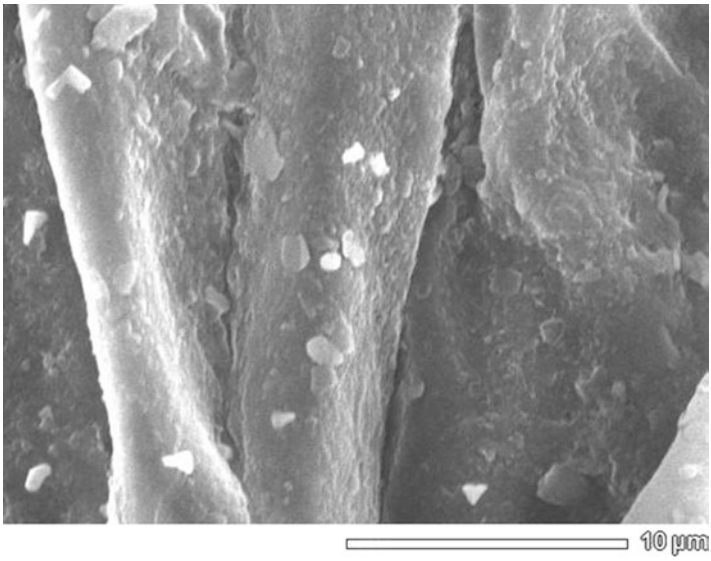

Fig. 13.27 The scan electron microscopy of surface structure of VAM roots in *Conocarpus erectus* L. plants

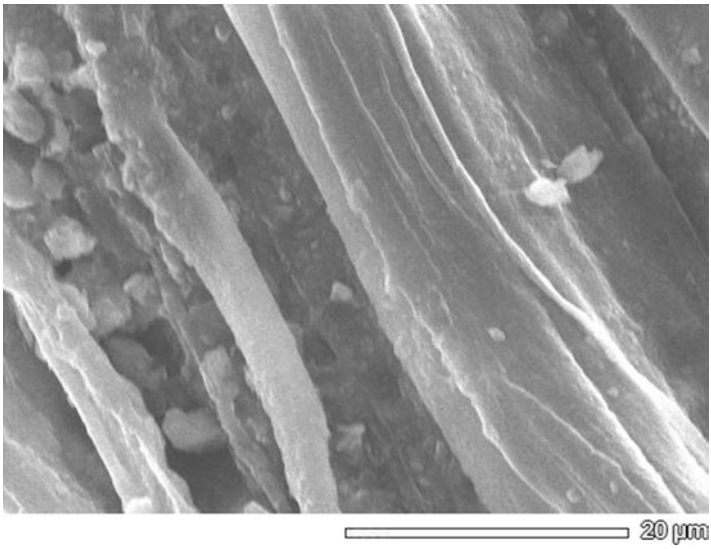

Fig. 13.28 The scan electron microscopy of surface structure of VAM + CO_2 roots in *Conocarpus erectus* L. plants

As used herein, MP system of the present disclosure can effectively remove CO_2 from the atmosphere coupled with generating high enzyme activity, i.e., amylase, protease, nitrate reductase and nitrite reductase activity, and other value-added biomass. As used herein, MP of the present disclosure can effectively remove CO_2 from the

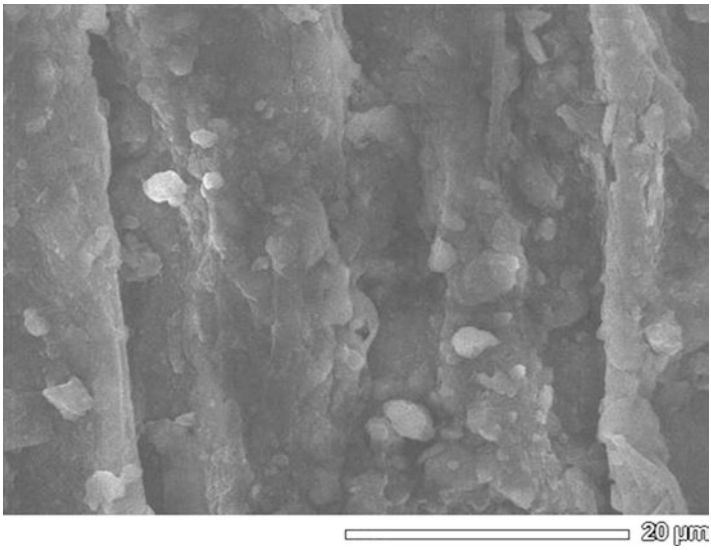

Fig. 13.29 The scan electron microscopy of surface structure of VAM + drought roots in *Conocarpus erectus* L. plants

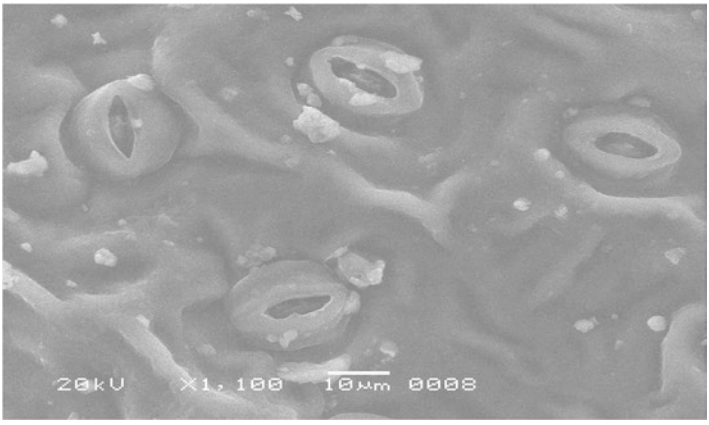

Fig. 13.30 Scan electron microscopy of control leaves of *Conocarpus erectus* L. visualizing stomata and nutrients

atmosphere coupled with strong root network simultaneously solubilizing insoluble P into soluble one to activate photobiological reactions and other nutrients for value-added biomass. In another trait, an isolated VAM *Glomus fasciculatum* species is provided which is characterized as (i) activator of biological reactions in plants and (ii) provides tolerance to plant in drought condition, (iii) has the ability to assimilate excess nutrient from soil, and (iv) has an ability to solubilize insoluble P into soluble posterity thereof. Also, in another trait, *Conocarpus erectus* L. plant species is provided which is characterized by the (i) ability to grow in existing

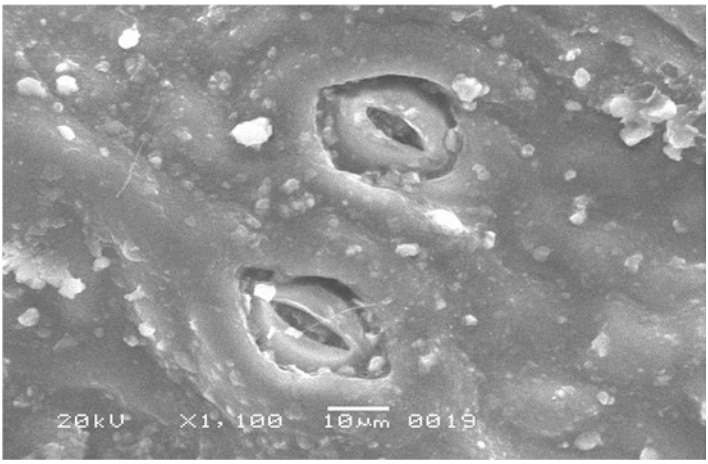

Fig. 13.31 Scan electron microscopy of VAM inoculated leaves of *Conocarpus erectus* L. visualizing stomata and nutrients

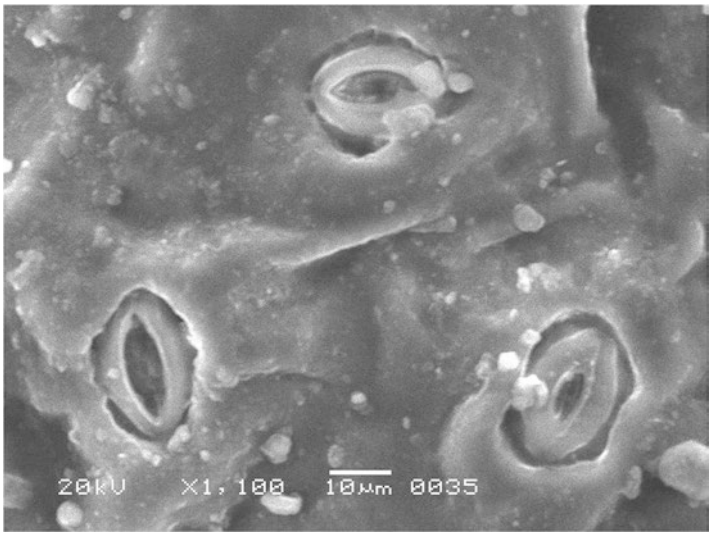

Fig. 13.32 Scan electron microscopy of VAM-CO2 inoculated leaves of *Conocarpus erectus* L. visualizing stomata and nutrients

ecological conditions, (ii) ability to concentrate carbon, and (iii) ability to accumulate more pigments or posterity thereof.

As used herein, the proverb "ability to accumulate high quantities" means the following: for starch and high-value pigments like chlorophyll and carotenoids, high quantities mean, for example, from 19 to 29% of dry weight and fresh weight from 4 to 10%.

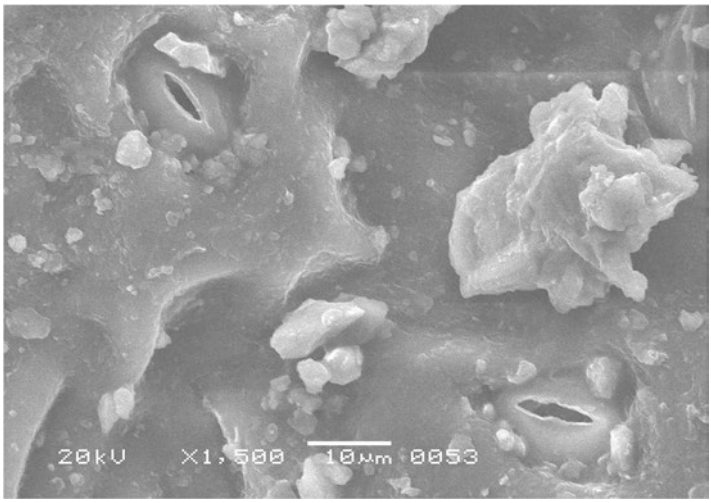

Fig. 13.33 Scan electron microscopy of VAM –drought inoculated leaves of *Conocarpus erectus* L. visualizing stomata and nutrients

As used herein, MP of the present disclosure can effectively remove CO_2 from the atmosphere coupled with strong branching pattern of the plant simultaneously capturing more light for value-added biomass and increasing branching pattern from 9 to 11%. In all aspect, MP system of the present disclosure can effectively remove CO_2 from the atmosphere coupled with large size of stomata to greater assemblage of CO_2 and higher K contents to regulate stomatal opening to other value-added biomass. In all aspect, MP system of the present disclosure can effectively remove CO_2 from the atmosphere coupled with pigments like chlorophyll a and b, carotenoids, mesophyll, and xanthophyll to store more light energy for other value-added biomass increasing chlorophyll a from 1 to 3%, chlorophyll b from 1 to 2%, and carotenoids from 2 to 6%.

In all aspects, MP system of the present disclosure can effectively remove CO_2 from the atmosphere coupled with producing high starch contents and other value-added biomass provided as a sink of CO_2 thereof. In all aspect, MP system of the present disclosure can effectively remove CO_2 from the atmosphere couple with activating ATP system of the plant for conversion of solar energy to chemical energy to other value-added biomass to provide as a sink of CO_2 thereof.

In all aspects, MP system of the present disclosure can effectively remove CO_2 from the atmosphere coupled with activating proline in leaf/root system of the plant that provided internal rehydration, whereas increase in proline content in leaves was from 3 to 17% and in roots 20 to 24%.

As used herein, MP system of the present disclosure can effectively remove CO_2 from the atmosphere coupled with activating phenol in leaf/root system of the plant for defense to other value-added biomass increasing from 23 to 40% in leaves and 24 to 35% in roots. As used herein, MP system of the present disclosure can effectively remove CO_2 from the atmosphere coupled with activating starch in leaf/root

system of the plant for carbohydrate to other value-added biomass increasing from 8 to 10% in leaves and 13 to 25% in roots.

As used herein, MP system of the present disclosure can effectively remove CO_2 from the atmosphere coupled with activating reducing sugar in leaf/root system of the plant in excessive concentration of CO_2 to other value-added biomass increasing from 2 to 20% in leaves and 11 to 22% in roots. As used herein, MP system of the present disclosure can effectively remove CO_2 from the atmosphere coupled with activating protein in leaf/root system of the plant to work at high temperature 40 °C to other value-added biomass increasing from 6 to 10% in leaves and 2 to 11% in roots.

As used herein, MP system of the present disclosure can effectively remove CO_2 from the atmosphere coupled with activating strong root system of the plant to assimilate large amount of nutrients from soil to other value-added biomass thereof. As used herein, MP system of the present disclosure can effectively remove CO_2 from the atmosphere coupled with an ability to assimilate large quantities of nutrients selected from the assembly comprising of nitrogen, phosphorous, Ca, K, and inorganic carbon, as well as an ability to accumulate large quantities of protein mass to other value-added biomass thereof. As used herein, MP system of the present disclosure can effectively remove CO_2 from the atmosphere coupled with generating high enzyme activity, i.e., amylase, protease, nitrate reductase and nitrite reductase activity, and other value-added biomass. As used herein, MP of the present disclosure can effectively remove CO_2 from the atmosphere coupled with strong root network simultaneously solubilizing insoluble P into soluble one to activate photobiological reactions and other nutrients for value-added biomass.

In one trait, an isolated VAM *Glomus fasciculatum* species is provided which is characterized as (i) activator of biological reactions and has the (ii) ability to activate photosynthetic activity to capture more CO_2, (iii) ability to assimilate excess nutrient from soil, and (iv) ability to solubilize insoluble P into soluble one at EMP condition or posterity thereof.

In another trait, *Conocarpus erectus* L. plant species is provided which is characterized by the (i) ability to grow in existing ecological conditions, (ii) ability to concentrate carbon, (iii) ability to accumulate more pigments, and (iv) ability to capture more light via strong branching or posterity thereof. As used herein, the proverb "ability to accumulate high quantities" means the following: for starch and high-value pigments like chlorophyll and carotenoids, high quantities mean, for example, from 31 to 48% of dry weight and fresh weight from 42 to 59%. As used herein, MP of the present disclosure can effectively remove CO_2 from the atmosphere coupled with strong branching pattern of the plant simultaneously capturing more light for value-added biomass and increasing branching pattern from 29 to 43%. In all aspect, MP system of the present disclosure can effectively remove CO_2 from the atmosphere coupled with large-size stomata to greater assemblage of CO_2 and higher K contents to regulate stomatal opening to other value-added biomass. In all aspect, MP system of the present disclosure can effectively remove CO_2 from the atmosphere coupled with pigments like chlorophyll a and b, carotenoids, mesophyll, and xanthophyll to store more light energy for other value-added biomass

increasing chlorophyll a from 7 to 11%, chlorophyll b from 4 to 7%, and carotenoids from 8 to 14%. In all aspect, MP system of the present disclosure can effectively remove CO_2 from the atmosphere coupled with producing high starch contents and other value-added biomass provided as a sink of CO_2 thereof. In all aspect, MP system of the present disclosure can effectively remove CO_2 from the atmosphere coupled with activating ATP system of the plant for conversion of solar energy to chemical energy to other value-added biomass to provide as a sink of CO_2 thereof.

In all aspects, MP system of the present disclosure can effectively remove CO_2 from the atmosphere coupled with activating proline in leaf/root system of the plant that provided internal rehydration, whereas increase in proline content in leaves was from 8 to 20% and in roots 11 to 22%. As used herein, MP system of the present disclosure can effectively remove CO_2 from the atmosphere coupled with activating phenol in leaf/root system of the plant for defense to other value-added biomass increasing 27 to 38% in leaves and 20 to 32% in roots. As used herein, MP system of the present disclosure can effectively remove CO_2 from the atmosphere coupled with activating starch in leaf/root system of the plant for carbohydrate to other value-added biomass increasing from 20 to 40% in leaves and 21 to 30% in roots. As used herein, MP system of the present disclosure can effectively remove CO_2 from the atmosphere coupled with activating reducing sugar in leaf/root system of the plant in excessive concentration of CO_2 to other value-added biomass increasing from 27 to 30% in leaves and 31 to 39% in roots. As used herein, MP system of the present disclosure can effectively remove CO_2 from the atmosphere coupled with activating protein in leaf/root system of the plant to work at high temperature 40 °C to other value-added biomass increasing from 13 to 21% in leaves and 5 to 15% in roots. In some embodiments, MP system of the present disclosure can effectively remove CO_2 from the atmosphere coupled with activating strong root system of the plant to assimilate large amount of nutrients from soil to other value-added biomass thereof.

As used herein, MP system of the present disclosure can effectively remove CO_2 from the atmosphere coupled with an ability to assimilate large quantities of nutrients selected from the assembly comprising of nitrogen, phosphorous, Ca, K, and inorganic carbon, as well as an ability to accumulate large quantities of protein mass to other value-added biomass thereof.

As used herein, MP system of the present disclosure can effectively remove CO_2 from the atmosphere coupled with generating high enzyme activity, i.e., amylase, protease, nitrate reductase and nitrite reductase activity, and other value-added biomass.

As used herein, MP of the present disclosure can effectively remove CO_2 from the atmosphere coupled with strong root network simultaneously solubilizing insoluble P into soluble one to activate photobiological reactions and other nutrients for value-added biomass.

Improving the biomass production and/or increasing the carbon fixation by the plant comprising introducing VAM fungi into plants, wherein the introduction of the natural biomaterial results inside activation of biochemical pathway followed by activated strong root and leaves system where the high chloroplast, starch, protein, amino acid having the enzymatic activity leads to biomass addition which in turns leads to young fuel (Wang et al. 2013).

As used herein, the ability to capture at high CO_2 from environment makes this bioengineered VAM/plant system extremely suitable for biological sequestration of CO_2 from flue gases emitted from power-generating plants as well as heavy traffic zone. This system can also accumulate high concentrations of pigments to capture more solar radiation and convert it to chemical energy which activates the carbon-carbon linkage for polymerization of glucose into starch and other biomass-related compounds. The bioengineered system capable to synthesize and accumulate large quantities of carbohydrates, cellulose, proteins, and lipids with high enzymatic activities possesses strong antioxidant activities (Pfeffer et al. 1999; White and Hammond 2008).

This bioengineered MP system can thrive at up to maximum CO_2/air and can be used as an ideal candidate for carbon sequestration and renewable biomass production.

As used herein, the fresh weight, dry weight, leaf area, branching pattern, stem diameter, strong deep root system, pigments, starch, proteins, proline, enzymes, and minerals as value-added biomass were higher in EMP > MP > DMP > CP.

- As used herein, bioengineered VAM/plant system proved to be the best emission controller/recycler of fossil fuel after its use which can convert emitted CO_2 into young fuel with the progression of oxygen.

The primary goal of current investigation (in search of new technologies) was the optimization of the photosynthetic process in the *Conocarpus* spp. This species commonly used in green belt of Karachi City. The strategy used to maximize photosynthesis in *Conocarpus* spp. was the use of VAM fungus as a native plant species in relation to absorption of CO_2 from megacities. The ability of the fungi to provide assistance in growth, increase in biomass, changes in the numbers of organ, and initiation of new leaves and root was tested. This indicates that biotechnologists can direct the results of photosynthesis for getting possible benefits in greening the environment via exchange of two primary gases, the production of assimilates, sugars, and starches, toward both vegetative and generative in a balance. *Conocarpus* spp. with VAM fungi showed expected response toward photosynthetic activity via showing dense branching pattern of leaves with larger surface area as compared to nonassociated plants. These modifications in VAM-associated plants indicate the direct link with photosynthetic activity (Azmat et al. 2016). It was suggested that in VAM-engineered plants, photosynthetic photon flux density (PPFD) reaching a unit surface per unit of time was found to be enhanced. That was credited to the leaf area index and number of leaf in VAM plants which help in maximizing the plants' access to available light. Light use efficiency by plants depends not only on the photosynthetic efficiency of plants but also on the efficiency of the interception of light and efficiency with which light is converted to chemical energy in photosynthesis (Subramanian et al. 2006; Subramanian and Charest 1995).

The new character of vesicular-arbuscular mycorrhizas (VAM) was established after longtime practices and investigation at laboratory scale that VAM fungus is the designer of plant for CO_2 capturing, which consequently balances the atmospheric gaseous redox reaction. It was recommended on the bases of experimentation that a

VAM fungus is a fresh "C" lover in comparison to other fungi which feed on dead materials and finally decompose it. The ability of VAM to provide assistance and increase tolerance of plants against various diseases does not have negative impact even though it survives on live plants. The plants in presence of fungal inoculation showed rapid growth, increase in biomass, and changes in the numbers of organ, and initiation of new leaves and root. These properties associated with fungal-associated plants were tested as a new design of plants for reduction of CO_2 from atmosphere. A direct link was reported with new design of plant through modified soil composition on enhanced photosynthetic activity related to the solubilization and availability of P (Marschner 2008; Velázquez and Rodriguez-Barrueco 2007). Light use efficiency by plants depends not only on the photosynthetic efficiency of plants as well as large surface area of leaves but also on the efficiency of the interception of light and efficiency with which light is converted to chemical energy through ATP in photosynthesis. Analysis of photobiological reactions established that VAM association increases the light-capturing capability of chlorophyll which works more rapidly in transformation of light energy to the ATP reaction center due to the large space available. It was concluded that after estimation of starch, sugar, and pigment analysis, and other variables of plants that the C*onocarpus* and VAM association may bring, the green revolution in controlling global warming which is the result of over-emittance of two gases, carbon dioxide and methane initiating extreme climate changes, results in remarkable increase in water vapor, carbon dioxide, methane nitrous oxide, and especially greenhouse gases due to contaminating constituents released as a result of industrial development, toxic waste, and deforestation.

It concluded that VAM association in plant kingdom is the natural gift to clean the atmosphere where VAM feed on fresh C from freshly prepared carbohydrates in leaves and also provide help in reduction of CO_2 from atmosphere with the release of oxygen. It was recommended that a VAM fungus is the cleaner of gaseous carbon via providing soil nutrient assistance leading to new design of plants. Native plant species may be the probable solution of sinking CO_2 from the atmosphere via speedy photosynthesis in carbon-concentrating plants, providing clean air for life on earth. It is the only natural processes, an ultimate source of life that can help in balancing the level of oxygen and carbon dioxide in the earth. As a matter of fact, that oxygen in the atmosphere is attributed to the process of photosynthesis. It indicates that one should search in technologies which can be helpful in releasing the current excess pressure of CO_2 from the atmosphere in a cost-effective way through internal modification of natural process of photosynthesis for better exchange rate in between CO_2 and O_2 (Azmat et al. 2017; Bago et al. 2003; Martins et al. 1997).

Patent citation covering various microbial methods for production of biomass and bioenergy

Cited patent	Filing date	Publication date	Applicant	Title
WO2007028611 A3	Sep 7, 2006	Jul 19, 2007	Masako Shinjoh	Process for Biomass Production Using a Microorganism with a Disrupted Glucose-Dehydrogenase Gene (gms 01)
US20140057327 A1	Aug 22, 2012	Feb 27, 2014	Omar Bagasra, Kamal Chowdhury, Verlie A. Tisdale, George E. Miller III, Rebecca Bullard-Dillard	Single Vessel Production of Butanol from Biomass Using Engineered Thermophilic Microorganisms
US20120115195 A1	Apr 30, 2010	May 10, 2012	Jay D. Keasling, Yisheng (Connie) Kang, Eric J. Steen, Gregory Bokinsky	Product of Fatty Acid Esters From Biomass Polymers
WO2007137401 A1	May 23, 2007	Dec 6, 2007	Dimitre Gueorguiev Karamanev, Vassili Porfirievich Glibin	Improved Biofuel Cell
EP2954043 A1	Feb 5, 2013	Dec 16, 2015	Vladimir Vujanovic, James J. Germida	Endophytic Microbial Symbionts in Plant Prenatal Care
US9200244 B2	Nov 16, 2012	Dec 1, 2015	Rudolf Ehwald, Lars Bähr, Arne Wüstenberg, Joel Herve Soh	Method for Culturing Photoautotrophic Microorganisms for the Production of Biomass
WO2016055879 A1	Aug 13, 2015	Apr 14, 2016	Escobar valeska Villegas, López sandra Mosquera, Uribe Luisa Fernanda Posada, Correa Educrecia Maria Ramírez, Gaviria Tatiana Zazini Cuellar, Castillo John Jairo Mira, Roldán luz Edith Argel	Process for Increasing Biomass and Spores Production of Plant Growth Promoting Bacteria of the *Bacillus* Genus
CA2833622 A1	Apr 30, 2012	Nov 1, 2012	Wan-Kei Wan, Darcy SMALL	Method to Enhance Growth of Biomass Constituents of Photosynthetic Microorganisms
WO 2015109265 A1	Jan 16, 2015	Jul 23, 2015	Renee M. Saville, Joshua A. Silverman, Eric G. Luning, Brandon D. Doss, Lorraine Joan Giver, Sol M. Resnick, Drew D. Regitsky	Microorganisms for the Enhanced Production of Amino Acids and Related Methods

(continued)

Cited patent	Filing date	Publication date	Applicant	Title
US 9365461 B2	May 23, 2014	Jun 14, 2016	Accelergy Corporation, Shanghai Advanced Research Institute of the Chinese Academy of Science	Integrated Processes for Producing Fuels and Biofertilizers from Biomass and Products Produced
US 5096481 A	Aug 30, 1990	Mar 17, 1992	David M. Sylvia, Amiel G. Jarstfer	Sheared Roots as a VA-Mycorrhizal Inoculum and Methods for Enhancing Plant Growth
US 5554530 A	Aug 4, 1994	Sep 10, 1996	J. Andre Fortin, Marc St-Arnaud, Chantal Hamel, Claude Chavarie, Mario Jolicoeur	Aseptic In Vitro Endomycorrhizal Spore Mass Production
WO 2013044212 A1	Sep 24, 2012	Mar 28, 2013	R. Stewart Smith, Ahsan Habib	Chitooligosaccharides and Methods for Use in Enhancing Soybean Growth
US20100255541 A1	May 16, 2008	Oct 7, 2010	Qiang Hu, Milton Sommerfeld	Advanced Algal Photosynthesis-Driven Bioremediation Coupled with Renewable Biomass and Bioenergy Production
WO1981003338 A1	Apr 27, 1981	Nov 26, 1981	J Litchfield, W Lawhon	Liquid Culturing of Sporulating, Ectomycorrhizal Fungi
CA2318925 A1	Jan 19, 1999	Jul 29, 1999	Alan Christopher Gange	Grass Treatment
US 8669082 B1	Aug 22, 2012	Mar 11, 2014	Omar Bagasra, Kamal Chowdhury, Verlie A. Tisdal, George E. Miller III, Rebecca Bullard-Dillard	Single Vessel Production of Butanol from Biomass Using Engineered Thermophilic Microorganisms
US20120190090 A1	Jan 24, 2012	Jul 26, 2012	Gregory Bokinsky, Jay D. Keasling	Microbial Conversion of Plant Biomass to Advanced Biofuels
US 9096859 B2	Jan 24, 2012	Aug 4, 2015	Gregory Bokinsky, Jay D. Keasling	Microbial Conversion of Plant Biomass to Advanced Biofuels
EP 2954043 A1	Feb 5, 2013	Dec 16, 2015	Vladimir Vujanovic, James J. Germida	Endophytic Microbial Symbionts in Plant Prenatal Care

Recent patent citation covering mycorrhizal application in soil for production of biomass and bioenergy

Cited patent	Filing date	Publication date	Applicant	Title
EP 2982241 A1	Aug 6, 2014	Feb 10, 2016	Eva Lucic, Louis Mercy	A Method of Mycorrhization of Plants and Use of Saccharides in Mycorrhization
WO201502860 A1	Aug 29, 2014	Mar 5, 2015	Symplanta Gmbh & Co Kg	System and Methods for Continuous Propagation and Mass Production of Arbuscular Mycorrhizal Fungi in Liquid Culture
US6271175 B1	Jan 19, 1999	Aug 7, 2001	Alan C. Gange	Grass Treatment
US6576457 B1	Dec 15, 2000	Jun 10, 2003	Sui-Sheng T. Hua	Fungal Media and Methods for Continuous Propagation of Vesicular-Arbuscular Mycorrhizal (VAM) Fungi in Root Organ Culture
WO2013098829 A1	Dec 30, 2011	Jul 4, 2013	Adholeya Alok	Novel Mycorrhizae-Based Biofertilizer Compositions and Method for Mass Production and Formulations of Same
US20150040629 A1	Dec 30, 2011	Feb 12, 2015	Adholeya Alok	Novel Mycorrhizae-Based Biofertilizer Compositions & Method for Mass Production & Formulations of Same
EP2797422 A1	Dec 30, 2011	Nov 5, 2014	Adholeya Alok	Novel Mycorrhizae-Based Biofertilizer Compositions and Method for Mass Production and Formulations of Same
US20110252847 A1	Dec 19, 2008	Oct 20, 2011	Torgny Näsholm, Henrik Svennerstam	Use of a Fertilizer Containing l-Amino Acid for Improving Root Growth and Growth of Mycorrhiza
US7901927 B1	Aug 8, 2006	Mar 8, 2011	Jerry R. Barrow, Mary E. Lucero	Transfer and Incorporation of Heritable Symbiotic Fungi into Non-host Plants
US20040211721 A1	May 24, 2004	Oct 28, 2004	Stamets Paul Edward	Delivery Systems for Mycotechnologies, Mycofiltration and Mycoremediation
WO2010037167 A1	Sep 30, 2009	Apr 8, 2010	Paul Robert Harvey, Steven Alan Wakelin, Maarten Harm Ryder	Use of *Penicillium* spp. to Enhance Plant Growth

(continued)

Cited patent	Filing date	Publication date	Applicant	Title
US20100021515 A1	May 16, 2007	Jan 28, 2010	Robin Duponnois	Novel Compositions of Fungal Inocula, Method for the Preparation Thereof, and Use Thereof for Improving the Growth of Cultures
WO2014160826 A1	Mar 27, 2014	Oct 2, 2014	Brett GYGI, John Kosanke, Patrick Reed	Compositions and Methods for Enhancing Plant Growth
EP2753177 A1	Sep 6, 2012	Jul 16, 2014	Peter Dahmen, Daniela Portz, Klaus Tietjen, Jean-Pierre Vors	Acyl-Homoserine Lactone Derivatives for Improving Plant Yield
US8524224 B2	Jan 31, 2011	Sep 3, 2013	Joan M. Henson, Kathy B. Sheehan, Russell J. Rodriguez, Regina S. Redman	Methods of Using *Curvularia* Strains to Confer Stress Tolerance and/or Growth Enhancement in Plants
WO2014160827 A1	Mar 27, 2014	Oct 2, 2014	Diego Omar Demares, Florencia Olivieri, Gabriel Osvaldo Gutkind	Compositions and Methods for Enhancing Microbial Stability
US 20080207448 A1	Jan 30, 2008	Aug 28, 2008	Donald H. Marx, Gregory Keith Lewis	Coated Seeds and Methods of Making Coated Seeds

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Recent Patents on Endophytic Fungi and Their International Market

14

Laith Khalil Tawfeeq Al-Ani

Abstract

An endophytic fungus is a very great microbe that can grow in all parts of plant, root, stem, leaf, and fruit. These fungi are alive inside the plant as symbiosis or mutualism. Through the life cycle of this type of fungi inside plant is coming from secreting secondary metabolite compounds that possible utilizing for plant and other fields. Many of these compounds can be a novel product. Therefore, this chapter offers the patents recently to show its importance for plants, industry, medicine, and ecosystem. Patents showed some of the novel isolates as genera *Neotyphodium* sp., *Muscodor* sp., *Curvularia* sp., and *Fusarium* sp. Also, many natural compounds were discovered as pyrrolizidine alkaloid, pericoannosin A, praeruptorin C, cytosporaphenone A, etc. There are many companies using these patents prepared in special formula to sell in international markets. This possibility is helpful to enhance the resistance of plants and humans from diseases without occurrence of any collateral damages. The international markets and research centers work together with patent may bring several new products of new strains or isolates and also new secondary metabolites of endophytic fungi to the markets. That can utilizing in different industries like as biopesticdes, and others that useful and to get the consumer confidence.

Keywords

Endophytes · PGPR · Biological control · Microbial formulations · Fusarium · Curvularia

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H. B. Singh et al. (eds.), *Intellectual Property Issues in Microbiology*,
https://doi.org/10.1007/978-981-13-7466-1_14

14.1 Introduction

Endophytic fungi are colonizing the internal tissue of plant. The "endophyte" as term first emerged in the late 1800s for the microorganisms that live in internal tissue of plants including leaf and stem (Wilson 1995; Porras-Alfaro and Bayman 2010; Gange et al. 2011), seed (Johnson et al. 2013), and root (Kwaśna et al. 2016; Singh et al. 2017). These are forming a set of plant-microbe interaction or called "symbiosis." While, several endophytic fungi produced mycotoxins through infection the seeds (Attitalla et al. 2010a, b).

Generally, endophytes include several microbes such as bacteria and fungi. Endophytic bacteria like PGPR are used in the agriculture to control plant diseases and enhance the plant growth (Al-Ani 2006, 2017a; Al-Ani and Al-Ani 2011; Mohammed et al. 2011,2013; Ray et al. 2017). Endophytic fungi are useful for plant by protecting it from plant pathogens including Trichoderma, nonpathogenic Fusarium, and others fungi (Al-Ani et al. 2013a, 2018; Al-Ani 2017b, 2018a, b, 2019a, b; Al-Ani and Albaayit 2018a, b), *Fusarium* (Al-Ani 2010; Al-Ani et al. 2013b; Al-Ani 2017b), mycorrhizae (Voříšková et al. 2017), *Penicillium* (Vega et al. 2006), *Colletotrichum tofieldiae* (Hiruma et al. 2016), *Curvularia* sp. (Teles et al. 2005), *Piriformospora indica* (Yadav et al. 2010), and other species.

Endophytic fungi mean the relation between fungi and plant without disease symptoms or called "symbiosis" that live inside the plant tissue without causing any disease. Also, it improved the longevity and photosynthetic capacity of plant without causing any demolition for the chemical and nutrient of life cycle under infection (El-Maghraby and Shebany 2014). Some of endophytic fungi can attack another part of plant through growing inside the plant systemically without incidence of any symptoms like some toxigenic species of *Fusarium* (Bacon and Hinton1996; Bacon et al. 2001), *Alternaria* (Tajet al. 2015), *Penicillium* (Vega et al. 2006), and *Aspergillus* (Palencia et al. 2010). Some endophytic fungi are pathogenic for other plants (Malcolm et al. 2013). On the other hand, endophytic fungi may induce many changes in the plants because it may produce mycotoxins. These changes include the morphology and physiology (El-Maghraby and Shebany 2014).

Endophytic fungi are known as enhancing the plant growth and biological control through inducing the change inside the cell metabolism of the plant. This happens after the endophytic fungi grow in spaces among cells or walls of the host plants. Endophyte can make bioactive chemical inside the plant that is used in life cycle such as (A) protection against plant pathogens and pests and (B) enhancement of plant growth (Owen and Hundley 2004). Some endophytic fungi can produce the bioactive chemicals that benefit it in the manufacture of medicinal compounds (Strobel 2003). Also, some will be as novel source to make biopesticides (Andrés et al. 2017), antioxidant, antibacterial, and anticancer (Rollando et al. 2017).

Two isolates of endophytic fungi *Alternaria alternata* and *Fusarium tricinctum* from leaves of *Solanum nigrum* are producing some phytohormones that are able to enhance the plant growth (Khan et al. 2015). Many isolated endophytic fungi of medicinal plant are producing the antibacterial compounds (Keswani et al. 2016; Kharwar et al. 2011). *Fusarium fujikuroi* as endophyte associated with *Taxus*

brevifolia is able to make gibberellins (Strobel and Daisy 2003). *Penicillium citrinum* LWL4 is induced of plant defense by the endogenous salicylic acid and jasmonic acid in the host sunflower plant against *Sclerotium rolfsii* stem rot (Waqas et al. 2015). The endophytic *Chaetomium globosum* isolated from the sterilize parts of plant *Nymphaea nouchali* that secreted several antimicrobial activities against very important bacteria *Staphylococcus aureus*, *Bacillus cereus*, *Pseudomonas aeruginosa*, and *Escherichia coli* (Dissanayakea et al. 2016). For mycotoxins that are produced by some endophytic fungi as toxigenic of *Chaetomium* species, five species of this genus produced a sterigmatocystin (Rollando et al. 2017).

14.2 Patents on Endophytic Fungi

Endophytic fungi are very attractive for the researcher to detect the new isolates or a novel chemical that includes the prominent of many countries such as the USA, the Kingdom of Saudi Arabia, Malaysia, New Zealand, Canada, Australia, India, China, the United Arab Emirates, Egypt, South Korea, Japan, Brazil, European countries, South Africa, and Jordan. In this chapter, some important patents on endophytic fungi (from 2000 to 2017) have been discussed. The patents of endophytic fungi comprised several fields in our life (Fig. 14.1). The fields are very

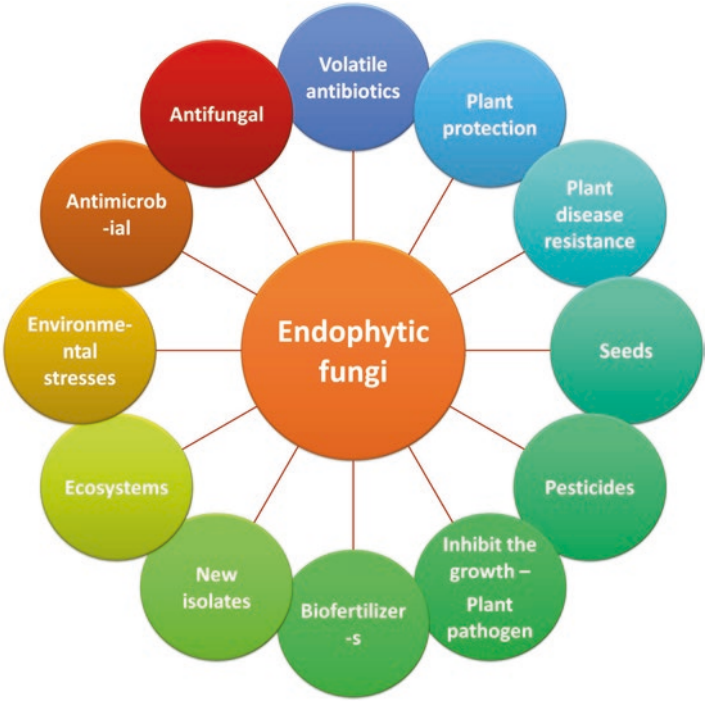

Fig. 14.1 Scheme showing the different fields of patents for endophytic fungi worldwide

interesting for the researchers and can be put under four general fields: (A) agriculture, (B) industry, (C) ecosystem, and (D) medicine.

14.2.1 Agriculture

14.2.1.1 Inducement of Plant Resistance and Enhancement of Plant Growth

Endophytic fungi are utilized worldwide as the agent in different fields of agriculture. Every time they detected a new isolate and taxonomic of endophytic fungi and then determine the role of this isolate for agriculture. Indeed, international patent of endophytic fungi in the field of agriculture has strong relevance with many novels of the traits. The traits are comprised of many main tools like protecting the plant from infection of diseases and pests, inducing systemic resistance and plant defenses, and enhancing the plant growth.

Many new patents were discovered and considered of the endophytic fungi that can be used in plant protection and inhibition of the plant pathogens. Green et al. (2011) isolate the novel endophytic fungi *Muscodor strobelii* that were able to protect the oil palm plant from plant diseases such as *Ganoderma boninense* and pests. These endophytic fungi can produce volatile compounds that kill the plant pathogens. Volatile compounds produced several chemicals after 14 days of *Muscodor strobelii* culture on PDA. Endophytic fungi from the grape as *Myrothecium verrucaria* can be used as a biocontrol agent instead of chemical pesticides against vine gray mold disease of grape that is caused by *Botrytis cinerea* (Zhi and Xiping 2017). Several antagonistic fungi can inhibit the growth of bacteria *Xylella fastidiosa* through producing radicinin that have antimicrobial activity (Rolshausen and Roper 2017). Umemura et al. (2012) obtained a glycosphingolipid and liposoluble substance that was extracted from filamentous fungus by using ethyl acetate (organic solvent). These chemicals can induce the plant resistance against the plant pathogens instead of fungicides. Some endophytic fungi can protect plants from diseases and pests. The endophytic fungi *Neotyphodium lolii* are protecting the grass plant from abiotic and biotic stress through raising the level of janthitrem epoxide compounds (Tapper et al. 2013). Also, the seed treatment of *Secale* spp. plant with some endophytic fungi conferred several levels of protection and also increased the resistance against plant diseases and pests (Hume et al. 2014, 2016). The soil, foliar, and seed of cotton were treated with spores of *Beauveria bassiana* and *Paecilomyces lilacinus* (endophytic fungi) that confer the protection against diseases and insect, as well as enhancement of the plant growth (Sword 2017). Therefore, some endophytic fungi can improve the plant growth and increase the production of seeds and yield.

Endophytic fungi can infect any part of the plant that is able to improve the plant growth and protection against diseases and pests by secreting several secondary metabolisms. Treating the seeds of a plant from the genera *Lolium* and *Festuca* with endophytic fungi of the genus *Neotyphodium* led to the improvement of the ability of plant to resist environmental stresses such as the toxic agents (West and Piper 2011). Several endophytic fungi such as *Coniothyrium* spp., *Cladosporium* spp.,

Penicillium spp., *Pseudeurotium* spp., and *Paraconiothyrium* spp. treated the wheat seeds that have the ability to enhance the seed vitality (mycovitalism), promote the plant growth and the plant nutrient uptake, increase the yield, and increase the resistance against plant pathogens and pests (Vujanovic and Germida 2014). The genera of fungi such as *Coniothyrium*, *Pseudeurotium*, and *Paraconiothyrium* are the novel endophyte strains that can produce the gibberellins and ABA. Then, Stewart and Brown (2016) prepared a suitable nutrient media to increase density of the colony-forming unit (CFU) of *Clonostachys rosea* strain 88-710 that is able to improve the plant vigor through combining with the root to produce the phytohormones as indole-3-butyric acid (IBA). The same strain of *Clonostachys rosea* is used to enhance the plant vigor of plant through spraying the foliar of plant and coating the seeds such as corn, wheat, and soybean (Brown2016). The conidia germination of *Clonostachys rosea* is tolerating many fungicide groups. Some of the endophyte is able to improve the agronomic characteristics of the cotton crop (Sword 2016). *Neotyphodium lolii* and *N. coenophialum* have the ability to reduce the toxicity of ryegrass and enhance the plant resistance against diseases and production of antifungal (Spangenberg et al. 2016). Endophytic fungi *Chaetomium globosum* can increase the biomass of *Salvia* plant and content of the component of both tanshinone and phenolic acids (Jian et al. 2017). Some endophytic fungi are mixed with compost to make a biofertilizer powder mixture (Idris et al. 2015; Jacobson et al. 2017).

14.2.1.2 Production of Antimicrobials

Endophytic fungi produce many antimicrobials which can be used against pathogenic fungi and bacteria, nematodes, and insects for plants and animals. Endophytic fungi *Neotyphodium* spp. of the grass *Elymus canadensis* can secrete secondary metabolites inside the plant which encourage the agronomic characteristics of a host plant (Young and Hopkins 2008a,b, 2011). *Muscodor albus* as novel endophytic fungi can produce volatile antibiotic compounds and can be analyzed by using the GC-MS (Strobel et al. 2010a). Two species of novel endophytic fungi of *Muscodor* sp. include *Muscodor albus* and *Muscodor roseus* that produce an active mixture of volatile antibiotics against plant diseases and pests (Strobel et al. 2010b). The chemical of polynucleotides and polypeptides was purified from a strain of *Muscodor strobelii*; these chemicals have the ability to inhibit or kill the plant diseases and pests (Green et al. 2010). Two isolates of fungi *Nodulisporium* spp. and *Ascocoryne* spp. produced some organic compounds such as polypeptides and can collect them, from the culture, fungal cells, and medium or from air space associated with the fungus and culture medium (Mann et al. 2012). Strains of *Muscodor albus* and *M. roseus* omitted several volatile compounds that have the active effect that relates with pesticides like nematicidal, bactericidal, fungicides, and insecticidal (Strobel et al. 2012a,b). Also, many volatile organic compounds can be produced from fungi *Hypoxylon* sp., *Muscodor* sp., and *Nodulisporium* sp. in growing suitable media (Strobel and Tomsheck2013). The culture of *Daldinia* sp. produces many volatile compounds that possibly kill or reduce the growth of plant pathogens (Ezra et al. 2016). *Chaetomium* sp. produces secondary metabolites at low cost (Zhao et al.

2017). A pyrrocidine compound of endophytic fungi was produced by fermentative production, and this compound is produced at the low cost and has antifungal and antitumor activity (Bin et al. 2017). The genus *Muscodor* sp. produced several volatile compounds including propanoic acid, 2-methyl; 1-butanol, 3-methyl, acetate; 1-butanol; and ethanol (Gandhi et al. 2017). *Stemphylium solani* can produce a novel compound and has the biocide effect against pathogens (Gonzálezet al. 2017).

14.2.2 Industry

Endophytic fungi are very interesting and distributed in all plants naturally. These fungi are playing an important role in industry such as feeding, incense, and biofuel. The patent of Craven (2010) found the method to infect the grass with several endophytic fungi that enhance the propagation of grass and increase the feed and biofuel. The mixture injection in xylem of agarwood (*Aquilaria sinensis* tree) induced the defense reaction and forms the incense through 6–24 months; this mixture is the mixing of solution (acetic acid and methanoic acid) and some fungi such as *Hypocrea jecorina*, *Colletotrichum gloeosporioides*, *Fusarium* sp., *Khuskia* sp., *Ampelomyces* sp., *Hypocrea lixii*, *Pestalotiopsis* sp., *Chaetomium* sp., and *Botryosphaeria rhodina* (Guan et al. 2012).

14.2.3 Ecosystem

Endophytic fungi can protect the plants from the environmental damage. A strain of *Curvularia* was treated with *Dichanthelium languinosum* grass in geothermal zone, which increases its tolerance against bad conditions such as thermal and drought (Henson et al.2007, 2013), by secreting the secondary metabolite compounds (Henson et al. 2011a,b). Inoculation of many seeds of different plants with endophytic fungi is beneficial for the environment; this occurred using the composition method with cardboard to remove the dioxide carbon from the atmosphere to reduce the warming of the world (Stamets 2008). In the genus *Neotyphodium* of endophytic fungi that infected the grass of both seeds and plant of the genera *Festuca* and *Lolium*, this infection played a role in enhancing the grass tolerance against stresses of environment, such as reduced or no toxicity from livestock or other grazing animals, heat, and drought (West and Piper 2008,2009). *Fusarium culmorum* isolated from the dune grass, *Leymus mollis*, in beaches of Washington State can stimulate the plants of both monocots and dicots against salt stress; this isolate can decrease the level of salinity in the soil (Redman and Rodriguez 2010). *Clonostachys rosea* can stimulate the plant against the environment stress (Stewart and Brown 2016).

14.2.4 Medicine

Coexistence of endophytic fungi in intercellular among tissues of the plant have proven the role importance its in enhancement the high bioactive resource of natural products and also novel products. The products can use them as possible in medicine field through pharmaceutical production that of them is anticancer, antioxidant, antiviral, etc. The novel strain of *Pestalotiopsis microspora* 12–30 can produce the novel compounds as 3,5,7 trisubstituted isobenzofuranone and 1,5,7 trisubstituted 1,3-dihydroisobenzofuran and derivatives that are possibly used as an antioxidant and antimycotic agent (Strobel et al. 2007). Endophytic fungi (strain no. MTCC5124) can produce a chemical structure camptothecin (camptothecinoids) that is used for anticancer activity (Puri et al. 2010). Also, it is possible to extract several chemicals from grass locoweed (swainsonine) that is enhanced by endophytic fungi Undifilum oxytropis; these chemicals can be used as antineoplastic, inhibiting metastasis and tumor cell growth (Jincheng et al. 2012).

Strain of *Aspergillus* sp. 085242 is able to produce a compound of asperterpenols A; this is a drug used to treat liver cancer and for the preparation of anti-hepatoma; this compound is a strong inhibitor for a hepatoma carcinoma cell (Yan 2014). Also, asperterpenols A form *Aspergillus* sp. 085242 that is used to prepare anti-ovarian cancer drugs (Xianrong 2016). Endophytic fungi *Cytospora* that is isolated from rhizosphere is able to produce a cytosporaphenone A compound that is used as an antineoplastic and antitumor drug; therefore, it is possibly used to be the new anticancer drugs (Hong et al. 2017). Many species of endophytic fungi were isolated of the grass Brachiaria-Urochloa; these endophytic fungi are the primary source of antibiotics, immunosuppressants, anticancer agents, and cholesterol-lowering drugs (Spangenberg et al. 2017).

A novel class of alkaloid compound could produce by fermenting the culture of fungi which is used as the antiviral agent to treat the herpes simplex virus type 1 (HSV-1) and also acceptable to use in pharmaceutical salts that used it for treated the disease caused by HSV-1 (Changlun et al. 2017). Novel pyrrolizidine alkaloid comprising penibruguieramine A and ophiopogonin B is extracted from an endophytic fungus *Penicillium* sp. GD6 that can be used in the pharmaceutical composition which is used in prevention and treatment of chronic nephritis (Di 2017). While Di and Deshun (2017) who invented a method to utilize pericoannosin A and praeruptorin C for prevention and treatment of acute cerebral infarction produced by the endophytic fungus *Periconia* sp.

14.3 International Market

The importance of endophytic fungi has appeared every time worldwide. There are many characteristics that attract researchers for discovering the new isolates. I found many isolates very interesting and can use them in the production of biofertilizers, biopesticides, natural product for the drug, and bio-industry. But, the exploitation of microorganism is very poor though abundant in the production of bioactive novel

compounds using different fields. But many centers of technology are utilizing the endophytic fungi in coating the seeds of crops and grass that they bring and sold in international market. The Texas Foundation Seed Service (TFSS) is a unit of Texas A&M AgriLife Research and is very active in seed and agricultural organizations in the USA, as well as AgriLife internal committees that have team including the Commercialization, Small Grains Advisory Committee, and Intellectual Property Management (Brown2010).

The endophytic fungi are used in the market by coating the seeds; the Adaptive Symbiotic Technologies in Seattle, Washington, brought market the first commercial product of microorganisms as endophytic fungi – enhancing the plant growth and selling the rice and maize (corn) seeds are coated with a mixture of fungi (Jones 2013). BioEnsure Company that used 28 states produces the seed formula of rice and corn treated with fungal strain that is ready to sell (Demarest 2015). Also, Adaptive Symbiotic Technologies (AST) is working on formulas for sugarcane, barley, cotton, and grasses, among others, which many companies such as Monsanto, DuPont, Bayer, and INCOTEC were testing the efficacy of BioEnsure product of the formula seeds (Demarest 2015). These examples indicate to use endophytic fungi with the substrate to make a mixture that can be doing a coating for seed. This mixture can stimulate the seed germination (mycovitalism) and protection of seed from diseases, pests, and abiotic stress. Also, they can produce biofertilizers containing endophytic fungi. Several rules are put to guarantee the quality of microbial-based fertilizers present on the market, and then they boost farmers to use it in the field (Malusá and Vassilev 2014).The companies of Novozymes and Symbiogenica are producing the microbial for agricultural crops that are possibly translatable to biofeedstocks. Novozymes company produces several microbial-based products such as Optimize® of TJ Technologies (tjtechnologiesinc.com) (Hamilton2014).

Muscodor albus is a novel isolate and already registered as patent, so that Marrone Bio Innovations got the license to use it and EPA approved the potential in using these isolates in agriculture (Lugtenberg et al. 2016). In New Zealand, it used the novel endophytic fungi through a company Avanex® Unique Endophyte Technology that is a registered trademark of Grasslanz Technology in Australia and New Zealand, and it used three endophyte fungi isolates of novel patent the genus *Neotyphodium* sp. that is comprised of AR601, AR94, and AR95 (Avanex Brochure 2017). More than 20 natural product-derived drugs are brought to international market worldwide from 2001 to 2005 as well as used in about 140 all major therapeutic areas (Butler 2005; Lam 2007).

14.4 Conclusion

Endophytic fungi have been isolated from leaf, stem, root, and fruit and have the high capacity to compete with other microbes by secreting many secondary metabolism compounds in space among tissues. These characteristics are the attract zone for several inventors to find a novel isolates or secondary compounds. The recent

patents have been separated to four points as it is assumed according to the type of service or benefit.

In this chapter, show a brief of patents of countries but there are many countries not including here, due to difficult reach it. While they found the role of patents in the agriculture field through inducing the plant resistance against the harsh conditions both biotic and abiotic stresses. The biotic condition as the bioenemies likes (A) plant pathogens include viruses, bacteria, nematode, fungi, viroids, and plant parasite, also, (B) pests such as mite and insect. Additionally, endophytic fungi are helping plant as mutualism by utilizing the nutritional for tissues and secreting compound enhancement of the plant growth like indole acetic acid and gibberellins. While, abiotic conditions are comprising salts in soil, pH, drought, cold, etc. Also, some patents are used to extract novel secondary compounds to treat the dangerous diseases such as anticancer, anti-inflammatory, antiviral, antioxidant, and antimycotic agent as well as used in industry like increasing the feed and biofuel.

The genera of endophytic fungi as *Neotyphodium* sp., *Muscodor* sp., *Curvularia* sp., and *Fusarium* sp. are novel isolates having the special characteristic in production of the secondary compounds which are useful for plants and human. Therefore, the technology agriculture companies exploited the patents of novel isolates and bring to international market under special formula for using in the fields from farmer or utilizing of natural product like pyrrolizidine alkaloid, pericoannosin A, praeruptorin C, cytosporaphenone A, and others in the drug products by specialized in pharmaceutical industries. The products of biofertilizers, biopesticides, Bio Natural Products, and bio-compounds in drugs are offered in the international market at special design which is confirmed by researchers in the specialist research centers. The confirmation must be displayed in different media such as TV, papers, and the Internet, so it may arrive to the consumers, and they encourage them to buy them and use them in the fields and insert them in manufacture of the drugs or other industries.

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Part III

Intellectual Property Issues in Pharmaceutical Microbiology

The Biopharmaceutical Social Contract and U.S. Patent Social Contract: Historical Antecedents and Recent Developments

15

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Abstract

The chapter starts by examining the Biopharmaceutical Social Contract in light of the historical Patent Social Contract. It reviews the importance of intellectual property protection for biopharmaceutical innovation, including regulatory data protection, trade secrets, undisclosed information, and patents. It further considers the impact of the Hatch-Waxman Act and more recent US intellectual property ("IP") developments that substantially alter the Patent Social Contract for biopharmaceutical inventions, arising out of statutory changes and Supreme Court precedent. In particular, it reviews patent law amendments resulting from US legislation (Biologics Price Competition and Innovation Act and the Leahy-Smith America Invents Act) and Supreme Court precedents (*Mayo Collaborative Services v. Prometheus Laboratories, Inc.*, *Molecular Pathology v. Myriad*

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H. B. Singh et al. (eds.), *Intellectual Property Issues in Microbiology*,
https://doi.org/10.1007/978-981-13-7466-1_15

Genetics, and *Cuozzo Speed Technologies, LLC v. Lee*). It explores the impact of *Mayo* and *Myriad* (broadening the exceptions to patent eligibility for products of nature) and *Cuozzo* (lowering the standard to prove patent invalidity) on biopharmaceutical innovations and provides future perspectives for proper balancing of the patent social contract with a move from a litigation-focused to an innovation-focused patent system for biopharmaceutical drug development.

Keywords
Biopharmaceutical · Patent social contract · Patents · Regulatory data protection · Trade secrets · Undisclosed information · AIA · BPCIA · IPR · Mayo · Myriad · Cuozzo

15.1 Introduction

In recent years we have seen renewed interest in the proposed Biopharmaceutical Social Contract, focusing on drug pricing and the public interest in ensuring affordable and sustainable assessment to medicines. The importance of patents has gotten short shrift in the discussion, and this chapter focuses on the historical understanding of the US patent system as a social contract providing mutual benefits to innovators and the public to ensure sustainable commercialization of novel healthcare products and their broad availability to the public.

Historically, patents have provided a strong base for commercialization of innovative healthcare products, akin to the foundation for a house. Life sciences patents provide incentive for the discovery research and early preclinical development for a new innovative drug (molecule). For highly regulated products like biopharmaceuticals, however, filing a patent application is an early step in a lengthy and challenging process of research and development that generates a vast amount of highly confidential and commercially valuable regulatory data. At the time of patent filing – and generally even at the point of patent issuance – most biopharma research programs have not reached the clinic, where the vast majority falls far short of full commercialization. Where patents protect the initial research yielding the new invention, regulatory data protection ("RDP"), often referring to the protection of "D" in the research and development (R&D) process, protects the development, including data generated during clinical trials, subsequent to the invention. If patents are the foundation of the biopharma house, RDP puts a roof over its head.

America's Founders provide key insights into the social contract role of patents in the commercialization and assimilation of new technologies for creation of social and economic benefit. From the earliest days of the American Republic, patent administration was placed at the apex of national economic policy, with impressive results. The more recent development of RDP norms also provides important lessons in terms of the overall importance of statutory and regulatory protection for so-called undisclosed information, e.g., commercially valuable trade secret regulatory data, long shared with health authorities as a condition of gaining marketing approval.

Rooted in the US Constitution, the patent system supplanted state-based patent systems and provided inventors with the opportunity to seek one patent for the entire country. In contrast, RDP recognizes the substantial effort required by the innovator to meet regulatory requirements and safeguards the confidential, commercially valuable regulatory dossier, also known as undisclosed information or essential trade secrets, of innovators. Taken together, patents and know-how protected by RDP and/or trade secrecy are the key research assets for any innovative biopharma company. Moreover, the large numbers of patents generated every year in the United States are critical in the technology transfer system as a market mechanism that small biotechnology start-ups, universities, and others use to generate licensing revenues and raise money for further R&D.

In this context, the increasingly challenging patent environment that has developed over the last decade – including US Supreme Court precedents (*Mayo Collaborative Services* vs. *Prometheus Laboratories, Inc.*,[1] and *Molecular Pathology v. Myriad Genetics*[2]), US Patent and Trademark Office ("USPTO") practice guidelines, and post-grant inter partes review ("IPR") processes – undermines the presumption of patent validity and erodes the exclusivities provided under the patent system, with unintended consequences including a greater reliance on trade secrets instead of patent protection and smaller investment in potentially life-changing genomic diagnostics and therapeutic innovations.

15.2 The BioPharmaceutical Social Contract vs. The Patent Social Contract

For many years, the functioning of the patent system has been described as a social contract between the inventor and the larger society. Commercializing life sciences inventions is highly dependent on both patents and trade secrets, even more so than other high-tech sectors, as IP may be an emerging biotech company's primary asset. As per US law, most patent applications are made public – published electronically – 18 months after filing. Following publication, the patent application is available to anyone with a high-speed Internet connection, along with the full filing history. Therefore, the patenting process makes critical contributions to scientific progress and knowledge availability to individuals at a global scale.

In this way, the patent system acts as a social contract that grants exclusive rights to inventors for a limited period of time in return for detailed disclosure of the invention for the benefit of all. The Patent Social Contract, however, depends on availability of quiet title for granted patent, i.e., that a granted patent will enjoy the presumption of validity – whether to exploit the invention exclusively or to enter into one or more licensing agreements, as appropriate. Instead, in the US patent system, right holders endure serial challenges that undermine the presumption of

[1] Mayo v. Prometheus, 566 U.S. ___ (2012).

[2] Association for Molecular Pathology v. Myriad Genetic, 569 U.S. ____ (2013).

validity for issued patents, eroding the Patent Social Contract and leading to perverse outcomes as discussed above.

Given the general unpopularity of patents in the popular media, it is perhaps unsurprising that Brent Saunders, chairman, president, and CEO of Allergan, announced a new social contract with patients via the CEO Blog in September 2016. While acknowledging the immense capital investment required for commercialization of innovative healthcare products, Saunders avoided any mention patents or marketing exclusivity (RDP). Skirting the issue of America's increasingly dysfunctional patent system, Saunders was lauded for his commitment to limit price increases and enhance access programs for low-income patients. Rather than calling for renewing the Patent Social Contract to provide the quiet title needed for sustainable biopharma innovation, Saunders restated the company's commitment to "innovation, access and reasonable pricing ideals" for medicines.[3] Accordingly, the Allergan social contract stressed innovation without exclusivity, an impossible equation that ignores the central importance of effective IP protection to an enabling environment for biopharmaceutical innovation.

Plaudits for the Allergan CEO predictably turned to brickbats in September of 2017 after the company pursued a highly creative solution in the quest for quiet title for patents relating to Restasis™, Allergan's flagship ophthalmology drug; "Restasis is Allergan's second best-selling product, behind the wrinkle treatment Botox, bringing in nearly $1.5 billion in 2016."[4] Faced with the threat of "double jeopardy" due to parallel USPTO Inter Partes Review (IPR)[5] and Hatch-Waxman Para IV judicial challenges to the Restasis patent, Allergan licensed the patent to the St. Regis Mohawk Tribe in order to assert sovereign immunity from IPR.[6] Predictably, the

[3] Allergan CEO Blog. 2016. Our Social Contract with Patients. https://www.allergan.com/news/ceo-blog/september-2016/our-social-contract-with-patients. Accessed 26 October 2017.

[4] Thomas, Katie. 2017. Patents for Restasis Are Invalidated, Opening Door to Generics. New York Times. https://www.nytimes.com/2017/10/16/health/allergan-restasis-patent-.html?_r=0. Accessed 26 October 2017.

[5] In 2011, Congress enacted the America Invents Act ("AIA") (*see* Leahy-Smith, America Invents Act (AIA), Pub. L. No. 112–29, 125 Stat. 284 (2011)) and created three new Post Grant Proceedings ("PGP") that can be initiated by a third party (not patent owner), including IPR, a new proceeding, intended to replace inter partes reexamination proceedings, in which third parties can actively play a role in challenging the validity of issued patents before the Patent Trial and Appeal Board ("PTAB") at the US Patent and Trademark Office. IPRs are designed to be a faster and less expensive proceeding than district court litigation, but IPR proceedings are quasi-judicial in nature and differ significantly from district court litigation; besides IPR, the other two PGPs are Post Grant Review ("PGR") and Post-Grant Validity Review of Business Method Patents, often referred to as Covered Business Method ("CBM"). PGR must be filed no later than 9 months after patent issuance or issuance of reissue. While the grounds for filing IPR are patent invalidity under 35 U.S.C. §§ 102 and 103 based on prior patents and publications, the ground for filing PGR is any ground for patent invalidity under 35 U.S.C. except for failure to comply with the best mode requirement. PGR, therefore, could also be used for invalidating Orange Book-listed patents issued within 9 months, particularly under a ground for patent invalidity other than under 35 U.S.C. §§ 102 and 103 based on prior patents and publications.

[6] Carroll, John. 2017. Allergan's tribal treaty in Restasis patent fight triggers a Congressional donnybrook. Endpoints News. https://endpts.com/allergans-tribal-treaty-in-restasis-patent-fight-triggers-a-congressional-donnybrook/. Accessed 26 October 2017.

lion's share of attention has gone to Allergan's ability to assert sovereign immunity due to its agreement with the St. Regis Mohawk tribe, with widespread outrage at how Allergan has defeated the intent of the IPR process. The sheer audacity of Allergan's approach of asserting sovereign immunity through a third party – and the relative weakness of the underlying patents that within weeks of the Allergan's tribal assignment were invalidated in court[7] – obscured the real threat to biopharmaceutical innovation from the erosion of quiet title.

The bottom line: the USPTO's IPR process and parallel judicial Hatch-Waxman challenges have created an unsustainable degree of uncertainty for patent holders, at least with respect to the innovative life sciences. In fact, Allergan's willingness to take this extreme pathway to extinguish the IPR process begs the question: can biopharma companies succeed without renewal of the patent social contract?

In this context, it may be helpful to review the foundations of social contract theory generally and with regard to the patent system. The principles underlying social contract theory were articulated first by seventeenth-century philosopher Thomas Hobbes. In the *Leviathan or The Matter, Forme and Power of a Commonwealth Ecclesiastical and Civil*,[8] Hobbes famously asserted that the absence of organized government with the power to enforce civil and commercial rights, i.e., the "state of nature," would result in a state of continual war[9]:

> Whatsoever therefore is consequent to a time of war, where every man is enemy to every man, the same consequent to the time wherein men live without other security than what their own strength and their own invention shall furnish them withal. In such condition there is no place for industry, because the fruit thereof is uncertain: and consequently no culture of the earth; no navigation, nor use of the commodities that may be imported by sea; no commodious building; no instruments of moving and removing such things as require much force; no knowledge of the face of the earth; no account of time; no arts; no letters; no society; and which is worst of all, continual fear, and danger of violent death; and the life of man, solitary, poor, nasty, brutish, and short.

As articulated by Hobbes, life outside of an established civil order is extremely unpleasant. In the state of nature or pre-social state, everyone has a right to all things, but no individual is guaranteed anything – this represents the first component of Hobbes' delineation of the social contract. While it is true that there are no limits placed on one by any higher power, by the same rationale, there exists no form of protection to which one can turn for assistance. Moreover, life is not worth all that much without the comforts provided by productive industry culture or society. The state of nature is more symbolic than actual, designed to demonstrate that a rational agent in such a situation would readily agree to enter into a social compact for reasons of self-preservation.

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[7] Thomas, Katie. *Op. cit.*

[8] Hobbes, Thomas. 2016. *Leviathan or The Matter, Forme and Power of a Commonwealth Ecclesiastical and Civil*. eBooks@Adelaide, The University of Adelaide Library. https://ebooks.adelaide.edu.au/h/hobbes/thomas/h68l/. Accessed 26 October 2017.

[9] *Id.*, Ch. 13.

Hobbes explication of the second component is the individual's capacity to live within a society and to seek at least a minimum level of material satisfaction without constant threats to his existence through allegiance to a sovereign. Hobbes' agent in the state of nature would lack all of those goods associated with life within the regulated state. This presages the third element in Hobbes' social contract theory, i.e., the psychological conception of the self, where the individual will pursue desires and ends through submission to an absolute sovereign, i.e., an all-powerful king or queen. The rational actor within Hobbes' scenario lays aside the right to all things in order to guarantee rights to the fruits of her own labor; this is also expressed as the only way to promote industry, develop culture, and elevate the overall quality of life and avoid constant insecurity, safeguard her life, and attain a measure of comfort and at least limited freedom.

As social contract theory has evolved over time, it has retained the basic structure of Hobbes' original formulation, with less pessimistic assumptions relating to the basic selfishness of man as it evolved through John Locke's writings on *Second Treatise on Government*[10] and subsequently through John Rawls' philosophy in *A Theory of Justice*.[11] The three common structural elements include (1) a pre-social state, (2) the agent and his individual capacities and interests for living within a society, and (3) the psychological conception of the self that can be advanced through the social contract.

Moving forward to the twentieth century, John Rawls provided most internally consistent and extensive revision of social contract theory. Building on the foundation of social contract theory provided by Hobbes and Locke, John Rawls constructed his definitional approach to justice in what he calls the well-ordered society, with the original position standing in for the pre-social state of nature.

Like Hobbes and Locke before him, Rawls employs the original position as an expository device in order to establish the assumptions which are critical to the well-ordered society. Rawls' agent in the original position is defined as a totally anonymous individual with no knowledge of his or her personal circumstances, individual qualities, likes, prejudices, or values (i.e., conception of the good). The claim is made in this way that an individual would be capable of unbiased choice through a shared lack of information. Accordingly, the agent in the original position is entirely neutral[12]:

> Among the essential features of this situation is that no one knows his place in society, nor does anyone know his fortune in the distribution of natural assets and abilities, his intelligence, strength and the like … The principles of justice are chosen behind a veil of ignorance.

The other major advance in Rawls' conception of the social contract is that not all agents are defined as having equal abilities or similar outlooks. If everyone had the

[10] Locke, John. 2005. *Second Treatise on Government*. http://www.earlymoderntexts.com/assets/pdfs/locke1689a.pdf. Accessed 26 October 2017.

[11] Rawls, John. 1971. *A Theory of Justice*. Cambridge: Belknap Press, Harvard University.

[12] *Id.* 12

same natural endowments, social status, personal wealth, etc., then the veil of ignorance would be unnecessary.

Through the artificial elimination of that knowledge, Rawls believes the veil of ignorance would result in the selection of "justice as fairness," i.e., "that the principles of justice are agreed to in an initial situation that is fair."[13] In sum, Rawls' agents are unaware of their own particular place in society and so have no choice except to choose rationally justifiable and fair principles of justice.

He calls the process of reasoning "reflective equilibrium," where all of the participants propose and debate premises for the fair organization of the civil state.[14] Rawls believes that this process would yield the greatest amount of liberty consistent with his principles of justice[15]:

> Since all are similarly situated and no one is able to design principles to favor his particular condition, the principles of justice are the result of a fair agreement or bargain. For given … the symmetry of everyone's relations to each other, this initial situation is fair between individuals as moral persons, that is, as rational beings with their own ends.

Rawls' agents are both autonomous and mutually disinterested, i.e., conceived as not having any positive or negative stake in each other's interests. With this in mind, Rawls outlines two principles of justice: equality in allocation of basic rights and responsibilities ("First Principle: Each person is to have an equal right to the most extensive total system of basic liberties compatible with a similar system of liberty for all.")[16] and some degree of compensation for the inevitable inequalities of wealth, social position, and/or authority ("Second Principle: Social and economic inequalities are to be arranged so that they are both a) to the greatest benefit of the least advantaged, consistent with the just savings principle, and b) attached to offices and positions open to all under the conditions of fair equality of opportunity.").[17] These principles require substantial explanation; however, the basic intent is clear: Rawls social contract envisions a society where no one takes advantage of any others, and no one shall gain at the direct expense of the other.

Moreover, the broader benefit of Rawls' social contract would flow to future generations, where in fact we have no way of knowing the natural endowments, social status, and economic class of our own descendants. In this context, the original position is not mere theory and applies equally in our own time.[18] Through the enforced ignorance of participants in the original position, future generations are protected and provided with the broadest degree of liberty consistent with principles of justice and fairness.

[13] *Id.* 12.
[14] *Id.* 20.
[15] *Id.* 13.
[16] *Id.* 302.
[17] *Id.* 14–15.
[18] *Id.* 209.

Accordingly, the original position is much more defensible as a basis for decision-making with regard to future generations than as a theoretical construct for the present generation (or the present generation in 1971). Rawls concludes that open access to positions of authority and the economic and social mobility that accompanies freedom of opportunity will advance both the interests of society and the individual who is rewarded according to his abilities. He also orders the two principles such that the second principle should not be allowed to override the first ("These principles are to be arranged in a serial order with the first principle prior to the second. This ordering means that a departure from the institution of equal liberty required by the first principles cannot be justified by, or compensated for, by greater social and economic advantages.").[19]

With this brief history and explication of social contract theory, the historical significance of the Patent Social Contract comes into focus. Like Hobbes' and Locke's agent in the state of nature, the individual innovator has no way to exclude others without the social contract of the national patent system. Like Rawls' parties in the original position, the patent system is designed to provide the greatest degree of liberty for individuals to pursue their own interests, consistent with the equality of opportunity. To fully understand the broader social and economic context of the Patent Social Contract in the United States, it may be helpful to review the historical roots of the US patent system, together with the more recent development of protection for regulatory data packages, also known as regulatory data protection or RDP.

15.3 Historical Social Contract Roles of Patents

America's founders recognized the importance of IP protection as an engine of creativity, innovation, and economic development, enshrining exclusive rights for authors and inventors in Article I of the US Constitution ("The Congress shall have the power to lay and collect taxes, duties, imposts and excises, to pay the debts and provide for the common defense and general welfare of the United States; but all duties, imposts and excises shall able uniform throughout the United States; … too promote the progress of science and useful arts, by securing limited times to authors and inventors the exclusive right to their respective writings and discoveries.").[20] So, it is worth revisiting early US history of patents, with an in-depth look at one particular inventor, Oliver Evans, and his Evans Mill System that revolutionized flour milling in the eighteenth century.

National patent protection and related technology transfer played a critical role in early US economic development, both in terms of providing a framework for the national economy and also establishing the United States as an agricultural export powerhouse from the earliest years of the American Republic. The Act of April 10, 1790, established the American patent system and created the Patent Board with

[19] *Id.* 61.

[20] US Constitution, Article I, §8, clause 8.https://usconstitution.net/xconst_A1Sec8.html. Accessed 26 October 2017.

members including then-Secretary of State Thomas Jefferson, then-Secretary of War Henry Knox, and then-Attorney General Edmund Randolph.[21] The Department of State was charged with overall administration of the new patent system, with the earliest patents signed President Washington, Thomas Jefferson, and Edmund Randolph.

15.3.1 Case Study in Early Tech Transfer: The Evans Mill System Patent

In this day and age, it may be hard to imagine the absolute priority accorded to patents by the Founding Fathers. To understand the importance of new technologies to the nascent US economy, it is worth taking a closer look at one technology that proved to be of particular interest to both George Washington and Thomas Jefferson.

Serial inventor Oliver Evans introduced a number of advanced agricultural and industrial processes over the course of his lifetime. Evans revolutionized the process of flour manufacture with the Evans Mill System, enshrined in US Patent No. 3. Recognized as the first mass production process, they automated the manufacture of high-quality flour in a fraction of the time associated with the fragmented and labor-intensive traditional methods for flour milling.[22]

Prior to the establishment of the federal patent system, Oliver Evans had been awarded exclusive patent rights in the State of Maryland, Pennsylvania and New Hampshire, which he relinquished in order to avail himself of federal patent rights. Generally speaking, patents provide "negative" rights: excluding all others from gaining benefit from the inventor's work for a fixed 20-year period. This does not guarantee that the patented invention will be profitable; in our own time, the vast majority of biopharma patented inventions fail to make it through the R&D process and do not reach the market as new healthcare products, and this may have been the same for inventors of new technologies during the colonial period and during the early days of the American Republic. In this context, the federal patent system proved much more effective than state-by-state patenting in advancing the assimilation and adoption of new technologies for creation of social and economic value.

In or around 1800, Thomas Jefferson also built a grist mill, realizing in retrospect that his millwright had relied heavily on Evan's technology. In 1808 Jefferson wrote to Evans to make amends and to provide payment for use of the technology: "I am informed and indebted to you for the machinery erected and interest on it, $89.60 [$1,545 today], which sum I therefore now remit you in a draft on the Bank of the United States."[23] Evans wrote back to Thomas Jefferson, expressing his "sincere thanks … I can say with truth that had all those who had used my improvements

[21] Press Release #02-26.2002. The U.S. Patent System Celebrates 212 Years.https://www.uspto.gov/about-us/news-updates/us-patent-system-celebrates-212-years. Accessed 26 October 2017.

[22] Moore, Sam. 2011. Oliver Evans' Improved Grist Mill. http://www.farmcollector.com/equipment/oliver-evans-improved-grist-mill. Accessed 26 October 2017.

[23] *Id.*

paid as generously as the President of the U.S., I might have been enabled to render my country much greater service."[24]

Looking forward, newly issued patents remain a critical market mechanism for technology transfer, where emerging biopharma companies, universities, and others leverage patents and related know-how to generate licensing revenues to support further R&D.

For innovative life sciences in particular, patents also play a critical role in monetizing the value of ongoing research programs for emerging biopharma companies – a very high-risk enterprise in which failure is more common than success. Now as then, a strengthened patent system would provide an economic boon to inventors and act as incentive to investors to invest capital in high risk and high reward life sciences R&D.

15.4 Regulatory Data Protection/Trade Secrets/Undisclosed Information

Development of RDP policies is a much more recent phenomenon as compared to the US patent system, dating back to the passage of the 1984 Drug Price Competition and Patent Term Restoration Act (PL 98-0417), and known as the Hatch-Waxman Act ("Hatch-Waxman"). The Hatch-Waxman Act created procedures regulated by the Food and Drug Administration ("FDA") for generic drug approval and market entry both before and after the brand name drug patents expire.[25] Consequently, the Hatch-Waxman Act allowed for an expedited pathway for generics to enter the United States, circumventing extensive procedures for new drug approval, which could not previously be done until the brand name drug patents expired. To achieve this result, the Hatch-Waxman Act reversed the decision in *Roche Products, Inc.*, *v. Bolar Pharmaceutical Co*.,[26] by enacting 35 USC 271(e)(1) which insulates generic manufacturers from infringement claims during their development of bioequivalent drug products, and restored a portion of the terms of the original innovators' patents that had been lost due to the testing required for FDA approval. The Hatch-Waxman Act also allowed a drug manufacturer to seek generic drug approval by submitting an Abbreviated New Drug Application ("ANDA").[25] The ANDA application process is shortened because rather than presenting preclinical and clinical data to establish safety and effectiveness (efficacy), the ANDA can piggyback on the safety and effectiveness data submitted by the original innovator in the New Drug Application ("NDA"). Thus, approval can be attained by simply establishing bioequivalence between the generic drug defined in the ANDA application and the original branded product.[25]

[24] *Id.*

[25] Finston, Susan K., Davey, N., et al. (2016). Mayo, Myriad, American Invents Act, and BPCIA: how has the United States pharmaceutical market been affected? *Pharm. Pat. Anal.* 5(3):59–167.

[26] Roche Products, Inc. v. Bolar Pharmaceutical Co., 733 F.2d 858 (Fed.Cir.1984).

In the Hatch-Waxman arrangement, manufacturers of branded drugs are required to list in an FDA-maintained "Orange Book" those product patents that cover the NDA-approved drug, indicating on a claim-by-claim basis which claims could reasonably be asserted against a generic version of the approved drug product.[27] In the case of drug products still covered by patents, after 4 years from the first approval, applicants may file an ANDA that includes a patent certification with respect to each patent listed in the Orange Book ("OB-listed patent") for the reference brand product. At that time, the ANDA applicant must certify that "(1) no patent is listed; (2) the subject patent has expired; (3) the applicant is not seeking approval until after the listed patent(s) expire; or (4) the patent is invalid, unenforceable, or will not be infringed by the manufacture or sale of the drug product for which the ANDA is submitted (the last certification is the so-called 'paragraph IV certification,' 'Para IV' or 'P-IV')."[28] In the scenario that the ANDA application demonstrates the original patent is invalid, unenforceable, or not infringed, the NDA holder ought to be notified by a "Para IV notice letter" of the certification. Further, the ANDA applicant must include a detailed statement for the basis of this assertion.[25]

Therefore, Hatch-Waxman fundamentally altered the pharmaceutical industry in America, establishing a market for copies of old drug innovations, which is now approaching 90% of total pharmaceutical sales in the United States.[29]

Due to concerns that introduction of new healthcare products in the United States was lagging behind Europe, Hatch-Waxman sought to "balance the benefits of greater competition from generic drugs with the benefits of having sufficient intellectual property protection to preserve the incentives to make the large, up-front, and risky expenditures necessary to develop new drugs successfully."[30] These IP protections included an explicit albeit limited period of marketing exclusivity for innovative drugs through regulatory data protection (RDP) and patent term restoration to make up for excessive time lost in the regulatory process. In the process, the US pharmaceutical industry became the largest supplier of medicines in the world, generating more drugs than any other nation and attracting Japanese, Indian, and European companies to conduct their research and development ("R&D") in the United States and to market products in America first.

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[27] Rosen, D.L.2007. Unlocking the Secrets of FDA's Orange Book: An Introduction to Therapeutic Equivalence, Drug Patents, Exclusivities, and More. https://www.foley.com/files/Event/be981bab-d77b-472e-9ff1-f55cd1f2d29b/Presentation/EventAttachment/f5b43aff-83d5-404a-81de-f61e1e769986/FDA%20Orange%20Book.pdf. Accessed 26 October 2017.

[28] Range, Brian. 2001. The ANDA Patent Certification Requirement and Thirty-Month Stay Provision: Is it Necessary? Digital Access to Scholarship at Harvard. https://dash.harvard.edu/bitstream/handle/1/8852164/Range.pdf?sequence=1. Accessed 26 October 2017.

[29] Association for Accessible Medicines. 2017. Generic Drug Access & Savings in the U.S. https://www.accessiblemeds.org/sites/default/files/2017-07/2017-AAM-Access-Savings-Report-2017-web2.pdf. Accessed 26 October 2017.

[30] Muris, Timothy. 2001. Competition and Intellectual Property Policy: The Way Ahead. https://www.ftc.gov/public-statements/2001/11/competition-and-intellectual-property-policy-way-ahead. Accessed 26 October 2017.

Before Hatch-Waxman, a pharmaceutical innovator's clinical data was not disclosed by the FDA to third parties. Hatch-Waxman created a new regulatory form of intellectual property protection, known as RDP, including a fixed period of marketing exclusivity for new products based on the clinical dossier submitted to the FDA as a condition of regulatory approval. RDP provides mutual benefits to both the original innovator and to the generic industry, which is able to employ the original clinical dossier after the expiration of RDP for purposes of gaining marketing approval for post-patent generic copies of innovative medicines.

Hatch-Waxman awarded a 5-year confidentiality period from the marketing approval date for new chemical entities ("NCEs") and 3-year protection for new applications of old entities, regardless of the status of the original patent. By prohibiting ANDA submission during the first 4 years after the originator's marketing approval, or 2 years from market approval of a new use of existing drugs, the RDP term restricts the powers of regulatory bodies involved in pharmaceutical product approval, initially protecting the confidentiality of all clinical and preclinical data such as drug interactions, efficacy, and dosing. Serving as the gatekeeper, the government conserves valuable judicial resources and protects the commercial interests of emerging biopharma companies.

Subsequent amendments have added additional periods of marketing exclusivity for orphan drugs providing a 3-year period of exclusivity for approval of new products demonstrating new uses for existing therapeutic molecules,[31] 7 years of exclusivity for designated orphan drugs,[32] and 6 months of exclusivity for pediatric use under the Federal Food, Drug and Cosmetic Act §§ 505(c(3) and 505 (j)(5)(F).[33] Moreover, following passage and implementation of the Biologics Price Competition and Innovation Act ("BPCIA") of 2009, the FDA also provides a separate 12-year term of exclusivity for biologics and a very limited class of large peptide drugs.[34] The BPCIA or Biosimilars Act was enacted on March 23, 2010, as a component of the Patient Protection and Affordable Care Act, Pub. L. No. 111-148. After this time period, the regulatory dossier remains confidential (and in fact is always referred to as "undisclosed information"). Second comers are permitted to reference the regulatory data on file with the FDA, though the data itself is never made public and remains the private property of the originator.

[31] 21CFR314.108. 2017. New drug product exclusivity. https://www.accessdata.fda.gov/scripts/cdrh/cfdocs/cfcfr/CFRSearch.cfm?fr=314.108&source=govdelivery&utm_medium=email&utm_source=govdelivery. Accessed 26 October 2017.

[32] 21CFR316. 2017. Scope of orphan-drug exclusive approval. https://www.accessdata.fda.gov/scripts/cdrh/cfdocs/cfcfr/cfrsearch.cfm?cfrpart=316&showfr=1&source=govdelivery&subpartnode=21%3A5.0.1.1.6.4&utm_medium=email&utm_source=govdelivery. Accessed 26 October 2017.

[33] Public Law 105–115. 1997. The Food and Drug Administration Modernization Act of 1997. https://www.gpo.gov/fdsys/pkg/PLAW-105publ115/pdf/PLAW-105publ115.pdf. Accessed 26 October 2017.

[34] H. R. 3590 – 686. 2009. https://www.fda.gov/downloads/drugs/guidancecomplianceregulatoryinformation/ucm216146.pdf.Accessed 26 October 2017.

More broadly, unlike the US patent system which provides a standard twenty (20)-year term of protection regardless of the nature of the invention, RDP periods in the United States vary considerably depending on the area of technology. Overall, the United States has enacted and/or implemented separate statutory or regulatory provisions relating to new chemical entities approved for use as drugs (5 years), biological or large molecules as therapies or vaccines (12 years), and agriculture chemicals (10 years).

Internationally, RDP has been formalized through the WTO Agreement on Trade Related Aspects of Intellectual Property Rights ("TRIPS"). Under Article 39.3 of the WTO TRIPS Agreement, WTO members are required to provide an effective period of exclusivity for confidential, commercially valuable undisclosed information. Nearly all OECD-level states and many emerging economies provide RDP for a minimum of 5 years, providing both marketing exclusivity and protection from disclosure of commercially valuable regulatory dossiers.

The bottom line: in contrast to the patent social contract, the protection given to RDP is provided in recognition of the substantial effort and investment required to generate the regulatory data needed by governments to ensure the safety and effectiveness of highly regulated healthcare products. This regulatory data is also viewed as undisclosed information, i.e., it would remain a trade secret but for the compelling interest of regulatory agencies in reviewing the data.

15.5 Patents, RDP, and the Patent Social Contract

As mentioned, the patent applicant is required to make a full disclosure of the relevant research, to enable anyone "skilled in the art" to replicate the invention. This is the social contract between the innovator and the public at large. Under US law most patent applications are made public within 18 months after filing, and following publication by the USPTO, the patent application is available to the general public, along with the entire file history of the application. This means that anyone around the world with an Internet connection can gain access to the accumulated knowledge contained in published patent applications and made available online by USPTO and so the patent system contributes to the progress of science with a massive knowledge base available to researchers around the world.

By contrast, innovative companies submit highly confidential, commercially valuable regulatory dossiers to health regulatory authorities as a condition of gaining marketing approval and in return receive a limited period of marketing exclusivity and a permanent assurance of confidentiality. This test data is required to demonstrate safety, quality, and efficacy of new products and would be protected as a trade secret if it were not required for regulatory approval. Far from a social contract, RDP represents an important limitation on the government's ability to make use of or disclose to others the proprietary data associated with new drug applications.

Both forms of IP protection are necessary; neither alone is sufficient. Running in parallel with the patent term, RDP is not a form of "ever-greening" for patented products and generally expires prior to the end of the patent term. This protection is provided purely in recognition of the investment of well over 1 billion dollars made in expensive and time-consuming preclinical and clinical trials that constitute the majority of the truly massive investment needed, on average, to bring one successful product to market, taking into account all of the research programs that fall by the wayside. Going forward to face the heightened challenges of growing global competition in life sciences, these IP protections will only be more important to US competitiveness in the twenty-first century.

With our increasing understanding of the human genome, patent standards have become tougher in the last decade for life sciences inventions, and entire areas of research have been made patent ineligible. A combination of regulatory reforms at the USPTO, Supreme Court precedents and other judicial decisions have all played a role in evolving patent standards. Increased patent filings and lengthier review times also have contributed to growing patent backlogs and a diminished rate of patent issuance, leading to a costlier process for smaller firms with increased uncertainty.

Patents provide innovators the exclusive ability to commercialize their inventions, meaning that being the first to invent something demonstrating a substantial advance allows for a limited window of exclusive financial benefit rewarding R&D efforts undertaken during the innovation process. Oftentimes, innovators can also license their products to generate additional revenue for further research. Despite these benefits, however, patent holders also face increased scrutiny after their idea is made public and therefore may experience more patent challenges after the grant.

Additionally, patenting in the context of regulated products is only one step in a lengthy R&D process, as these products require further review by a regulator. In the case of a biological drug or genetically modified seed or other biotech product, for example, there are also extensive regulatory processes under the authority of the US Food and Drug Administration (FDA) and the Environmental Protection Agency ("EPA"). Accordingly, for a novel biopharmaceutical or agro-biotech invention (e.g., drought-resistant seeds), an effective patent term could be 10 years, 8 years, or even less.

In biotechnology it also helps to be an optimist: fewer than 1 in 10,000 successfully patented inventions will grow up to be a successful life sciences product. Even among those products, fewer ultimately break even. At the same time, patents and know-how protected by trade secrecy may represent the key assets for a small biotech company that has not yet reached the commercialization stage. Thus, the large patent volume generated annually in the United States is crucial in allowing technology transfer to act as a market mechanism employed by small biotechnology start-ups and academia to generate revenues from licensing for further research.

15.6 Weaknesses in the Patent Social Contract: The AIA, BPCIA, and Judicial Precedents

The hollowing out of patent protection for certain classes of biotechnology inventions may have far-reaching and unintended consequences for development and assimilation of a broad class of innovative life sciences technologies for creation of social and economic benefit. In parallel with sweeping legislative changes, two Supreme Court decisions, *Mayo* and *Myriad*, substantially expand exceptions to patentable subject matter for natural phenomenon with broad impact on patentability of genomic diagnostics and perhaps unintended fallout relating to additional emerging technologies.

15.6.1 Changes to Patent Procedures: The AIA and Establishment of the PTAB

The BPCIA or Biosimilars Act was enacted on March 23, 2010, as a component of the Patient Protection and Affordable Care Act, Pub. L. No. 111-148. The America Invents Act ("AIA") was passed in 2011, with key provisions of the AIA coming into effect on September 16, 2012, and on March 16, 2013, with profound impact on the patent system. The AIA introduced two major changes to the patent process, including a shift from a first-to-invent ("FTI") to a first-to-file ("FTF") and establishing broader opportunities for administrative challenges to patents through establishment by USPTO of the Patent Trial and Appeal Board ("PTAB") under lower thresholds for standard of proof and claim construction. We will briefly discuss both issues in this chapter, and how they have eroded quiet title for patent holders, but a lengthier conversation on these issues can be found in Finston et al.[25]

First, by changing US patent law from an FTI to an FTF system, the AIA harmonized American law with other patent jurisdictions such as the European Patent Office ("EPO") and the Japan Patent Office ("JPO").[25] This is important for innovators who hope to patent their invention in a number of countries, as prior US policy allowed for ideas to be protected on the date of conception, but these rights could be lost in other jurisdictions if a patent application was not appropriately filed. Another advantage of such a change includes greater transparency and predictability, as inventorship declaration based on filing date is far simpler to implement than determining which inventor came up with the idea first. This date could then be used on a global scale to prevent inconsistencies between various jurisdictions.

On the contrary, critics note that the FTF system disproportionately impacts individuals and smaller entities, as the pressure to file early is high, and larger corporations with armies of researchers have more resources to do so. Filing many patents without cost constraints could create a thicket that blocks out start-ups with better ideas but less cash. The patent race also promotes the need for legal counsel earlier on in the research process, which could prove burdensome for independent researchers or burgeoning firms. This increase in cost multiplies internationally, given the need for Patent Cooperation Treaty (PCT) filings to ensure protection in major

Table 15.1 IPR statistics for OB-listed patents, 2012–August 2017

Year	2012	2013	2014	2015	2016	2017
OB-listed patent asserted in district court and IPR instituted	24	45	72	108	69	21
OB-listed patent asserted in district court and IPR *not* instituted	7	6	17	24	29	10
OB-listed patent asserted in district court and IPR filed	31	51	89	132	98	31
OB-listed patent asserted in district court and IPR instituted/OB-listed patent asserted in district court and IPR filed (%)	77.4%	88.2%	80.1%	75.8%	71.8%	67.7%

Data – courtesy of Lex Machina

global markets and the timing of national phase filing requirements. Accordingly, independent inventors and/or emerging biotechnology companies invariably face substantially higher IP management costs at earlier stages of research under the FTF system.[25] Moreover, the patent prosecution process for life sciences inventions has become increasingly burdensome for individual inventors and emerging biopharmaceutical companies due to the increased costs and protracted time periods required for USPTO review. Finally, the FTF system is said to encourage frivolous patents that may not demonstrate complete enablement of the invention.[25] Thus, patent offices should be careful when granting applications, as approved patents with limited implementation could be used against non-patenting innovators who truly deserve credit.

Further erosion of the patent social contract in the context of the Hatch-Waxman scheme has resulted from the USPTO PTAB Inter Partes Review (IPR) process implemented under the AIA. The new PTAB IPR post-patent review proceedings undermine the presumption of validity for granted patents that provides quiet title to innovators. While this may have significant impact for many industries, the PTAB IPR review process has had a profoundly adverse impact on biopharma in particular.

Of the many factors parties consider in deploying the IPR/ANDA interplay, the first is the IPR institution rate. Table 15.1 below shows the IPR statistics for OB-listed patents from 2012 to August 31, 2017.

As shown in Table 15.1, the institution of IPR for OB-listed patents asserted in district court has declined from a peak of 88.2% in 2013 to 67.7% in 2017. Yet, the institution rate of OB-listed patents asserted in district court in 2017 as of August 31 is still relatively high.

A second factor is the standard of claim construction. The Supreme Court decided in *Cuozzo Speed Technologies, LLC v. Lee*[35] that the AIA contains an express and clear conferral of authority to the USPTO to promulgate rules governing its own proceedings in IPR. In *Cuozzo*, the Supreme Court confirmed the rule-

[35] Cuozzo Speed Techs., LLC., v. Lee, 579 U.S., _____ (2016).

making authority of the PTAB in interpreting claims under the "broadest reasonable interpretation" (BRI) standard and affirmed the holding of the Court of Appeals of the Federal Circuit ("CAFC") that institution decisions by the PTAB (i.e., whether or not to grant a post-grant trial) are not appealable.

Cuozzo addressed the divergence of claim interpretation standards between PTAB – where claims are construed broadly under the preponderance of evidence rule – and Article III Federal Courts – where claims are construed narrowly under the clear and convincing evidence rule. In particular, the Court had to make this decision because the AIA did not provide any guidance on claim construction, and therefore this decision was being made by the USPTO. Justice Breyer affirmed in Cuozzo that it was appropriate within the USPTO's rule-making authority for the PTAB to use the BRI standard for claim construction.[25] More specifically, the BRI standard adopted by the USPTO was found reasonable given the "text, nature, and purpose of the statute,"[36] i.e., 35 U.S.C. §314. This decision therefore created a window for patent challenges before the PTAB as it sanctioned the use of BRI by the PTAB. Namely, *Cuozzo* dictated that despite evidence that Congress wanted to establish a trial-like proceeding, IPR is more like a specialized agency proceeding, not a judicial one.[37] The practical effect of this ruling is that the claims of the challenged patent are often construed more broadly by the PTAB than they would be by the district court, which applies the more restrictive Phillips claim construction standard. Currently, the extent to which the broader interpretation of the claims by the PTAB results in invaliding patents that would otherwise be found not invalid by the district courts remains a matter of some debate, although it is beyond debate that the invalidity rates experienced in IPR proceedings far surpasses those in the district courts. In light of *Cuozzo*, an IPR filer (which may or may not be a generic drug company) may elect to file much earlier, even significantly in advance of any Para IV filing, in an effort to short-circuit the Hatch-Waxman litigation/framework. And any interested party can file an IPR challenge, such as Kyle Bass' Coalition for Affordable Drugs, which has filed a number of IPRs.

A third factor is the differential rate of success between PTAB and district courts, as well as the patent type being challenged (e.g., in the pharmaceutical industry: active pharmaceutical ingredient, formulation, and method of use patents).[25] One study has shown that API patent owners succeed at far higher rates than method of use or formulation patent holders (60% vs. 24% and 4%, respectively). Thus, cases involving a new drug prevail most.

Given the high rate of institution of IPR trials based on OB-listed patents as shown in Table 15.1, the broadest reasonable interpretation (BRI) standard for claim interpretation, and the higher success of invalidating API patents, one would expect to see a greater number of challenges by generic companies before the PTAB (specifically relating to API patents, which are generally considered the hardest to invalidate in the traditional district court), as the process is cheaper, faster, and recently validated by the Supreme Court in *Cuozzo*. Thus, a two-pronged strategy for

[36] *Id*. 13.

[37] *Id*. 12–17.

challenging patents has emerged in the pharmaceutical industry: as Hatch-Waxman litigation is started at the district court level, the identical patents are challenged at the PTAB – though the timings for the patent challenges in the district court and PTAB could vary depending on the facts of each case.[25]

Though a boon for innovators with short product development cycles, the PTAB IPR process has been described as a bane to innovative life sciences, where patenting occurs at close to the start of a lengthy, costly, and highly regulated commercialization process. As demonstrated in the recent Allergan Restasis patent controversy, generic manufactures routinely get "two bites from the apple," pursuing judicial review before a district court, while the same patent is challenged for validity in the PTAB under a lower standard of proof and easier claim construction.

In brief, the PTAB process reverses the burden of proof, eliminating the presumption of validity of an issued patent. In addition, the decision by the judiciary to defer to PTAB decisions – despite the difference in standards of proof – has elevated an administrative process to the level of judicial review of a lower court. In effect the operation of the PTAB cedes the District Court's fact-finding process to the USPTO and itself is the subject of litigation as a potential violation of separation of powers.

15.6.2 The BPCIA

While the focus of the AIA was to fundamentally alter the entire patent system, BPCIA was a narrower piece of legislation aimed at creating an abbreviated pathway for follow-on biological products, or biosimilars, that demonstrated therapeutic equivalence to the approved reference product. Biologics are created through living tissue, including animals, plants, cell culture, bacteria, and viruses, unlike their pharmaceutical counterparts which are chemically manufactured. For this reason, they present an increased complexity, and unlike generic drugs, the abbreviated pathway for biosimilars does not necessarily require the molecule to be identical to the original biologic.[25]

Biologics are on the frontier of biopharma innovation, as they have successfully treated indications in spaces including cancer, cardiology, and immunology with increased genomic targeting. Every year, biological products are becoming a larger share of the FDA's approved medicines, with 12 approved in 2015 and 50% of these gaining priority review.[25] However, they do have the downside of greater R&D spending due to manufacturing challenges, and therefore increase the cost on the healthcare system.

Intended to parallel the Hatch-Waxman Act, the 2009 BPCIA legislation aimed to grow patent disputes before FDA approval by creating an abbreviated pathway for biosimilars to enter the market. Given the substantially more complex nature of biological drug development, as well as increased challenges of commercialization, biosimilar development has remained costly compared to generic versions of chemical entities that flooded the market after Hatch-Waxman. If more biosimilars were to enter the market, however, this could certainly change.

Thus far, only large and highly sophisticated generic producers (Teva, Celltrion, and Novartis Sandoz) have entered the US market through the abbreviated biosimilars pathway. Further, Eli Lilly (with Boehringer Ingelheim), Amgen, and Pfizer – all traditionally large companies – have dominated the biopharma space more broadly, reflecting high clinical research costs. Namely, smaller firms cannot afford to generate the safety and efficacy data required and additionally are not able to attract physicians to their possibly riskier biosimilars. In particular, regional generic behemoths such as Dr. Reddy's and Sun Pharma have focused their attention on marketing biosimilars in less regulated markets outside of the United States.[25]

The BPCIA's framework describing the process of information exchange regarding patent infringement between the biosimilar applicant and reference product sponsor has been termed the "patent dance," and this has been dominated by companies liked Celltrion, Sandoz, Amgen, Hospira (now Pfizer), and Apotex. Under 42 U.S.C. §262(*l*), the "patent dance" is the process whereby "the bio-similar applicant and the reference product sponsor exchange information regarding the application for the bio-similar; in particular, the parties exchange information regarding patents that may be the subject of litigation regarding the proposed bio-similar product."[38] Given that it is only optional for the biosimilar applicant to disclose relevant information as per recent judicial interpretation, BPCIA has reduced transparency for the innovator by allowing for the "patent dance" to be circumvented. This undermines Congress's initial idea to establish an efficient resolution during the reference product sponsor's market exclusivity. Yet, others argue that this legislation is still in its early days, and there will be a lag before the Courts comprehensively interpret and work out various provisions of the BPCIA.[25]

Nonetheless, major firms around the world including the largest generic manufacturers (e.g., Teva, Sandoz, Celltrion, Apotex) are applying for biosimilar approval, and this is occurring at an increasing annual rate.[25] With more biosimilars entering the market, the law is mostly working in the way it should. While Congress has focused on patent and biosimilar policy, the Supreme Court must now fill the substantive gaps, including the "natural phenomenon" and "law of nature" exceptions to eligibility.

15.6.3 *Mayo* and *Myriad*

The Supreme Court questioned the patented eligibility of genomic diagnostic tests in *Mayo*, ruling that "Prometheus Laboratories' patents relating to methods of treatment for serious gastrointestinal autoimmune illness (Crohn's disease) fail to meet patent requirements set out in 35 U.S.C. § 101, as falling within the exception to patentable subject matter for the law of nature."[25] The Question Presented, or QP, is meant to crystallize a controversy into a few lines when submitting a petition for

[38] Potter, Amanda. 2015. Interpreting the BPCIA – Is the "Patent Dance" Mandatory? *The Columbia Science and Technology Law Review*.http://stlr.org/2015/03/31/interpreting-the-bpcia-is-the-patent-dance-mandatory/. Accessed 27 October 2017.

certiorari to the Supreme Court and can determine whether Justices take the case. The petitioner's counsel in *Mayo* mastered the "elevator pitch" and presented a calculated QP that made a powerful impact on the Justices, who lacked a basic understanding of the scientific method:

> Whether 35 U.S.C. § 101 is satisfied by a patent claim that covers observed correlations between blood test results and patient health, so that the claim effectively preempts all uses of the naturally occurring correlations, simply because well-known methods used to administer prescription drugs and test blood may involve "transformations" of body chemistry.

Thereby, the QP in the case made a new and complex diagnostic methodology that optimized therapy for Crohn's disease patients analogous to an observation of the sun rising in the east. The Supreme Court agreed that Prometheus did not demonstrate an inventive step beyond observing a law of nature. More specifically, the test determining a critical relationship between metabolites and thiopurine dosage levels when treating gastrointestinal autoimmune illness was seen as a simple observation, and in a 9-0 decision the Court ruled that this natural phenomenon could not be patentable. The Supreme Court further acknowledged that while this decision may be unfavorable to the diagnostics industry, and thereby limit access of diagnostics to patients, their job is not to comment on policy but rather to make judgments on the law.[25] The Justices instead urged Congress to create more nuanced policy that may foster innovation in the diagnostic sector through increased protection of ideas.

Critics of this decision note that the Court in *Mayo* failed to precisely differentiate between patentable and unpatentable process claims in which a law of nature is a limiting step. The decision also failed to provide a key resolution regarding two prior conflicting decisions, enabling both USPTO examiners and lower courts to bar patent eligibility one limitation at a time, at the expense of biopharmaceutical innovation.[25] This unintended consequence as a result of the Court's decision was only compounded the following year in *Myriad.*

In the *Myriad* decision, the Supreme Court invalidated DNA patent claims for *BRCA1* and *BRCA2* genes to be used to predict likelihood of ovarian and breast cancer in high-risk patients, but upheld diagnostic testing of the genes' cDNA, which is synthetically replicated. The company Myriad determined both the sequence and location of the two genes, isolated the DNA without modification, and claimed this product as an invention. In a 9-0 decision, the Supreme Court in *Myriad* determined that the company's claims do not meet patent eligibility standards under 35 USC §101, which is the Patent Act's law of nature exception:

> Myriad's DNA claim falls within the law of nature exception. Myriad's principal contribution was uncovering the precise location and genetic sequence of the *BRCA1* and *BRCA2* genes. *Diamond v. Chakrabarty*, 447 U.S. 303, is central to the patent-eligibility inquiry whether such action was new "with markedly different characteristics from any found in nature," *id*., at 310. Myriad did not create or alter either the genetic information encoded in the *BCRA1* and *BCRA2* genes or the genetic structure of the DNA. It found an important and useful gene, but groundbreaking, innovative, or even brilliant discovery does not by itself satisfy the §101 inquiry.

Importantly, this decision distinguishes claims on DNA fragments *BRCA1* and *BRCA2* from those relating to cDNA, allowing for genetic inventions that "create or alter genetic information" [39] to be patented, such as synthetic DNA created in the laboratory, known as complementary or cDNA. Thus, this opinion creates a slippery slope regarding the product of nature exception with no clear definition provided. Furthermore, products of nature with varying degrees of complexity are conflated (e.g., leaf picked from a tree vs. chromosomes containing 500–600 genes like *BRCA*).[25] While the Supreme Court may have intended to prevent private ownership of DNA material, it failed to draw a clear precedent: should all genes and even their products not be considered for patentability by the law of nature exception?

Experts have found the Justices in the *Myriad* decision to lack coherence in their opinion, as they simultaneously reaffirmed the congressional responsibility to substantiate patent policy but also issued a far-reaching ruling to invalidate all DNA patents. *Mayo* and *Myriad,* in the opinion of these experts, have left much confusion in their wake, as it is still unclear what constitutes law of nature and what is patentable subject matter.[25] In reality, scientific progress relies on replicating or relying on laws of nature, and thus the Supreme Court ought to take leadership on making this crucial distinction more apparent.

At the end of the day, either the Supreme Court or Congress should address this issue of needing more clarity by distinguishing patentable subject matter from natural phenomena with explicit limits. The biopharmaceutical industry also desires that the Court recognizes the high costs and efforts of identifying natural correlations, genetic mutations, and other biologically occurring phenomena and subsequently applying them to create ingenious diagnostics and therapeutics. Conceptualization of these discoveries and commercialization to patients in need, through the scientific method, is no easy task.

15.7 Conclusion: The Way Forward

This chapter has looked back to look forward: reviewing and the growing impact of RDP for innovative life sciences to identify possible ways forward to renew the Patent Social Contract. It is all too easy to view the lessons of the past as irrelevant to best practices for present-day IP policies relating to innovative life sciences. In fact "what's past is prologue" [40] – we need to learn from the past to seek a way forward to renew the patent social contract to ensure an enabling environment for commercialization of emerging life sciences technologies in the twenty-first century.

[39] Myriad Genetic, 569 U.S. ____ (2013), 11.

[40] Shakespeare, William. 2005. The Tempest, Act 2, Scene 1.https://www.playshakespeare.com/the-tempest/scenes/957-act-ii-scene-1. Accessed 26 October 2017.

15.7.1 What Have We Learned?

Our nation's founders placed a premium on the US Patent System to spur innovation, replacing state-by-state patenting with a national system proved effective in building the national economy, adding to the knowledge base, and providing additional benefits through the assimilation of new technologies for social and economic benefit. This Patent Social Contract was based on a presumption of validity of issued patents. The primacy of the patent system in the earliest days of the Republic is underscored by the fact that each issued patent was signed by not one but three cabinet officials – Secretary of State Thomas Jefferson, Secretary of War Henry Knox, and Attorney General Edmund Randolph – before signing by President George Washington.

Moving forward into the twentieth century, Hatch-Waxman was envisioned as a "Grand Bargain," balancing early generic entry with new incentives for sustainable biopharmaceutical innovation. The dramatic increase in Hatch-Waxman Para IV litigation over time, however, curtails the statutory 20-year patent term for biopharmaceutical patents. Under Hatch-Waxman Paragraph IV, generic pharmaceutical manufacturers generally challenge the innovator's patent on day 1 of year 4 following FDA approval, i.e., an average of 5–10 years prior to patent expiration. Beyond Hatch-Waxman litigation incentives that have taken on a life of their own, recent patent amendments instituted the USPTO IPR process, creating "double jeopardy" for patent holders facing continuing judicial challenges under Hatch-Waxman and further eroding quiet title needed for sustainable investment in innovative life sciences.

In the meantime, US Supreme Court's *Mayo* and *Myriad* precedents have expanded exceptions to subject matter eligibility, with ambiguous rulings that have left a wake of uncertainty and curtailed investment into potentially lifesaving diagnostic and prognostic inventions considered "products of nature" and therefore ineligible for patent protection.

We have also seen in this context that RDP is an important, independent form of IP that cannot substitute for effective patent protection for life sciences inventions and that has itself been pared back for the increasingly important peptide class of biotechnology healthcare products.

15.7.2 Where Do We Go from Here?

The time has come to renew the Patent Social Contract through restoration of effective patent protection and an assumption of 'quiet title' for the innovative life sciences, including important diagnostic and prognostic inventions. We need to move from a litigation-focused to an innovation-focused patent system for biopharmaceutical drug development, ensuring quiet title through restoring the presumption of validity for issued patents, and providing clear guidelines for patentable subject matter to spur commercialization of potentially lifesaving emerging technologies. Innovation without exclusivity is unsustainable.

Dynamics of Topics in Antimalarial Patents: Comparison Between the USPTO and SIPO

16

Bo Kyeong Lee and So Young Sohn

Abstract

For the past several decades, considerable efforts have been made to roll back malaria, but contributions in this field have not been clearly investigated thus far. In this context, this paper explores research topics of malaria patents and compares their time-series trends. In particular, we compare the dynamics of antimalarial patent topics between the United States Patent and Trademark Office (USPTO) and the State Intellectual Property Office (SIPO) of the People's Republic of China using a dynamic topic modeling (DTM) approach. Thus far, more patents have been applied in the USPTO with a drastic increase in the number of malarial patents. Eventually, patent application in the SIPO has become more frequent in comparison to that of the USPTO after 2013. In addition to the two different patenting trends between the USPTO and SIPO, topics of technological fields identified by the DTM approach are rather different for the two patent offices. Topics of mosquito prevention methods, such as a net and diagnostic tool, were found only in the SIPO, while in the USPTO, topics for specific vaccines in different stages were identified. In both, the SIPO and USPTO, topics of malarial medicine were common, and interestingly, two topics related to malarial medicines made using natural resources were observed in the SIPO. As such, our findings confirm that despite the common goals to eliminate malaria, different technological fields have evolved in the two major patent offices, based on the interests of the applicants and environmental conditions. Such distinctions shed light on necessity and effect complementary cooperation between the developed and developing worlds.

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H. B. Singh et al. (eds.), *Intellectual Property Issues in Microbiology*,
https://doi.org/10.1007/978-981-13-7466-1_16

Keywords
Malaria · Patent analysis · Dynamic topic modeling · Latent Dirichlet allocation

16.1 Background

Exposure to malaria is strongly related to poverty. Although there are vaccines and treatments for malaria, people living in the least developed countries continue to be at risk of death from malaria (Trouiller et al. 2002). The World Health Organization (WHO) reported that there were approximately 212 million malaria cases and an estimated 429,000 deaths in 2015. In general, children under 5 years of age and pregnant women are at highest risk, and inhabitants of the sub-Saharan Africa are the most severely affected.

In order to control malaria, several approaches can be adopted, such as controlling malaria vector, improving diagnostic methods, and improving treatment. Long-lasting insecticide-treated bed nets (LLIN) and indoor residual spraying (IRS) are popular vector control methods. These strategies have led to a decline of infection in some highly endemic countries, such as Rwanda and Zambia (Kokwaro 2009). Furthermore, diagnostic methods and medicines have become readily available due to international efforts. The WHO promoted "Roll Back Malaria" to eliminate malaria death by 2010 (Guerin et al. 2002; Narasimhan and Attaran 2003), while numerous efforts have been made to control malaria. However, malaria continues to be an economic and social burden due to the resistance of the prevention and treatment methods – artemisinin and insecticide (Newby et al. 2016).

Thus, continuous efforts to develop new vaccines, medicines, and insecticides are needed (Greenwood and Mutabingwa 2002; Trouiller et al. 2002; Cotter et al. 2013). However, malaria is being overlooked by drug manufacturers and other organizations, such as government agencies and the news media.

Pharmaceutical companies in the developed countries do not encourage developing and producing treatments for neglected diseases as these diseases are not profitable (Pecoul et al. 1999; Ridley et al. 2006). Furthermore, malaria is a burden to the developing world, while it is not the public health concerns in the developed world. Therefore, the underlying motives of pharmaceutical companies in developed nations for antimalarial research and development (R&D) are mostly to highlight social responsibility rather than the earnest needs of their own country. For instance, most antimalarial projects are the results of the "Medicines for Malaria Venture" (MMV), which was launched to encourage private companies' participation in developing antimalarial products by building alliances with the public sector.

On the other hand, China is one of the developing countries with the technological capabilities to develop new and effective malaria medicine while simultaneously continuing to face the risk of malaria. Although cases of malaria within the Chinese mainland declined, the disease unexpectedly re-emerged in the last decade (Huang et al. 2017). Thus, the Chinese government and researchers have paid significant attention to rolling back malaria by developing antimalarial technologies.

Furthermore, the Chinese government utilizes malaria-related technology transfer as a key for strategic alliance with certain Southeastern Asian and African countries lagging behind in R&D capacity.

For the past several decades, most antimalarial inventions have been proposed in the developed world, particularly in the United States of America (the United States), but China, which is the largest developing country, began to achieve progress in antimalarial technology. Despite the considerable global efforts in antimalarial R&D, contributions in this field have not been clearly investigated thus far (Jana et al. 2012; She et al. 2016).

The aim of this study is to explore the research topics of malaria patents and compare their time-series trends. In particular, we compare the dynamics of antimalarial patent topics in the United States Patent and Trademark Office (USPTO) to those in the State Intellectual Property Office (SIPO) of the People's Republic of China. In order to identify the patent topics and their dynamics over time, we employ a dynamic topic modeling (DTM) approach (Blei and Lafferty 2006).

Exploring patents can accelerate the development of technologies and innovations by providing incentives for future inventions. Furthermore, a comparison of research paths between developed and developing countries shows the core technological competences of individual countries. Lastly, investigation of patent information can be used to direct policies and guide decisions (Triplett 1999; Lichtenberg 2001; DiMasi et al. 2003; Hubbard and Love 2004; Clark et al. 2011).

16.2 Malaria Patents

We retrieved patents which were applied to the USPTO and SIPO[1] for the year ended 2016. We found that 2833 patents were applied in the USPTO since the first patent in 1974. In the SIPO, the first patent was applied in 1985 and the total number of malaria-related patents was 879.

As shown in Fig. 16.1, in the USPTO, an increasing number of patents were applied from the early 1990s, and malaria-related patent applications in this patent office reached a peak in the early 2000s. The overall recent USPTO application trend declined after the global financial crisis. On the other hand, the number of malaria-related patent applications in the SIPO was small in comparison to the USPTO. However, it began to drastically increase after the early 2000s. Eventually, more patents were applied in the SIPO than in the USPTO in 2013.

For each patent office, the proportion of the first applicant's nationality is shown in Fig. 16.2. In both the patent offices, the proportion of native applicants is a majority. In the USPTO, applicants from 35 nations have participated in applying malaria-related patents, while those from 25 nations have done in the SIPO.

[1] The search term is designed to retrieve patents, including malaria-related words, such as "antimalarial" within their titles and abstracts, and also A61P-033/06 in its International Patent Classification (IPC): (((malaria*).TI., (malaria*).AB., or (A61P-033/06).IPC.) and (@ AD<=20161231)).

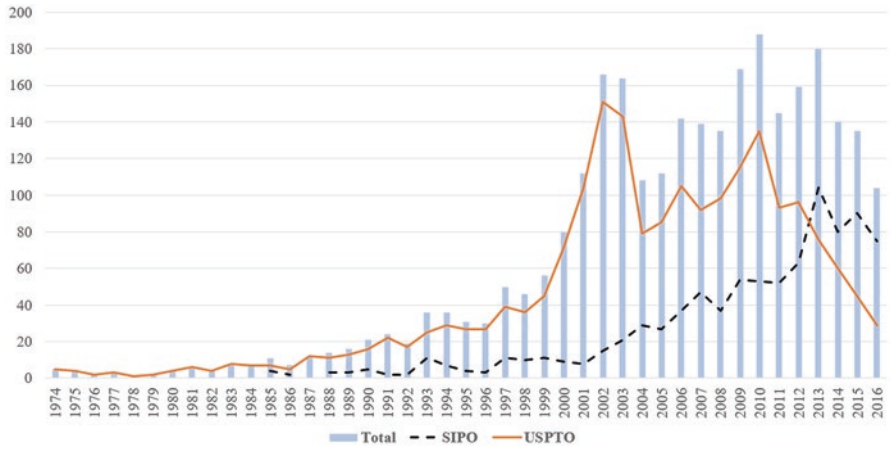

Fig. 16.1 Development trend of malaria patents

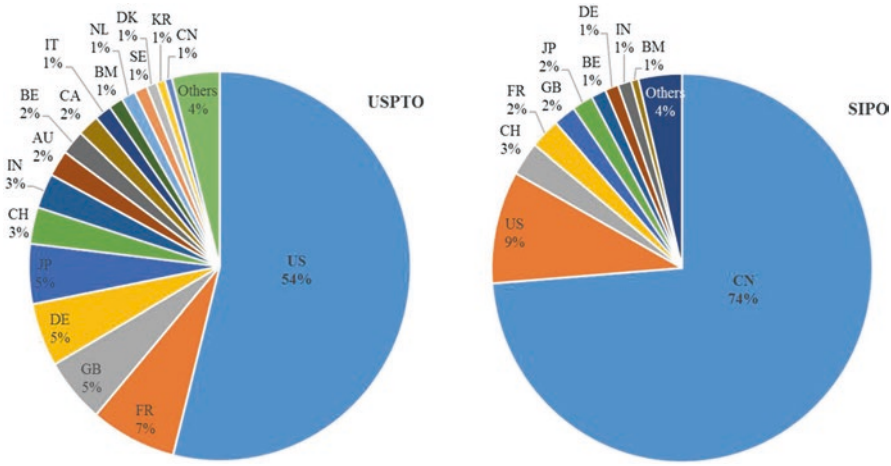

Fig. 16.2 Nationality (*US* United States of America, *FR* France, *GB* United Kingdom of Great Britain and Northern Ireland, *DE* Germany, *JP* Japan, *CH* Switzerland, *IN* India, *AU* Australia, *BE* Belgium, *CA* Canada, *IT* Italy, *BM* Bermuda, *NL* Netherlands, *SE* Sweden, *DK* Denmark, *KR* Korea, and *CN* China) of the first patent application: left, USPTO; right, SIPO

The major applicants and their nationalities according to the patent office are shown in Table 16.1. Institute Pasteur from France has the largest number of patents in the USPTO, and the government of the United States (represented by the Secretary of the Army and the Department of Health and Human Services) has continuously applied for a considerable number of malaria-related patents.

Similar to the patent application trend shown in Fig. 16.3, majority of the patents from major applicants – Suzhou Siju Biomaterials Co., Ltd., Shandong University, Suzhou Institute of Nano-Tech and Nano-Bionics, and Chinese Academy of

Table 16.1 Applicants and their nationalities

Patent office	Applicant (nationality)	Number of patents	Patenting activity
USPTO (2833)	Institute Pasteur (FR)	42	Continuously patenting between 1998 and 2012
	SmithKline Beecham Corporation (US)	37	Peak during 2001–2002
	The United States as represented by the Secretary of the Army (US)	33	Continuously patenting between 1979 and 2016
	Human Genome Sciences, Inc. (US)	25	Peak during 2005–2007
	The United States as represented by the Department of Health and Human Services (US)	22	Continuously patenting between 1983 and 2016
SIPO (879)	Suzhou Siju Biomaterials Co., Ltd. (CN)	31	Peak during 2013–2014 (applied 29 patents in 2013)
	Shandong University (CN)	17	Peak after 2014
	Suzhou Institute of Nano-Tech and Nano-Bionics, Chinese Academy of Sciences (CN)	10	All patents are applied in 2014
	East China University of Science and Technology (CN)	8	Continuously patenting after 2008
	Guilin Pharmaceutical Co., Ltd. (CN)	8	Peak during 2005–2006
	F. Hoffmann-La Roche AG (CH)	8	Peak in 1990s

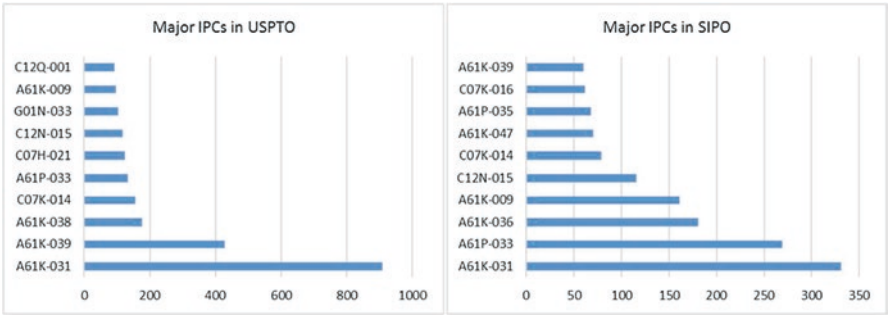

Fig. 16.3 Major IPCs of malaria patents

Sciences – were applied recently. F. Hoffmann-La Roche AG is a non-Chinese applicant and its patenting activity has not continued.

The IPC describes the technological field and application scope of a patent. The ten major IPCs in the USPTO and SIPO are shown in Fig. 16.3 and Table 16.2.

In both the patent offices, the largest IPCs of malarial patents are A61K-031, which deals with "Medicinal preparations containing organic active ingredients." Similarly, several sub-IPCs of A61 (medical or veterinary science and hygiene) are commonly found as major IPCs in the USPTO and SIPO, while some sub-IPCs, such as A61K-036 ("Medicinal preparations of undetermined constitution containing material from algae, lichens, fungi or plants, or derivatives thereof, e.g.,

Table 16.2 Description of the major IPCs

IPC	Description
A61K-031	Medicinal preparations containing organic active ingredients
A61K-039	Medicinal preparations containing antigens or antibodies
A61K-038	Medicinal preparations containing peptides
C07K-014	Peptides having more than 20 amino acids, gastrins, somatostatins, melanotropins, derivatives thereof
A61P-033	Antiparasitic agents
C07H-021	Compounds containing two or more mononucleotide units having separate phosphate or polyphosphate groups linked by saccharide radicals of nucleoside groups
C12N-015	Mutation or genetic engineering; DNA or RNA concerning genetic engineering; vectors, e.g., plasmids; or their isolation, preparation, or purification; use of hosts thereof
G01N-033	Investigating or analyzing materials by specific methods
A61K-009	Medicinal preparations characterized by special physical form
C12Q-001	Measuring or testing processes involving enzymes or microorganisms
A61K-036	Medicinal preparations of undetermined constitution containing material from algae, lichens, fungi or plants, or derivatives thereof, e.g., traditional herbal medicines
A61K-047	Medicinal preparations characterized by the non-active ingredients used, e.g., carriers or inert additives; targeting or modifying agents chemically bound to the active ingredient
A61P-035	Antineoplastic agents
C07K-016	Immunoglobulins: proteins produced by B cells, made up of two identical heavy and two identical light chains, held together by interchain disulfide bonds

traditional herbal medicines") are found as an essential scope only in the SIPO and not in the USPTO. Thus, the comparison of major IPCs indicates that although R&D efforts to eliminate malaria have focused on developing medicines and vaccines, the specific scopes may differ according to the actors of the R&D activity.

IPC describes the purpose of a patent and its fundamental technologies, but is limited in identifying the specific technological fields. Furthermore, pharmaceutical materials or compounds for antimalarial purposes have changed overtime due to the drug-resistance of the plasmodium. Considering this background, we apply the DTM approach to malaria patents and compare major topics between the USPTO and SIPO and their time-series trends in the next section.

16.3 Dynamics of the Antimalarial Technological Fields

16.3.1 Research Design of the Dynamic Topic Modeling

Dynamic topic modeling (DTM), which was proposed by Blei and Lafferty in 2006, is based on latent Dirichlet allocation (LDA), which is a generative topic modeling approach. LDA assumes that every document is a mixture of topics with a probability distribution and that topics are represented by their own probability distributions of

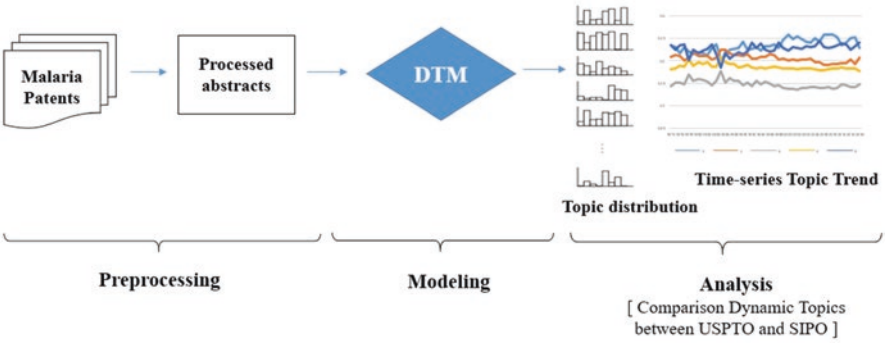

Fig. 16.4 Research design

terms from all the documents (Blei et al. 2003). This topic modeling approach has been widely used in recent bibliometric literature (Choi et al. 2017; Lee and Sohn 2015).

As LDA captures the topics of a set of documents only once, it is limited to examining the changes of topics over time. In this context, DTM was introduced as an extended model of the LDA that captures the evolution of topics over time in a probabilistic perspective by exploiting the temporal structure of a set of documents (Blei and Lafferty 2006).

As shown in Fig. 16.4, we apply a DTM approach to the abstracts of the malaria patents and identify the major topics in each patent office. This study selects the number of topics that can maximize dissimilarity between the topics according to the method proposed by Deveaud et al. (2014). Further, we compare the topics of the USPTO and SIPO, and their evolutions over time, in order to understand the two nation's efforts in rolling back malaria thus far.

16.3.2 Results of the Dynamic Topic Modeling

Malaria patents from the USPTO can be categorized into five topics as shown in Table 16.3. The first topic, "Application of antimalarial treatment in autoimmune disease," includes patents of antimalarial medicine which can be extensively utilized to treat autoimmune diseases, such as rheumatoid arthritis and Alzheimer's disease. As the researchers found that antimalarial medicine, such as chloroquine, is effective to cure inflammation and autoimmune diseases, significant efforts have been made in developing pharmaceutical products for cancer, Alzheimer's disease, and rheumatoid arthritis based on antimalarial medicine. This R&D approach focuses on dealing with the diseases prevailing in the developed nations rather than developing medicines for malaria itself. A significant and growing interest in topic 1 in the United States is represented by a higher proportion in comparison to other topics, as shown in Fig. 16.5.

The second and fourth topics encapsulate the technologies for inventing vaccines. In general, the different types of malaria vaccines can be categorized by

Table 16.3 Malaria-related patent topics: USPTO

	1	2	3	4	5
Topic	Application of antimalarial treatment in autoimmune disease	Preerythrocytic vaccines	Basic science for malaria	Asexual blood-stage vaccines	Compounds of malaria treatment
Words	Compounds	Protein	Cell	Antigen	Group
	Treatment	Peptide	Parasites	Vaccine	Alkyl
	Substituted	Acid	Blood	Response	Hydrogen
	Salts	Synthetic	Antimalarial	Surface	Atom
	Compositions	Cell	Enzyme	DNA	Substituted
	Inhibitors	Antigen	Sample	MSP	Carbon
	Acid	Cells	gpD	Transmission	Halogen
	Prophylaxis	Immunogenic	Red		Salts
			Dosage		
	Inflammatory	Vaccines	Oral		Alkoxy
	Alzheimer	Target			Hydroxyl
	Rheumatoid	Vectors			Phenyl
	Arthritis	Epitopes			Rand
	Cancer	Circumsporoz-oite			Aryl
					Methyl
					Nitrogen
Patent example (IPC)	US 6432933	US 5972351	US 7338766	US 8153140	US 8530491
	Glycol and hydroxyphosphonate peptidomimetics as inhibitors of aspartyl proteases (A61K-031)	*Plasmodium falciparum* MHC class I-restricted CTL epitopes derived from preerythrocytic stage antigens (A61K-039)	Compositions and methods for treating infections using cationic peptides alone or in combination with antibiotics (A61K-038)	Chimeric MSP-based malaria vaccine (A61K-039)	Antimalarial compounds with flexible side chains (A61K-031)

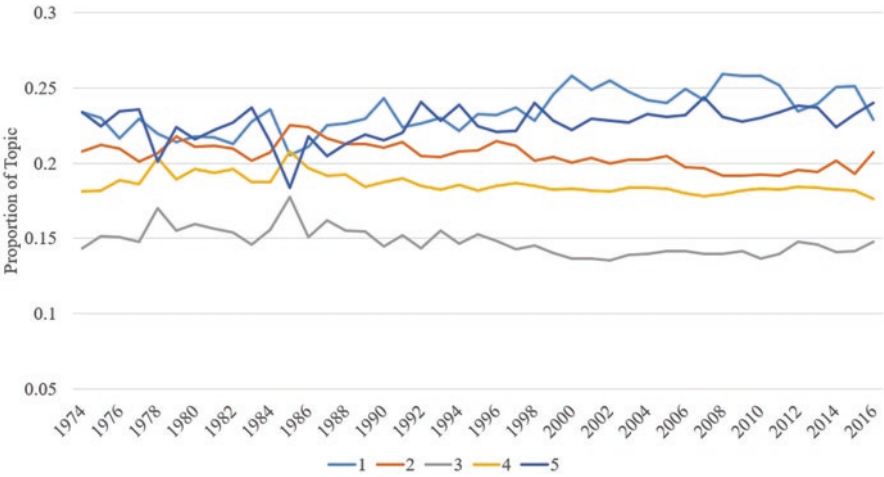

Fig. 16.5 Time-series dynamics of malaria-related technology topics: USPTO

following the stages of parasite development – preerythrocytic and erythrocytic stages (asexual blood-stage). The former stage vaccine aims to make antibodies to neutralize sporozoites or kill the parasite-infected hepatocytes, while the latter stage vaccine elicits antibodies and T-cell responses (Girard et al. 2007). The second topic captures the preerythrocytic stage vaccines, which are derived from the circumsporozoite protein, and the fourth topic refers to the asexual blood-stage vaccines based on merozoite surface proteins (MSP). These two topics have been developing continuously over a span of four decades as shown in Fig. 16.5. The third topic shows a minimum proportion among the topics and concerns the basic science of malaria, including the mechanism of parasites.

The topics in the SIPO can also be classified into five (Table 16.4), and their time-series trends are shown in Fig. 16.6. The overall trend of the topics revealed that patents in the SIPO are indented unlike from the ones in USPTO, and this inconsistent trend became more severe from the late 2000s. Such a pattern of topics is interpreted as many applicants, who had relatively short R&D experience in comparison to those in the USPTO, paid attention to a wide variety of antimalarial technologies after the late 2000s.

The results of the SIPO do not encapsulate a topic on malaria vaccines, but treatment methods using indigenous intellectual properties, such as topic 1, "Artemisin in combination therapy," and topic 3, "Traditional herbal therapy," are revealed. These two topics are relevant to IPC "A61K-036" which is revealed as the major technological field only in the SIPO by the frequency of IPCs. Topic 5 of the SIPO is similar to topic 5 of the USPTO. These three topics represent the technological fields of antimalarial medicine.

As the medicinal effects of artemisinin, which is extracted from *Artemisia annua*, were known to the Chinese scientist – Youyou Tu – who won a novel prize for her discoveries concerning therapy against malaria in 2015, a considerable number of

Table 16.4 Malaria-related technology topics: SIPO

	1	2	3	4	5
Topic	Artemisinin combination therapy	Protection tool	Traditional herbal therapy	Diagnostic method	Compounds of malaria treatment
Words	Artemisinin	Mosquito	Chinese	Detection	Compound
	Medicine	Body	Medicine	Polypeptide	Pharmaceutical
	Artesunate	Net	Radix	Kit	Treatment
	Obtain	Anopheles	Traditional	Protein	Substituted
	Drying	Sealing	Grams	Containing	Alkyl
	Agent	Valve	Herb	Device	Salt
	Raw	Floating	Rhizome	Gene	Acid
	Powder	Prevent	Toxic	Diagnosis	Deacetylase
	Oil	Fabric	Herbal	Shown	Heterocyclic
	Compound	Platform	Fructus	Blood	Histone
	Cyclodextrin	Protection			
		Patch			
Patent example	CN 101125127	CN 2013-10023331	CN 2012-10182829	CN 102103141	CN 101031295
	Artemisinin derivatives freeze-dried preparation and preparation method (A61K-009)	Tree shade mosquito trapping device (A01M-001)	Traditional Chinese medicine for treating intractable malaria (A61K-036)	Immunity-chromatography kit for rapid diagnosis of malaria and its pathogen species and preparation method thereof (G01N-033)	Medicinal composition for prevention or treatment of parasitic protozoan infection (A61K-031)

patents for topic 1 have been applied in the SIPO. Furthermore, after identifying the resistance to artemisinin in the vicinity of the Mekong river in Cambodia and Myanmar, patents related to artemisinin-based combination therapies have been actively applied in the SIPO. Such antimalarial material from indigenous resources – both plant and knowledge – is a distinctive research area in the SIPO in comparison to the USPTO.

In addition, topics 2 and 4 are not found in the results of the USPTO. Thus, we can interpret that relatively more interests have been paid to these fields in the market and R&D sectors in China in comparison to those in the United States. Topic 2 encapsulates LLIN and IRS, which are popular vector control methods. The technological intensity for topic 2 is relatively lower than the invention of medicines or vaccines, but such technologies have led to a decline in infections in some highly endemic countries, such as Rwanda and Zambia (Kokwaro 2009).

Furthermore, although the proportion of diagnostics in topic 4 is lower than the total proportion of topics related to antimalarial medicine (topics 1, 3, and 5), this technological field has received significant attention in the SIPO (She et al. 2016).

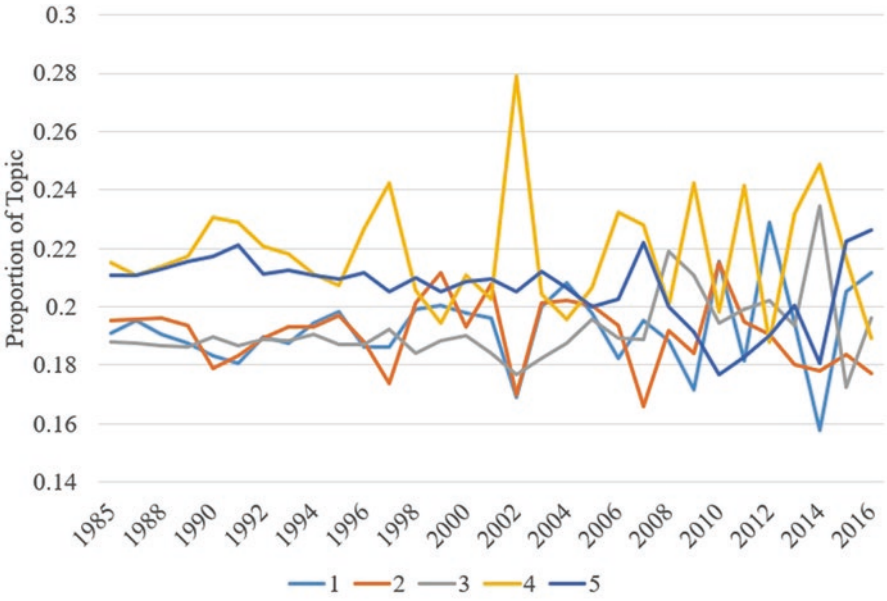

Fig. 16.6 Time-series dynamics of malaria-related technology topics: SIPO

Our findings confirm that despite the common goals of eliminating malaria, different technological fields have evolved in the two major patent offices, based on the interests of the applicants and environmental conditions.

16.4 Discussion

For the past several decades, considerable efforts have been made to roll back malaria. Most antimalarial innovations have been proposed in the developed world, particularly the United States, but China, which is the largest developing country, began to achieve progress in antimalarial technology. Despite the considerable global efforts in antimalarial R&D, contributions in this field have not been clearly investigated thus far (She et al. 2016).

In this context, we explored the research topics of malaria patents and compared their time-series trends. In particular, we compared the dynamics of antimalarial patent topics between the USPTO and SIPO. The application of malarial patents peaked in 2002 and 2010 for the USPTO, but began to decrease after 2010. On the other hand, considering the SIPO, despite a relatively late start of patenting activity in comparison to the USPTO, a number of malarial patents increased drastically and eventually outperformed the USPTO after 2013.

Technological developments and innovations to reduce the prevalence of malaria are more likely when a country such as China has the relevant technological capabilities and a sufficient market. China has recently promoted R&D efforts to control

malaria, which is reflected in the increased number of malaria patents in the SIPO, as majority of the recent assignees of malaria patents in this patent office are Chinese.

In addition to the two different patenting trends between the USPTO and SIPO, the technological field topics identified by the DTM approach were rather different in these two patent offices. Topics of mosquito prevention methods, such as a net and diagnostic tool, were found only in the SIPO. On the other hand, in the USPTO, topics of specific vaccines in different stages were identified. In both the SIPO and USPTO, topics on malarial medicine were common, and interestingly, one of the malarial medicines made from natural resources was revealed in the SIPO.

Technological fields in the SIPO included various methods from a net to a diagnostic tool, while those in the USPTO were confined to pharmaceutical inventions. One can expect that such differences are owing to the disparities in indigenous technological capabilities between the developing and developed countries. In addition, the two patent offices showed distinctive approaches in pharmaceutical inventions. In the USPTO, antimalarial medicine evolved to be applied to different diseases, such as rheumatism, which is in demand in the developed nations, while several antimalarial medicines-related patents applied in the SIPO were based on the utilization of indigenous resources.

The development of antimalarial medicines using traditional knowledge and natural resources has been paid significant attention not only in China but also other developing countries. For example, *Andropogon leucostachyus* in Brazil and *Streptomyces ballenaensis* in Costa Rica have been studied as new materials for antimalarial medicines, comparable to the usage of *Artemisia annua*. Similar to the knowledge of biotechnology that has been mostly invented in the developed world and protected by the intellectual property system, indigenous resources and traditional knowledge are now being considered as intellectual property after the Nagoya protocol (Lee and Sohn 2016). Thus, collaboration between developed and developing countries to facilitate exchange of knowledge and natural resources through the Nagoya protocol can be a new strategy to roll back malaria. Protection of extensive intellectual properties from technologies to national resources provides an opportunity for collaborative efforts to eliminate malaria through technological advancement.

Acknowledgment This work was supported by the National Research Foundation of Korea (NRF) grant funded by the Korea government (MSIP) (2016R1A2A1A05005270).

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Evergreening: An Equivocal Affair in Pharmaceutical Industries

17

Surbhi Shriti, Akansha Jain, and Sampa Das

Abstract

Laws protecting the intellectual property (IP) are one of the most obscurely defined laws. All the members of the World Trade Organization abide by the legal agreement signed between the countries to regulate the IP rights between the member countries *known as Agreement on Trade-Related Aspects of Intellectual Property Rights (TRIPS). Developing countries especially India amended the Patent Act in 2005 in order to strengthen* its administration revolving around IP Rights and tuned it according to the TRIPs Agreement, with an exceptional spotlight on the pharmaceuticals. The main idea behind this amendment was to prevent the process called evergreening. Evergreening is a process where pharmaceutical industries try to extend the duration of a patent under the disguise of increasing the therapeutic efficiency of the drug. Public access to the patented drug can also increase as an outcome of this act by shunning redundant guarding to the inventor. India pledged to curb evergreening which was evidently observed by the recent Supreme Court verdict on the case of Novartis AG v. Union of India (UOI) and Ors. The aim of this chapter is to provide a clear understanding of evergreening so that an unbiased view can be established both towards the best of public interest and protection of the inventor's right.

Keywords

Patents · TRIPs · Evergreening · Indian Patent Act

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H. B. Singh et al. (eds.), *Intellectual Property Issues in Microbiology*,
https://doi.org/10.1007/978-981-13-7466-1_17

17.1 Introduction

17.1.1 Background

Of late, the pharmaceutical industries are experiencing massive policy changes in protection rights scenario. Many big pharmaceutical organisations have lost patent security for their profitable blockbuster solutions, and despite the fact that an expanded measure of funds are spent on innovative work (R&D), they are facing several issues. As an outcome, they start to largely rely on their current patents and go to their most extreme to augment benefits from them. This prompts characteristic patent approach by these organisations, i.e. evergreening where pharmaceutical firm expands the existence of a patent, in this case, a medication by getting extra 20-year licences for minor iteration or insignificant reformulations of the medication, without fundamentally expanding the remedial viability (Granstrand and Tietze 2015). Such practices might be addressed from two opposing point of views.

The law of licences gives selective rights; Indian Patent Act's Chapter II, 1970, Section 3 (d) rebuffs the exploitation of its existing position. The intersection of intellectual property law between Indian Patent Act's Chapter II, 1970 Section 3 (d) and Section 84 has been argued. Chapter II of the Indian Patent Act, 1970 Section 3 (d) imposes that:

> *(d) The mere discovery of a new form of a known substance which does not result in the enhancement of the known efficacy of that substance or the mere discovery of any new property or new use for a known substance or of the mere use of a known process, machine or apparatus unless such known process results in a new product or employs at least one new reactant.*

Whereas Section 84 states:

> *(1) At any time after the expiration of three years from the date of the grant of a patent, any person interested may make an application to the Controller for grant of compulsory licence on patent on any of the following grounds,*
>
> *(a) That the reasonable requirements of the public with respect to the patented invention have not been satisfied, or*
>
> *(b) That the patented invention is not available to the public at a reasonably affordable price, or*
>
> *(c) That the patented invention is not worked in the territory of India.*

When the above-mentioned affair is applied to Indian pharmaceuticals, the issue turns out to be considerably complicated. One of the most research-intensive industries in the world is that of pharmaceuticals (Bansal et al. 2009). Expenditures on research and development as well as their respective clinical trials are very high. Moreover, there remains always a possibility of imitating the new product, hence, protection of patent becomes very crucial (Domeij 2000). Evergreening comprises diverse carefully planned strategies to utilise this elite privilege to its maximum performance which largely falls on the border of both lawful and unlawful behaviour. This book chapter tries to examine the thin boundary dividing the utilisation and the abuse of pharmaceutical licences with a major attention on evergreening.

Patent security generally prompts a limiting infrastructure so that the patent proprietor has a critical control over cost and supply on the pertinent market. In this way, the market is exceptionally controlled to ensure the security and productivity of the patent that is accessible for patients. Likewise, range of price is discussed nationwide beforehand so that medication is endorsed for prescription. The incidence and scope of laws governing patents have differed according to place and time.

17.1.2 General Perception

The composition of the international pharmaceutical industry is exclusive: it has a two-level structure (Taggart 1993). The first level comprises the innovators, often large and multinational, and the second level has generic companies (Gunther and Breuvart 2005), which manufacture generic adaptation of a drug when the licence's term has been completed. Moreover, the biotechnology companies are emerging as third level (Domeij 1998). These organisations devote their actions to development and typically do not have the capacity to deliver or manufacture pharmaceuticals to buyers. These organisations generally collaborate with first-level organisations. These companies frequently associate with innovator companies for the step down processing of patented medicines from its end and rely on actual marketing by the first-level companies.

Between innovators, rivalry becomes the most important issue in the inventive progress. Their R&D exercises go for building up another drug or improving an officially existing pharmaceutical patent keeping in mind the end goal, i.e. to stay competitive. Moreover, rivalry happens amongst originators and generic organisations. It is seen that when a pharmaceutical item goes off patent, generic medicine by generic organisations will show up for marketed. These organisations by and large assert on the benefits of cost of the prescription and consequently contribute less or no funds on R&D.

In recent times, the partition between the innovators and generic company is gradually dissolving. This can be validated specially in Asian, Eastern European and Latin American markets where the consumer's financial conditions are mediocre. Affording such expensive brand name drugs become a daunting task for such developing countries. Therefore, generic companies like Guangdong BeiKang Pharmaceutical Company Ltd. (China) were acquired by AstraZeneca in 2011 (Murphy and Liberatore 2009), and Zentiva, Kendrick and Medley were acquired by Sanofi all of which were functioning in market.

17.1.3 The Crucial Role of Innovation

One of the key aspects of the pharmaceutical sector is that it is typically portrayed as extremely inventive and knowledge intensive. In the global arena, this particular sector sees maximum investments in its R&D. Advertising expenses surpassing

funding on R&D is a remarkable characteristic in this field. Research-based pharmaceutical are hence required to develop new and improved substances to remain profitable as well as stay in competition. Nevertheless, the pharmaceutical sector is unsteady corporate: R&D projects are frequently prolonged and ambiguous with a high failure rate. Likewise, the timeline for launching a brand novel medication in the marketplace is lengthy; generally it takes 0–12 years from initial discovery to the actual launch available on the market. Only 1 in 10,000 compounds reach the market as a medication.

Owing to the high risks involved, the enterprise is reliant on earnings from the goods that really achieve its place in the market in order to recuperate their funds. Even slight healing enhancements in already present invention can cause extended profitability. This is normally called incremental innovation, a strategy maximum innovator organisation employ in (Rosenberg 2009). Incremental innovation promotes discovering minor novelty of a drug or treatment that emerges from consequent R&D, totally built on the concept of an already available product which has the similar mode of action. The consequence is a second-generation product, also identified as a "follow-on product". Nowadays, few innovators invest less in R&D than they earlier did. In its place, they rely upon biotechnology companies for the latest compound manufactured that can be bought by them. As the huge innovator organisations cope with placing the drugs available in the market, it is much needed from biotechnology companies to do greater innovation in the future.

The profit fundamentally causes some undesirable outcome on the pharmaceutical industries. There were few allegations contradicting the options of investments in R&D. As already discussed, to fund a new innovation is very expensive affair. This results in biased selection of those medications which can be fulfilling and likely to offer a higher profit on the enterprise's funding. As a result, priority is given to investing in researches for tablets consumed in first world countries over the pills sold in third world countries.

17.1.4 The Launch of Novel Pharmaceutical in Market

The life cycle of a pharmaceutical can be partitioned into three phases:

- The prelaunch phase
- The promoting and deals phase
- A later phase when the patent licence terminates and entry of generics becomes likely

The means of the patents' commercialisation is entirely controlled by a horde of principles for pharmaceutical organisations for subsequent exploration.

17.1.5 Generic Entry

After the expiry of patent licence of a medicine, its generic variants are allowed to enter the pharmaceutical market. The section of generics more often results in decrease in cost and an increase in supply. In this way, laws are intended to improve and empower the passage for these organisations by offering a shortened course to accomplish proper market entry. By utilising the originator medication as indication, the generic organisation spares time and can come into the market more swiftly. Likewise, the generic organisation doesn't require investing large funds in R&D and doesn't have different expenses identified with development of solutions. Thus a generic medicine is defined as:

> *A medicinal product which has the same qualitative and quantitative composition in active substances and the same pharmaceutical form as the reference medicinal product, and whose bioequivalence with the reference medicinal product has been demonstrated by appropriate bioavailability studies.* (DIRECTIVE 2001/83/EC OF THE EUROPEAN PARLIAMENT AND OF THE COUNCIL 2001)

Previously prior to 2005, a generic company was only able to utilise the innovator's pharmaceutical product as point of reference which was further minimised if the patent licence was yet to be over or was still available in the market. Upon introduction of amendment, these generic organisations were able to exploit their market up to 8 years after the end of the pharmaceutical patent's licence. Likewise, a generic organisation isn't obligated to lead preclinical tests and clinical trials to get a marketing approval.

17.1.6 Generic Substitution

Generic substitution is a prevalent partisan apparatus which is required to build proper platform for utilisation of generics. The government can reduce expenses on costly medication by permitting drug stores to trade recommended medication during circumstances where less expensive generic adaptation are accessible, expenses on costly medication can be reduced on behalf of the government. Additional motivation behind generic substitution, certain endorsing propensities of innovators can also be changed.

17.2 Evergreening of Pharmaceutical Patents

Patent holders to extend the privileged position they enjoy during exclusivities adopt a variety of strategies when their patents are about to expire. This kind of approach is also known as evergreening which is widely common in pharmaceutical industries (Shadowen et al. 2011; Singh et al. 2016). As soon as the patent expires, their main contenders become the second-tier generic companies on whose arrival

there is a general decline in cost and demand of these branded products. To counteract this sudden competition and to secure their market position, the Innovator Company tends to respond through various measures. These measures have been defined by various terminologies. Some reports refer such approaches as "life cycle management strategies" which toil upon common goal by maximising benefits by working as a "tool box" (Domeij 2013). The report suggests a variety of such strategies as potentially anticompetitive, including patent clusters, patent litigation, life cycle strategies for follow-on products and interventions before national regulatory authorities. This may partake a harmful impact on generic struggle, hampering its survival in the market and a damaging delivery and cost of drugs, particularly in the developing countries.

17.3 Evergreening of Patents in India

The commencement of a fresh patent regime was marked by establishment of Indian Patents Act (Amendment) in 2005 for the protection of the privileges of individual patent holders. This act was realisation of the commitment which India had towards the World Trade Organization on the consensus on Trade-Related Aspects of Intellectual Property Rights. It is addressed mainly by the following points:

- *Implementation of the meaning of 'pharmaceutical substance';*
- *Omission of 'mere discovery of new form of known substance' and the 'new use for a known substance'*; and
- *Production of commodities which may be approved for 'patent protection in the new regime.* (Dhar and Gopakumar 2006)

Moreover, a new explanation of the term "new invention" was added. Few limitations were included in the "scope of patentability" as discussed earlier in Section 3(d) mentioned earlier. This act was India's attempt to strike a balance towards all different participants like local generic pharmaceutical industries, NGOs, the scientific communities, International MNCs and the IP lawyers.

Since the establishment of TRIPs Agreement, WTO members perceived the necessities of the underprivileged nations for proper healthcare. In 2001, they concocted WTO Doha Ministerial Declaration for public health (WTO Doha Ministerial Declaration 2001). The Declaration's implementation was totally neglected by all pharmaceutical industries as they ignored the need to diminish the costs of the meds, particularly for the treatment of sicknesses like tumour and HIV/AIDS. This shows that international organisations don't feel the need to deal with the medical issues of the developing nations enough. Consequently, the strategies encouraging the accessibility of drugs at a reasonable price to the deprived individuals, globally, have been confirmed futile.

According to Property Rights Report, 2006, countries are able to approve legislation and assessment guiding principles necessitating a standard of ingenuity that would avoid evergreening patents from being granted thus substantiating the

accuracy of the IPR. Furthermore, it expresses that the TRIPS Agreement offers freedom to WTO adherents to find out the obstacles requisite for the ingenious measure (WHO Public Health, Innovation and Intellectual Property Rights Report 2006). Luckily, TRIPS agreement allows countries to formulate their patent law according to financial condition of their citizens. Given that, India's commitment towards the availability of drugs towards the upheaval of its socio-economically poor class was clearly visible in the latest judgement of India's Supreme Court on Novartis patented drug "Gleevac" (Table 17.1).

17.4 Case Study of Novartis Versus Supreme Court, 2013

Recently a lot of interest was garnered by the judgement passed by the Indian Supreme Court on the Novartis patent application for setting a stern benchmark of non-blatant approach for patents. This hearing was perceived as a combat between giant pharma and health aid groups in India. This latest chronicle at the Supreme Court traces its path back to the year 1998 when Novartis, a Swiss-based pharmaceutical giant, filed a patent application for drug named Gleevec (Zimmermann 1998) (or Glivec, in Europe) based on the fact that it invented its beta crystalline form of imatinib mesylate, which is the salt form of the free base. This drug is used to treat chronic myeloid leukaemia and gastrointestinal stromal tumours (GIST) and different forms of cancer (Novartis AG v. Natco Pharma and Others, Controller of Patents and Designs 2005). However, during that era patents were not granted to pharma or agrochemical product. When TRIPS Agreement came into effect, India opted for setting up a "mailbox" to adjust during transitioning period, and hence this patent was kept in "mailbox". In the meantime, Novartis set the cost of the drug per patient as USD 2666 per month. However, some generic companies started producing it at USD 177–266 per month.

The patent application was once again processed when such products came under patent laws in 2005. Keeping the amendment inserted in Section 3 (d) of the Patent Act in 2005 regarding the effectiveness of the medicine in mind, Assistant Controller of Patent and Design, Chennai Patent Office, rejected the application due to absence of novelty and nonobviousness. Since the appellate board was yet to be convened, Novartis filed a series of appeal in Madras High Court pleading that Section 3(d) of Patent (Amendment) Act 2005 is in defiance of Article 14 of the Constitution and not in compliance with the TRIPS Agreement. This appeal was again rejected by Madras high court holding that it does not have enough authority to determine whether domestic laws are in contrary to treaties signed by India at International level. To combat this, Novartis filed Special leave petition in 2006 in Supreme Court of India. Novartis contended that the patent had improved efficacy over other polymorphs with better flow properties, thermodynamic stability and bioavailability. The apex court rejected these contentions saying that efficacy in view of Section 3d was improvement in therapeutic value instead of physical value.

Table 17.1 Lawsuits on patent infringements in India

S.No.	Court	Plaintiff	Defendant	Drug	Cost of patented drug	Cost of generic version	Decision
1.	High Court of Delhi March 19, 2008	F. Hoffmann-La Roche Ltd	Anr. vs Cipla Limited	Erlotinib (Tarceva) lung cancer medicine	Rs 4800 per tablet	Rs 1600 per tablet	Decision went in favour of Cipla
2.	High Court of Bombay January 19, 2015	Farbewerke Hoechst Aktiengesellschaft Vormals Meister Lucius & Bruning a Corporation etc.	Unichem Laboratories	Uni-Tolbid tablets anti-diabetic	NA	NA	Granted ad interim injunction restraining Unichem from manufacturing the tablets
3.	High Court of Delhi Oct 07, 2015	Merck, Sun Pharma (Co Plaintiff)	Glenmark Pharma	Sitagliptin phosphate (Januvia) anti-diabetic	–	30% cheaper	Refused to impose an injunction on Glenmark's sale of Sitagliptin. Case still in court
4.	Intellectual Property Appellate Board Nov 2, 2012	Roche Pharma	Sankalp Rehabilitation trust and Wokhardt	Pegasys (hepatitis C drug)	73,000 per month	7900 per month	Decision went in favour of Sankalp Rehabilitation Trust

5.	High Court of Delhi	Roche Pharma	Cipla	Valcyte, (HIV/AIDS) antiviral medication for transplant patients	NA	NA	Pending in Delhi High Court
6.	High Court of Madras Nov 25, 2005	Wockhardt Ltd.	Hetero Drugs	Nadifloxacin, antibiotic for the treatment of *Acne vulgaris*	NA	NA	Granted ad interim injunction restraining Hetero from infringing its exclusive marketing rights on nadifloxacin
7.	Intellectual Property Appellate Board Mar 02, 2013	Bayer	Natco Pharma	Nexavar (kidney cancer)	Rs 30,000 a month	Rs 5400 a month	IPAB upheld Natco's compulsory licence. Decision went in favour of Natco
8.	Indian Supreme Court April 01, 2013	Novartis Pharma Ltd	Union of India and others	Glivec (beta crystalline form of imatinib)	$20–$30 per pill	$2 per pill	Supreme Court held that beta crystalline form of imatinib mesylate is not patentable

According to the court, the goal of developing a patent system was to reduce the further extension of the patent after the completion of its term of 20 years so that generic firms can manufacture and market the medicine.

The Court asserted that Amendment was proposed:

- To avert evergreening
- To grant effortless access to the Indian citizens for life saving drugs
- To discharge their constitutional duty of providing healthcare to its citizens

It is significant to remember that the judgement in no way contradicted the patent laws. It extraordinarily considered public interest while coming on a decision on this case. Here, a general understanding has to be developed that the right to health is very important in many parts of the world but is not achieved due to lack of accessibility of medicine which is largely dependent on the cost. Hence decisions such as these allow the poor populace to gain access to the patented drugs at affordable prices.

17.5 India's International Commitment

Innovations in India has always been embraced and endorsed which has been relayed to the international communities by India's approach towards developing strong intellectual property protection system and dealing with problems arising from introduction of new technology. We can clearly see this in the several mutual accords of India with different countries such as Germany, Australia, the USA and many other countries which is noted in the official website of Patent Office of India. This memorandum of understanding or MoU is aimed to reinforce assistance for advantage of industry, research and populace of the specific countries' intellectual property offices. As far as IP rights are concerned, this MoU tries to stroke phases of civic responsiveness and human resource management. The MoU signed between Ministry of Commerce and Industry of India and The Federal Department of Economic Affairs of Switzerland on Intellectual Property in 2007 had offered for a joint commission primarily for the following purposes:

- To protect Intellectual Property at national level
- To share experiences between the two countries
- To develop constant support in area of traditional knowledge and geographical indication

The Patent Cooperation Treaty (2001), of which India is a member state, seeks the following obligations:

- To involve in the development and growth of science and technology
- To improvise the current legal security of innovation
- To increase the speed of access to the availability of documents describing the technical information regarding the new inventions to the public

When we try to closely assess global obligation of India with new innovation in sight, we see that community wellbeing is significantly considered with utmost priority. Importance is duly given to contribution towards science and technology but without compromising public health and welfare. Hence, it should be noted that the characteristic of evergreening is evidently influencing the health and welfare of the general masses. Since, India is a welfare country, the Constitution binds her to consider public welfare with paramount importance.

17.6 An Equilibrium Between the Patients and Patents

Mere description of problems resulting from the stringent patent regulations on evergreening of the patent cannot be sufficed. Recommending a key for these troubles also becomes imperative. This calls for a need to establish an equilibrium between the patent laws and their extension and maintaining a reasonable price for the patented drugs to increase affordability of the drugs. There are different means that can facilitate the decline in the value of patented drugs.

17.6.1 Compulsory Licencing

This kind of licencing ensures the accessibility of drugs to poor section of society as well as maintaining of low price of drug though patented as allowed by India's Patent Act (Patents (Amendment) Act, Section 68, 2005). Compulsory licencing allows permission to non-patent holders of the drug for manufacturing patented drug (Mathur 2012). India granted its first compulsory licence ever in March 2012. A cancer drug called Sorafenib tosylate patented by Bayer was licenced to an Indian generic drug manufacturer Natco Pharma. Non-governmental groups reportedly welcomed the decision (Estavillo 2012).

17.6.2 Mutual Benefit Programmes

It is expected from the Government to provide better healthcare which is accessible to different strata of the society as India is already burdened with persistent issues like small income and shortage of healthcare facilities. Important medicines are within limited reach of the common man. Patented or not, access to lifesaving and crucial medicine is very less. For this reason, the government should make certain that access to basic health facilities is increased.

17.7 Conclusion

Patent evergreening tends to promote unfair abuse of competition. Improved IP scrutiny might curb this malpractice. This will in turn help in the removal of major obstacle in the entry of generic companies which provide cheaper and safer drugs available for the common masses. Landmark decisions such as Novartis foster a sense of better understanding of a very complicated territory called evergreening in IP practices. Earlier to the Novartis judgement, India had instigated persuasive pharmaceutical companies to generate licences to domestic generic companies to formulate their patented drugs. Now, the Supreme Court's decision will set an important example, which may transfigure foreign drug companies' insight towards India. Anyhow, whether there are new patents or not, demoralising innovators with excessively strict legislation will leave us with no new innovative drug development, and consequently no generic companies in developing countries including India will see the light of the day. So it becomes a prerequisite that we strike a balance between promoting innovation by flexible polices for the originator companies and encouraging generic companies which bring safer and cheaper drugs for masses.

Acknowledgements Surbhi Shriti is grateful to CSIR, New Delhi, for financial assistance under UGC Fellowship scheme. Akansha Jain is grateful to Department of Science and Technology, Govt. of India, New Delhi, for financial assistance under Start-up Research Grant (Young Scientist) Scheme (YSS/2015/000773). Sampa Das acknowledges Indian National Science Academy for her Senior Scientist Fellowship.

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Emerging and Resurgent Arboviral Diseases: Global Vaccine Patent Landscape and the Case for Immunome

18

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Abstract

Emerging and resurgent arboviral diseases are a major public health problem for developing countries, particularly in Latin America and Africa, for the severity of their symptoms and lethality. Vaccines are recognized as the most powerful preventive, low-risk and cost-effective interventions. For this reason, vaccines against these arboviral diseases could have an extensive impact on global health. Nevertheless, many gaps persist in innovation and technological development of these vaccines and it is necessary and urgent to accelerate new funding mechanisms and incentives, such as "patent pools", with active participation of manufacturers in developing countries, to assure their cost-effectiveness, efficacy and minimize their potential adverse effects. In this global scenario, intellectual property, especially patents documents, have emerged as a crucial issue for vaccine development. The global patent landscape for vaccines against these four arboviral diseases has undergone drastic changes in the past 5 years, with breakthroughs resulting from advances in molecular biology and genetic engineering: DNA vaccines, recombinant vaccines based on antigens expressed in vectors (viral, bacterial, yeast) and vaccines obtained through reverse vaccinology, with

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H. B. Singh et al. (eds.), *Intellectual Property Issues in Microbiology*,
https://doi.org/10.1007/978-981-13-7466-1_18

the selection of potential candidates at the genetic level rather than the protein level. Our main aim is to transcend the conventional debate on vaccine development and ethical, regulatory and policy issues, already explored in many scientific publications in the past three decades and determine which of these issues should be considered new and specific to this new perspective. Finally, an adequate use of patent documents, as indicated here, can be a valuable source of information, supporting technological prospect tools in more effective knowledge governance strategies.

Keywords
Arboviral diseases · Vaccines · Patents · Zika Chikungunya · Dengue

18.1 Introduction

Emerging and resurgent arboviral diseases are a major public health problem for developing countries, particularly in Latin America and Africa, for the severity of their symptoms and lethality. In the Latin American region, Brazil has been particularly affected by Zika, Dengue and Yellow Fever, transmitted by viruses of the *Flaviviridae* family, genus *Flavivirus* and by Chikungunya, transmitted by a virus of the *Togaviridae* family, genus *Alphavirus*. In the last two decades, the rapid global dissemination of Dengue, the emergence of Zika and Chikungunya in Brazil and the risk of re-urbanization of yellow fever in the country, particularly in large metropolitan areas such as in Rio de Janeiro, have become a major concern for international and national policy makers. Changing eco-social conditions, such as climate change, poverty, intensification of travel and increasing populational mobility, with poor sanitation and garbage collection, have contributed to the rapid global proliferation of *Aedes* mosquitos and thus to the increasing number of human and non-human hosts infected by arboviruses. These conditions have aggravated the complex global epidemiological scenario and have dramatically increased the demand for new vaccines and therapeutic strategies, challenging research priority-setting (Wilder-Smith et al. 2017). Co-infections of these four arboviral diseases have complicated this scenario and antibody dependent enhancement (ADE) of populations previously exposed to Dengue has emerged as a strong hypothesis to explain Zika congenital syndrome and neurological disorders (Possas et al. 2017) and might pose barriers to vaccine development against both diseases.

Vaccines are recognized as the most powerful preventive, low-risk and cost-effective interventions. For this reason, vaccines against these arboviral diseases could have an extensive impact on global health.

The main challenge for emerging developing countries, particularly affected by these diseases, is to assure more effective knowledge governance strategies (Foss 2007; Foss et al. 2010) to accelerate the vaccine availability for their populations, overcoming persisting gaps through public-private partnerships and technology transfer agreements.

Nevertheless, many gaps persist in innovation and technological development of these vaccines and it is necessary and urgent to accelerate new funding mechanisms and incentives, such as "patent pools", with active participation of manufacturers in developing countries, to assure their cost-effectiveness, efficacy and minimize their potential adverse effects. Vaccine innovations require increasing investments in high-throughput screening of new vaccine antigens and candidates and access to new vaccine adjuvants, with new platforms supported by multi-stakeholder manufacturing facilities.

In this global scenario, intellectual property, especially patents documents, have emerged as a crucial issue for vaccine development. The global patent landscape for vaccines against these four arboviral diseases has undergone drastic changes in the past 5 years, with breakthroughs resulting from advances in molecular biology and genetic engineering: DNA vaccines, recombinant vaccines based on antigens expressed in vectors (viral, bacterial, yeast) and vaccines obtained through reverse vaccinology (Sette and Rappuoli 2010), with the selection of potential candidates at the genetic level rather than the protein level.

We present here a global overview of the current scenario for these new vaccine patent deposits and the new developments in this area, stressing the need to overcome current scientific and technological gaps.

From this perspective, we stress the urgent need for new global scientific and technological initiatives supporting the development of new biotechnology-based vaccines, which will be key to deal with these emerging and resurgent arboviral infectious diseases and to support global surveillance.

Finally, considering the current gaps to vaccine development identified in the patent documents and related literature, we make considerations on the need to approach vaccine innovation and development against arboviral diseases from new conceptual frameworks, supported by recent breakthroughs in immunology. We describe and discuss a new strategy, Immunome, emerging from the Genome Project, which might result in a paradigm change in understanding immune response and clinical outcomes to vaccines and comment related ethical, regulatory and policy barriers that should be overcome for its successful implementation.

18.2 Eco-social Approach: Emerging and Resurgent Diseases

Emerging and resurgent arboviral diseases, such as Dengue, Zika, Yellow Fever and Chikungunya, are no longer confined to tropical regions and to the most economically disadvantaged areas of the globe, but threaten other countries, including developed nations such as the US and European countries. Therefore, the conceptual approach to arboviral diseases should shift from a traditional tropical neglected disease framework, focused on the poorest countries, to a new emerging and resurgent disease paradigm recognizing their complexity, in a global eco-social perspective and the urgent need for novel cross-disciplinary perspectives and methodologies. These vector-borne arboviral diseases deserve therefore more public health attention. An eco-social approach should be urgently put in place in order to anticipate

risks and provide interventions before the emergence and global spread of these arboviral diseases.

The first and crucial challenge is understanding the complexity of ecosystems, in a comprehensive perspective, which is crucial to addressing these arboviral vector-borne diseases with complex dynamic cycles involving human and non-human primates and blood-feeding vectors, such as *Aedes* mosquitoes. The importance of an ecological perspective is often missed in public health and epidemiological surveillance, and the absence of this perspective might explain previous failures in dealing with unexpected pandemics. These complex conditions affecting the evolution, introduction, mutations, variations, and adaptations of arboviruses in new ecological niches should be understood from this perspective. In addition, it is important to understand that evolution is not progressive, rather it occurs in opportunistic and unpredictable ways. The notions that usually prevail in global public health and epidemiological surveillance approaches include equilibrium-oriented points of view, assumptions of linearity, and teleological perspectives. However, these notions must be overcome to deal with disease evolution in complex ecosystems and with its unpredictability (Possas 2016).

Another challenge is related to social and cultural issues. Although genetic, immunological, and environmental conditions are important, understanding the social, economic and cultural aspects of the vulnerable populations is also necessary because a pathogen requires a receptive population in order to cause disease. The specific social issues contributing to the outbreak of arboviral diseases include rapid urbanization in conditions of extreme poverty, leading to intense deforestation that favors the contact of populations with unknown vectors and pathogens, as well as the intensification of international travel and population mobility. In addition, social vulnerabilities to new disease are not only a consequence of socioeconomic conditions, but also of the social behaviors related to risk, disease, vaccine and treatment perceptions. Vaccine refusal, often based on exacerbated perception of adverse effects, mistakenly disseminated by the media and internet, can become an important public health obstacle and has emerged as a recent cultural phenomenon. It is therefore important to understand cultural and behavioral barriers when dealing with the emergence of new diseases and new vaccine and therapeutic strategies.

18.3 Global Epidemiological Scenario: Arboviruses

The global scenario for the four main infectious arboviral diseases has become increasingly complex, with new demands for vaccine innovation and development. We provide here an over-view of the four diseases in our study: yellow fever, dengue, Chikungunya and Zika.

18.3.1 Yellow Fever (YF): Risk of Re-urbanization

Yellow fever, an acute viral hemorrhagic fever, is considered one of the most dangerous infectious diseases and a scourge to mankind, due to its high lethality. The disease originated in Africa, from where it spread to Brazil, other American countries and Europe through the slave trade in the seventeenth century, North America and Europe. It is difficult to provide precise global data on yellow fever outbreaks, due to the current barriers to differential diagnosis of hemorrhagic fevers in the remote poorest regions of the world, where access to services is very difficult or even inexistent. Forty seven countries in Africa (34) and Central and South America (13) are either endemic for, or have regions that are endemic for, yellow fever. A modeling study, which has been a reference for international vaccine policies (Garske et al. 2014) estimated the global burden of yellow fever during 2013, indicating alternative scenarios from 84,000 to 170,000 severe cases and 29,000–60,000 deaths, 90% of them in Africa (WHO 2017a, b). Interestingly, the disease is common in tropical areas of South America and Africa, but not in Asia, probably as a result of genetic diversity and peculiar genetic characteristics of the Asian populations and/or cross-protection by other *flavirus* infections. Since the 1980s, the number of cases of yellow fever has been globally increasing. This increase has been attributed to more people living in cities in areas contiguous to forests, increased populational mobility, with travel intensification, and changing climate. The Brazilian Ministry of Health has reported from December 2016 an ongoing outbreak of yellow fever, which has remained for decades in the country in a sylvatic cycle, but now with concerns on the risks of re-urbanization of the disease in a near future, in the largest metropolitan areas of the country, particularly Rio de Janeiro. The first cases were reported in the State of Minas Gerais in December 2016, but confirmed cases have since been reported in the neighboring states of Espírito Santo, São Paulo and Rio de Janeiro. Cases have occurred mainly in rural areas, with most cases being reported from Minas Gerais state, with some cases resulting in death. Health authorities in the affected states, with assistance from the Brazilian Ministry of Health, are conducting mass vaccination campaigns among unvaccinated residents of affected areas.

Brazilian public manufacturer Bio-Manguinhos from Oswaldo Cruz Foundation is the main global producer of yellow fever vaccine. Yellow fever is the only one, of the four arboviral diseases in this study, with a highly effective and efficacious vaccine, providing in most cases a long-lasting protection, available at very low costs, in spite of some rare but severe adverse effects. New innovative vaccines now in development worldwide for yellow fever are an attempt to minimize these adverse effects.

18.3.2 Dengue: Dramatic Global Increase

Upwards 390 million people in the world are infected by Dengue every year, with 90 million of severe cases and the remaining 300 million with benign or asymptomatic cases, usually not diagnosed and/or reported. The disease has been reported in

125 countries, the incidence has increased 30-fold in the last 5 years and with the rapid global spread of its mosquito vectors, *Aedesaegypti* and *Aedesalbopictus,* this number tends to dramatically increase (Bhatt et al. 2013; WHO 2017a, b). The poorest countries in Africa and Latin America, such as Brazil, have been particularly affected by the disease.

Currently, there are no effective vaccines or therapies against Dengue virus (DV) and the four variants of the DV make this challenge even more complex. Several novel strategies are ongoing. Some of the muse live-virus attenuated vaccines for dengue 1, which is critical since virus-neutralizing epitopes have been found to be complexes only found in the whole, intact virus. Other types of vaccines use denatured viral proteins or dengue virus domains taken out of the whole virus context, a strategy leading to the generation of sub- or non-neutralizing antibodies which in turn puts the patient at risk for developing dengue hemorrhagic fever upon secondary exposure. Companies are searching innovative technologies to develop safe and effective live-virus vaccines coupled with a low-cost system of manufacture. One of them, Arbovax created a strategy based on the straightforward concept of developing stable mutations of arboviruses that can replicate successfully in insect cells but grow poorly in mammalian cells, thus creating live, attenuated host-range mutant virus vaccines for any virus that has an insect vector and for which a cDNA clone can be produced. Immunogenicity and safety of three novel live, attenuated host-range DV vaccines containing deletions in the transmembrane domain of Dengue virus serotype-2 (DV2) E glycoprotein were evaluated by Arbovax in African green monkeys. Groups of four monkeys received one dose each of test vaccine candidate with no boost. Two vaccines, DV2ΔGVII and DV2G460P, generated neutralizing antibody in the range of 700–900 PRNT50. All three vaccine strains decreased the length of viremia by at least 2 days. No safety concerns were identified.

Another strategy is focused on the use of chimeric proteins for immunization. Studies have attempted to determine the human antibody response against dengue virus by characterizing human anti-dengue monoclonal antibodies. Prior to this work, most immunological studies on dengue infections had been conducted in mice, which are not a natural host for dengue and which produce a very different antibody response. One of the conclusions to come out of the human studies is that the dominant human antibody response against the dengue virus surface proteins, membrane (prM and M) and envelope (E, soluble envelope protein, sE), is non-neutralizing and cross reactive against the four serotypes of dengue. These non-neutralizing, cross-reactive antibodies are the primary cause of the antibody dependent enhancement of disease. This presents problems for the development of a dengue vaccine that uses the entire prM and E proteins. Even if a vaccine formulation using full length prM and E can induce a broad neutralizing response against all four serotypes, when the neutralizing antibody response wanes over time, the dominant non-neutralizing response will remain and prime vaccine recipients for severe disease if they are ever infected again. It is not yet clear how long the neutralizing vaccine response would endure or when vaccine recipients might become at risk for disease enhancement, but there are few examples of vaccines that induce lifelong protection. An invention (Isern and Michael 2017) relates to a chimeric protein and

methods for producing a chimeric protein for immunizing an individual against dengue and dengue clinical outcomes, and for treating an individual susceptible to infection or infected with dengue virus. In some embodiments, the chimeric protein could be used to create a treatment composition for an infected individual, while in others the chimeric protein could be used to produce a live attenuated vaccine, or a subunit vaccine that is not replicative. The chimeric protein is created by substituting a portion of yellow fever virus (YFV) envelope protein, Flavivirus yellow fever virus, with a portion of any of the strains of dengue virus (DENV) envelope protein, Flavivirus dengue virus. In one embodiment, the chimeric protein of the invention is created using YFV 17D strain envelope protein. Although the example is limited to YFV envelope protein, in other embodiments it is envisioned the chimeric protein may be created using the envelope protein of any flavivirus, for example West Nile Virus, St. Louis encephalitis, Dengue Fever virus, Japanese encephalitis, and Kunjin virus, and substituting any of the four strains of DENV envelope protein. These and other new vaccine developments against Dengue ongoing worldwide are attempting to find a highly effective and efficacious vaccine, against the four variants of the Dengue virus, at low costs and without severe adverse effects.

18.3.3 Zika

The emergence of the severe Zika outbreak in 2015 in Brazil rapidly spread to other countries in the Americas and to other continents, and resulted in 220,000 confirmed cases of Zika infection in the Americas and more than 80 countries affected by the disease (WHO 2017a, b). It was declared by WHO to be an international emergency (decision recently lifted), attracting global vaccine initiatives. There has been in recent months a sharp decrease in global number of cases, probably due to herd immunity and seasonal factors in Brazil, the country where the disease emerged as a large outbreak and spread to other countries in the Americas and worldwide.

The rapid global spread of Zika mobilized global concern and several governmental and non-governmental initiatives were created and attracted significant global funding for its prevention and treatment. Nevertheless, it is still not clear whether there will be a viable market for a vaccine, once one is eventually approved. Sanofi Pasteur, a leading vaccine manufacturer, recently announced its decision to give up its Zika vaccine project, one of most important vaccine candidates. The sharp decrease in the number of cases, possibly due to herd immunity and seasonal variations, which would prevent the spread of the disease in exposed populations, could explain recent withdrawal from funding sources to Sanofi, such as the US Biomedical Advanced Research and Development Authority (Barda), and the perception of the company that probably there will not be a viable market for this vaccine. Another explanation could be the perception from the company that cross-reactivity with Dengue and antibody dependent enhancement, a strong hypothesis to explain devastating complications on babies before birth, might be an important barrier for vaccine development. However, if Zika starts to spread again, this withdrawal from Sanofi Pasteur may become an important gap. But fortunately,

there are several other vaccine candidates against Zika vaccine ongoing, developed by other manufacturers. Several strategies are ongoing for a Zika vaccine: viral vector, inactivated virus, VLP, Live attenuated, DNA, Protein, mRNA, Peptide. A recent study (Lagunas-Rangel et al. 2017) shows that most of the 38 vaccine ongoing projects for Zika are recent and still in pre-clinical stage (84%) and only 3% of them have reached Phase II.

The US National Institutes of Health-NIH is developing a DNA-based Zika vaccine and there are now 18 other agencies and companies around the world developing Zika vaccines. Recently Inovio Pharmaceuticals and GeneOne Life Science, from South Korea, announced approval to initiate a phase I human trial to evaluate Inovio's Zika DNA vaccine which has induced robust antibody and T cell responses in small and large animal models. Other international initiatives funded by anonymous private donors, such as the Zika Cure Alliance (CuraZika), by the University of Pittsburgh in cooperation with Fiocruz in Brazil, are also supporting vaccine development. These new vaccine candidates are mostly based on platforms for dengue vaccine: inactivated, live attenuated, live vectored, chimeric, virus-like particles (VLP), subunit protein, DNA. Several Brazilian institutes are now involved in these recent initiatives. Bio-Manguinhos/Fiocruz is developing Zika vaccines in different partnerships and platforms: inactivated, 17 D Yellow Fever/Zika chimeric virus in tissue culture, subunit E protein and VLP expressed in tobacco.

Evandro Chagas Institute, in collaboration with the US Texas University Medical Branch, is developing an attenuated Zika vaccine. The Butantan Institute is developing an inactivated vaccine in partnership with the US Barda. Another recent study in collaboration between Harvard University and the University of São Paulo has shown that a single immunization of a plasmid DNA vaccine or a purified inactivated virus vaccine provides complete protection in susceptible mice against challenge with a ZIKV outbreak strain from northeast Brazil. Finally, the University of Pittsburgh in collaboration with Fiocruz/Aggeu Magalhães Research Institute is now developing a Zika vaccine using a new version of LAMP technology under the sponsorship of the CuraZika program (Possas et al. 2017).

18.3.4 Chikungunya

Outbreaks were reported in Africa, Southern Europe, Southeast Asia, and islands in the Indian and Pacific Oceans. In late 2013, Chikungunya was found for the first time in the Americas on islands in the Caribbean. In Brazil 230.410 cases of Chikungunya were reported in 2016 (Ministry of Health Brazil 2017). Symptoms include fever and joint pain and typically occur 2–12 days after exposure. Other symptoms may include headache, muscle pain, joint swelling and rash. Most people are better within a week, but in some cases the joint pain may last for months. Chikungunya virus (CHIKV) can lead to severe rheumatic disease in humans.

As with DV, there are no current vaccines or therapeutics available for CHIKV. Some companies, such as Arbovax, are developing vaccines for CHIKV using the same method to generate host-range viral mutants. Arbovax analyzed five

host-range CHIKV vaccines in a mouse model and assessed for joint swelling, generation of neutralizing antibodies and protection from challenge. One of these vaccines produced no inflammation and no detectible viremia post-challenge (Brown and Hernandez 2003; US Patent 6.589.533).

18.3.5 Antibody-Dependent Enhancement: Zika and Dengue Interactions

The scientific debate on the immune mechanisms possibly involved in Zika and Dengue interactions (Halstead 2017) have stressed the need for understanding the immune responses that might be involved in the possible impacts of previous immunity to DENV through infection or vaccination on protective immunity and/or disease enhancement in individuals exposed to ZIKV infection. The ADE hypothesis remains controversial but should be examined, considering its implications for development of vaccines against both diseases.

Recent experimental studies have provided evidence supporting the hypothesis that the dengue virus may contribute to ADE and severe disease in Zika infections. The results of an in vitro study surprised researchers with high levels of Zika replication detected in the presence of dengue antibodies in cultured immune cells (Paul et al. 2016). In sequence, another study has also reported similar results, showing that certain different antibodies to dengue virus react to Zika but not strongly enough to neutralize the virus (Dejnirattisai et al. 2016). Instead, when blood plasma from patients who had recovered from dengue was added to cell cultures infected with Zika, this study found that the ZIKV replication increased by 100-fold. Other experimental studies on ADE have provided evidence in this same direction (Barba-Spaeth et al. 2016; Priyamvada et al. 2016; Rivino and Lim 2016).

In contrast, the opponents of this ADE hypothesis argue that this enhancement would not be specific for Zika since flavivirus antibodies have been known for decades in the scientific literature to cross-react with other flavivirus antigens, including those of dengue virus, when diluted to the adequate concentration. However, this argument does not permit dismissing the possibility that ADE may contribute to the severity of Zika cases in newborns and adults (Possas et al. 2017).

The findings that dengue virus antibodies may partially neutralize ZIKV and strongly stimulate its replication in vitro, although controversial, should not be disregarded at least as a hypothesis for further investigation. If confirmed, Dengue and Zika vaccines might induce antibody enhancement against both viruses, with severe adverse effects in vaccines.

18.4 Patent Landscape: New Vaccine Developments

The global vaccine landscape has undergone drastic changes with the advent of vaccines as multipatented products (Possas et al. 2015). Patent documents have the function of protecting an invention, so it is common for it to refer to the various

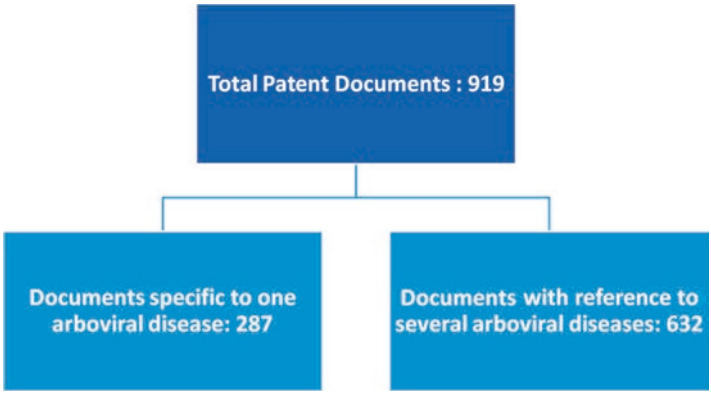

Fig. 18.1 Search results in specific and multi-disease patent groups (1963–2017). (Source: Federal University of Rio de Janeiro, School of Chemistry. Information System on the Chemical Industry (SIQUIM). Derwent Innovation Index)

diseases which may be related to the subject invention of protection. Using the same type of treatment (identification of keywords in the abstracts and subsequent reading of the titles) the documents were separated into two main groups, those specific for a particular pathology and those more general that cite the diseases focus of this study. The search for patent documents was carried out in the Derwent Innovation Index database available from the CAPES journal portal. The search strategy was elaborated considering the classification of the Derwent Manual Code[1] for arboviruses and vaccines and the keywords identified in the title or summary of the documents, for the pathologies selected in this study.

In order to retrieve patent documents related to these pathologies, the following keywords were used in the strategy: dengue or yellow fever or Zika or Chikungunya or arbovirus. The classification Derwent Manual Code presents a specific classification for arboviruses (B14-A02A2) and two for vaccines (B14-S11 and C14-S11) incorporated into our methodological strategy, since the purpose of the study is to produce, formulate, develop and use vaccines. Based on this strategy, 941 patent deposits were identified, considering the indexing period in the base from 1963 to September 2017. These data were imported into the VantagePoint® software for treatment and analysis of data from the patent documents.

Considering their titles, the patent documents were classified into two large groups: those specific for one disease e those related to multiple diseases, as indicated in Fig. 18.1.

Figure 18.2 indicates interesting features in the temporal evolution of the patent documents for vaccines against specific arboviral diseases/pathogens. It shows that

[1] Derwent Manual Code is a classification attributed in the Derwent Innovation® database to all the patent documents indexed in it. This classification also has a hierarchical structure, such as the International Classification of Patents, although in less detail. The Manual Codes divide the technological knowledge contained in the patent documents into 21 sections.

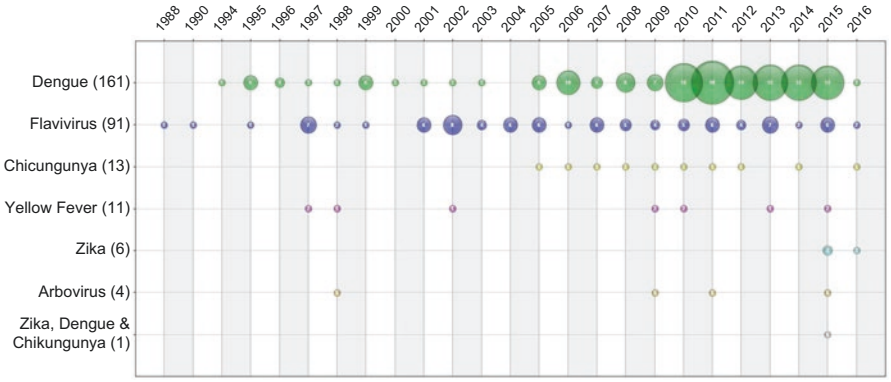

Fig. 18.2 Temporal evolution of specific patent documents for arboviral diseases/pathogens. (Source: Federal University of Rio de Janeiro, School of Chemistry. Information System on the Chemical Industry (SIQUIM). Derwent Innovation Index)

the global efforts so far have evolved mainly in the direction of vaccines against Dengue, which is now the major challenge. Important gaps remain, particularly in innovation and development of vaccines against Zika and Chikungunya and improvement of Yellow Fever vaccine, reducing its adverse effects.

Table 18.1 provides an overview of the patent documents in our search according to the main patent holders for vaccines against arboviral diseases/pathogen, with the US Department of Health and Human Services leading with 29 patents.

It should also be noted in Table 18.1 that the main vaccine patent holders did not submit, in the period considered in our search, specific patent documents for Zika, probably protected by confidentiality. Nevertheless, as indicated in previous Fig. 18.2, there are from other patent holders six patent documents directed to this pathology, with the enterprise Valneva Austria leading with three deposits.

18.5 Genetic Diversity and New Vaccines: The Case for Immunome

The immune system is a highly complex system, based on a structured and coordinated expression of a wide array of genes and proteins. One of the major gaps in vaccine innovation, particularly affecting the development of new vaccines against arboviral diseases, is related to the inability of scientists to explain the diversity of individual immune responses and clinical outcomes to the same vaccine and how this diversity relates to innate and acquired immunity.

The human immunome, a specific set of genes and molecular structures underlying the capacity of the immune system to fight disease, is estimated at 100 billion times larger than the Human Genome Project in terms of data output. Because of this scale, scientists have never been able to characterize the core parts by which the immune system responds to pathogens and develops a disease. It is only recently that dramatic advances in sequencing technologies and bioinformatics,

Table 18.1 Patent documents per main patent holders: specific arboviral diseases/pathogens

Main patent holders	Total documents	Patent documents per specific disease/pathogen					
		Dengue	Flavivirus	Chikungunya	Yellow fever	Arbovirus	Zika
US Dept Health and Human Services	29	15	13	1			0
Sanofi Pasteur	24	13	10		1		0
Us Sec of Army	15	10	4	1			0
Acambis	11	1	10				0
Takeda Vaccines	10	7	3				0
Us Sec of Navy	10	7	2			1	0
Inst Pasteur	8	4	4				0
Int Cent Genetic Eng& Biotechnology	7	7					0
Univ Texas System	7		4	2	1		0

Source: Federal University of Rio de Janeiro, School of Chemistry. Information System on the Chemical Industry (SIQUIM). Derwent Innovation Index

exponentially extending their capacity, have made possible for the first time uncovering the complexity of the human immunome (Crowe and Koff 2015).

Immunome, a bioinformatics resource, has been conceived for the characterization of the human immune system. It contains information about immunity related proteins, their domain structure and the related ontology terms and contains also information about the localization and mechanisms involved in the coding genes.

Determining the core parts of the immune system in the human immunome could drastically transform how we diagnose, prevent and treat disease through the identification of new biomarkers while enabling highly targeted, computationally designed vaccines and therapies that reduce time and risk of product development.

The Immunome Program of the Human Vaccines Project, will sequence in a global collaborative 7 to 10-year effort, receptors from a group of genetically diverse individuals in several continents, and determine the structure and function of a key subset of receptors. Through an open-source procedure, data will be made available to researchers across the world (Koff et al. 2014; Crowe and Koff 2015).

In this Program, laboratory analyses of bio-specimens will be combined with an array of other genetic, lifestyle and health information provided by volunteers to help researchers to identify individual genetic differences that contribute to diverse immune responses. The initial study will assess immune responses of ten healthy adults (ages 40–80) to a licensed hepatitis B vaccine (considered an ideal model to study human immunological protection) and it is expected that this study will expand to include several hundred people – from neonates to the elderly in middle and low income countries.

The Immunome Program can thus bring crucial information to the development of more effective vaccines against arboviral diseases. Vaccine manufacturers in

developing countries particularly affected by these diseases, should be actively involved in its international scientific and technological collaborations.

18.6 Ethical and Regulatory Barriers

A better understanding of the immune system will therefore require from the Immunome Program of the Human Vaccines Project not only clarifying the biological processes involved in immunity, autoimmunity, and anomalous responses to antigens, but also sharing a huge amount of data from international scientific collaboration, with ethical and regulatory implications. There will be in this Program international cooperation in the areas of bio-banks and bio-repositories, as the project will involve the collection of samples necessary for solving complex issues, such as the ones related to genetic diversity and implications for the immune response.

Consequently, the Immunome Program will require, for its success, well designed international collaboration for rapid and fast track access to bio-banks and bio-repositories, including the ones in developing countries. A bio-bank is a repository that stores and manages biological samples known as bio-specimens for use in research. The bio-bank in the Immunome Project will support the collection, analyses, storage and distribution of bio-specimens for research use.

We list below potential ethical and regulatory barriers to Program implementation:

1. Ethical guidelines for sharing bio-specimens and information: need for harmonization and cultural issues in informed consent;
2. The difficulties in creating adequate local ethical evaluation procedures with the necessary flexibility;
3. The long delays in project evaluation and excess of bureaucratic steps;
4. Virtual inexistence of acceptable “fast track” review processes for evaluating priority and emergency projects;
5. Lack of flexible regulatory procedures for sharing bio-specimens and samples;
6. Legal constraints in access to bio-repositories and to bio-bank information;
7. The difficulties in defining the standard of care to be provided during clinical trials;
8. Intellectual property: confidentiality and constraints to patent information sharing;
9. Inadequate incentives for patents: “patent pools” and awards.

18.7 Final Considerations

Innovative vaccines projects against the four main arboviral diseases (Dengue, Zika, Yellow Fever and Chikungunya) have recently emerged worldwide with novel strategies, such as reverse vaccinology, as indicated in the patent documents described here: vectors for expression (such as adenovirus, measles virus and yellow fever),

DNA vaccines, live attenuated vaccines, subunit vaccines, inactivated virus vaccines, VLP, LAMP and SAM (novel self-amplifying mRNA).

Nevertheless, most of these projects are in pre-clinical, phase I and phase II stages. New and more effective knowledge governance strategies and incentives, such as "patent pools" and awards, will be necessary to globally accelerate vaccine development for these diseases, with active participation of vaccine researchers and manufacturers from developing countries, particularly affected by these diseases.

In addition, a major challenge has been identified: the need to explain the diversity of individual immune responses and clinical outcomes to the same vaccine and how this diversity relates to innate and acquired immunity, a major gap that the Immunome Project could contribute to overcome, now that dramatic advances in sequencing technologies and bioinformatics, exponentially extending their capacity have made make possible for the first time uncovering the complexity of the human immunome, a specific set of genes and molecular structures explaining the capacity of the immune system to fight disease.

Another important challenge is related to the need to clarify the mechanisms involved in antibody dependent enhancement of Zika in populations previously exposed to Dengue infection, a controversial issue that might be detrimental to the development of vaccines against both diseases.

A third challenge is related to the need to overcome ethical and regulatory barriers and bureaucratic constraints particularly affecting the developing countries, with possible detrimental consequences for international collaborative efforts in Immunome research and development.

The Immunome scientific strategy will generate a huge and complex amount of data and will require a new paradigm in approaching complex decision making processes involving ethical, regulatory and policy issues, particularly in the developing and middle income countries. We suggest a knowledge governance framework should be conceived, in long-term approach, including a broad range of issues, such as priority setting for research, development and innovation funding; incorporation of international collaborative initiatives into national science, technology and innovation policies; intellectual property and patent sharing; communication of results and community participation.

Scientists, technologists, policy makers and community leaders in developing and middle-income can bring important contributions to these novel strategies. Our main challenge now is to transcend the conventional debate on vaccine development and ethical, regulatory and policy issues, already explored in many scientific publications in the past three decades and determine which of these issues should be considered new and specific to this new perspective (Singh et al. 2016).

Finally, an adequate use of patent documents, as indicated here, can be a valuable source of information, supporting technological prospect tools in more effective knowledge governance strategies.

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Intellectual Property Issues Surrounding Antimicrobial Agents

19

Gerard Marshall Raj and Neel Jayesh Shah

Abstract

The burden of antimicrobial resistance (AMR) is on a consistent rise worldwide. Antibiotics still remain as the principal armamentarium in combating infectious diseases despite profound improvements in the field of infection control and vaccination technology. WHO also recommends national action plans for mitigating AMR and appropriate financial support to attain the same. Implementation of the "Global Action Plan on Antimicrobial Resistance (GAP-AMR)" is essential for the development and conservation of antibiotics for which the WHO along with the "Drugs for Neglected Diseases Initiative (DNDi)" is creating a "Global Antibiotic Research and Development Partnership". The three parallel objectives of this independent product development partnership are antimicrobial and point-of-care diagnostics R&D, conservation, and access to existing antimicrobials. One of the ways to procrastinate, if not preclude, the time travel back to the "pre-antibiotic era" is to optimize the IP practices, thereby creating a congenial environment for all the stakeholders. Striving for a balance between strict antimicrobial patenting practices and broader access to innovative antimicrobials is an indispensable "trade-off" for the mere existence of antimicrobials. This chapter discourses about the connection between antimicrobial R&D and the pharma industry, the contribution of patents in antimicrobial discovery, the alternative antimicrobial patenting practices, and the Indian scenario.

Keywords

Pharmaceutical patents · Antimicrobial resistance · Antibiotics · TRIPS · WTO · WHO

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H. B. Singh et al. (eds.), *Intellectual Property Issues in Microbiology*,
https://doi.org/10.1007/978-981-13-7466-1_19

19.1 Introduction

The burden of antimicrobial resistance (AMR) is on the rise consistently worldwide and it accounts for 700,000 deaths, annually (WHO 2014). Antibiotics still remain as the principal armamentarium in combating infectious diseases despite profound improvements in the field of infection control and vaccination technology. However, the need for newer antimicrobials is not well echoed from the pharma industry's perspective. Compared to the 1980s only a few of the major pharmaceutical companies are involved in antibiotic research and development (R&D) (Harbarth et al. 2015; Huttner et al. 2013).

A recent interagency joint symposium held by the World Health Organization (WHO), the World Trade Organization (WTO), and the World Intellectual Property Organization (WIPO) emphasized the importance of a universal cooperation of worldwide governments, regulatory agencies, pharmaceutical companies, and other stakeholders to curtail the spread of AMR (WTO 2016).

This chapter discourses about the connection between antimicrobial R&D and the pharma industry, the contribution of patents in antimicrobial discovery, the alternative antimicrobial patenting practices, and the Indian scenario.

19.2 Antimicrobial Development and the Pharma Industry

As suggested by the Infectious Diseases Society of America (IDSA), the European Society of Clinical Microbiology and Infectious Diseases (ESCMID), and other agencies, the antimicrobial pipeline is drying up gradually but definitely for the past few decades. The number of under-trial antibiotics against multidrug-resistant Gram-negative bacteria is particularly bleak (Outterson et al. 2007; Silver 2011; Renwick et al. 2016). The main reason is the apprehension surrounding the pharma industries in getting their requisite returns on investment (ROI). Many models have been suggested to boost up the antimicrobial R&D. One such is delinking the volume of sales from the reward paid for a new antibiotic; this could curb the occurrence of overuse of antibiotics and also incentivize investments in R&D of antibiotics (Laxminarayan 2014; WHO 2015; Outterson et al. 2016).

Path-breaking strategies like a "transferable intellectual property right" (TIPR) or "wildcard" patent and "patent term extensions" are suggested to revamp the production of novel antimicrobial drugs. In TIPR, the conventional connection between innovation and reward is severed. By virtue of bringing about a novel antimicrobial drug to the market, the pharmaceutical company will be granted with additional years of marketing authorization for their bestselling drug. This disengagement of patenting from marketing rights is the so-called "wildcard" patent. The other strategy is to extend the patent period for antimicrobial drugs, thereby giving the companies a longer effective patent life. Patent extensions are in vogue in pharmaceutical industry, for example, the Hatch-Waxman Act (USA) and Supplementary Protection Certificates (EU) given as compensation for the time lost in regulatory approval.

However, some advocate against the propaganda of antimicrobial research and development pipeline is really empty (Bassetti et al. 2017; Brüssow 2017). The opponents are of the thought that the current antimicrobial R&D environment is not as bleak as it is considered (Table 19.1), and they are against the "wildcard" patent and "patent term extensions" policies. They believe that by providing "wildcard" patents, the estimated financial burden in developing a newer antimicrobial can be more than ten times the current cost. Direct transparent funding of research would be preferred than that generated by these "wildcard" patents as they would act like hidden taxes on heart disease, chronic obstructive pulmonary disease, asthma, depression, and other common ailments to fund antimicrobial R&D.

Likewise, "patent term extensions" for antimicrobials can be detrimental for improving global public health. Companies may slow down the normally aggressive innovation process owing to the extended patent period, and this may have a negative cost cutting on antimicrobial R&D. Secondly, the antimicrobials will be set at a higher price for a longer duration of time due to delay in the entry of generic counterparts. Finally, in a patent-based incentive system like this, the pharma companies are pushed to inappropriately increase the sales of their antimicrobial products in the last few years just before patent expiry in sharp contrast to the more judicious use of antimicrobials which is advised (Outterson et al. 2007).

Table 19.1 Novel antimicrobial classes

Year	Antimicrobial class
1930s	Sulfonamides
1940s	Penicillins
	Cephalosporins
	Aminoglycosides
	Chloramphenicol
1950s	Tetracyclines
	Macrolides
	Glycopeptides
	Rifamycins
1960s	Quinolones
	Lincosamides
	Trimethoprim
2000s	Streptogramins
	Oxazolidinones
	Lipopeptides (daptomycin)
	Ketolides (telithromycin)
	Glycylcyclines (tigecycline)
	Pleuromutilin (retapamulin)
	Glycolipopetide (telavancin)
2011	Macrocyclic lactone (fidaxomicin)
2012	Diarylquinoline (bedaquiline)

Adapted from Outterson et al. (2007)

19.3 The Roles of Patents on Novel Bullets Against Microbes

The dependence of antibiotic innovation on patents and other IP rights is well exemplified by the discoveries of the early "magic bullets," viz., sulfa drugs, penicillin, and streptomycin. Some of the breakthrough antimicrobials, however, had the support in various other ways like the academic university-drug industry collaborations and wartime emergencies (Sampat 2015).

19.3.1 Sulfa Drugs, Penicillins, and Streptomycin

In fact it was the firm enthusiasm toward patent that pushed Bayer, the German pharma giant, to work on the sulfonamide group of antimicrobials. Bayer went on to acquire a process patent (DE 607537) for Streptozon (the first sulfa drug). Once, after obtaining the patent, the global distribution of Prontosil (previously known as Streptozon) had increased (Lesch 2007; Jayachandran et al. 2010). The fear of "reverse engineering" was existent even those times due to lack of "process patent," which led to initial restricted access to certain countries like France (Hager 2006).

Similarly, it was the acquisition of patent by the US Department of Agriculture (USDA) scientists, who worked along with Florey and Chain and developed a medium for mass production of penicillin, which sustained the development of penicillin (Neushul 1993).

Streptomycin was given a "composition of matter" patent (US 2,449,866) by the US Patent Office (USPTO). Selman Waksman and his student Albert Schatz were the patentees of this natural drug product (streptomycin) obtained from the actinomycetes. Not only that a natural product (though purified) was given a patent for the first time but also that by patenting streptomycin, patentability of subsequent antibiotics was ensured (Kingston 2004; Woodruff and Selman 2014).

19.3.2 Changes in Patenting and Drug Regulatory Practices

The subtle role of patents and exclusivity on the successive phases of the antibiotic revolution and vice versa had also been known, like the discovery of streptomycin and other follow-on antibiotics led to changes in the patenting practices world over. One such example is the move away from the requirement of "flash of creative genius" (the way in which the inventions were made) for patentability and toward "nonobviousness" or "inventive step" requirements, especially for pharmaceutical patents, in the 1950s and 1960s (Dutfield 2009; Raj et al. 2015). The semisynthetic and synthetic penicillins were some of the early examples for the involvement of third-party patenting agencies (viz., the "Research Corporation") for acquiring pharmaceutical patents. The coinciding patent claims by three independent pharma companies on three broad-spectrum antibiotics (chlortetracycline, oxytetracycline, and tetracycline) led to "cartelization" in the pharma industry for the first time.

"Cartelization" is a business model wherein a group of commercial enterprises collude to limit competition within an industry or market.

The inception of drug regulatory practices was partly due to patent-related monopolies in antibiotics which used to result in overprescribing and higher prices. And conversely, it is also stated that the rise of drug regulation led to the need for firm patent protection. The practice of compulsory licensing also came into existence (Carpenter 2010).

In line with these thoughts, the US Food and Drug Administration (FDA) had initiated the Generating Antibiotics Incentives Now Act (GAIN Act) to promote the development of newer antimicrobials. Under this GAIN Act, some of the molecules were given the status of Qualified Infectious Disease Product (QIDP). QIDP designation will help in two ways, one is to expedite the drug review process and the other is to provide with additional 5 years of marketing exclusivity. An add-on 6 months of exclusivity is also provided for companies which develop a companion diagnostic test for the indication (FDA Voice. GAIN Act 2014; Brown 2013). Similarly, the European Commission (EC), an institution of the European Union (EU), and the European Federation of Pharmaceutical Industries and Associations (EFPIA) representing the European pharmaceutical industry have joined arms by donating 1 billion euros each to a project named Innovative Medicine's Initiative (IMI) for the development of novel, safe, and effective antimicrobials (Kirby 2012).

Majority of the prospective antimicrobials under trial are semisynthetic and synthetic derivatives of known natural antibiotics (precisely named so, as antimicrobials of natural origin are termed as "antibiotics"). However, some antimicrobials are derived from known microbiological agents and very few from novel microbiological strains. Under such circumstances, the innovators are in a catch-22 situation as it is essential for them to register the new microbial strain in any recognized depository as per the Budapest Treaty. Once deposited a registration number is given to the strain which could be quoted in the patent specification; the advantage is that the depositor is exempted from describing the strain, and the disadvantage is the huge registration money to be paid (Saha and Bhattacharya 2011).

The erstwhile effect of antimicrobial patenting was in a way thought to facilitate the progress in other areas of medicine, viz., anticancer chemotherapy and transplantation immunotherapy (Le Fanu 2002).

19.4 Optimal Practices in Antimicrobial Patenting

The intricacies surrounding patenting antimicrobial agents are obvious. As discussed earlier, a purely patent-based pharma industry by providing "wildcard" patents and "patent term extensions" for antimicrobials could be unfavorable to all the stakeholders. The following are some of the alternative approaches.

19.4.1 Compensation for the Patent Owner for Valuable Innovation

Valuable and outstanding innovations are to be rewarded appropriately, and this could be the best market-based remedy for inadequate innovation in the field of antimicrobial research.

Unlike, the chronic disease states like heart diseases or diabetes, the antibiotics are usually prescribed episodically and for a short course of time. Depending on the setup, the insurance agencies, the governmental organizations, or the general public are hesitant to pay substantially higher prices for antimicrobial drugs. However, it should be borne in mind that infections similar to cancers can pose a huge economic burden on the society. Hence, it is the duty of the pharma industry to emphasize the cost-effectiveness statement in antimicrobial R&D like they defend in oncology to fetch high financial returns.

Secondarily, higher costs can, in turn, limit the irrational use of antimicrobials. However, the negative effects of access to high-priced drugs can arise especially for the patients from developing countries (Outterson et al. 2007).

As compensation to delinking antimicrobial R&D from sales, the pharma companies bringing about newer antimicrobials can be rewarded in a staged manner, i.e., a minimum base reward and subsequent annual payments based on the long-term clinical effectiveness of the antimicrobial agent. The ideal scenario would be to provide incentives to novel antimicrobial drugs irrespective of them being developed either for last-resort use or immediate therapeutic value (Outterson et al. 2016).

The European Investment Bank (EIB), under the EU, created an "InnovFin Infectious Diseases Finance Facility (IDFF)" which provides between 7.5 million and 75 million euros to companies actively participating in antimicrobial-related research. Recently, the EIB signed a MoU with AntibioTx A/S, a private Danish biotechnology company, for 20 million euros to develop a new class of antibiotics (European Investment Bank 2017).

19.4.2 Compensation for the Patent Owner for Antimicrobial Conservation

The drug regulatory agencies can restrict the use of an antimicrobial temporarily so as to increase the time to AMR; however, in doing so the companies lose profits. Hence, the patent holder (market authorization holder) has to be judiciously compensated by means of either direct monetary payments or offering a "full patent buyout" (Outterson et al. 2007).

However, a more preferable option is to go for a "partial patent buyout" in which the IP rights are licensed to a global coordinating body, and the right and responsibility to manufacture and market the drug are still vested with the pharma company. The drug company would still be compensated for appropriate antimicrobial

conservation resulting in optimal antimicrobial access to the areas in need (Outterson et al. 2016).

19.4.3 Enhanced Public Funding of Antimicrobial Research and Development

Public-funded R&D is preferable to private-funded R&D. The most direct and efficient route to foster antimicrobial R&D is to increase the long-term governmental research grants from the various organizations, such as the National Institutes of Health (NIH) in the USA, Medical Research Council (MRC) in the UK, and Indian Council of Medical Research (ICMR) in India. The public funding for antimicrobial research is particularly more relevant during the early preclinical phase of drug development (Outterson et al. 2016).

The importance of public–private partnerships (PPPs) is also not to be undermined (Outterson et al. 2007; Boucher et al. 2013); PPPs are particularly more necessary during the clinical phase of drug development (Outterson et al. 2016). The Biomedical Advanced Research and Development Authority (BARDA) of the US government had recently awarded a fund of 200 million USD to GSK for the development of novel antibiotics (Laxminarayan 2014); the IMI existent in the EU is another example for growing PPPs in the field of antibiotic R&D (Kirby 2012).

The IMI-driven DRIVE-AB (Driving Re-InVEstment in R&D and responsible AntiBiotic use) conglomeration comprising of 9 private and 14 public partners from around 12 countries is a unique initiative helping in co-evolvement of both rational antibiotic use and replenishment of the antibiotic pipelines (Harbarth et al. 2015). DRIVE-AB is one of the seven other projects started under the aegis of New Drugs 4 Bad Bugs (ND4BB) program of IMI by creating innovative public–private collaborative partnerships for the discovery and development of novel antimicrobial agents. COMBACTE (Combating Antibiotic Resistance in Europe), TRANSLOCATION (finding new ways of getting antibiotics into bacteria and stopping bacteria from expelling the drugs), ENABLE (to develop new drug for Gram-negative bacteria), COMBACTE-CARE, COMBACTE-MAGNET, and iABC (inhaled Antibiotics in Bronchiectasis and Cystic Fibrosis) are the other projects envisaged under ND4BB (New Drugs for Bad Bugs (ND4BB) [Internet] 2017).

The importance of multinational cooperation to fight against AMR is highlighted by the introduction of the "Transatlantic Taskforce on Antimicrobial Resistance (TATFAR)" linking the USA and the EU (European Commission. Research & Innovation.Health.[Internet] 2017).

The BEAM Alliance (Biopharmaceutical companies from Europe innovating in AntiMicrobial resistance) is a group of 40 biopharmaceutical companies from 11 European countries dedicated to develop novel antimicrobials; currently, in this forum, there are around 95 antibacterial products in development (BEAM Alliance Position Paper [Internet] 2015).

19.4.4 Reimbursement for Health-Care Providers for Antimicrobial Conservation

For known reasons, conservation and restoration of antimicrobials can be much cheaper than creating an entirely new antimicrobial drug. Conservation could be achieved through traditional techniques of health promotion, infection control, upgraded diagnostic testing, stewardship of available antimicrobial drugs (optimizing antibiotic utilization), and subsidies for preferred therapies (Laxminarayan 2014).

Innovations in the settings of microbial diagnostic and susceptibility testings are necessary to ward off irrational antimicrobial prescribing practices and to assure that the best antimicrobials are prescribed empirically. The recent award of 1 million euros worth "Horizon prize for better use of antibiotics" given to Minicare HNL (a diagnostics company) by the EC is a good example for the support the innovative easy-to-use diagnostics are garnering globally. Minicare HNL developed a finger prick test that can diagnose in less than 10 min a bacterial infection and also if a patient can be treated safely without the need for antibiotics (European Commission. Research & Innovation.Health.[Internet] 2017).

Rapid Identification of Respiratory Tract Infections (RID-RTI), Chips4Life (C4L), and RApid Point-of-Care test Platforms for Infectious Diseases (RAPP-ID) are some of the other missions which uphold the necessity for innovation in diagnostic modalities in the field of microbiology (How EU funding contributes to public health and tackles antimicrobial resistance [Internet] 2017).

In developing countries, subsidy plans for artemisinin-based combination therapy for malaria and multidrug therapy for tuberculosis are examples for subsidies for preferred therapies (Outterson et al. 2007; Boucher et al. 2013).

19.5 Indian Perspectives

19.5.1 TRIPS and India

The pharmaceutical patenting practices can be divided into two eras, i.e., before 2005 and after 2005, as during this change over India became a signatory of the TRIPS (Trade-Related Aspects of Intellectual Property Rights) agreement under the WTO. Owing to this, two drastic changes happened in the patent system in India. First, the duration of patent protection was extended to a period of 20 years from a period of 7 years. The second and most significant modification was that the patents have to be granted to the composition of the product ("product patent") and not just the process in making them ("process patent").This was a huge blow to the Indian pharmaceutical industry, especially the smaller ones, as they now have to focus more attention on their R&D activities. The effects of this change were far-reaching; the Indian pharma companies, especially the smaller ones, which once dwelled on "reverse engineering" (a process of manufacturing the same drug using a different process, acquire the patent, and sell the drugs at a lower price than the original

innovator company), had to reinvent themselves and strengthen their R&D activities (Raj et al. 2015).

The effect of this change in trend toward "product patent" on antimicrobial use was studied by Chaudhuri et al. (Chaudhuri et al. 2003) in India. They carried out counterfactual simulations of how the prices, profits, and consumer welfare would have been affected had the fluoroquinolone class of drugs been patented for use in India like in some of the other countries. The results portrayed the adverse influence of TRIPS on the Indian economy. It was estimated that the annual welfare loss could be around 144 million USD to 450 million USD if appropriate patents were enforced on the fluoroquinolones (ciprofloxacin, norfloxacin, ofloxacin, and sparfloxacin). They also decomposed the consumer welfare loss into a "product variety" effect, an "expenditure switching" effect, and a "price adjustment" effect and reiterated the importance of these components on policymaking.

19.5.2 Antimicrobial Resistance in India

AMR is as rampant in India as globally; it has been estimated that the worldwide consumption of antibiotics between 2000 and 2010 increased by 36% with India accounting for around 75% of this increase along with other BRICS (Brazil, Russia, India, China, and South Africa) countries. India was the largest consumer of antibiotics for human health care in the year 2010.

Currently, almost 50% of total value of drugs sold is antimicrobials in India, and AMR is bound to occur with such high proportions of antimicrobial use. Availability of prescription antibiotic drugs as over-the-counter products and undue compensation given to the physicians are some of the reasons for this exaggerated use. Both overuse and misuse of antimicrobials can result in AMR (Laxminarayan et al. 2016; Laxminarayan and Chaudhury 2016; Humphreys and Fleck 2016).

In line with the "Global Action Plan on Antimicrobial Resistance (GAP-AMR) (WHO 2015), 2015" released by the WHO, the "National Action Plan on Antimicrobial Resistance(NAP-AMR) (National Action Plan on Antimicrobial Resistance(NAP-AMR) 2017), 2017–2021" was drafted by the Core Working Group under the aegis of the Ministry of Health and Family Welfare, Government of India, and released in April 2017. Along with the five objectives outlined in the GAP-AMR, the national action plan included a sixth objective. More precisely called as a strategic priority, the sixth objective was to strengthen India's leadership on AMR. The three focus areas for attaining this objective are international, national, and state level collaborations in all matters concerned with AMR.

19.5.3 Antimicrobial Research in India

In a country like India, innovation in terms of reliable and affordable point-of-care diagnostics to detect both the infective agent and its sensitivity to common antibiotics would be more sensible as the chances for acquiring new broad-spectrum yet

affordable antibiotics are meagre (Laxminarayan 2014; WHO 2015). As per the Consultative Expert Working Group on Research and Development (Consultative Expert Working Group on Research and Development [Internet], 2012) established by WHO, at least 0.01% of GDP should be spent for health needs in the developing nations which like other countries India is yet to achieve; the same trend continues in antimicrobial R&D.

India is 1 of the 26 participating members of the "Joint Programming Initiative on AMR (JPIAMR)" initiated by the EU for coordination among the countries across the globe. JPIAMR was set up to unify the dispersed funding and research efforts and to maximize research by a joint multinational collaborative venture (Joint Programming Initiative on Antimicrobial Resistance [Internet], 2017).

There are 96 patents (as of August 2016) filed by the Indian investigators related to antimicrobial research which appears to be promising. However, the majority of the researches were restricted to modified antimicrobial formulations, description of antimicrobial properties of known synthetic or natural antimicrobial products, and development of nanoparticle-based antimicrobial agents. There is deficient research into the mechanisms of resistance and rapid antimicrobial susceptibility diagnostic testings. More importantly, there is no clinical research on any novel antimicrobial agent, and antimicrobial research is only at experimental or in vitro level in India which is very disappointing.

On grounds of ROI, the drug companies and academia have focused on chemical alteration of existing agents rather than on attempting to discover innovative antimicrobial compounds. This trend continues even as some of the major pharmaceutical companies in India have increased their expenditure on R&D to over 40-folds in the past 10 years (Das et al. 2017).

The Antimicrobial Resistance Surveillance and Research Network (AMRSN) (ICMR 2016) was established by ICMR in 2013 to estimate the AMR prevalence of six pathogenic microbes. Though not found to be optimally functioning (Das et al. 2017), the recent release of Antimicrobial Guidelines (AMGL) (ICMR 2017) by ICMR for empiric management of ten common infectious syndromes was based on the data collated by the AMRSN. This reflects the partial success achieved by the surveillance system in India. Hence, the need of the hour is to further strengthen the existing AMRSN so that the nationwide surveillance system is more well-regulated and coordinated.

19.6 Conclusion

As per the WHO's GAP-AMR-2015, international collaborative research between the developing and developed nations is the basis for attaining the "objective 5" to overhaul AMR. The "objective 5" is to "Develop the economic case for sustainable investment that takes account of the needs of all countries, and increase investment in new medicines, diagnostic tools, vaccines and other interventions." WHO also recommends national action plans for mitigating AMR and appropriate financial support to attain the same (WHO 2015). Implementation of this GAP-AMR is

essential for the development and conservation of antibiotics for which the WHO along with the "Drugs for Neglected Diseases Initiative (DNDi)" is creating a "Global Antibiotic Research and Development Partnership" (WHO 2017a). The three parallel objectives of this independent product development partnership are antimicrobial and point-of-care diagnostics R&D, conservation, and access to existing antimicrobials (WHO 2017b).

As per the recent WHO statements, we are actually marching insidiously toward an era in which even trivial infections can kill a person like in the "pre-antibiotic era" – the now more appropriately rechristened term called the "post-antibiotic era." One of the ways to procrastinate, if not preclude, this medical debacle is to optimize the IP practices, thereby creating a congenial environment for all the stakeholders. We should strive for a balance between stricter antimicrobial patenting practices and broader access to innovative antimicrobials – which is an indispensable "trade-off" for the mere existence of antimicrobials.

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Flexibilities Under the Indian Patents Act for Use of Pharmaceutical Inventions

20

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Abstract

Prior to 2005, the Indian Patents Act, 1970 (hereinafter 'the Patents Act') did not provide for patent protection on pharmaceutical products; an important consequence of such a patent regime was the growth of a robust generics drug industry in India which earned India the title of the 'pharmacy of the developing world'. In 2005, India amended its Patents Act to provide patent protection to pharmaceutical products. This had a direct consequence on generic drug manufacturers in India who can no longer commercially sell generic versions of patented drugs in India until the drugs go off patent. On the other hand, access to medicines (the right of the public to affordable medicines) is a key concern for India and other developing and least developed countries. Certain provisions in the Indian patent law are aimed at ensuring access to medicines by striking a balance between patent-holders' rights and public interest. This chapter focusses on the flexibilities in the Patents Act, such as compulsory licensing and section 107A of the Patents Act, which allow for certain uses of patented drugs by third parties, and section 3(d) of the Patents Act which prevents ever-greening of pharmaceutical patents. The chapter discusses landmark judgments such as *Bayer Corporation v. Union of India*, *Novartis v. Union of India* and the more recent judgment of the Delhi High Court in *Bayer Corporation v. Natco Pharma Ltd. and Alembic Pharmaceuticals Ltd.* The chapter concludes with the role of public interest in guiding the interpretation of patent law provisions by Indian courts and the issues surrounding the court's interpretation of these provisions.

Keywords

Indian Patents Act · Pharmaceutical patents · WTO · TRIPs

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H. B. Singh et al. (eds.), *Intellectual Property Issues in Microbiology*,
https://doi.org/10.1007/978-981-13-7466-1_20

20.1 History of Pharmaceutical Patent Protection in India

The first patent regime in independent India was the Indian Patents and Designs Act, 1911 which allowed patents to be granted on both products as well as processes. In October 1948, the Indian government established a Committee (presided over by Dr. Bakshi Tek Chand, a retired Judge of the High Court of Lahore) to review patent law in India and to bring the country's patent system in line with national interests. The Tek Chand Committee submitted an interim report in August 1949 following which the Indian government made certain amendments to the 1911 Act (*vide* Act 32 of 1950) which related mostly to compulsory licensing provisions. However, these amendments were cumbersome to implement and in 1957, the Indian government appointed Justice N. Rajagopala Ayyangar to propose revisions to the patent law. The Ayyangar Committee submitted its report[1] in September, 1959. This led the Indian Parliament to enact the Patents Act, 1970 (hereinafter the original Patents Act 1970) which incorporated the recommendations of the Ayyangar Committee. The original Patents Act 1970 did not provide for patents on medicines or drugs and only the processes or methods of manufacturing the medicines and drugs could be patented. The Act based on the recommendations of the Ayyangar Committee disallowed patents on pharmaceutical products to prevent monopoly on medicines and to ensure that medicines remain affordable to the public at reasonable prices.

By not allowing patents on pharmaceutical products, the Patents Act 1970 led to a booming generic drugs industry in India as Indian companies could 'reverse engineer' or make copycat versions of foreign drugs without paying any licensing fee to foreign companies. This further enabled Indian generic drugs companies to sell cheap versions of foreign drugs at a fraction of their cost in India and other countries. India became one of the leading exporters of generic drugs in the world, earning itself the title of 'pharmacy of the developing world'.

However, India was compelled to substantially amend its patent law when it became a member of the World Trade Organisation (WTO), an intergovernmental organisation which sets down rules related to international trade. As a member of the WTO, India was obliged to bring its national patent law in line with the Agreement on Trade-Related Aspects of Intellectual Property Rights (TRIPS)[2] – one of the provisions in the TRIPS Agreement is that members must generally provide patent protection for *any* invention including products in *all* fields of technology. Thus, India enacted the Patents (Amendment) Act, 2005[3] in 2005 which repealed section 5 of the original 1970 Act and allowed patents on pharmaceutical products.

It is worth pointing out here that India's 1970 patent law which denied pharmaceutical product patents was in line with the laws of other European nations, as almost all European countries did not allow patent claims on pharmaceutical products at that time. One might wonder then why the TRIPS Agreement mandated

[1] Ayyangar Committee, *Report on the Revision of the Patents Law* (1959) 39. https://spicyip.com/wp-content/uploads/2013/10/ayyangar_committee_report.pdf. Accessed 6 March 2017.

[2] Available at: https://www.wto.org/english/docs_e/legal_e/27-trips.pdf.

[3] Act No. 15 of 2005. Available at http://www.wipo.int/wipolex/en/details.jsp?id=2407

WTO members to provide patents on pharmaceutical products. The shift from non-patenting to patenting of pharmaceutical products through the TRIPS Agreement took place mainly because of the pressure exerted by the United States during the negotiation of the WTO Agreements, to protect the interests of US pharmaceutical companies.

While the present Patents Act does provide patents on pharmaceutical products (so long as they fulfil the general criteria of patentability- novelty, non-obviousness and industrial utility), the Indian patent law contains provisions to guard against wrongful exploitation of pharmaceutical patents by patent owners. Two important provisions in this regard are section 3(d) and compulsory licensing provisions. A third provision in the Patents Act, namely section 107A allows a patented invention to be used by third parties for the purposes of research. We shall now explore each of these three provisions and their interpretation through landmark judgments.

20.2 Section 3(d) of the Patents Act

To be patentable, an 'invention' must be new, non-obvious and capable of industrial application.[4] The Patent Examiner applies the test of novelty, non-obviousness and industrial utility to allow or reject patent applications. However, before applying the aforementioned 'substantive test of patentability', the Examiner must ascertain whether the subject matter of the invention is itself patentable, by applying section 3 of the Patents Act. Section 3 enumerates the list of inventions which are not patentable under the Patents Act- examples of non-patentable inventions under section 3 are traditional knowledge, computer programs per se and inventions which could be contrary to public order or morality. Section 3 can therefore be considered a subject-matter patentability test and if any invention (over which a patent is claimed) falls under section 3, it is not patentable under the Act.

Section 3(d) of the Patents Act specifies inter alia that the mere discovery of a new form of a known substance which does not result in the enhancement of the known efficacy of that substance is not a patentable invention. The explanation to section 3(d) states that salts of known substances shall be considered to be the same substance, unless they have significantly different properties with regard to efficacy.

Section 3(d) plays a key role in determining patentability of chemical compounds especially in the field of pharmaceuticals. The landmark case involving section 3(d) is *Novartis v. Union of India*[5] which was decided by the Supreme Court of India in 2013.

[4] Defined in section 2(1) (j) of the Patents Act.

[5] Civil Appeal Nos. 2706–2716 of 2013.

20.2.1 Novartis v. Union of India

20.2.1.1 Background and Facts

Jürg Zimmermann, a scientist working with Novartis (a Swiss multinational pharmaceutical company) invented some derivatives of the chemical compound N-phenyl-2-pyrimidine-amine. One of the derivatives was CGP 57148[6] in free base form (known as 'Imatinib') which was capable of inhibiting certain protein kinases and possessed anti-tumour properties. Imatinib was used in anti-tumoral drugs and drugs against atherosclerosis to treat warm-blooded animals. The US Patent Office granted a patent on Imatinib[7] (hereinafter Zimmermann Patent) on May 28, 1996.

Using Imatinib in free base form, Novartis first produced Imatinib Mesylate (the methanesulfonic acid addition salt of Imatinib) and then the beta crystalline form of Imatinib Mesylate. Novartis then filed a patent application for the beta crystalline form of Imatinib Mesylate in the Chennai Patent Office on July 17, 1998.[8] The beta crystalline form of Imatinib Mesylate is a therapeutic drug for treating chronic myeloid leukemia and certain kinds of tumours and marketed under the brand name 'Glivec'/'Gleevec' by Novartis. Novartis claimed that the beta crystal of Imatinib Mesylate had more beneficial flow properties, better thermodynamic stability, lower hygroscopicity, and was easier to store and process. Novartis stated all the improved properties of the beta crystal in comparison with the alpha crystalline form of Imatinib Mesylate. Novartis also produced expert evidence that the beta crystal had much higher bioavailability as compared to Imatinib in free base form.

Novartis' patent application for Glivec was opposed in five separate opposition petitions by Cancer Patients Aids Association, Natco Pharma Ltd., Cipla Ltd., Ranbaxy Laboratories Ltd. and Hetro Drug Ltd. under the pre-grant opposition mechanism provided in section 25(1) of the Patents Act which allows any person to oppose a patent application on certain specific grounds such as prior use, non-patentable subject matter of the invention etc. After hearing all the parties, the Assistant Controller of Patents and Designs rejected Novartis' patent application on January 25, 2006. The Assistant Controller held that Novartis' invention did not fulfil the novelty and the non-obviousness test because Glivec was anticipated by prior art (namely, the Zimmermann patent) and obvious to a person skilled in the art (as Glivec was disclosed by the Zimmermann patent specifications). Further, the Assistant Controller was of the opinion that Glivec was not patentable under section 3(d) of the Patents Act.

Novartis appealed against the Assistant Controller's order in the Intellectual Property Appellate Board (IPAB) which dismissed the appeal petitions on June 26, 2009. The IPAB held that while Glivec fulfilled the novelty and non-obviousness tests, the subject-matter of the invention (namely, the beta crystalline form of Imatinib Mesylate) was not patentable under section 3(d). Novartis appealed directly

[6] 4-(4-methylpiperazin-1ylmethyl)-N-[4-methyl-3-(4-pyridin-3-yl)pyrimidin-2-ylamino)phenyl] benzamide.

[7] US Patent No. 5,521,184.

[8] Application No. 1602/MAS/1998.

against the IPAB's order before the Supreme Court (SC) under Article 136 of the Constitution (special leave to appeal).

The SC had to deal with legal issues such as whether Glivec (the beta crystalline form of Imatinib Mesylate) satisfied the test under section 3 (d) and whether Novartis was entitled to a patent on Glivec even if the invention was novel and non-obvious, but failed to satisfy the test under section 3(d).

20.2.1.2 Court's Analysis

a. *Legislative history of section 3(d)*

The Court delved into the legislative history of patent law in India particularly that of section 3(d) of the Patents Act. The SC noted that when the Bill to allow product patents for pharmaceutical and agricultural chemical substances was introduced in the Indian Parliament in December 2004, it was met with a great deal of scepticism by members of the Opposition, who highlighted that big pharmaceutical companies would rely on product patents to *"artificially extend the period of patent to keep competitors out and keep the prices of the patented product high"*. The opposition to the Bill was strong not just within India but also in countries abroad, as the Bill would directly impact India's ability to supply 50% of the cheapest drugs in the world to under-developed and developing countries. One of the members of the Opposition expressed concern that the Bill was vague about the 'ever-greening effect' of the provision (e.g. where companies might try and extend patent protection over a drug by claiming a patent over various forms of the same drug). Ever-greening delays entry of cheap generic versions of drugs and the public is compelled to purchase expensive patented drugs till the time the patent on a drug is in force.

Interestingly, to demonstrate the harm that would follow ever-greening of patents, the Opposition cited the example of Novartis' Glivec which costs Rs.1,20,000 per month in India and whose generic versions cost only Rs. 8000 to Rs. 10,000 in India.

The 2005 Amendment Act which was finally passed by the Parliament to provide product patents differed significantly from the 2004 Bill because the Act included the words, "the mere discovery of a new form of a known substance which does not result in the enhancement of the known efficacy of that substance" and an explanation in section 3(d). The Indian government brought about changes in amendment with the objective of preventing ever-greening under section 3(d).

b. *Meaning of 'efficacy' in section 3(d)*

As provided in the explanation to section 3(d), the salts, pure forms and other derivatives of known substance are considered to be the same substance unless they differ significantly in properties with respect to efficacy. In order to determine whether Glivec satisfied the section 3(d) requirement, the Court had to determine the meaning of efficacy in section 3(d) as the term 'efficacy' is not defined in the Patents Act. The SC in para 180 held, "the test of efficacy would depend upon the function, utility or the purpose of the product under consideration. Therefore, in the case of a medicine that claims to cure a disease, the test of efficacy can only be

therapeutic efficacy" [emphasis supplied]. Further, the court said, "therapeutic efficacy of a medicine must be judged strictly and narrowly" [emphasis supplied].

After holding that efficacy in section 3(d) refers to therapeutic efficacy, the Court went on to examine whether Glivec had greater therapeutic efficacy as compared to Imatinib in free base form. Novartis had argued that Glivec had better physical attributes than the free form of Imatinib in terms of solubility, more beneficial flow properties, more thermodynamic stability, less hygroscopicity and greater bioavailability.

It is important here to highlight that Novartis in its patent application in India had claimed that it had invented the beta crystalline form of Imatinib Mesylate proceeding directly from Imatinib in free base form and therefore, Novartis sought to show enhancement of efficacy of Glivec in comparison with Imatinib in its free base form. The SC, however, rejected Novartis' argument and was of the opinion that Novartis must show the enhanced efficacy of the beta crystal form of Imatinib Mesylate with respect to the non-crystalline form of the salt, Imatinib Mesylate.

The SC in its judgment noted that Novartis had launched Glivec in the US market on the basis of the Zimmermann patent and much before the US patent for the beta crystalline form of Imatinib Mesylate was granted to Novartis on May 17, 2005. This is important because when furnishing information for its New Drug Application (NDA) before the US Food and Drug Administration (FDA), Novartis had listed the active ingredient of the drug as Imatinib Mesylate and Novartis declared that the Zimmermann patent covered the "composition, formulation and/or method of use of Imatinib Mesylate).

Interestingly, Novartis in its patent application in the Chennai Patent Office had claimed that the Zimmermann Patent ended at Imatinib in its free base form and did not cover Imatinib Mesylate. Novartis' patent application was possibly intended to evidence a high level of inventive step in producing the beta crystal of Imatinib Mesylate directly from Imatinib in its free base form, than if Novartis had been claiming that it manufactured the beta crystalline form of Imatinib Mesylate from Imatinib Mesylate in its non-crystalline form. On the basis that Novartis had declared to the US FDA that the active ingredient in Glivec was Imatinib Mesylate and that Imatinib Mesylate was itself covered by the Zimmermann patent, the SC held that Imatinib Mesylate (non-crystalline) was known from the Zimmermann patent and was the substance immediately preceding the beta crystalline form of Imatinib Mesylate. Accordingly, the Court held that the comparison of the properties of the beta crystal must be done with the non-crystal of Imatinib Mesylate and not Imatinib in its free form.

The Court found that Novartis had not shown any enhancement of efficacy, or solubility of the beta crystal with Imatinib Mesylate. The SC also said that the high solubility of the beta crystal (as claimed by Novartis w.r.t. Imatinib) could very well be a property of Imatinib Mesylate since salts in general are more soluble than compounds in free base form.

In examining whether the other properties of the beta crystal (such as more beneficial flow properties, better thermodynamic stability and lower hygroscopicity) amounted to enhancement of efficacy under section 3 (d), the Court held that not all

advantageous properties of an invention would be considered, but only those that directly related to 'therapeutic efficacy'. The Court also emphasised that every form of a particular substance has some properties which inhere in that form (e.g. solubility in salts and hygroscopicity in polymorphs), therefore properties of a chemical form of a substance which are by virtue of that form would not qualify as enhancing the efficacy of a particular substance. Accordingly, the court ruled that the physico-chemical properties of the beta crystal outlined above have nothing to do with therapeutic efficacy and therefore, must be disregarded under section 3(d).

On the point that the beta crystal had 30% increased bioavailability compared to Imatinib in free base form, the court held that increased bioavailability alone will not necessarily lead to enhancement of therapeutic efficacy. Accordingly, the court held that the beta crystalline form of Imatinib Mesylate failed the test of section 3(d).

c. *Section 3(d) does not bar all forms of incremental inventions*

The SC clarified that section 3(d) does not bar patent protection for all incremental inventions of chemical and pharmaceutical substances. The judgment highlighted that a new product in chemicals (especially pharmaceuticals) does not necessarily mean something which is produced from the scratch. Rather, a product could be new even if it is different from a previous version or better than the earlier products. Where patent protection is claimed for a pharmaceutical chemical which is a new form of a known substance, the said invention must pass the test of section 3(d) (and the explanation under section 3(d)) in addition to the substantive criteria of patentability (novelty, non-obviousness and industrial application).

d. *Novartis' application for Glivec- An attempt at evergreening?*

In its closing remarks, the SC pointed out a troubling aspect of the matter, namely, that when Glivec was sold in the US in 2001, it was marketed as Imatinib Mesylate and not Imatinib Mesylate in its beta crystal form. Even when Glivec was marketed in India in 2003, on its packaging the drug was described as Imatinib Mesylate Tablets 100 mg and each tablet was said to contain 100 mg Imatinib (as Mesylate). The packaging made no reference to Imatinib Mesylate in beta crystalline form. Therefore, what was sold by Novartis as Glivec was in fact Imatinib Mesylate and not beta crystalline form of Imatinib Mesylate as claimed by Novartis in its India patent application. The court said that it was conceivable therefore that by claiming a patent on the beta crystal form of Imatinib Mesylate and claiming it to be the drug, 'Glivec', Novartis was in fact trying to patent Imatinib Mesylate which was not permissible in India.

In clarifying that 'efficacy' in section 3(d) refers to 'therapeutic efficacy' in case of pharmaceuticals, the Novartis judgment ensured that pharmaceutical companies did not unfairly extend patent protection term for their drugs. This in turn has ensured that the entry of cheaper and generic versions of life-saving drugs is not delayed in the market.

20.3 Section 84 of the Patents Act

Section 84 provides for issuance of compulsory licences by the Controller on a patented invention. Under this provision, any 'interested person' may apply to the Controller of Patents (hereinafter Controller) for grant of a compulsory licence on a patent (at any time after the expiry of 3 years from the date of the grant of the patent) on either of the following grounds:

(i) The reasonable requirements of the public with respect to the patented invention have not been satisfied.
(ii) The patented invention is not available to the public at a reasonably affordable price
(iii) The patented invention is not worked in the territory of India

An important condition for grant of compulsory licences is that an applicant under section 84 must (before applying for a compulsory licence) have made efforts to obtain a licence from the patent-holder on reasonable terms and conditions and the efforts to obtain such a licence must have been unsuccessful.

The landmark case on section 84 is *Bayer Corporation v. Union of India*[9] which dealt with the first compulsory licence granted by India under section 84.

20.3.1 Bayer Corporation v. Union of India

20.3.1.1 Background and Facts

Bayer Corporation, a US-based pharmaceutical corporation, invented a drug, Sorafenib Tosylate (brand name 'Nexavar'), to treat kidney cancer i.e. Renal Cell Carcinoma (RCC) and liver cancer i.e. Hepatocellular Carcinoma (HCC). In 1999, Bayer filed for a patent on Nexavar in the US and an international patent on Nexavar under the Patent Co-operation Treaty (PCT) in 2000. On July 5, 2001 Bayer applied for the Nexavar patent in India which was granted on March 3, 2008. On December 6, 2010 Natco, an Indian drug manufacturing company, approached Bayer for a voluntary licence to manufacture and sell Nexavar in India. Natco proposed to sell Nexavar at a price less than INR 10,000 per month of therapy as opposed to INR 280,428 per month of therapy charged by Bayer. Natco sought to obtain the voluntary licence on such reasonable terms and conditions as would enable Natco to sell Nexavar at an affordable price to the public. On December 27, 2010 Bayer rejected Natco's application for a voluntary licence on Nexavar.

On July 29, 2011 (3 years after the grant of the Nexavar patent to Bayer on March 3, 2008) Natco applied to the Controller for a compulsory licence on Nexavar under section 84 on the ground that all the three conditions for granting a compulsory licence were fulfilled. In its compulsory licence application, Natco also proposed to sell Nexavar at Rs. 8,800 per month of therapy.

[9] W/P No. 1323 of 2013.

On November 18, 2011 Bayer opposed Natco's compulsory licence application under section 87 which allows the patentee or any other person to oppose a compulsory licence application. After hearing both Natco and Bayer, the Controller granted a compulsory licence on March 9, 2012 to Natco to manufacture and sell Nexavar; the Controller allowed Natco to sell Nexavar at INR 8800 for 1 month of treatment, and directed Natco to pay Bayer a royalty at the rate of 6% of Natco's net sales of Nexavar. Bayer appealed against the Controller's order in the IPAB which on March 4, 2013 upheld the Controller's order to grant compulsory licence but increased the rate of royalty payable to Bayer from 6% to 7%. Bayer challenged the IPAB order[10] before the Bombay High Court.

20.3.1.2 Court's Analysis

a. *Reasons behind compulsory licensing*

The Bombay High Court first examined the reason behind compulsory licensing in patent law. The court observed that the purpose behind grant of monopoly rights such as patents was to ensure that patent holders utilised their invention for the benefit of the society; this was possible only when the inventor made their inventions available for the use and enjoyment of the public. Accordingly, the Paris Convention for the Protection of Industrial Property 1883 (hereinafter Paris Convention), which was perhaps the first international treaty on patents, allowed member countries to provide legislative measures to ensure due working/exploitation of the patent. The Patents and Designs Act, 1911 also contained provisions for compulsory licensing to prevent abuse of the patent by the patent holder.

The court noted the public interest objective in providing for compulsory licences, namely to protect public health and promote access to medicines. WTO members in 2001 adopted Declaration on the TRIPS Agreement and Public Health (also known as Doha Declaration) wherein they affirmed the right of member countries to provide for compulsory licensing provisions to protect public health. The court then proceeded to examine the grounds for grant of a compulsory licence under section 84(1).

b. *'Reasonable requirements of the public'*

The first ground for grant of a compulsory licence under section 84(1) is when the "reasonable requirements of the public with respect to the patented invention have not been satisfied". Section 84 (7) lays down the circumstances when the reasonable requirements of the public shall be deemed to not have been satisfied- one such circumstance is when due to the refusal to grant a voluntary licence by the patentee, the supply of the invention is not to an adequate extent [emphasis supplied].

[10] Bayer Corporation v. Union of India, The Controller of Patents, Natco Pharma Ltd., Order OA/35/2012/PT/MUM.

Bayer argued that the reasonable requirement of the public with respect to Nexavar had to be calculated in the context of the number of patients in need of the patented drug. Bayer argued that such a calculation which should have been carried out by the authorities before the grant of compulsory licence was not done in the present case. The court rejected Bayer's argument ruling that the quantum of the patented drug required by the public could not be calculated on a mathematical basis. The court pointed out that in calculating whether Nexavar met the reasonable requirement of the public, the Controller had in fact relied on the figures in the Globocan 2008 report which had been put forth by Bayer. The Controller also relied on the figures provided by Bayer in affidavits of its Country Medical Director, Mr. Manish Garg, wherein Mr. Garg had stated that an aggregate of 8842 patients would require Nexavar; Bayer had supplied Nexavar to only about 200 patients in 2011.

Bayer argued before the court that the quantity of the patented drug supplied by Cipla (which was manufacturing Nexavar without Bayer's permission) should be added to the amount supplied by Bayer to ascertain whether the reasonable requirement of the public w.r.t. Nexavar was being met. Interestingly, Bayer had earlier also filed a patent infringement suit against Cipla which was pending in the Delhi High Court. The court held that Cipla's supply of Nexavar could not be taken into account to calculate reasonable requirement under section 84; this was because the supply of drugs by Cipla was uncertain as it could be stopped at any time if the Delhi High Court issued an injunction in the patent infringement suit. The court clarified that Cipla's supply would have been relevant under section 84 only if Bayer had condoned Cipla's supply of Nexavar; on the contrary, Bayer had opposed Cipla by filing a patent infringement suit.

The court pointed out that in Form 27 (an annual statement filed with the Controller by a patent holder to show the extent to which they have worked their invention in India), Bayer had not included Cipla's sale of Nexavar and therefore, Bayer could not now rely on Cipla's sale to prove that the reasonable requirements of the public under section 84 were being met.

Finally, the court held that in respect of medicines, the adequate extent test under section 84(7) had to be 100% satisfied, i.e. the patented drug had to be made available to every patient by the patent-holder. According to the court, this was in line with the Parliament's reason behind providing for compulsory licensing, and the Doha Declaration to ensure access to medicines for all. The court ruled that Bayer had failed to satisfy the reasonable requirement of the public under section 84.

c. *Availability of the invention at a 'reasonably affordable price'*

The second criterion for granting a compulsory licence under section 84(1) is non-availability of the patented invention to the public at a reasonably affordable price. According to the court, the reasonably affordable price had to be determined on the basis of the relative price being offered by the patent holder and the applicant after hearing any other party opposing the compulsory licence application. The court took into account the price of Nexavar sold by Bayer (INR 284,000 per month of therapy) and the price proposed by Natco (INR 8800 per month of therapy) and

held that the reasonably affordable price was necessarily the price offered by Natco as it established that Bayer's price was not a reasonably affordable price.

Bayer argued that the reasonably affordable price must reflect the research and development (R&D) costs of Bayer as well as the R&D costs incurred on failed drugs. Bayer submitted that taking into account its R&D costs and a reasonable profit, its price was a reasonably affordable price. Natco produced evidence that Bayer had recovered the total amount of R&Ds costs from 1994 up to 2004 in 1 year itself. Based on Natco's evidence and the fact that Bayer had not produced any evidence such as balance sheet etc. to establish its R&D costs, the court found that Bayer had not established that its price was a reasonably affordable price.

A significant fact was that as very few people in the US (less than 200,000) suffered from cancer of RCC and HCC, Nexavar was classified as an 'orphan drug' in the US i.e. the US government reimbursed 50% of Bayer's R&D costs for Nexavar. Therefore, in the absence of evidence by Bayer, the court was not convinced that Bayer's R&D costs when factored in would amount to the price which it was charging for Nexavar.

One of the affordability arguments put forth by Bayer was that its Patient Assistance Programme (PAP) w.r.t. Nexavar enabled poorer patients to pay for 3 days' worth of medicines and obtain medicines for the remaining 27 days of a month for free; Bayer argued that its PAP initiative made Nexavar affordable for poor patients in India. The court rejected the argument on the ground that medicines supplied under PAP were available only to particular patients depending on whether the patients satisfied certain pre-existing criteria and at the discretion of Bayer and the doctor attending the patients. The court clarified that the requirement under section 84 (1)(b) was that the patented drug should be available at a reasonably affordable price to 'any member' of the public and not particular patients as was the case under PAP.

d. *Working of the patented invention in the territory of India*

The last ground under section 84(1) for grant of compulsory licence is non-working of the patented invention in the territory of India. One of the issues in the case was the meaning of working the patented invention in the territory of India. Bayer argued that the 'local working' requirement under section 84 was met by importation of Nexavar in India, whereas, the Indian government (respondent) contended that Bayer was required to manufacture Nexavar locally in India i.e. section 84(1) (c) referred to 'local manufacturing'. The Indian Government submitted that this would enable technology transfer to India.

Interestingly, the Controller had interpreted section 84(1)(c) to require local manufacturing, whereas, the IPAB was of the opinion that the local working requirement could also be met by importation of the invention if the patent holder could satisfy the authorities under the Patents Act that it was not possible to manufacture the invention in India. The IPAB ruled that importation by itself did not amount to non-fulfilment of the local working condition and that local working of the invention would have to be decided on a case to case basis. The court agreed with IPAB's

reasoning and held that the local working requirement under section 84(1)(c) did not necessarily refer to local manufacturing in all the cases. However, the Bombay HC did not explicitly rule on the issue whether Bayer had met the local working requirement under section 84(1)(c).

The court highlighted that public interest should always be fundamental in deciding cases involving compulsory licence for medicines as the reason behind compulsory licensing was to make patented inventions available to the society in adequate numbers and at a reasonable price. The court dismissed Bayer's petition after finding that the first and second grounds under section 84 for grant of a compulsory licence were satisfied.

Bayer subsequently filed a special leave petition (SLP) [(C) NO(S). 30145/2014] in the Supreme Court against the Bombay HC order. However, the SC found no reason to entertain the SLP and dismissed Bayer's petition without discussing the merits of the case.

20.4 Section 107A of the Patents Act

Section 107A of the Patents Act is the research exemption in Indian patent law which provides that the act of making, using, selling or importing of a patented invention by a third party, if done for the purpose of submission of information required under any law in India or abroad to regulate the manufacture, use, sale or import of any product, would not amount to patent infringement. Section 107A is also known as the Bolar exemption after a famous US case, *Roche Products v. Bolar Pharmaceuticals*, which involved a similar provision in US patent law.

The Bolar exemption is particularly important for Indian pharmaceutical companies as it enables them to carry on research to develop generic versions of patented drug during the term of patent and get approval for the generic drugs to sell them in the market immediately after the patented drug goes off-patent. If there was no Bolar provision in patent law, pharmaceutical companies would have to wait for a patented drug to go off-patent before they could use the patented drug to make and get market approval for the generic drugs. Conversely, this would have led to 'evergreening' of patents as patented drugs (in the absence of a Bolar exemption) would have continued to enjoy monopoly in the market even after the expiry of their patent term, until the generic drugs were launched in the market. The Delhi High Court recently ruled on the scope of section 107A in *Bayer Corporation v. Natco Pharma Ltd. & Alembic Pharmaceuticals Ltd.*[11]

[11] W.P. (C) No. 1971/2014 & CS (Comm) No. 1592/2016.

20.4.1 Bayer Corporation v. Natco Pharma Ltd. & Alembic Pharmaceuticals Ltd.

20.4.1.1 Background and Facts

After Natco was granted a compulsory licence to manufacture Bayer's Nexavar, Natco started manufacturing Nexavar under the brand name 'Sorafenat'. In 2014, Bayer filed a writ petition[12] in the Delhi High Court on grounds that Natco's export of Sorafenat violated the terms of the compulsory licence. While the petition was pending, the Delhi HC granted a temporary injunction restraining Natco from exporting Sorafenat. Natco then filed an interim application[13] asking the court for permission to export 1 kg of active pharmaceutical ingredient (API) of Sorafenat to conduct development/clinical trials in China. The Delhi HC allowed Natco's application under section 107A. However, the order was successfully appealed by Bayer, and Natco was restrained by the court from exporting Sorafenat during the pendency of Bayer's writ petition. Bayer also filed a separate patent infringement suit[14] in the Delhi High Court against Alembic Pharmaceuticals Ltd. (an Indian pharmaceutical company) which was manufacturing and exporting Rivaroxaban (Bayer's patented anti-coagulant drug); Alembic argued that its export of Rivaroxaban fell under section 107A. Both the petitions filed by Bayer (against Natco and Alembic) concerned the issue whether the export of a patented drug for the purposes of submission of information to a regulatory authority was allowed under section 107A. The Delhi HC clubbed the two petitions and delivered its order on March 8, 2017.

It is important here to note firstly, that many Indian pharmaceutical companies are large API manufacturers for foreign pharmaceutical companies which are increasingly outsourcing API manufacturing to Asian countries as a means to reduce the cost of developing medicines. API is the 'active' component of a drug or that component of a drug which produces the 'effects' of a drug. The API can be contrasted with the 'excipient' of a drug which is used as a medium for the API and is used to deliver the drug to the body. It appears that in this case, Natco and Alembic were manufacturing the APIs of Bayer's patented drugs and exporting them for the purpose of submission of information to drug regulatory authorities abroad.

Secondly, generic drug manufacturers engage in the process of developing generic versions of patented drugs during the patent term so that by the time the patent on those drugs expires, the generic drugs are ready to be launched and sold in the market without delay. Before the generic drug companies can sell their products in the market, they are required to submit information to the drug regulatory authorities in the country where they intend to sell the drug; the information includes proof of 'bioequivalence' of the patented drug and the generic drug. According to the United States Food and Drug Administration (FDA), two drugs are said to be bio-equivalents of each other when there is no significant difference in the rate and extent to which the APIs of the two drugs become available at the site of drug action

[12] W.P. (C) 1971/2014.

[13] CM 9687/2014.

[14] CS (COMM) No. 1592/2016).

when the drugs are administered. The Bolar provision aids the submission of information (such as bioequivalence) to regulatory authorities by generic drug manufacturers, as it allows generic drug companies to use the patented drug (without the permission of the patent-holder) to prove its bioequivalence with the generic drugs to the drug regulatory authorities.

Bayer's primary argument in this case was that section 107A allows sale/use/importation of a patented invention for the purpose of submission of information only within India, and therefore export of the patented product for the purpose of submission of information to any authority outside India is not permitted under section 107A.

20.4.1.2 Court's Analysis

a. *Section 107A permits the sale of a patented product outside India for uses related to section 107A*

Bayer advanced a number of arguments to support that export of a patented invention is not covered under section 107A. Bayer argued that section 107A only permits the information generated in India to be transferred abroad and not the sale of the invention. The court rejected this argument for the reason that even if the information required by foreign drug regulatory authorities was generated in India, such information may not be accepted by the drug regulatory authorities situated in other countries. Therefore, it becomes essential to allow a patented drug to be exported to other countries under section 107A in order to generate information in accordance with the guidelines of the drug regulatory authorities.

Secondly, Bayer argued that the word 'selling' used in section 107A referred to 'selling of the patented invention within India' and not abroad. The court relied on the dictionary meaning of 'selling' and held that the word 'selling' does not contain any geographical limitation. Therefore, the court rejected Bayer's argument.

Bayer argued that section 107A specified acts allowed under section 107A as 'making, constructing, using, selling or importing' a patented invention; since the word 'exporting' is not mentioned, section 107A does not allow for the export of a patented invention. The court rejected this argument on grounds that the right to export is part of the fundamental right to freedom to practise any profession, occupation, trade or business under article 19(1) of the Constitution. The court held that the right to export being a fundamental right in this case can be curtailed only by an express statutory provision.

An interesting argument of Bayer was that export under section 107A should be prohibited because there was no way to determine whether an export allegedly under section 107A was indeed for the purposes (submission of information) mentioned in section 107A. Further, if exports under section 107A were allowed, Indian courts would have no jurisdiction to monitor the use of the patented invention after it had been exported. The court rejected this argument and held that if Bayer found that a particular export under section 107A was not in fact for the reasons stated in section 107A, the patentee could enforce their rights in the courts of the country where the patented invention had been exported.

b. *Permitting export of a patented invention under section 107A does not violate TRIPS*

Bayer also argued that article 31(f) of TRIPS (which allows WTO members to provide for patent exceptions in their law) allows third party/government uses only where the use of the patented invention is predominantly for the domestic market of that WTO member; therefore, export of Bayer's product should not be allowed under section 107A.

The court rejected Bayer's interpretation of article 31(f). The court reasoned that section 107A is not a patent exception and therefore, article 31(f) would not be applicable. According to the Delhi HC, section 107A was not a patent exception because it was enacted for the purpose of submission of information (to regulatory authorities) to commercially sell the drug only after the expiry of the patent. Further, the court emphasised that TRIPS allowed WTO members to enact measures necessary in public interest and therefore, export under section 107A does not violate TRIPS.

For the above reasons, the Delhi HC ruled that section 107A permitted export of a patented invention so long as the export is for the purpose mentioned in section 107A. Bayer had argued in its petition against Natco that Natco's export of Sorafenat violated the terms of the compulsory licence because under a section 84 compulsory licence, Natco only had the right to manufacture Nexavar in India and not export the product outside India. However, the court ruled that Natco's rights under section 107A were not affected by the compulsory licence under section 84; the HC clarified that any export under section 107A by Natco is only to obtain regulatory approval outside India and not to commercially sell the invention outside India. Therefore, Natco's export under section 107A does not violate the compulsory licence under section 84.

The HC dismissed Bayer's petitions against Natco and Alembic. It is important to highlight that the court in its judgment stated that export for the purpose of submission of information to regulatory authorities is permitted under section 107A even if done for profit. The position taken by the court supports Indian pharmaceutical companies which manufacture and export API for pharmaceutical companies situated outside India.

Bayer subsequently appealed against Alembic[15] and Natco.[16] In April 2019, the Division Bench of the Delhi HC ruled in favour of Natco and Alembic. The Delhi HC's judgment is significant as it broadened the scope of the Bolar provision to promote public interest. The court recognised that it was important to allow export of a patented invention outside India to obtain regulatory approval for selling the drug in the (importing) country once the patent on the drug expired. This in turn would facilitate the timely launch of generic medicines in the market and ensure access to medicines.

[15] RFA (OS) (COMM) 6/2017.

[16] LPA 359/2017.

20.5 Conclusion

In all the judgments analysed above, public interest- access to medicines and health- was an important factor in the court's reasoning and also the main reason for enacting provisions like section 3(d), compulsory licensing and section 107A. In the Novartis case, for instance, the Supreme Court recognised that the Indian Parliament in providing patent protection to pharmaceutical products had to balance its obligations under TRIPS on one hand and India's commitments to promote public health on the other. Similarly, in the Nexavar compulsory licence case the Bombay HC emphasised the role of public interest while granting compulsory licences under section 84. In the Bolar provision petitions concerning export under section 107A, we see that the Delhi HC has in fact elevated the Bolar provision to the status of a 'right' which cannot be read as an exception to a patentee's exclusive rights. The court even went a step further and held that the right to export under section 107A is a fundamental right under the Constitution of India and cannot be restricted except by legislative enactment.

India has faced backlash by countries in the West, especially the United States over use of these provisions to uphold public interest over patentee's rights. The US in its annual Special 301 report which monitors the level of IP protection in various countries, has repeatedly criticised section 3(d) and the possible use of compulsory licensing as posing challenges to the US pharmaceutical industry and adversely affecting international trade. However, these fears are ill-founded and the flexibilities in Indian patent law are TRIPS-compliant. Till date, only one compulsory licence, namely, the compulsory licence on Nexavar has been issued under section 84; while other compulsory licence applications were filed in India after Nexavar, they were unsuccessful mainly because the Indian Patent Office applied the section 84 requirements stringently during examination of the compulsory licence applications. Further, section 3(d) is justified under article 27 (2) of TRIPS which allows WTO members to exclude certain inventions from patentability to protect human health.

Notwithstanding the minimum standards for IP protection mandated by TRIPS, member countries have the right to enact public interest measures which may be contrary to the right-holders' interests. It bears noting that these provisions in the Indian Patents Act are flexibilities which are allowed to WTO members under TRIPS. The provisions by themselves perhaps would have meant little, if not for the broad interpretation given to them by Indian courts. As patent cases involving public interest are increasingly being litigated in the country, the continuing future of the Indian generic drug industry will depend upon the interpretation of patent law flexibilities by the Indian judiciary. This in turn will impact access to medicines in India and other parts of the world.

Industrial Applications of *Pseudomonas fluorescens*: A Patent Survey

21

Prakash Jyoti Kalita and Ratul Moni Ram

Abstract

Unscrupulous human activities have imposed some serious problems on earth right from global warming to environmental pollution. A high time has reached to take some serious actions against these devastating activities in order to save our planet from any further deterioration. A quantum of research has already been done to figure out some simple and cost effective measures to tackle these problems. In order to achieve these goals, many techniques are being employed among which use of microbial agents and their products is gaining widespread popularity. Microorganisms are both beneficial and hazardous to flora and fauna in different aspects, so it entirely depends upon us to discriminate between them and thereby to figure out the beneficial strains. Among the various beneficial microbial agents, the bacterium *Pseudomonas fluorescens* is showing some promising role. In last few decades, plenty of work has been done on application of the bacterium in various sectors viz., sewage water treatment, bioremediation, biofilters construction, treatment of petroleum wastes and many more. The use of this bacterium is not limited only towards combating environmental pollution but it has shown a potential role in the agriculture sector as well. It has been widely used for the preparation of bio-fertilizers as many strains of *P. fluorescens* have tremendous ability of dissolving the phosphate in the soil which is generally present in complex form and is not readily available to the plant. In addition to it, the bacterium has been used even for the production of bio-herbicide and bio-pesticides for controlling weeds and phytopathogens which makes it a successful PGPR overall. Application of the bacterium as a biocontrol agent enables to

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H. B. Singh et al. (eds.), *Intellectual Property Issues in Microbiology*,
https://doi.org/10.1007/978-981-13-7466-1_21

reduce the annual global consumption of various hazardous chemicals which generally impose some serious threats to environment as well as to human health. Overall it may be stated that *P. fluorescens* have got multifarious applications and this chapter will briefly deal with certain such invention discovered in the recent decade.

Keywords
Pseudomonas fluorescens · Bioremediation · PGPR

21.1 Introduction

Plant growth-promoting rhizobacteria (PGPR) are a diverse group of microorganisms that play a key role in disease suppression and plant growth promotion by triggering plant defense. The activation of plant's own defense mechanism against infection by the plant pathogen can be systematically activated upon exposure of plants to PGPR strains. This phenomenon is known as induced systemic resistance (ISR). However, the resulting elevated resistance by the source upon pathogen attack is called systemic acquired resistance (SAR) (Keswani et al. 2016a, b; Ram et al. 2018).

P. fluorescens is one of the most popular PGPR species studied so far and it encompasses a group of common gram negative, rod-shaped bacterium that colonizes in the vicinity of soil, water and plant surface. It secretes a soluble greenish fluorescent pigment particularly under low iron availability conditions. *P. fluorescens* requires a minimal media for their growth and grows well in media supplemented with any carbon sources (Palleroni 1984). Since they are found in abundance in the rhizospheric zone, *P. fluorescens* strains are being extensively studied for their beneficial attributes to the plant macrosystem i.e. biocontrol and bioremediation of various organic compounds. The rhizosphere acts as a nutrient-rich habitat and harbors a wide range of microorganisms that each can have beneficial, harmful or neutral effects on the plant (Berendsen et al. 2012).

Many members of the bacterium have been reported to be potential agents for the biocontrol against seed and soil borne fungal diseases (Hoffland et al. 1996; Wei et al. 1996; Gera Hol et al. 2013). In addition to it, specific strains of *P. fluorescens* and *P. putida* have found to be plant root colonizers and in turn cause significant yield increase (Schroth and Hancoc 1982; Weller 1988; Parke 1990a, b) and produce certain antagonistic secondary metabolites (Hass and Defago 2005). *P. fluorescens* suppress plant pathogens by various mechanisms that encompasses production of antibiotics (Fravel 1988; Thamashow and Weller 1990; Keel et al. 1992), parasitism (Prasad et al. 2015; Lugtenberg and Kamilova 2009; Van der Ent 2009), siderophores (Kloepper et al. 1980; Leong 1986; Schippers et al. 1987) and lysis (Ordentlich et al. 1987; Campbell and Ephgrave 1983), volatile compounds (Voisard et al. 1989; O'Sullivan and O'Gara 1992) or through induced systemic resistance (van Loon et al. 1998).

Due to the multifarious applications of *P. fluorescens* in various sectors viz., sewage water treatment, bioremediation, biofilters construction, treatment of petroleum wastes etc., there are numerous patents involving its beneficial aspects all over the globe. This chapter covers the important attributes of *P. fluorescens* which has been patented in the last two decades.

21.2 *P. fluorescens* as a Biocontrol Agent

Few years back a survey data came out which shows that around 9 thousand insect and mite species, 8 thousand weeds species and 50 thousand species of plant pathogens attacks the agriculturally important crops and thereby reduces the annual crop production worldwide to a significant level (Zhang et al. 2011). In order to control these pathogens a huge amount of pesticides, insecticides or fungicides are used but more than 70% of these used chemicals are not absorbed by the plants instead they infiltrate into the soil and contaminates the ground water (Fan 2017). Hence, it has become very important to develop some biological formulations which can replace the use of these harmful pesticides. In order to perform this recently *P. fluorescens* biovar 1 bacterium having the deposit number DSM 25556 has been used and was found to be showing inhibitory activities against *Xanthomonas arboricola* pv. *pruni, Ralstonia solanacearum, Erwinia amylovora* and *Pseudomonas syringae* pv. *syringae* (Bazzi and Biondi 2013a, b).

In recent past considerable amount of research has been done in the field of plant pathology and other applied sciences for finding out curative measures to tackle various agriculturally important plant diseases, but soil borne diseases have not received much attention hence many more work has been started in this field. Soil borne diseases can be dealt with hazardous chemicals available in the markets supplied from various renowned companies but the use of these chemicals leave considerable amount of residues which in turn impose serious threat to the human health and other organisms (Singh et al. 2016a, b, 2017). So, in order to overcome this problem it is better to deal with the biocontrol agent and one such example is the use of *P. fluorescens*. The bacterial based formulation can be used to treat many soil borne diseases like root rot, set rot, wilt, collar rot, red rot, rhizome rot, damping off, stem rot, club rot and apart from them even the diseases like blight, blast, leaf spot and anthracnose (Heydari and Pessarakli 2010). The invention suggests that the combination of the bacterial based formulation (Bio Fungicide) with enzymes, fats and growth promoting molecules provides significant control over the soil borne diseases and other diseases mentioned above (Patel and Patel 2011).

Another invention has provided a suitable method for the preparation of the biopesticide by combining equal amount of *Trichoderma harzianum* and *P. fluorescens* that was obtained from liquid as well as solid fermentation which was carried out separately. The formulation was obtained by mixing both the biocontrol agent in 1:1 ratio and was used for the treatment of several soil borne diseases of agriculturally important crops, and have reportedly shown significant amount of control over these pathogens (Rao and Ramchandran 2007).

21.3 *P. fluorescens* Based Biocontrol Agents for Management of Fungal Diseases

Fungal pathogens are responsible for causing a huge annual loss and in order to control them globally a huge amount of chemicals are used (Agrios 1988; Baker 1987). But as these chemicals impose serious threat to the environment so now a day's bio-control agents are given more preference (Cook 1993). In continuation with this the present invention shows that the potential use of *P. fluorescens* strain P469 TSKM B-1982 as a biocontrol agent. The strain was isolated from the rhizosphere of winter wheat in Krasnodar Krai. This strain shows a significant suppressive activity against a range of phytopathogenic fungal genera viz., *Alternaria*, *Colletotrichum*, *Fusarium*, *Rhizoctonia*, *Phoma*, *Phytophthora*, *Oospora* and *Erwinia* (Aslan et al. 2004).

Another such excellent example is the use of *P. fluorescens* against gray mold which is caused by a fungus *Botrytis cinerea*. This disease is found mostly in the bedding plants and it can spread quickly and hence can damage any healthy parts of the plants. The present invention discloses a method for the preparation of Biofungicide by combining the dispersible granules of *Trichoderma* and *P. fluorescens*. For the preparation of water dispersible granules 20–30% of *Trichoderma*, 15–20% *P. fluorescens*, 5–10% wetting agent, 6–10% adhesive, 10–15% disintegrating agent and 15–44% of carrier was mixed and pelletized. The granules so obtained were then utilized for the control of gray mold disease and interestingly it has shown a significant control over this deadly disease (Zekai et al. 2011).

Sugarcane smut is another such type of devastating disease of sugarcane caused by the fungus *Sporisorium scitamineum*. In order to control this disease a group of Chinese researcher has made the potential use of *P. fluorescens* strain HN58 as a biological pesticide. The strain has a significant inhibitory effect on the sugarcane smut whip disease and as it is non- toxic in nature and environment friendly as well, so in near future it can be used for controlling the spread of this disease (Pinggen et al. 2017).

Powdery mildew is another important fungal disease that affects a huge range of crops and thereby leads to huge annual losses (Gautam 2015). The present invention deals with the use of a *P. fluorescens* strain with an accession number of CCTCC NO: M 2014274 for controlling this disease. This strain of *P. fluorescens* shows significant inhibiting effect over *Sphaerotheca fuliginea* with an inhibition zone diameter of 28 mm. Hence, the results shows that this bacterial strain can be potentially used for controlling powdery mildew of cucumber, strawberry and tobacco (Rui et al. 2017).

Black shank is a soil borne disease caused by the pathogen *Phytophthora parasitica* var. *nicotianae* this pathogen has a broad host range and can infect a wide range of crops (Gallup et al. 2006). In order to control this disease the present invention makes the use of *P. fluorescens* XF10 with the preservation number CGMCC No.13703. Results show that the extracellular metabolites and the volatile products of the *P. fluorescens* significantly inhibit the growth of this pathogen. Therefore this strain can be used as an effective biofungicide for the control of black shank (Ruiping et al. 2018).

In 2016 a group of Russian researchers have found that the *P. fluorescens* strain VKM B-2955D can be used as a potential bio-control agent. This strain suppresses the development of many phytopathogenic fungi and some deadly bacteria's due to their ability to produce an antibiotic known as phenazine. Further this strain have the ability to dissolve the complex inorganic phosphate present in the soil mostly in insoluble form which in turn makes it available for the plant and subsequently contributes to their overall growth (Anokhina et al. 2018). Another research group from Korea has reported that the *P. fluorescens* strain sense BB2 also bears antifungal activities and can be used for making a potential bio-fungicide (Joon 2013).

21.4 *P. fluorescens* Based Biocontrol Agents for Management of Bacterial and Viral Diseases

Similarly, like fungi bacteria and viruses are also known to cause deadly diseases in plants and there are a huge range of viruses and bacteria's known that badly infects the crops. Hence, it is essential to design suitable strategies in order to control the disease spread. Till date many approaches has been used which include right from conventional method to genetic engineering approaches but this invention has shown the potential use of bio-control agent for controlling the spread of viral diseases in plants. *P. fluorescens* strain Gpf01 [KCCM10642P] has been used for the control of many viral diseases which includes cucumber mosaic virus (CMV), Tobacco mosaic virus (TMV) (Hak et al. 2006).

Bacterial blight of rice is caused by the infectious agent known as *Xanthomonas oryzae* it carries a high epidemic potential and can destroy almost all varieties when suitable condition prevails. Huge amount of research work has already been done on this pathogen to find out possible ways to reduce its damage. Among the various ways devised till date use of biocontrol agent is quite promising one. This invention makes the use of *P. fluorescens* strain Migula 1895 KACC10072 for its control which bears potential antimicrobial activity against *X. oryzae* (Jae-Hwa et al. 2011). The current invention shows the inhibitory effect of the *P. fluorescens* strain RP15 with an accession number CGMCCNo.7061 over *Phytophthora capsici* (Shuzhen et al. 2014). Recently *P. fluorescens* strain (2)-16′ has been used for the control of tomato bacterial wilt disease it was used in the seedling culture medium. Generally the biocontrol agents were inoculated via soil drenching, root dipping or seed coatings. It has been observed that the presence of biocontrol agent suppresses the spread of bacterial wilt. The suppression mechanism is mainly attributed by antibacterial metabolites produced by these biocontrol agents which in turn hinders the growth of the pathogen (Chuanzhen et al. 2012). Another such invention shows the potential use of the *P. fluorescens* pf27 in the control of potato disease caused by *Bemesia tabaci*. Apart from this the biopesticide formulation is extremely useful in the control of potato black scurf, late blight of potato, potato scab disease and many harmful pests of tomato and cotton (Jian et al. 2017). The black spot of walnuts is caused by the pathogen *Xanthomonas juglandis* which causes huge loss to its production. The present invention aims at providing a suitable biological agent for the control of this

disease. *P. fluorescens* strain GH2-1 with an accession number of CGMCC No. 14743 shows potential inhibiting activity against this pathogen and thereby serve as a reliable biological agent for controlling this disease (Chunhua et al. 2017).

Apart from using *P. fluorescens* as a potential biocontrol agent against soil borne diseases, fungal, bacterial or viral diseases one of the research group has shown its potential use as a bioherbicide against certain weeds (Kennedy et al. 1991; Quail et al. 2002). Annual bluegrass and rough bluegrass are common weeds of golf courses, lawns and athletic fields. For their control generally herbicides are used but because of the toxicity imposed by these herbicides, now several alternatives were looked upon by the researchers among which biocontrol agents are the most promising one. A biocontrol formulation containing one or more strains of *P. fluorescens viz P.fluorescens* biovar B strain XJ3, *P. fluorescens* biovar B strain XS18 and *P. fluorescens* biovar A strain LRS 12 were used with a carrier which is agriculturally acceptable. The formulation can be applied directly on the soil or can be used to treat the seeds also it can be used in combination with fertilizers and herbicides. For efficient activity of the biocontrol agent the suggested dose of bacteria varies from 10^5 to 10^{11} cfu bacteria per square meter of land (Kennedy 2016).

21.5 Suitable Methods for the Preparation of Biopesticide Formulation

In past researchers generally produce *P. fluorescens* biocontrol formulation by inoculating it in Kings B broth and subsequently using talc powder as a carrier. But the major drawback of this process is that this method involves only liquid fermentation and excludes solid fermentation which in turn results into the inferior quality of the biocontrol agent formulation. Different group of researchers have used various types of carriers but nobody has used Pongamia cake, neem cake or wheat bran for the solid fermentation of *P. fluorescens*. These authors have devised a method where *P. fluorescens* is initially inoculated in the Kings B broth then liquid fermentation in 5–10% pongamia cake and finally followed by solid fermentation in sterile de oiled Pongamia cake (Rao 2012).

21.6 Industrial Applications of *P. fluorescens*

Pulp is a lignocellulosic fibrous material which is prepared by separating cellulose fibers from wood or fiber crops. Wood pulp serve as an important raw material in the paper industries, pulping is mainly done chemically or mechanically but this patent has introduced a new method by using biological bacterial solution in the process of pulping. This method makes the use of a complex microbial flora which includes *Bacillus* sp., *Rheinheimera tangshanensis, P. fluorescens, Acinetobacter lwoffii,* and *Wickerhamomyces anomalus* for the pulping process (Jia 2015).

Another research group has made the potential use of *P. fluorescens* strain with an accession number of CGMCC No. 5974 in liquid pulping method. The bacterial

liquid pulping comprises of defibering, steam sterilizing, rough pulping and fine pulping. Even during this process the waste liquid which was produced is further recycled into methane and subsequently the methane was used as an energy resource or for the preparation of organic fertilizer (Ping 2015).

The use of biological agent is not limited to only pulping industries but now days it can be used even for the production of ethanol. For the production of ethanol the major sugars viz glucose, xylose, arabinose, galactose, and mannose present in cellulose and hemicellulose can be metabolized to ethanol by incubating them with a suitable biological agent. For this purpose many recombinant microorganisms are used one such work includes the construction of a recombinant polypeptide bearing a carrier peptide and a passenger polypeptide which is fused to the lyase, cellulose, laminarinase or lipase. Microorganism bearing such construct is incubated with the metabolizable organic compounds to obtain ethanol (Yoshikuni et al. 2011).

21.7 Role of *P. fluorescens* in Biotechnology

In most of pharmacological studies, genetic engineering, medical sciences and in many more applied sciences it is essential to study the protein of interest which has therapeutical importance, medical importance or important role in development of any living organism. In order to study such proteins it is essential to purify the recombinant protein which is always a challenging task. So, designing a host which can significantly increase the amount of recombinant proteins produced can definitely improvise the research in the concerned field. One such invention includes the use of a *P. fluorescens* cell population which bears one or more genomic mutations. The mutations have reportedly increased the level of extracellular secretion and hence can be used for the production of proteins like chemokines, blood proteins, antibodies, proteases, kinases and many more. The mutant population has been assigned an accession number PTA-8981 and PTA-8982 and was deposited in the American type tissue culture collection (Rettalack and Chew 2010). *P. fluorescens* has recently been used as a suitable host for expressing recombinant proteins from plants. For this the researchers have made some codon optimized maize genes and used these for expressing in *P. fluorescens.* The codon optimized plant protein was combined with the bt booster (BTB) nucleic acid molecule which in turn has increased the efficiency of its expression in the bacterial host to a fair amount (Kelkar and Woosley 2017).

All living organisms contain phospholipids and they serve as the major component of the plasma-membranes in combination with cholesterol and glycolipids. To convert these phospholipids into commercially useful products many phospholipase enzymes were used. The present invention shows the potential use of phospholipase B from *P. fluorescens.* The enzyme has a gene length of 1272 bp and it codes for a zymoprotein with a molecular weight of approximately 45.8 kDa. An expression vector and a recombinant host of the phospholipase B has been obtained from colibacillus recombinant plasmid. The recombinant phospholipase produced by this method shows considerable of lipase activity and a fair amount of stability at low

temperature. The modified phospholipids produced via these recombinant enzymes can be used in industries in grease refining or as a phospholipids emulsifying agent (Fangyan et al. 2011).

EPSP synthase is an enzyme which is produced mostly by the microorganisms and plants, this gene has gained attention when it was reported that it was the prime target of the herbicide glyphosate. However, with subsequent research many resistant genes from different sources were reported which either metabolize glyphosate or show resistance towards this. Such type of resistance genes is very important in the field of genetic engineering for the purpose of making herbicide resistant crop species. The present invention shows the presence of one such resistant EPSP synthase gene in *P. fluorescens*. The gene encodes a protein of around 445 amino acids and shows a high homology with the EPSP synthase gene from *Agrobacterium rhizogenes* CP4 (Xiaoyan et al. 2012). Another invention shows the potential use of *P. fluorescens* in immuno-magnetic bead-enzyme-linked immunoassay. In this method the carboxyl magnetic beads were coupled with a *P. fluorescens* polyclonal antibody. This method has the potential to detect its antigen up to the similar level as of the conventional ELISA method. Further this method serves as a potential tool for detecting quickly and accurately the *P. fluorescens* pollution in food items such as milk (Xianjun and Wei 2017) (Table 21.1).

LAMP is an isothermal nucleic acid amplification technique unlike the polymerase chain reaction (PCR) technology where the reaction is carried out at different temperature, LAMP is carried out at a constant temperature and hence it does not require a thermal cycler. The same technique has been used for the purpose of rapid detection of *P. fluorescens* in a sample. The kit composed of a set of five primers which can allow the efficient amplification of their target within a short period of time with high efficiency and accuracy and at a low cost. Hence, this kit offers an easy a fast way to detect the presence of *P. fluorescens* in any sample under study (Jun et al. 2013).

21.8 Pharmaceutical Applications of *P. fluorescens*

A recombinant vaccine was made by incorporating the DNA encoding an antigen that can stimulates a potent immune response into bacterial and mammalian cells, further the antigen expressed in these cells can be purified and used for subsequent studies. The similar technique has been used for making an effective vaccine against the Gram-negative bacteria *P. fluorescens* which can potentially infect a variety of economically important fishes which includes carp, tilapia and many more. The infection caused by these bacteria induces a disease in fish known as Redskins disease which leads to a huge economic loss. Till now there has been no vaccine discovered to cure this disease and most of the fish famers rely mostly on the antibiotics only for its cure. The current invention shows the method of making the recombinant vaccine from the *P. fluorescens* amino acid sequence in the sequence list SEQ ID No. 1. After the PCR amplification of the product it was combined with a carrier p EASY-E2 and was cloned in the eukaryotic expression plasmid p E478 and was

Table 21.1 A representative list of patents relating to *P. fluorescens*

S. N	Patent number	Applications of *P. fluorescens*	Reference
1.	CN 106520638A	Applications of *pseudomonas fluorescens* for preventing powdery mildew of plants	Rui et al. (2017)
2.	US9657298B2	Developed recombinant bacterial strains comprising heterologous nif genes in its genome, and capable of fixing nitrogen	Soto et al. (2017)
3.	US9713333B2	Reported the antagonistic effect of *Pseudomonas fluorescens* bacteria strain ATCC BAA-477 over *Ganoderma* infection in oil palm	Loh and Abdullah (2017)
4.	US9578884B2	Reported the weed suppressive activity in the *P. fluorescens* strain ACK55, *P. fluorescens* strain NKK78 and *P. fluorescens* strain SMK69	Kennedy (2017)
5.	EP2553102B1	Reported the potential use of *P. fluorescens* for the production of recombinant toxin proteins viz. CRM 197, diphtheria toxin, pertussis toxin, tetanus toxoid fragment C etc.	Retallack et al. (2015)
6.	CN103397099B	Devised a quantitative method for the detection of *P. fluorescens* in the rhizosphere soil by using fluorescent quantitative PCR	Jianrong et al. (2015)
7.	CN 102888358B	*Pseudomonas fluorescens* and biological bacteria liquid pulping method	Ping (2015)
8.	CA2545610C	Developed a improved expression system by using *P. fluorescens* for the production of recombinant proteins	Schneider et al. (2014)
9.	US8349593B2	Used *P. fluorescens* for the production of succinic acid amide compound	Kitamura et al. (2013)
10.	US8455218B2	Developed a method for obtaining soluble hG-CSF protein from *P. fluorescens*	Jin and Chew (2013)
11.	CN 102382879B.	Developed *Pseudomonas fluorescens* LAMP (loop-mediated isothermal amplification) detection agent and kit	Jun et al. (2013)
12.	CN 102614504B	Developed recombinant protein vaccine from *Pseudomonas fluorescens*	Li and Yonghua (2013)
13.	WO2013130680A1	Reported that *P. fluorescens* strain ATCC 55799 bears antibacterial properties against some phytopathogenic microorganisms	Asolkar et al. (2013)
14.	EP2836612A1	Reported that *P. fluorescens* with deposit number DSM 25556 have inhibitory activities against many pathogens	Bazzi and Biondi (2012)
15.	US 8168172B2	Process for the production of organic formulation of bio-pesticide *Pseudomonas fluorescens*	Rao (2012)
16.	WO2011123139A1	Developed a method for the production of recombinant CRM197 protein in *P. fluorescens*	Retallack et al. (2011a, b)
17.	WO2011118896A1	Developed a method for the production of sialidase from *P. fluorescens* strain jk-0412	Park et al. (2011)

(continued)

Table 21.1 (continued)

S. N	Patent number	Applications of *P. fluorescens*	Reference
18.	EP2314602A1	Developed a improved expression system by using *P. fluorescens* secretion systems	Retallack et al. (2011a, b)
19.	US7815903B2	Developed a method for the commercial production of biopesticides by using *P. fluorescens*	Khan et al. (2010)
20.	US7658851B2	Successfully used *P. fluorescens* for waste water treatment	Nelson and Rawson (2010)
21.	WO2010008764A1	Reported *Pseudomonas fluorescens* strains for production of extracellular recombinant protein	Rettalack and Chew (2010)
22.	US7595173B2	Designed a suitable method for the low cost production peptides, including antimicrobial peptides (AMPs), by using *P. fluorescens*	Krebs et al. (2009)
23.	US7553656B2	Developed some mutant strains of *P. fluorescens* which produces large amounts of alginate	Gimmestad et al. (2009)
24.	KN 100828566B1	*Pseudomonas fluorescens* k4 having excellent ability of denitrification of NO and NH_3 from industrial wastewater	Ho et al. (2008)
25.	US20070292918A1	Developed a method for the heterologous expression of recombinant protein in *P. fluorescens*	Stelman et al. (2007)
26.	US20060147438A1	Used *P. fluorescens* biotype B E34, *P. fluorescens* biotype C WH19, *P. fluorescens* biotype C WH6 for the control of grassy weeds	Azevedo et al. (2006)
27.	WO2005069913A3	Provided a suitable method for the efficient production of a recombinant mammalian protein by expression in a pseudomonad	Retallack et al. (2005)
28.	RU2235771C	Prepared a formulation containing *Pseudomonas fluorescens* p469 effective against plant diseases caused by phytopathogenic fungi and microorganisms	Aslan et al. (2004)
29.	US6509177B1	Developed a method for the production of pseudomonic acid A antibiotic from *P. fluorescens*	Szell et al. (2003)
30.	EP0758385B1	Expressed the chimeric *Bacillus thuringiensis* toxin comprising a cryIF core N-terminal toxin portion and a heterologous C-terminal protoxin portion from a cryIA(b) toxin or cryIA(b)/cryIA(c) chimeric toxin in *P. fluorescens*	Schwab and Thompson (2003)
31.	US6495362B1	Reported that the *P. fluorescens* NBRI 1303 (ATCC 55939) was effective in suppressing plant pathogens, including *Fusarium oxysporum f. sp. ciceri, Rhizoctonia bataticola* and *Phthium* sp. in chickpeas	Nautiyal (2002)

(continued)

Table 21.1 (continued)

S. N	Patent number	Applications of *P. fluorescens*	Reference
32.	WO2002036795A3	Developed a method for the production of menthol by using a steriospecific lipase enzyme isolated from *P. fluorescens*	Chaplin et al. (2002)
33.	US6048713A	Found that *P. fluorescens* HP-72-B13 and *P. fluorescens* HP-72-Br5 have antagonist property against pathogenic fungi of the genera *Pythium, Rhizoctonia, Sclerotinia and Gaeumannomyces* spp.	Murakami et al. (2000)
34.	US5980747A	Devised a method for the storage of *P. fluorescens* and its subsequent use for bioremediation	Vandenbergh et al. (1999)
35.	US5962624A	Discovered a method for the production of polyesters by using *P. fluorescens*	Vonderhagen et al. (1999)
36.	US5741663A	Developed a bacteriological growth medium selective for *P. fluorescens*	Russel (1998)
37.	US5711945A	Used *P. fluorescens* for reducing the pitch content of pulps and pulpwoods which can be used for making cellulosic products	Blanchette et al. (1998)
38.	US5344769A	Used *P. fluorescens* for the production of polyesters	Witholt et al. (1994)
39.	EP0472494A3	Reported that the *P. fluorescens* strain CGA 266446, CGA 266447, CGA 267356, CGA 270293, CGA 270294 shows antagonistic effect against the pathogens *Rhizoctonia solani* and *Pythium ultimum*	James et al. (1992)
40.	WO1990001327A1	Reported the inhibitory action of *P. fluorescens* against root rot in peas caused by Aphanomyces fungus	Parke (1990a, b)

subsequently expressed in the *Escherichia coli* BL21 (DE3). The vaccine prepared by this technique has shown a promising effect by decreasing the infection rate up to nearly 81% (Li and Yonghua 2013).

Sialic acid belongs to a family of naturally occurring carbohydrates it has been reported that microbes express sialic acid-specific lectins which helps bacterial cells to attach themselves with the host cell. Similarly, gram negative bacteria's use certain endogenous transport system to acquire sialic acid from external environment. This invention shows a potential way to degrade this sialic acid by using the sialic acid degrading enzyme produced by the *P. fluorescens* strain sense JK-0412. The author have shown a possible way to make drugs by using this strain which can potentially degrades this sialic acid molecule and thereby help in treating viral infection, cancer etc. (Yong-il et al. 2012).

21.9 *P. fluorescens* and Bioremediation

Industries, agricultural practices and domestic households produces huge amount of waste water which in turn causes pollution to the ground water and fresh water resources. In order to overcome this problem previously several methods have been devised which in turn can treat the contaminated water. This invention provides an insight about potential use of *P. fluorescens* K4 (KCCM 10841P) strain for this purpose. This strain can degrade high concentration of nitrogen oxide and ammonia components through denitrification. Hence, by using this biological agent industrial waste water can be treated to remove the toxic ammonia compounds (Ho et al. 2008). Similarly, *P. fluorescens* strain SJTE-2 with a preservation number CGMCC No.6587 has been used for degrading the estrogen substance oestrone, 17-Beta-estradiol, estriol and polycyclic aromatic hydrocarbon substance naphthalene, luxuriant, bisphenol A. The bacterial strain can use estrogen as its sole carbon source thereby it grows over it and decompose it within a short period of time depending upon the concentration of estrogen present in the source. Generally it can degrade 17-beta-estradiol within a period of 1 day if it is present at a concentration of 1 mg/L similarly in case of 50 mg/L concentration it usually takes 7 days to decompose 17-beta-estradiol up to 90%. Hence, this strain can be used efficiently for degrading all these aromatic hydrocarbons in the environment with a higher efficiency than ever before (Rubing and Jianhua 2014).

In this highly advanced world almost all of the industrial operation requires huge amount of petroleum products every day. These petroleum products right from there processing to industrial use emits very high amount of toxic materials which then pollutes almost all the land, air and fresh water resources. Hence, in past few decades this problem has drawn the attention of most of the scientific communities to find out effective measures to tackle this problem. The present invention has contributed albeit towards this, the author has used *P. fluorescens* strain SJTD-2 with a preservation number of CGMCC No.6586 to degrade the petroleum products. The bacterial strain can grow on the medium containing C18-C24 long-chain alkane or petroleum products (500 mg/L) and can degrade it completely within 1 day. Similarly, it can decompose C18-C24 long-chain alkane or petroleum products (200 mg/L) within 36 h and 2 g/L of crude oil in 7 days (Rubing et al. 2013).

Likewise these industrial or household activities even the agricultural activities is also significantly contributing the pollution and among which one of the major agent is the use of toxic and hazardous chemicals for the control of pest. Chlorpyrifos is among one of such toxic chemical which can cause serious health problems in human being because at higher dose it inhibits cholinesterase enzyme which in turn over stimulates the nervous system ultimately leading to nausea, respiratory paralysis or even death. Once sprayed on the crops it is not completely absorbed by the plants and hence the left out residues pollutes the environment. By keeping in view its hazardous nature many work has been done to find out some possible ways to degrade this toxic chemical. The present invention makes the use of *P. fluorescens* strain CHZYR6 3 as a biocontrol agent to decompose this chemical. This strain produces an enzyme that can efficiently degrade chlorpyrifos residue in water, soil

and vegetables. Further, the process of preparation of crude extract of the enzyme from this strain is easy, efficient, cost effective and has broad application prospects (Wei et al. 2014).

Apart from these another potential hazardous compound is heavy metals which now days contributing a lot to the rise in pollution levels. Heavy metals cause serious toxicity when they come in direct contact with the human body. The major sources of these heavy metals are usually industrial wastes and unscrupulous mining activities. In recent time many work has been done to find some ways to remove these hazardous metals from the infected resources, the present invention shows the use of *P. fluorescens* strain BM07 for this purpose. It is a cold induced strain of *P. fluorescens* which secretes exo biopolymer which in turn precipitates the heavy metals viz mercury or cadmium and thereby serves as a potent bioremediation agent for the removal of heavy metals from the contaminated resources (Chul et al. 2012).

21.10 Potential Use of *P. fluorescens* as a Biofilters

The need for culturing fish under controlled environment has resulted into the development of aquaculture facilities. In the aquaculture 95% of the water is recirculated and hence it has to be kept clean and fresh because a huge amount of ammonia is liberated into the fish tanks by the fishes during their protein metabolism (Lloyd 1992; Wood 1993; Smutna et al. 2002). The purification operation in turn can be carried out by using some biofilters; the present invention shows the use of *P. fluorescens* strain HF-3 with an accession number CCTCC NO: M2014274 as a biofilter. This strain has the capacity to remove 94.61% nitrite from the aquaculture after 48 h of treatment. Similarly, from the shrimp culture it can remove 94.35% of nitrite via its denitrification process after a period of 48 h. Not only this it can even remove 90% of nitrite from the sewage also hence it can serves as a potential agent for purifying all these water resources (Yuqiang et al. 2016).

21.11 *P. fluorescens* in Plant Growth Promotion

Plant growth promoting rhizobacteria (PGPR) are root-colonizing bacteria that form symbiotic relationships with plants. These bacteria's generally help in solubilising the phosphorus in the soil thereby help the plants in phosphorus uptake. However, the concentration of these PGPRs in soil is very limiting and hence they can solubilize only a limited amount of phosphorus which is not at all sufficient for the plants. Hence, in order to make the phosphorus available to the plants many researchers have developed different biofertilizers formulations by using different phosphorus-solubilising strain, of *P. fluorescens.*

The *P. fluorescens* CLW17 strain with a collection number of CCTCC NO. M 2010158 has been reported to be highly efficient in solubilising the insoluble phosphates of tricalcium phosphate, iron phosphate, aluminum phosphate etc. thereby it makes the phosphorus available to the plant in its rhizosphere zone and contributes

significantly in the growth of the plant (Jiahong et al. 2011). Another invention has disclosed that the *P. fluorescens* JW-JS1 strain shows strong phosphate solubilising ability from tricalcium phosphate and hydroxyapatite in the treated seedlings of NL-895poplar. Results revealed a significant rise in the uptake capability of poplar plants thereby contributing to their overall growth (Liu et al. 2010). Similarly, *P. fluorescens* CKD18 strain with a preservation number of CGMCC No.3227 have been reported to be highly efficient in dissolving phosphate which in turn allows better absorption of N, P and K in plants thereby promote better growth. The strain has been used for making bio-fertilizers and shows promising effect when applied in the field (Wenliang et al. 2011). Another strain of *P. fluorescens* which was known as FXW-HS7A has been deposited in the China Center for Type Culture Collection under the accession number CCTCC M 2012260. This strain has the capability to dissolve the phosphorus from the insoluble fraction of tricalcium phosphate, iron phosphate, aluminum phosphate and hydroxyapatite and makes it available in the free form which in turn is efficiently absorbed by the plants (Mingyan et al. 2013).

It is a well known fact that the plant cell cultures serves as a good source for the production of secondary metabolites like phytopharmaceuticals which can be induced *via* biotic changes. *P. fluorescens* N21.4 is one such biological agent which can be used to stimulate the plant culture to increases its content of isoflavones, anthocyanin. This in turn can strengthen the plants defense mechanism to withstand against the pathogenic attack (Parejo et al. 2011).

21.12 Conclusion

Agriculture is one of the most important sectors now days as it is dealing with the most challenging task of meeting the demand of global food supply. But there are several factors which significantly affect the global productivity and among which plant diseases are the major problem to be dealt with. In past decade many advanced technologies has been used to better understand this plant-pathogen interaction during disease establishment in order to develop suitable method for controlling these diseases (Kalita and Ram 2018). In past the most potent method used for controlling these plant diseases includes the use of various types of hazardous chemicals. These chemicals are quite effective in controlling these diseases but they have a major problem as they leave huge amount of residues. These residues in turn pollute the environment and are highly toxic to human beings as well. Hence, this has compelled the scientific communities to focus more and more on the development of biological control agent instead of using these toxic chemicals. *P. fluorescens* is one of such example which is emerging as a potential biocontrol agent against various bacterial, fungal or even viral diseases. The major benefit of these Bio-control agents is that they are environmental friendly, easy to manufacture as well as cost effective. The use of *P. fluorescens* is not limited to only as a biocontrol agent but it has been used for the purpose of bioremediation as well. Many researchers have used these bacteria for the removal of toxic chemicals from the sewage as well as fresh water resources. Apart from this even some researcher has used them for the

development of vaccines against certain deadly diseases of fishes. So, in a nut shell this bacterium shows a huge potential towards the welfare of human being and hence more and more research work should be carried out to make full use of this bacterium.

Conflict of Interest The authors declare that they have no conflict of interest.

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