Ethical, Patent, and Regulatory Issues in Microbial Engineering

8

Sumer Singh Meena and Anee Mohanty

Abstract

Engineered microbial systems are finding application in various sectors and are predicted to revolutionize variety of fields such as health care, food and agriculture industries, paper, textile, and environmental remediation. With the rapid advancements in technology for production of genetically modified organisms, there is also ever-increasing debate on social, ethical, and legal implications of such technologies. For these cutting-edge technologies to be commercialized and become the basis of successful business ventures, there is a need to protect these inventions through regimes of intellectual property rights (IPR). In addition to legal protection, the innovation must meet the regulatory framework keeping in mind the societal concerns. Ethical concerns are intertwined with genetically modified microorganisms and questions like are scientists "interfering with nature" or "playing god" are being widely debated. This chapter elaborates on the evolution of patent system for biological material, patent landscape of microorganisms across the globe, various ethical concerns, and the way forward.

Keywords

Genetically modified microorganisms · Intellectual Property Rights (IPR) · Patents · TRIPS · IDA · Bioethics

S. S. Meena · A. Mohanty (✉)
Department of Biotechnology, Dr. B. R. Ambedkar National Institute of Technology (NIT), Jalandhar, India
e-mail: mohantya@nitj.ac.in

V. Singh et al. (eds.), *Engineering of Microbial Biosynthetic Pathways*,
https://doi.org/10.1007/978-981-15-2604-6_8

8.1 Introduction

The history of exploiting microorganisms for production of food and beverages dates back to thousands of years. There are credible molecular evidences now that ancient civilizations in China, Egypt, Mesopotamia, and Greece have been using microorganisms for fermentation of grains and fruits (McGovern et al. 1996, 2004; Samuel 1996; Valamoti et al. 2007). Louis Pasteur's work on lactic acid and alcohol fermentation and later microorganisms as causative agents of diseases was a milestone discovery in microbiology (Gal 2008; Pasteur 1857) which led to search for newer fermentation techniques and improving the efficiency for production of various economically important products. In the twentieth century, scientific advancements made it clear that microbial genome possesses enormous potential to synthesize hundreds and thousands of complex molecules with diverse application. Now various industries are centered around microbial products starting from vaccines, antibiotics in health-care industry to harvesting renewable sources of energy from microbial biomass and food processing industries using an array of microbial enzymes and whole-cell microorganisms as biocatalysts (Vitorino and Bessa 2017).

Synthesis of bioactive compounds in living systems are often controlled by complex regulatory pathways comprising of dozens of genes. Thus, production and isolation of industrially important compounds in economically efficient ways would require manipulation and optimization of metabolic networks and if required addition of new genes or entire pathways to reprogram the microbial systems (Ginsberg et al. 2014). In the last couple of decades, breakthrough in genetic engineering and next-generation sequencing technologies are enabling the scientists with required methodology and genome information for engineering prokaryotic and eukaryotic cells. Microbial engineering holds enormous potential to change human lives; as cost of health care would reduce, greener and cheaper sources of renewable fuels would fulfill the energy requirement of the ever-increasing population, and resource recovery from waste material and higher yield from agriculture would be facilitating sustainable living (Smanski et al. 2016).

The ability to apply engineering principles to living systems for redesigning the existing microorganisms or the pursuit to even construct completely novel biological entities or designing tailor-made living entities is raising serious legal, ethical, and social issues. This chapter aims to elaborate on the various aspects of intellectual property rights, ethical, biosafety, and regulatory issues pertaining to microbial engineering.

8.2 Patent-Related Issues in Microbial Engineering

Microbial engineering involves manipulating the microbial cells for creating new products or processes. The engineered microorganisms are designed to enhance the yields of industrial chemicals such as enzymes, vitamins, amino acids or alcohol, biopolymers, or other disease-fighting agents such as vaccines, antibiotics, or simply

probiotics for enhanced immunity by colonization of human guts. Exploitation of microbial systems for value-added products are benefiting plethora of industries such as pharmaceuticals, biomedical, agroindustry, energy sector, and food processing industries. Thus engineered microbial systems designed to solve specific problems with practical application need to be commercialized to earn revenue and bring economic prosperity to the inventor and nation. The profitability of such ventures will also provide much required impetus to R&D activities in related fields.

In order to commercialize a product first, it needs to be protected from unfair copying and competition. Therefore, the novel engineered microorganisms are subjected to intellectual property rights (IPRs) which will not only be rewarding for the inventor but also will pave the way for exploring the unrecognized and untapped commercial utility of such inventions. IPRs grant legal protection to the creation of human mind and could be inventions of scientific, literary, or artistic nature, for specified amount of time to its creator or inventor. There are various types of IPRs like copyrights, industrial designs, trademarks, and patents, and depending on the nature of innovation, it can fall into one of the categories.

IPRs concerning a novel variety of genetically modified microorganisms, plant species, animal cell lines, genes, and any process of isolation or modification of biomolecules like DNA, RNA, proteins, and metabolites fall into the category of patents. Patents are legal rights conferred to inventors for fixed number of years after satisfying few conditions such as novelty, industrial application, nonobviousness, and full disclosure (Webber 2003). This legal right gives monopoly to the patentee to manufacture, sell, and import the patented product or process for a stipulated period of time. Ever since the rapid development in biotechnology, legal rights pertaining to novel life forms have been under serious debate partly because of differences in sociocultural and economical standings of nations. Though all the major technologies in the past that pushes the frontier forward have been faced with certain amount of resistance and tension, genetic modification of organisms is mostly perceived as commodification of life and an attempt to play with nature. Therefore, there is wide variation in patent laws across the globe, and this is even more apparent when it comes to patenting life forms. However, patenting of live forms especially microorganisms is not new as patents were granted to novel variety of yeasts used in brewing and baking industries in 1833 in Belgium and in 1843 in Finland (Webber 2006).

8.2.1 TRIPS Agreement: Patenting Microorganisms

The extent of legal protection to engineered life forms varies across different countries. For any biological material to be eligible for patent application, it still has to fulfill the basic criteria of patentable subject matter, i.e., inventive step, nonobviousness, and industrial utility as applicable to any other technology. So, any new organism or genetically modified microbe must be different from the already existing form in terms of character and/or usage. As stated earlier, there is a wide variation in patenting methodology adopted in different countries, one such

variation is mere isolation and purification of microorganisms or their genes cannot be patented in some countries, whereas in USA it can still be patented. As the profits from bioprospecting are rising tremendously over the years, the inconsistencies in patent laws have led to heated debate over ownership rights of patents (Wynberg and Laird 2007).

To reduce the distortion in patent laws and to enable seamless movement/trade of products and processes arising of biological patents, TRIPS (Trade-related Aspects of Intellectual Property Rights) agreement was signed by the member countries of WTO. It is aimed at bringing coherence in IPR policies of all member countries (Matthews 2003). TRIPS was negotiated in Uruguay Round of the General Agreement on Tariffs and Trade (GATT) between 1989 and 1990 and is administered by the WTO (Drahos 2002). It is mandatory for all the member states of WTO to enforce the minimum standards of IP protection, and noncompliance could lead to punitive action like sanction/fines. The developing nations were having some apprehensions that scope of patentability is too wide and may impede the social and economic welfare of less affluent nations.

Section 27 of TRIPS states that "patents shall be available for any invention, 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 section reiterates the basic tenets of patentability of be novelty, nonobviousness, and industrial application, but the noteworthy thing is it brought all fields of inventions at par with each other as far as patenting is concerned and made non-discrimination its underlying principle.

With this TRIPS brought microorganisms also under the ambit of patent protection and therefore many nations modified their domestic patent laws and have now started patenting of microorganisms. From 2005, all the member countries had to allow microbial patenting if was not allowed earlier (Sekar and Kandavel 2002).

8.2.2 Budapest Treaty, Deposition of Microorganisms, and IDA

As patent laws globally require full disclosure of invention during patent application in such a way that person skilled in the art could comprehend the full invention and its working. In case of microbial patents or patenting of their genetic material or any compounds derived from them, drawings or mere description would be highly insufficient, and the need for microbial samples to be deposited in a culture collection for patent application was felt internationally. Therefore, Budapest Treaty on the International Recognition of the Deposit of Microorganisms for the Purposes of Patent Procedure was signed in 1977 and was enforced in 1980 and is administered by WIPO (World Intellectual Property Organization). As of June 2019, there are 82 countries which are party to this treaty, and it led to the creation of IDA (International Depository Authority). IDA ensures that a patent applicant needs to deposit the biological material in only one of the recognized culture collections and eliminated the practice of depositing in every country where the patent is filed. Examples of IDAs are American Type Culture Collection (ATCC), the European

Collection of Cell Cultures (ECACC), Japanese Federation of Culture Collections, and the Deutsche Sammlung von Mikroorganismen und Zellkulturen (DSMZ), Microbial Type Culture Collection and Gene Bank (MTCC) in India. The IDAs accept a wide range of biological materials which include microbial cultures (e.g., viruses, algae, fungi, bacteria), animal cell lines, hybridomas, plant cell lines, genetic material (including DNA fragments), vectors along with the host used for expression of a gene, spores, etc. (www.wipo.int/budapest/en/idadb). These culture collections also alleviate the problems related to storage, transportation, handling of diverse biological samples and could very well be transformed into biological resource centers with legal mandate for benefit sharing internationally (Sekar and Kandavel 2004).

8.2.3 Status of Microbial Patenting in Developed Countries

Article 27.3(b) of TRIPS agreement does not allow member states to exclude microorganisms from patents (Kothamasi et al. 2011). However, the agreement neither defines the term "microorganism" nor elaborates on the scope of protection. Another important thing is under Article 27.1 of TRIPS, subject matter must be an invention and not mere discovery. So, this raises a very pertinent question of whether mere isolation of microorganisms that exist in nature comes under patentable subject matter. Across the globe there seems to be more or less an agreement that any substance occurring in nature should not be patentable without significant human intervention.

8.2.3.1 US Patent System

This varies widely with some countries like USA taking a liberal stand on this by allowing patents on microorganisms which were isolated and purified from a consortia in laboratory and their existence was not known previously (Martin and Vermeylen 2005). US patent regime for biological materials have also gone through transitional phase and initially did not allow for patenting of living organisms. Only after the landmark judgment of supreme court of USA in the *Diamond v. Chakrabarty* case (Kevles 1994; Robinson and Medlock 2005) in 1980, the status changed to "all inclusive" or "include anything made by man under the sun." This was one of the first well-known case of engineered microbial system to get a patent. The applicant had genetically modified a bacterium of the genus *Pseudomonas* with catabolic plasmids capable of degrading oil spills. Initially the United States Patent and Trademark office (USPTO) studying the claims accepted that the bacterium does not occur in nature, but the application was rejected on the ground that subject matter was "living organism." An appeal against USPTO decision was filed in Supreme Court, and the court decided in favor of the applicant in an epoch marking verdict. The court ruled that the issue is not between living and nonliving nature of subject matter but between product of nature and human made invention (Chakrabarty 2010). Almost three decades later, US patent system has undergone various changes

and now take a liberal stand to bring a variety of living materials under the ambit of patent laws.

Here another pertinent question to ask is whether patenting of engineered microbial systems would also entail the gene responsible for designing the microbe patentable? In the case of Association for Molecular Pathology v. Myriad Genetics, Inc., 569 U.S. 576 (2013), Justice Clarence Thomas, of Supreme Court pronounced the verdict and held, "A naturally occurring DNA segment is a product of nature and not patent eligible merely because it has been isolated, but cDNA is patent eligible because it is not naturally occurring" (Ingram 2014). Biotechnology and pharmaceutical companies are taking advantage of this rule and patenting cDNA which is an edited version of original gene.

As a leading country in biotechnological innovation, the number of patents in US concerning microbial systems have increased many folds in past few years. With new issues with bio-patents, the legal system also needs to be modulated to be more accommodating. In 2013, American Invent Act was introduced in US which changed the status quo from first-to-invent to first inventor-to-file (Schafer 2013) to encourage filing of more patents in time-bound manner. This law also enlarges the scope of post grant opposition by third parties to increase transparency.

8.2.3.2 European Patent System

European nations have unified patent policy which is mostly derived from two documents, European Patent Convention (EPC) and the Biotechnology Directive, 1988 (Kranakis 2007). A unique feature of European patent system which is not present in American system is inclusion of a "public order and morality" clause under Section 53(a). Some other inventions are also not allowed for the purpose of patenting which are listed under Section 52 of EPC. The national IP laws of European nations also have their own approach when it comes to granting of biological patents.

8.2.3.3 Status of Patenting Microorganisms in Developing Countries: Case Study of India

Indian patent system is quite similar to European system and takes a firm stand by excluding preexisting phenomena, and creation of nature cannot be patented (Senan et al. 2011). The Indian Act of 1970 regulates the patent protection in India. This act has undergone many amendments over the years especially after signing the TRIPS agreement to meet its obligation for free and fair trade (Ganguli 2004). Patent amendment act of 2002 allowed patenting of microorganisms. Another major change that took place in 2005 was the deletion of Section 5 of Indian Patent Act, 1970, which allowed for only process patent paving the way for product patents. Indian patent system still does not allow patenting of process of production of plants, animals, or plant and animal as a whole or part of it only exception being the microorganisms. However, this could create confusion as the word "microorganism" has neither been defined clearly in TRIPS agreement nor by Indian patent system. Overall, the amendments made to the Indian patent system have been successful in removing the red tape and attracting more patent filing involving microbial processes

and engineered microbial systems, and this would augur well for the economy of the country (Balachandra Nair and Ramachandranna 2010; Mishra et al. 2019).

8.3 Ethical Concerns

Ability to alter life forms, even creating novel life forms and making them into profitable business ventures, raises many questions of legal, ethical, and societal concerns. The most contentious issues out of all is the issue of "owning life" which also leads to questions over use, transfer, and dissemination. The following section would deal with all such issues pertaining to engineered microbial systems.

8.3.1 Societal Concern and Public Trust

It is not surprising that a powerful technique like genetic engineering having the potential to create novel life forms would raise ethical security and safety concerns. The major concern being these technologies might blur the line between what is natural and what is not.

8.3.2 Biosafety and Bioterrorism Concern

As these engineered microorganisms could be created for various purposes, concerns about creating engineered pathogenic microorganisms for bioterrorism purposes also loom large in the psyche of common people. These biosecurity concerns were triggered in early twenty-first century when scientists were able to create Influenza virus (Tumpey et al. 2005) and cDNA of polio virus (Cello et al. 2002) in lab. If these technologies are easily accessible, then "biohackers" could use them to unleash terror attacks by creating more virulent strains of pathogen.

Another health concern of engineered microbial system is the potential use of these bugs in therapeutic clinical trials. Human body harbors many microorganisms in various anatomic site, and their role in digestion and immunity is increasingly becoming clear. In this regard, therapeutic microbiota enrichment like fecal microbiota transplantation (FMT) have shown promising result for treating recurrent *Clostridium difficile* infection (Van Nood et al. 2013). Success of these studies led to the investigation of FMT studies for treatment of other diseases like inflammatory bowel disease, treatment of graft versus host disease in hematopoietic cell transplant patients, reduction in intestinal carriage of multidrug-resistant organisms (Woodworth et al. 2017). U.S. Food and Drug Administration (FDA) is closely monitoring these cases and is bringing regulations and requirements to study the potential risks associated with such studies and the long-term effect of altering the microbiota.

8.3.3 Accidental Release and Environmental Implication

Potential release of these engineered microorganisms can lead to severe environmental and health hazards. Unlike air or water pollution which might dissipate over time, engineered microbes if released to environment will multiply and could pose grave threat to naturally occurring microbes in soil, water, air, or other parts of ecosystem. Our experience of introducing plant or animal species to new geographical areas in the past has created many ecological disasters, e.g., fungus introduced from Asia to North America killed half of its chestnut trees (Steiner et al. 2017), and many such examples of creating invasive species exist. Therefore, thorough assessment of genetically modified microorganisms and their effect on environment needs to be assessed before their release (Clark 2006) as they might have unpredictable and emergent properties.

It is felt that in the rat race of patenting life, the multinational corporations might have the tendency to only conduct short-term trials which may be highly inadequate as the long-term effects will be unknown. To avoid such scenarios, many patent systems across the world have "public health" clause in the patent laws, and inventions which are likely to be injurious to public health do not qualify for patents. Regulations should be put in place for thorough evaluation of whether the invention has undergone detailed biosafety trials or not, and these safety check points would go a long way in mitigating the fear in the minds of general public.

8.3.4 Economical Concern: Costlier Health Care or Food Products Only Available to Rich

Patents are in nature negative legal rights which bar others from using the patented technology and grant monopoly to the inventor for a stipulated amount of years. According to some human rights activists, this might increase the gap between rich and poor where patented technologies that are costlier are only available to rich out of reach for the poor, disadvantaged minorities, women, and underdeveloped world. These fears were raised by few nations after TRIPS agreement where it was felt that bringing everything under the IPR regime will make quality health care unaffordable to people in least developed parts of the world. To address these concerns, Doha Declaration on the TRIPS Agreement and Public Health was adopted by the WTO Ministerial Conference of 2001 in Doha which kept essential medicine and life-saving drugs out of the patent regime and gave flexibility to member nations to deal with any public health crisis.

Similar apprehensions exist for application of engineered microbial systems in agricultural industries. Farmers unconsciously act as selection agents in the development of microbial resources/germplasm, but their role goes unrecognized as multinational corporations acquire the rights of microbial resources, and there is no equitable profit-sharing mechanism in place (Kothamasi et al. 2011).

Regulatory mechanisms should be put in place such that ownership and commercialization of genes, genomes, and genetic information which might result in new food or health-care products is not out of reach for some sections of the society.

8.4 The Way Forward

Arguably, microbial engineering holds the potential for new industrial revolution with the production of cheaper drugs, disease-resistant plant variety, increasing soil fertility, enhanced crop growth, greener fuels, bioactive compounds for preservatives, color, fragrance enhancer, bioremediation of recalcitrant compounds to just name a few. However, proper regulatory mechanisms should be put in place to avoid any malicious attempt to misuse these technologies. Various checks and balances like screening of companies and thorough biosafety documentation before granting patents, creating awareness about biosecurity issues among scientists and general public alike, formation of professional society, including civic society members as stakeholders in decision-making process for granting patents for engineered microbial systems, will go a long way. There might not be an appropriate "one size fits all" approach with diverse systems and technologies in place, so regulatory bodies must take into account a wide range of perspectives about risk, economic impact, scientific progress, and moral reasoning in dealing with commercialization of genetically modified microorganisms.

References

Balachandra Nair R, Ramachandranna PC (2010) Patenting of microorganisms: systems and concerns. J Commer Biotechnol 16(4):337–347

Cello J, Paul AV, Wimmer E (2002) Chemical synthesis of poliovirus cDNA: generation of infectious virus in the absence of natural template. Science 297(5583):1016–1018

Chakrabarty AM (2010) Bioengineered bugs, drugs and contentious issues in patenting. Bioeng Bugs 1(1):2–8

Clark EA (2006) Environmental risks of genetic engineering. Euphytica 148(1–2):47–60

Drahos P (2002) Negotiating intellectual property rights: between coercion and dialogue. In: Global intellectual property rights. Palgrave Macmillan, London, pp 161–182

Gal J (2008) The discovery of biological enantioselectivity: Louis Pasteur and the fermentation of tartaric acid, 1857—a review and analysis 150 yr later. Chirality 20(1):5–19

Ganguli P (2004) Patents and patent information in 1979 and 2004: a perspective from India. World Patent Inf 26(1):61–62

Ginsberg AD, Calvert J, Schyfter P, Elfick A, Endy D (2014) Synthetic aesthetics: investigating synthetic biology's designs on nature. MIT press, Cambridge

Ingram T (2014) Association for Molecular Pathology v. Myriad Genetics, Inc.: the product of nature doctrine revisited. Berkeley Tech. Law J 29:385

Kevles DJ (1994) Ananda Chakrabarty wins a patent: biotechnology, law, and society, 1972–1980. Hist Stud Phys Biol Sci 25(1):111–135

Kothamasi D, Spurlock M, Kiers ET (2011) Agricultural microbial resources: private property or global commons? Nat Biotechnol 29(12):1091–1093

Kranakis E (2007) Patents and power: European patent-system integration in the context of globalization. Technol Cult 48(4):689–728
Martin G, Vermeylen S (2005) Intellectual property, indigenous knowledge, and biodiversity. Capital Nat Social 16(3):27–48
Matthews D (2003) Globalising intellectual property rights: the TRIPS agreement. Routledge, Abingdon
McGovern PE, Glusker DL, Exner LJ, Voigt MM (1996) Neolithic resinated wine. Nature 381 (6582):480
McGovern PE, Zhang J, Tang J, Zhang Z, Hall GR, Moreau RA et al (2004) Fermented beverages of pre-and proto-historic China. Proc Natl Acad Sci U S A 101(51):17593–17598
Mishra VK, Verma H, Singh G (2019) Recent development of patent in Indian scenario with special reference to microbial patents. In: PGPR amelioration in sustainable agriculture. Woodhead Publishing, Sawston, pp 159–166
Pasteur L (1857) Mémoire sur la fermentation applée lactique. Mémoire sur la fermentation alcoolique. Mallet-Bachelier, Paris
Robinson D, Medlock N (2005) Diamond v. Chakrabarty: a retrospective on 25 years of biotech patents. Intell Prop Tech Law J 17(10):12–15
Samuel D (1996) Investigation of ancient Egyptian baking and brewing methods by correlative microscopy. Science 273(5274):488–490
Schafer M (2013) How the Leahy-smith American invents act sought to harmonize United States patent priority with the world, a comparison with the European patent convention. Wash Univ Global Stud Law Rev 12:807–828
Sekar S, Kandavel D (2002) Patenting microorganisms: towards creating a policy framework. J Intell Prop Right 7:211–221
Sekar S, Kandavel D (2004) The future of patent deposition of microorganisms? Trends Biotechnol 22(5):213–218
Senan S, Haridas MG, Prajapati JB (2011) Patenting of microorganisms in India: a point to ponder. Curr Sci 100(2):159–162
Smanski MJ, Zhou H, Claesen J, Shen B, Fischbach MA, Voigt CA (2016) Synthetic biology to access and expand nature's chemical diversity. Nat Rev Microbiol 14(3):135–149
Steiner KC, Westbrook JW, Hebard FV, Georgi LL, Powell WA, Fitzsimmons SF (2017) Rescue of American chestnut with extra specific genes following its destruction by a naturalized pathogen. New For 48(2):317–336
Tumpey TM, Basler CF, Aguilar PV, Zeng H, Solórzano A, Swayne DE et al (2005) Characterization of the reconstructed 1918 Spanish influenza pandemic virus. Science 310(5745):77–80
Valamoti SM, Mangafa M, Koukouli-Chrysanthaki C, Malamidou D (2007) Grape-pressings from northern Greece: the earliest wine in the Aegean? Antiquity 81(311):54–61
Van Nood E, Vrieze A, Nieuwdorp M, Fuentes S, Zoetendal EG, de Vos WM et al (2013) Duodenal infusion of donor feces for recurrent Clostridium difficile. N Engl J Med 368(5):407–415
Vitorino LC, Bessa LA (2017) Technological microbiology: development and applications. Front Microbiol 8:827
Webber PM (2003) A guide to drug discovery: protecting your inventions: the patent system. Nat Rev Drug Discov 2(10):823–830
Webber PM (2006) Patenting of microorganisms. Nat Rev Drug Discov 5(1):13–13
Woodworth MH, Sitchenko KL, Carpentieri C, Friedman-Moraco RJ, Wang T, Kraft CS (2017) Ethical considerations in microbial therapeutic clinical trials. New Bioeth 23(3):210–218
Wynberg R, Laird S (2007) Bioprospecting: tracking the policy debate. Environ Sci Policy Sustain Dev 49(10):20–32