Patent Law Fundamentals for Biomedical Scientists

57

Srikumaran Melethil

Abstract

The major objective of this 2-part chapter is to introduce, demystify and advance the knowledge of patent law among biomedical scientists. Part I presents a discussion on the significance of understanding patent law concepts among scientists, followed by an introductory excursion into fundamental patent law concepts and terminology in the United States, such as intellectual property, novelty, anticipation, utility, non-obviousness, enablement, person of ordinary skill in the art, patent infringement, specification, and claims. Part II is geared more toward pharmaceutical scientists and discusses patent litigation between brand names and generic companies to illustrate the application of these concepts in patent prosecution and litigation. It is hoped that this chapter will serve as a starting point for biomedical scientists to foray into the area of patent law.

Keywords

Patent law · Biomedical scientists · Intellectual property · Non-obviousness · Commercialization of research · Novelty

57.1 Introduction

Patent law, at its heart, is mostly (if not, all) about commercialization of an inventor's intellectual property (IP). Simply put, it is about seeking financial gain from the creativity (inventions) of an inventor. Such gain also provides peer-recognition incentives to develop new products for the market, which is beneficial for the overall well-being of society. Development and marketing of pharmaceuticals, automobiles, computers, and communication and entertainment devices such as mobile phones and video games comprise a small sample of such useful products. Patent law attempts to provide a paradigm to strike a balance between the economic interests of the individual (inventor) and society at large.

The major objective of this introductory chapter on United States patent law is to introduce, demystify [1] and advance the knowledge of patent law among biomedical scientists, especially those involved in the discovery and development of pharmaceuticals. Therefore, the primary focus is to explain fundamental patent law concepts and

Disclaimer: Information and opinions presented in this chapter are strictly for educational purposes. It should not be construed as legal advice. Readers should consult a patent practitioner, such as a patent attorney or agent for specific advice on their patent needs.

S. Melethil (✉)
University of Missouri – Kansas City (Schools of Pharmacy and Medicine), Kansas City, MO, USA
e-mail: melethils@umkc.edu

G. Jagadeesh et al. (eds.), *The Quintessence of Basic and Clinical Research and Scientific Publishing*,
https://doi.org/10.1007/978-981-99-1284-1_57

procedures, and their applications using pharmaceutical patent litigation cases. To promote understanding of the subject matter, a comparison is made to the daily activities of research scientists. For example, the procedure to obtain a patent resembles the steps a scientist undertakes to develop a research proposal to a funding agency or to publish a paper in a peer reviewed journal.

An obvious question may relate to the presence and significance of this chapter on law, an apparent stranger in a book, otherwise devoted to science. A thorough understanding of patent law concepts is important to all biomedical scientists for the following three reasons: First, they enable them to better understand and appreciate the commercial potential of their research. Traditionally, scientists, especially in academia, have focused on the originality, quality and impact of their work, key requirements to obtain financial support for their research and ensuing publications in leading journals in their respective fields. Academic recognition also means job security (i.e., tenure, mobility) and financial success. But this culture of science is changing. During the last two to three decades, the commercialization of scientific efforts in academic institutions has become important, as seen by the establishment of technology transfer ("tech transfer") offices in a growing number of universities in the United States (US). The primary function of these offices is to assist in the commercial success of the ongoing research at their respective institutions (e.g., obtaining patents, establishing start-up companies). Such success has recently become part of the tenure dossier of faculty. Budgetary shortfalls from traditional sources are the single most important reason for this change in the academic culture [2]. Second, such knowledge enables scientists to communicate more effectively and work with patent attorneys and agents who traditionally develop strategies to prepare patent applications to obtain a patent from the United States Patent and Trademark Office (USPTO) for their inventions. Such interactions are inevitable, because, in this author's opinion, patent law involves more science than any other area of legal practice. Due to this, a science background is required to become a patent attorney or patent agent. Later in this chapter, a case is presented where a company lost its patent on a multi-billion dollar ("blockbuster") drug. In this author's opinion, this loss was likely due to a lack effective communication between pharmaceutical scientists and patent attorneys at that company (see The Prilosec Case, Part II). Third, a scientist with an understanding of patent law can have additional career advancements and upward mobility in today's marketplace, especially at start-ups, where a scientist often has interdisciplinary responsibilities.

At the outset, a key point must be made: There is considerable tension at the interface of law and science for both scientists and lawyers alike. This cultural clash between the disparate disciplines of law and science can be best stated in the following quote from a publication of the National Academy of Sciences [3]: "Because there is a general lack of understanding of each culture, these interactions often lead to a cognitive friction that is both disturbing and costly to society." Therefore, any effort to introduce patent law to scientists is a formidable task. To make this introductory chapter on patent law more understandable to a community of scientists, analogies to the field of science are often made to better explain patent law concepts and jargon to the readership.

Patent law basics are covered in Part I of this chapter. Discussion of selected cases is included in Part II to illustrate how the patent law concepts presented in Part I are applied in legal disputes (patent litigation). The following references published by the author provide additional information to better understand this chapter [4, 5].

57.2 Part I: Patent Law Fundamentals

57.2.1 What Is Intellectual Property (IP)?

The world intellectual property organization (WIPO) defines IP as follows [6]: It "refers to creations of the mind, such as inventions; literary

and artistic works; designs; and symbols, names and images *used in commerce* (emphasis added)."

WIPO goes on to explain the social, legal, and commercial issues related to IP [6]:

> [IP] is *protected in law* by, for example, patents, copyright and trademarks, which enable people to earn recognition or financial benefit from what they invent or create. By striking the right balance between the interests of innovators and the broader public interest, the IP system aims to foster an environment in which creativity and innovation can flourish (emphasis added).
>
> For a quick read on patents and other types of IP, such as copyrights and trademarks, the reader is referred to a publication authored by Miller and Davis [7].

57.2.2 Intellectual Property Explained

A simple example is presented to illustrate the legal meaning of IP. Inventor A constructs a mouse trap. Is that IP? Yes, from the ordinary meaning of the phrase "IP", because it is a product of inventor A's mind (intellect), and s/he owns it. But is it IP according to patent law? For example, can Inventor A make and sell his/her mouse trap on the open market ("inventions . . . used in commerce" from WIPO's definition)? It depends [8] on answers to certain key questions: (1) Are there other mouse traps sold on the market? (2) If the answer is Yes, are any of them "patent protected" (more on patent rights later)? and (3) Is A's mouse trap *legally* different (with respect to design, material and technology used, etc.) from all other patented mouse traps on the market? For now, if the answer to question 3 is "yes", then Inventor A can market the mousetrap, preferably with patent protection to prevent others from copying and selling A's mousetrap on the open market. A leading entrepreneur however does not believe in protecting his inventions via patents [9].

57.2.3 Inventive Steps

In patent law, an invention is created by a two-step process, namely conception and reduction to practice.

57.2.3.1 Conception Defined

Conception has been defined as the *complete performance* of the *mental part* of the *inventive act* and it is "the formation in the mind of the inventor of a definite and permanent idea of the *complete* and *operative* invention as it is thereafter to be applied in practice . . . [10] (emphasis added).

This is a critical step and *must* be done by the inventor(s).

57.2.3.2 Reduction to Practice Defined

Reduction to practice may be an actual reduction [i.e., making the invention] or a *constructive* reduction which occurs when a patent application on the claimed invention [patent application] is filed [11] (emphasis added).

Unlike conception, reduction to practice may be performed by anybody working under the direct and close supervision of the inventor.

57.2.3.3 Conception and Reduction to Practice Explained

To better understand these two steps, consider the previous example: Inventor A conceives an idea for a mouse trap (along with all the necessary details and drawings). Next, Inventor A has two options: S/he can make it himself/herself or hire somebody else (Contractor B) to build the mouse trap (reduction to practice). In the latter option, inventor A must provide Contractor B with all the *critical* details of making the mousetrap. Contractor B is considered an extension of Inventor A's hands and does not have any intellectual input. Note that Contractor B is *not considered* an inventor.

57.2.4 Constitutional and Policy Bases for Patents Defined [12]

One of the powers (responsibilities) granted to the Congress by the US Constitution (in pertinent part) is "To promote the *Progress of Science* and *useful Arts*" by securing for *limited Times* to . . . *Inventors* the *exclusive Right* to their respective . . . *Discoveries*" (emphasis added).

57.2.4.1 Constitutional and Policy Bases Explained

The US Constitution [13] provides the legal basis to establish a patent system to promote scientific development and the commercialization of such development for economic success in the US. Based on the authority delegated by Congress, the USPTO has developed a reward system that gives inventors exclusive rights to their inventions for a limited time with the provision that they publicly disclose their inventions. "It is hoped that such disclosure will promote innovations to the patented invention." This is sometimes called the patent bargain: limited-time monopoly in exchange for full disclosure.

57.2.5 Rights of a Patentee (Patent Owner) Defined [14]

A patent, in simple terms, is a *property right* granted by the US government to a patent holder for a limited time.

Ownership of a patent gives the patent holder the right *to exclude* others from:

1. making,
2. using,
3. offering for sale, selling, or
4. importing into the United States

the invention claimed in the patent.

57.2.5.1 Patentee Rights Explained

In simple terms, others are legally prohibited from the four activities stated above. These rights are "negative "in nature in that they are exclusionary. As noted with the mouse trap example, obtaining a patent on his/her mouse trap does not automatically give Inventor A the right to make and sell it on the open market.

Like all other property owned by inventor A (such as land, house, automobiles, bank accounts, etc.), s/he can sell, bequeath, transfer (assign) or license (allow another party to make and market the mouse trap for a fee) the mousetrap, during the life of the patent. Currently, this limited time (patent term) is 20 years from the effective filing date of the patent application [15]. Given the time needed for patent prosecution (the process used by the USPTO to evaluate a patent application and issue a patent, the effective patent life is less than 20 years. For example, patent prosecution on average takes 3.4 years for a drug and 4.4 years for a biological [16].

57.2.6 Patenting of Inventions (Patent Eligibility)

An invention must meet the following two major criteria to obtain an utility patent. First, it must belong to one of the four legal ("statutory") categories, namely, process, machine, manufacture, or composition of matter (see next section for more details). Second, the invention must be directed at the patent-eligible subject matter. For example, "abstract ideas, laws of nature, and natural phenomena (including products of nature)", referred to as judicial exemptions, are patent ineligible, "because they are the basic tools of scientific and technological work" and "granting them patent rights may impede innovation rather than promote it [17]". Inventions directed at nuclear weapons are also patent ineligible by law [18]: "No patent shall . . . be granted for any invention or discovery which is useful *solely* in the utilization of special nuclear material or atomic energy in an atomic weapon (emphasis added)."

The facts of the ultimate patenting of the genetically engineered oil eating bacteria would provide insights into certain legal steps involved in obtaining a patent [19]. The USPTO at first rejected the patent application for this oil eating bacteria stating that it did not fit *into* any of the four statutory categories. After the applicant legally challenged this rejection, the case worked

its way to the US Supreme Court, the final arbiter of all legal disputes including patent matters. In a close (5 - 4) decision, it overruled the USPTO and a lower court, with that now famous and often quoted line in patent law circles, "Anything under the sun that is made by man is patentable [20]." More details of this breakthrough case in the biotechnology area and the inventor can be found in this reference [21].

57.2.7 Classification of Utility Patents

Classification [22]: Utility patents are classified into the following categories: "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 therefor, . . . (emphasis added)."

57.2.7.1 Patent Classification Explained

Accordingly, the mouse trap being a machine, is eligible for a utitlity patent.

57.2.8 Types of Patents

Patents are broadly classified based on the subject matter of the invention, namely, utility, plants, and designs.

57.2.8.1 Patent Classification and Types Explained

Utility patents are the focus of this chapter and include the four (process, machine, manufacture and composition of matter) statutory categories mentioned in Sect. 57.2.7. Examples of each of these categories are a machine (e.g., the hypothetical mouse trap discussed), a manufacture (e.g., oil eating bacteria), a composition of matter (e.g., a new drug) and a process (e.g., a method to treat pain, discussed in Sect. 57.2.11.1).

57.2.9 Patent Eligibility Requirements

57.2.9.1 Overview of Patent Eligibility Requirements

In addition to being patent eligible (discussed in Sects. 57.2.6 and 57.2.9), the invention must also be new (referred to as the "novelty" requirement), be useful (referred to as the "utility requirement") and be non-obvious ("the non-obviousness" requirement. The Specification section of a patent application must also include sufficient details to enable (referred to as the "enablement" requirement) a person having ordinary skill in the art, a PHOSITA, (explained in Sects. 57.2.9.4 and 57.2.9.5) to make and use the invention ("practice the invention"). In the mouse trap example, Inventor A must provide enough details for a PHOSITA to make the mouse trap to meet the enablement requirement

Meeting the non-obviousness requirements is the biggest obstacle to obtaining a patent. As stated, these commonly used words, such as non-obviousness and enablement have distinct legal definitions (legal constructs) and might therefore be confusing to individuals new to patent law. Each of these requirements are discussed next in detail.

57.2.9.2 Novelty/Anticipation Defined

This requirement states (in pertinent part):

> A person shall be entitled to a patent *unless* the claimed invention was patented, described in *a* printed publication, or public use, on sale, or otherwise . . . available to the public before the effective filing date the claimed invention; . . . [23].

57.2.9.3 Novelty/Anticipation Explained

Note that all the exceptions stated recognize the concept of priority, i.e., being the first to invent, which is crucial in obtaining a patent. The USPTO has further clarified the meaning of novelty and anticipation:

A claimed invention [i.e., an application for a patent] may be rejected [by the USPTO] . . . when the invention is *anticipated* (or is "not novel") over *a disclosure* that is available as prior art (emphasis added). An invention (claim) to be rejected on the basis that it was anticipated, requires that ". . . *a* disclosure must *teach* [describe] every element required by the claim . . . [24]. The words, *a disclosure*, in the previous quote (reference 24) refers to a single reference, as was explained in the following court case: "A claim is anticipated only if each and every element as set forth in the claim is either found, either expressly or inherently described in a single prior art reference [25].

57.2.9.4 Non-obviousness Defined

From a conceptual perspective, non-obviousness may be distinguished from novelty (anticipation) in that this requirement takes a broader consideration of prior art (i.e., more than a single prior art disclosure, such as pertinent publications, patents, and disclosures can be combined to reject an invention (claim [26])):

1. A *patent for a claimed invention may not be obtained*,
2. notwithstanding that the claim is not identically disclosed as set forth in the [novelty section],
3. if the differences between the claimed invention and the prior art are such that the claimed invention as a whole,
4. would have been obvious before the effective filing date of the claimed invention
5. to *a person having ordinary skill in the art [PHOSITA],*
6. to which said claimed invention pertains.

57.2.9.5 Prior Art and PHOSITA Explained

A central question then is: How are novelty and non-obviousness determined in patent law? Two steps are involved in this process. The first step is to conduct a "prior art search" to identify *all* existing information relevant to a given invention. In fact, a patent examiner conducts such a search to evaluate the patentability of the invention described in a patent application. This is like a literature search conducted by scientists prior to starting a research project to determine critical issues relating to the proposed project, such as its originality, significance, experimental design, materials, and methods. In the second step, the determination of non-obviousness and novelty is done from the perspectives of a "person having ordinary skill in the art" (often referred to as a PHOSITA) after having evaluated the information gathered from the prior art search. The USPTO defines a PHOSITA as follows [27]:

The person of ordinary skill in the art is *a hypothetical person* who is presumed to have known the relevant art at the *time of the invention*. Factors that may be considered in determining the level of ordinary skill in the art may include: (a) "type of problems encountered in the art;" (b) "prior art solutions to those problems;" (c) "the rapidity with which innovations are made;" (d) "sophistication of the technology; and" (e) "educational level of active workers in the field. . . . In many cases, a PHOSITA will be able to fit the teachings [information] of multiple patents [and/or publications] together like pieces of a puzzle (emphasis added)."

Understandably, a PHOSITA is someone knowledgeable of the subject matter, like a reviewer of a scientific manuscript, who comments on its publication merits. In the mousetrap example, another mousetrap maker or those with formal training (such as a degree or apprenticeship) in mousetrap making would be a PHOSITA. In the biotechnology area, a PHOSITA is often someone with a Ph.D. degree in a related field, like molecular biology or biochemistry.

57.2.10 Enablement Defined

Enablement [28]: The patent application (specification section) should provide sufficient information for a PHOSITA to be able to make and use ("practice") the invention described in the patent application: "The specification shall contain a *written description* of the invention, and of the manner and process of making and using it, in

such full, clear, concise, and exact terms as to *enable* any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the *best mode* contemplated by the inventor of carrying out his invention. [29].

57.2.10.1 Comments on Enablement

The evolving nature of patent law in the US can be noted from the fact that on November 3, 2022, the US Supreme Court agreed to hear arguments to "fine tune" the proper standard to be used for enablement. (https://www.natlawreview.com/article/supreme-court-to-consider-enablement-requirement visited November 26, 2022).

57.2.11 Overview and Significance of Patent Claims

Claim(s) in a patent must clearly define the invention and are therefore an important, if not the most important, part of a patent application [30]. Further, the "specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter which the inventor . . . regards as the invention [31]. Claims define the boundaries of an invention (claim), formally referred to as its "metes and bounds". This is analogous to a real estate property (like a home) where the owner erects a fence to clearly mark its boundaries. Patent infringement occurs when somebody encroaches on the "metes and bounds" of an invention (patent claim). To continue the analogy, infringement of a patent is conceptually like trespassing on somebody's property.

57.2.11.1 Explanation of Claims

Selected claims from a patent relating to a pharmaceutical product to treat pain are shown next [32]. Consider each claim as a separate invention; note that the claims are related.

What is claimed is [numbers refer to individual claims]:

[Claim] 1. A *method* of effectively treating pain in humans *comprising* orally administering to a human on a once a-day basis an oral sustained release dosage form containing an *opioid analgesic or salt thereof* which upon administration provides a time to reach maximum plasma concentration (*Tmax*) of said opioid in *about 2 to about 10 h* and a maximum plasma concentration (C_{max}) which is *more than twice* the plasma level of said opioid at *about 24 h* after administration of the dosage form, and which dosage form provides effective treatment of pain for about 24 h or more after administration to the patient (emphasis added).

Claim 1 is called an *independent* claim because it is not dependent on any other claim. It is also a "broad" claim in that it does not state the specific opioid and includes all opioids used to treat pain. The patent title describes the invention as a whole: a method to treat pain over a period of 24 h in humans by administering a sustained release dosage form (could be a tablet, capsule, etc.) containing an opioid (specific opioid not mentioned) once a day. The claims also list other *metes and bounds* of the invention:

1. the time of maximum concentration (T_{max}) occurs between 2 and 10 h after administration, and
2. the maximum plasma concentration (C_{max}) observed following oral administration is more than twofold the concentration observed 24 h after dosing.

A competitor who markets a product that overlaps the details in Claim 1 above should expect an infringement lawsuit from the owner of this patent.

[Claim] 2. The method of Claim 1, wherein T_{max} occurs in about 2 to about 8 h after oral administration of said dosage form."

Claim 2 is a dependent claim because it depends on Claim 1. It claims everything in Claim 1, except that the T_{max} time range is narrower, occurring between 2–8 h, versus the 2–10 h in claim 1. It is a "defensive" strategy in claim drafting. If Claim 1 is rejected by the examiner for some reason (e.g., not supported by the

information presented in the Specification), the narrower range is more likely to be allowed by the patent examiner, and the inventor obtains a patent on the narrower range T_{max} range. Note that these ranges ("boundaries") are based on a clinical understanding of treating pain with opioids on the part of the inventor.

[Claim] 3. The method of Claim 1 wherein T_{max} occurs in about 6–8 h after oral administration of said dosage form.

[Claim] 3 further shortens the T_{max} interval.

1. The method of Claim 1 wherein that said opioid analgesic is morphine sulfate.

As explained, Claim 1 includes (claims) all opioid analgesics. However, claim 4 is narrower than Claim 1 in that it is directed at (claims) morphine sulfate, and has a greater chance be being allowed by the patent. (Remember, when one files a patent examiner application, the applicant is not sure which claims will be allowed by the patent examiner, like when an author submits a manuscript to a peer-reviewed journal). Therefore, the patent applicant makes all claims vital to the invention supported by the Specification.

57.2.12 Process for Obtaining a Patent (Patent Prosecution)

The first step usually is to file *a non-provisional* patent application with the USPTO disclosing the invention in great detail, as required by the agency. Drafting this application requires an in-depth knowledge of both, the scientific aspects of the invention, and the legal format and submission requirements. Understandably, it is a joint and challenging task for the inventor(s) and patent professionals, such as patent attorneys or agents. A detailed discussion of patent prosecution is beyond the scope of this introductory chapter on patent law. Instead, a short and modified outline of this process focused on scientific details is discussed below to generally introduce the reader to the application process; procedural formalities and legal requirements, such as the filing of specific forms and inventor oath or declaration, have been omitted to avoid confusion for a starting reader. Detailed instructions can be found in standard texts, such as that by Sheldon [33].

The non-provisional application should contain Specification and Drawings (if needed) sections [34]. The Specification section (abbreviated here to avoid confusion) should have the following technical and procedural details in the order shown below [35]:

(1) Title of the invention… (2) Cross-reference to related applications, [This can have implications for the effective filing date of the patent application] …, (7) Background of the invention, (8) Brief summary of the invention, (9) Brief description of the several views of the drawing, [if drawings are included], (10) Detailed description of the inventions, (11) A claim or claims…, and (13) Sequence Listing [for nucleotides and/or amino acid sequences, filed separately from the specifications].

Biomedical scientists would immediately recognize the similarity between the Specifications and Drawings sections of a patent application and a scientific manuscript prepared for publication in a peer-reviewed journal. As in a manuscript, the specification section includes experimental details, such as materials and methods used, results obtained, and conclusions relating to the invention. The Specification section ends with the claims.

57.2.12.1 Patent Application Review

The application is reviewed by USPTO experts (i.e., patent examiners) in the subject matter of the invention. This part is analogous to a peer review of a scientific manuscript or grant application. During the patent prosecution process, the inventor (or his agent, usually the patent attorney or agent) has limited opportunities, including a face to face to interview with the examiner, to respond to ("rebut") a patent examiner's in-writing ("office actions") criticisms ("rejections" and/or "objections") relating to the patent application. The difference between a rejection and an objection is explained below:

> "The refusal to grant claims because the subject matter is unpatentable is called a rejection; The term "rejected" is used by a patent examiner when the substance of the patent claims sought are deemed unallowable under U.S.C. 101, 102, 103 and/or 112. If the form of the claim (as distinguished from its substance is improper), an "objection" is made. An example of a matter of form as to which an objection is made is dependency of a claim on a previously rejected claim [36].

All rejections and objections by the examiner must be resolved prior to the granting ("allowance") of a patent. Final rejections by the USPTO can be challenged in the courts, as noted with the oil eating bacteria case [20].

57.2.13 Provisional Patent Application (PPA)

Briefly, a PPA is primarily for placeholder purposes, i.e., to establish a priority date for the invention [37]. It is like a non-provisional patent application, but a major difference is that a PPA application does not need to state any claims. It is important, however, that the Specification should support (provide data) the claims to be listed in a future non-provisional application, which must be filed within 12 months from the filing date of the PPA to benefit from its filing date priority. It automatically expires 12 months from the filing date, is not examined and cannot be extended.

57.3 Part II: Drug Patent Litigation (Applications of Patent Law Fundamentals)

57.3.1 Overview of Patent Litigation

In this part, litigation ("drug war" [38]) between generic and brand name (innovator) companies, where the patent owner (brand name company) lost, is used to provide a glimpse of how patent law concepts described in Part I are applied in the court. These cases mostly involve blockbuster drugs (annual sales of $1 billion or more) because they also generate considerable business and public interest. Brief summaries of each case are presented to explain the pertinent patent law principle involved in each of these cases. Legal citations are provided to allow the reader to pursue an in-depth reading of these cases, though it is not required to understand the information presented in this chapter. The legal basis for these cases is the Hatch-Waxman Act which is briefly described next.

57.3.2 The Hatch-Waxman Act [39]

This Act was passed in 1984 to primarily provide a pathway to market generic versions of patented drugs in the US. It has two major objectives aimed at balancing the interests of the stakeholders, namely, the brand name and generic drug companies, and the consumer (patient): (1) To encourage innovation by providing better patent protection to brand name drug companies, i.e., the development of new drugs, and (2) to foster competition in the pharmaceutical industry by providing a legal and regulatory pathway to market (hopefully, less expensive) generic versions of brand name drugs.

57.3.2.1 Hatch-Waxman Procedural Details

Under this Act, a new drug application (NDA) submitted to the FDA by an innovator (brand name) drug company for approval of its new drug must also include patent numbers and expiration dates of all patents that claims, either the drug (active ingredient and/or composition or formulation) or the method of use (i.e., indication). The FDA is *required* to list these patents in the FDA's "Orange" book, a commonly used abbreviation for its lengthy formal title, Approved Drug Products with Therapeutic Equivalence Evaluations. The Orange book can be easily found online at the FDA website (www. FDA.gov). This information serves as a public notification of any patent protection afforded a drug in the US.

When an amended new drug application (ANDA) is submitted to the FDA by a generic company for approval of a generic version of a patented drug, it must certify to one of the following:

1. the drug has not been patented,
2. patent on the drug has expired,
3. the generic version of the drug will not be marketed prior to the expiration of the patent(s) on the drug, or
4. the generic version of the drug will not infringe the patent(s) covering the drug or the patent(s) are invalid (i.e., patents listed in the Orange Book) This is commonly called a Paragraph IV certification based on the Roman numeral nomenclature used in the Hatch-Waxman Act.

The generic company must also notify the patent holder about its ANDA and explain why the *generic version will not infringe the patent (s) listed in the Orange Book* or why *these patent (s) is/are invalid*. This sets the stage for litigation.

FDA's role in patent matters with respect NDA and ANDA applications is ministerial, i.e., the agency must list the patents included in an NDA application. In addition, FDA approvals of NDA and ANDA applications are independent of patent issues. Patent issues between brand name and generic companies are settled in Federal courts.

57.3.3 Patent Litigation: Specific Cases

57.3.3.1 The Prilosec Case [40]: A Generic Company "designed around" a Dosage Form to Avoid Patent Infringement

Legal Background: For Kremers Urban Development Co. (KUDCo) to infringe Claim 1 of the '505 patent, its product must have all the components ("elements') cited in Claim 1 of the '505 patent listed below.

Case Details: Omeprazole is the active ingredient of the proprietary drug Prilosec® marketed by Astra Aktiebolag (Astra) and patent protected by US Patent No. 4,786,505 (the '505 patent) and US Patent No. 4853, 230 (the '230 patent). At the time of litigation (decided in 2002), it had an annual worldwide sale of $6 billion; US sales accounted for $4 billion. KUDCo., a small generic company, submitted its ANDA application to the FDA for approval of generic omeprazole with a Paragraph IV certification that its product would not infringe Astra's patents. Astra disagreed and filed a patent infringement lawsuit.

Claim 1 of the '505 patent became the deciding issue for Astra's infringement allegation, which reads as follows (in pertinent part):

> An oral pharmaceutical preparation *comprising*,
> a core region *comprising* an effective amount of a material selected from the group consisting of omeprazole plus an *alkaline reacting compound*, an alkaline omeprazole salt plus an alkaline reacting compound and an omeprazole salt alone; (emphasis added).
>
> As a procedural matter in general, Paragraph IV certification by a generic company and the counter arguments by the patent holder are decided in court by an evaluation of the pertinent patent claims.

The KUDCo. microtablet has three components: a core, a sub-coat and an enteric coat. It was found that the sub-coat and the enteric coat of this microtablet did not differ from that claimed in the '505 patent. But it does not have an alkaline reacting compound in its core like Astra's tablet. Therefore, the two tablets are different. Thus, the court ruled that KUDCo did not infringe Astra's patents and it could legally market generic versions of omeprazole, a big win for this small generic company at that time.

For those readers who are drug formulators, omeprazole is acid labile, and the addition of the alkaline reacting compound was likely to protect it during the tablet manufacturing process. KUDCo using newer technology designed around Prilosec®. The '505 patent was issued in 1988, more than a decade before this litigation. Though speculative, if the pharmaceutical scientists and patent attorneys at Astra had worked closely, they might have better seen this major weakness of the '505 patent and might

have reformulated their tablet without the alkaline reacting agent. Readers may recall from Part I that excluding others is the major right of a patentee.

For completeness's sake, three other generic companies, namely Andrx Pharmaceuticals, Cheminor Drugs and Genpharm, Inc. also tried to market their generic versions of Prilosec®. They failed to do so because their tablets were found to infringe Astra's patents.

57.3.3.2 The Prozac® Case (Double Patenting Invalidity) [41]

Legal Background: In lay terms, the law of double patenting prohibits issuing two patents for the same invention. Even common sense would support this prohibition because it would unfairly extend the life of a patent on a given invention. Legally, this is stated as:

> "[T]he extension of exclusive rights [patent protection] through claims in a later patent that are *not patently distinct* from claims in an earlier patent" (41). The *italicized* segment relates to the criteria for novelty and non-obviousness requirements discussed earlier.

Case Details: Fluoxetine is the active ingredient of Prozac®, Eli Lilly's proprietary blockbuster drug. It is used to treat depression and anxiety. Barr Laboratories submitted an ANDA in December 1995 for generic fluoxetine with Paragraph IV certification challenging the validity of Lilly's patents. In response, Lilly brought legal action alleging that Barr's ANDA application infringed its patents. Eli Lilly had two patents to protect Prozac®; US Patent No. 4,626,549 (the '549 patent, which issued on December 12, 1986) and the US Patent No 4, 590, 213 (the'213 patent, which issued on May 20, 1986). The court compared the following two critical claims listed below to determine if they were "patentably distinct":

> "A *method of blocking the uptake of serotonin by brain neurons in animals* comprising the administering to said animal of fluoxetine [claim 7, the '549 patent, the later patent']," and
>
> "A *method for treating anxiety in a human subject in need of such treatment* which comprises the administration to such human an effective amount of fluoxetine or norfluoxetine or pharmaceutically acceptable salts thereof [claim 1, the '213 patent, the earlier patent"]

These two claims are the same because the mechanism of action of fluoxetine is by blocking serotonin uptake in the brain [41] They are, therefore, not patentably distinct. Barr Laboratories won the case, giving it legal authority to market its generic version of Prozac®.

57.3.3.3 The Prometheus Case (Patentable Subject Matter, a "101" Issue) [42]

Legal Background: "[L]aws of nature, natural phenomena, and abstract ideas are not patentable" (e.g., $E = mC^2$) (42).

Case Details: Mayo Clinic (herein after Mayo) used diagnostic tests sold by Prometheus Laboratories (hereinafter Prometheus) based on the latter's two patents: U.S. No. 6,355,623 (the '623 patent), and 6,680,302 (the '302 patent) Mayo stated in 2004 that it planned to market its own version of a similar diagnostic test. Prometheus filed an infringement suit against Mayo.

Claim 1 of the '623 patent (vital to the case) states:

> A *method of optimizing therapeutic efficacy* for treatment of an immune-mediated gastrointestinal disorder, comprising: (a) administering a drug providing 6-thioguanine (6-TG) 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 8 × 10 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 8 × 10 red blood cells indicates a need to decrease the amount of said drug subsequently administered to said subject (emphasis added).

In pertinent part, the trial court concluded that claim 1 of the '623 patent, which identifies the therapeutic range for 6-TG, covered natural laws, and thus, the subject matter of the '623 patent was not patentable (invalid), and ruled in favor of Mayo. However, the appeals court reversed the trial on the issue of patentability and ruled that the '623 patent is valid, but Mayo's method infringed the patented method claim of Prometheus. On appeal by Mayo, the Supreme Court agreed to listen to arguments on the patentability of Claim 1 of the '623 patent. This Court, concurred with the lower (trial) court, and ruled the Prometheus patent invalid, stating [42]:

Anyone who wants to make use of these laws must first administer a thiopurine drug and measure the resulting metabolite concentrations, and so the combination amounts to nothing significantly more than an instruction to doctors to apply the applicable laws when treating their patients.

In other words, the stated invention (claim) is a fundamental law and, therefore, cannot be patented (a "101" issue). This decision shook up the diagnostic industry, with one author saying, "The new patent eligibility analysis provided in *Mayo* has narrowed the breadth of patent eligibility for diagnostic methods] [43].

57.3.3.4 The Bayer Case (Obvious to Try) [44]

Legal Background: When an invention is a result of solving a problem using methods that would have been obvious to a PHOSITA based on information in the prior art ("teachings"), then that invention fails to overcome the non-obviousness barrier and becomes patent ineligible. The Supreme Court had laid down the following standard for such situations in the KSR case [45]:

"When there is a design need or *market pressure* to solve a problem, and there are a finite number of identified, predictable solutions, a person of ordinary skill has a good reason to pursue the known options within his or her technical grasp. If this leads to the anticipated success, it is the product not of innovation but of ordinary skill and common sense. In that instance, the fact that a combination was obvious to try might show that it was obvious under §103 (emphasis added)."

Often patent decisions made in cases involving one technical/scientific discipline (subject matter) are applied to cases involving a different subject matter. Patent(s) in the KSR case dealt with automobiles (specifically, accelerator pedals) and this standard was applied to the Bayer drug case.

Case History: Bayer markets a patent protected drug Yasmin® [46], a female contraception drug. Barr, planning to market a generic version of this drug, filed its ANDA application along with a Paragraph IV certification that the claim central to the patent directed at Yasmin® is invalid. Bayer files suit alleging infringement. The outcome of the case depended on the validity of the Claim 1 (the invention in the '531 patent), which reads:

"A pharmaceutical composition comprising from about 2 mg to 4 mg of *micronized* drospirenone particles, about 0.01 mg to about 0.05 of 17α-ethynlestradiol, and one or more pharmaceutically acceptable carriers, the composition being in an oral dosage form exposed to the gastric environment upon dissolution and the composition being effective for oral contraception in a human female [marketed as Yasmin®] (emphasis added.)"

Bayer had solved a particular drug formulation problem relating to the drug drospirenone by using methods suggested in the prior art. Specifically, since the drug is poorly water soluble, Bayer scientists used micronized particles of the drug particles (see Claim 1 of the '531 patent) to improve the dissolution properties of Yasmin® (and hence its bioavailability or gastrointestinal absorption). The patent examiner, as might be expected, rejected this claim as obvious during patent prosecution based on prior art. In response to the rejection, Bayer countered by citing another

prior art publication that did not support ("teaches away" from) micronization, because the increased surface area resulting from micronization, could promote greater destruction. The examiner then allowed the claim and allowed the patent to issue. After a detailed examination of the science involved, the court sided with Barr, invalidating the '531 patent. The legal victory allowed Barr to market its generic version of Yasmin®.

57.4 Concluding Remarks

Legal complexities and nuances have been omitted in this chapter to promote an understanding of patent law fundamentals among the anticipated readership consisting of biomedical scientists. It is hoped that such understanding would encourage them to include the patentability of their research as one of the indices of innovative research. It is also hoped that the information provided here will promote more effective communication between biomedical scientists and patent attorneys and agents.

References

1. Everyday words such as comprising, consisting, novelty, anticipation, and obviousness are legal constructs in patent law
2. Personal Observations
3. Anon (2001) A convergence of science and law. National Academy Press, Washington, D.C.
4. Patent Law Basics For Scientists (So, you want to make money from your inventions?). https://youtu.be/LbdmqjjVU_0
5. Melethil S (2005) Patent issues in drug development: perspectives of a pharmaceutical scientist attorney. AAPS J 7(3):E723–E727
6. What is intellectual property? https://www.wipo.int/about-ip/en/
7. Miller AR, Davis MH (1990) Intellectual property: patents, trademarks and copyright, 2nd edn. West Publishing Co., St. Paul, MN
8. Legal humor: all answers to legal questions should begin with the phrase, *it depends*
9. Elon Musk, CEO of SpaceX does not believe in obtaining patents related to materials used to build the company's spaceships. https://www.cnbc.com/2022/09/21/why-elon-musk-says-patents-are-for-the-weak.html. Accessed 26 Nov 2022
10. Conception, Manual of Patent Examination Procedure (MPEP) 2138.04
11. Reduction to practice MPEP 2138.05
12. United States Constitution, Article I, §8, cl 8
13. The United States Constitution was ratified in 1788 and has been in force since 1789
14. 35 United States Code (U.S.C). 261 Ownership; assignment
15. The effective filing date may be earlier than the actual filing date if priority to a previous application is invoked
16. Burger, J, Dunn, JD, Johnson, MM, Karst, KR, Shear, WC. How drug life-cycle management patent strategies may impact formulary management. https://www.ajmc.com/view/a636-article. Accessed 12 Nov 2022
17. Patent subject matter eligibility MPEP 2106
18. Atomic Energy Act of 1954. Section 151(a) (42 U.S.C. 2181(a)
19. Microorganisms having multiple compatible degradative energy-generation plasmids and preparation thereof, US Patent No. 4,259,444. Inventors: Ananda M. Chakrabarthy
20. Diamond v. Chakrabarty, 447 U.S. 303 (1980)
21. Davey N, Rade RR (2021) Chakravarti, Anand Mohan 'Al' Chabrabarty 1938-2020. Nat Biotechnol 39:18
22. 35 U.S.C. § l01 – Inventions patentable
23. 35 U.S.C. § 102 - Conditions of patentability; novelty (paragraph (a)(1))
24. Anticipation – Application of 35 U.S.C. 102, MPEP 2131
25. Verdegaal Bros. v. Union Oil Co. of California 814 F. at 628, 631
26. 35 U.S.C. § 103 - Conditions of patentability; non-obviousness subject matter
27. Level of Ordinary Skill in the Art, MPEP 2141.03
28. 35 U.S.C 112 (a) Specification
29. This requirement is seldom a cause for rejection
30. "To coin a phrase, the name of the game is the claim." Giles Rich, then Chief Judge of the Federal Circuit (CAFC), The Extent of the Protection and Interpretation of Claims, American Perspectives, 21 Int'l Rev. Indus. Prop. & Copyright L., 497, 499 (1990)
31. 35 U.S.C 112 (b) [A] patent application specification shall conclude with one of more claims particularly pointing out and distinctly claiming the subject matter which the inventor . . . regards as the invention
32. Method for treating pain by administering 24-hour oral opioid formulations. US Patent No. 5, 672, 360, issued 9/30/1997. Inventors: Richard S. Sackler, Robert F Kalco and Paul Goldenhelm; Assignee: Purdue Pharma L.P
33. Sheldon JG (2022) How to write a patent application, 3rd edn. Patent Law Institute, New York
34. 37 Code of Federal Regulations (C.F.R.) 1.77 (a) Arrangement of application elements
35. 37 C.F.R.) 1.77(b) Arrangement of application elements

36. Quinn G. Understanding the patent process: rejection vs. objections. https://ipwatchdog.com/2016/04/02/patent-process-rejections-vs-objections/id=67761/. Accessed 3 Dec 2023
37. Provisional application for patent. https://www.uspto.gov/patents/basics/types-patent-applications/provisional-application-patent. Accessed 18 Nov 2022
38. McLean B. A Bitter Pill Prozac made Eli Lilly. Then along came a feisty generic maker called Barr Labs. Their battle gives new meaning to the term 'drug war'. https://money.cnn.com/magazines/fortune/fortune_archive/2001/08/13/308077/index.htm. Accessed 26 Nov 2022
39. Drug Price Competition and Patent Term Restoration Act of 1984, Public Law 98–417
40. Astra Aktiebolag v. Kremers Urban Development Co. 222 F. Supp2d 423 (S.D.N.Y. 2002) (defendants that lost are not included in the citation)
41. Eli Lilly & Co. v. Barr Laboratories, Inc., 222 F.3d 973 (2000) (US Court of Appeals, Federal Circuit)
42. Mayo Collaborative Servs. v. Prometheus Labs., Inc. 566 U.S. 66 (2012) (US Supreme Court case)
43. Dorn BR (2013) *Mayo v. Prometheus*: a year later. ACS Med Chem Lett 4(7):572–573
44. Bayer Pharma v. Barr Laboratories, (575 F3d. 1341) (2009) For a less legalistic and brief summary of the case, visit https://www.courtlistener.com/opinion/208257/bayer-schering-pharma-ag-v-barr-laboratories/. Accessed 5 Dec 2022
45. KSR Int'l Co. v. Teleflex Inc. 550 U.S. 398, 421 (2007) (US Supreme Court case)
46. Pharmaceutical composition for use as a contraceptive. US Patent No. 6,787, 531 (the '531 patent)