Patent Issues in Drug Development: Perspectives of a Pharmaceutical Scientist-Attorney

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ABSTRACT

The major purpose of this article is to emphasize the need for pharmaceutical scientists to have a better understanding of patent fundamentals. This need is illustrated by analyses of key scientific and legal issues that arose during recent patent infringement cases involving Prozac, Prilosec, and Buspar. Economic incentives for drug discovery and development clash with societal needs for low-cost pharmaceuticals in the United States and all over the world. The Hatch-Waxman Act of 1984 was enacted to promote public health by balancing the interests of brand name and generic companies. Patent protection, which provides a monopoly for a limited time, is aimed to provide such incentives. Creation of patents requires the interaction between scientists and lawyers, an endeavor made difficult by the differing intellectual spheres of their respective disciplines. Therefore, in the first place, a thorough understanding of patent fundamentals among pharmaceutical scientists will help them work more efficiently with patent attorneys. Second, it will enable them to appreciate the strengths and weaknesses of individual patents, which is critical in developing strategies amidst the ongoing patent tug-of-war between brand-name and generic companies.

KEYWORDS: Hatch-Waxman Act, Brand Drugs, Generic Drugs, Patent Strategies, Paragraph IV certification, ANDA, Prozac, Buspar, Prilosec

INTRODUCTION

> "When he was in the company of chemists, he spoke as a lawyer, and when with lawyers, he was a chemist. And when with the chemical patent lawyers, he didn't mind being just a fifty-fifty chemist-lawyer. They had his problem, too. It was like a group therapy. Patent lawyers had a profound sympathy for each other." (Charles L. Harness: *An Ornament to His Profession*)[1]
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> "[A patent] is simply an invitation to a law suit. . . . [I have] lost all faith in patents, judges and everything else relating to patents." (Thomas Alva Edison, owner of ~1000 United States patents)[2]

Patents on 65 drugs with weekly sales in the $2 to $10 million range expired in 2003.[3] Loss of market share is estimated to be ~40% within the first year after patent expiration. In addition, the pharmaceutical pipeline is "drying up" (ie, fewer new drugs are entering the market).[4] Therefore, when the patent on a drug expires, brand-name companies are increasingly seeking patent extension for the drug through innovative products such as clinically superior formulations of the drug (eg, new drug delivery systems, controlled release) and chemico-pharmacological modifications (ie, improvements in the pharmacokinetics or side effect profiles, single isomer drugs, prodrugs). Creating and protecting or attacking pharmaceutical patents requires close interaction between 2 groups of professionals, namely pharmaceutical scientists and lawyers. It also requires a good understanding of key concepts of each other's discipline. The division of labor can be summarized as "Scientists invent, Lawyers patent." However these 2 groups do not communicate effectively because ". . . there is a general lack of understanding of each culture, [and] these interactions often lead to a cognitive friction that is both disturbing and costly to society."[5] Analysis of patent infringement cases involving 3 "blockbuster" (having annual sales of a $1 billion or more) drugs (*infra*) from 2000 to 2002 supports this statement. These examples were selected to introduce pharmaceutical scientists to the certain central scientific and patent questions that arose during litigation of these drugs and that received much attention in legal, industrial, and public press circles. It is hoped that this discussion will also initiate serious efforts to promote interdisciplinary educational programs in the area of pharmaceutical sciences and patent law. It is also hoped that training of future pharmaceutical scientists will include an effective dose of patent fundamentals.

THE HATCH-WAXMAN ACT

The Drug Price Competition and Patent Restoration Act of 1984 (popularly called the Hatch-Waxman Act, "Act") was an attempt to resolve 2 major issues: (1) regulatory delays in marketing of pharmaceutical products faced by innovator (also called pioneer or research) drug companies and (2) difficulties generic drug companies had at that time in marketing generic versions of pioneer products following expiration of pertinent patent(s).[6,7] In practical terms, this Act made the

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following 3 important provisions: (1) it provided for the extension of the term of one existing patent for innovator drugs; (2) it made provisions for the marketing of generic versions of patented drugs on the day after patent expiration; and (3) it provided opportunities to challenge the validity of patents issued to innovator drug companies.

Of relevance to this discussion is the patent listing requirements for innovator companies and the opportunities for generic companies to challenge the validity of the listed patents. Briefly, the Act requires that the innovator drug company submit patent information with respect to its new drug application (NDA). The United States Food and Drug Administration (FDA) then lists this information in the so-called "Orange Book" (Approved Drug Products with Therapeutic Equivalence Evaluations). It is important to note that the agency has a purely ministerial role and does not have the authority to examine the propriety of the listed patents. This matter is decided by the courts. If the generic company complains to the FDA about improper patent listing by the innovator, the agency refers this inquiry to the innovator but takes no action to "delist" such patents.

A company intending to market a generic version of a listed drug must certify one of the following regarding the patents listed in connection with the innovator's NDA: (I) it has not been patented; (II) the applicable patent has expired; (III) the patent will expire on a given date and that the generic version will not be marketed before that date; or (IV) the listed patent is not infringed or invalid. Certification under the (IV) certification (called paragraph IV certification) is the most complicated of the 4 certifications. The generic company is also required to notify the innovator about the abbreviated NDA (ANDA) filing and explain the reasons why it believes the generic version will not infringe the listed patent or the listed patent is invalid. Upon notification, the innovator company has 45 days to file an infringement suit; the Act permits such action by the patentee though in reality no infringement has taken place. If such a suit is filed, the FDA withholds the approval of ANDA for 30 mo or till the case is decided. The outcome of the case will dictate further FDA actions. For example, if the generic product is found not to infringe ("does not read," in patent law terminology) on the patented claims, the ANDA is approved.

Patent Components: Claims and Description

A brief explanation of the 2 pertinent and important components of a patent, namely, claims and description of the invention, are presented to promote understanding of the cases to be discussed. The reader is referred to the easily readable (for scientists) text by Pressman on the patenting process[8]; a text published by Aspen Press is recommended for those who wish a more in-depth legal analysis of patent issues.[9] Claims define the "metes and bounds" of a patent, analogous to a fence that marks the boundaries of real property. The description of the invention, where the details of the invention including supporting data are included, should "enable" a person with "ordinary skills in the art" to make the claimed invention. In an infringement case, one major effort is to study the claims to ascertain what is precisely claimed. Note that while patents are issued by United States Patent and Trademark Office (USPTO), infringement issues are dealt with in the courts.

Pharmacological Issues - The Prozac Case: Double Patenting

In plain language, the term "double patenting" means that one cannot obtain 2 patents for the same invention. Stated more formally, double patenting prohibits the issuance of "more than one patent that claims the same or substantially the same invention to the same inventorship entity or a common assignee of several inventorship entities."[10]

The facts of this case, *Lilly v Barr*,[11,12] are as follows: Barr Laboratories Inc ("Barr") filed an ANDA in December 1995, along with a paragraph IV certification under the Hatch-Waxman Act, seeking approval from the FDA to market fluoxetine (the active ingredient of Prozac, marketed by Eli Lilly and Co, "Lilly") to treat depression. Lilly then filed a suit alleging that Barr's ANDA application infringed claim 7 of Lilly's 4 626 549 patent (the "549" patent). Barr argued, *inter alia,* that this claim was invalid for double patenting. After several legal maneuvers at the trial and appeal courts, the issue that was finally examined was whether claim 1 of 4 590 213 (the "213" patent) issued previously to Lilly covered the same invention as that in claim 7 of the "549" patent, which had expired in April 1994.

A double-patenting analysis by the court, in pertinent part, determines if the differences between the 2 claims are "patently distinct." If they are not distinct, then the later claim cannot be allowed. Claim 7 of the "549" patent essentially reads: A method of blocking the uptake of serotonin by brain neurons in animals comprising the administering to said animal of fluoxetine. Claim 1 of the "213" patent essentially reads: A method of treating anxiety in a human subject in need of such treatment, which comprises administering to said human an effective amount of fluoxetine.

Testimony provided by scientific experts from both Eli Lilly and Barr agreed that administration of serotonin results in blocking neural serotonin uptake. Based on this testimony, the court stated that "serotonin uptake inhibition is a natural biological activity [...an inherent property...] that occurs when fluoxetine hydrochloride is administered to an animal . . . such as a human, for any purpose, including treating of anxiety."[12] Therefore, the court concluded that "no patentable distinction exists between administering fluoxetine

hydrochloride for treatment of anxiety [claim 1 of "213" patent] and the inhibition of serotonin uptake administration of fluoxetine hydrochloride [claim 7 of the "549" patent]."[12] In other words, the "549" patent was invalid for reasons of double-patenting. In this connection, it is interesting to note that the suggested (see description sections) oral doses (1–50 mg/dose given from 1–4 times a day with a total daily dosage of 1–200 mg/day/human) for the claimed compounds including fluoxetine to inhibit serotonin reuptake (claim 7 of the "549" patent) overlaps with that (20–80 mg/day) for treating anxiety (claim 5 of the "213" patent). This ruling allowed for the marketing of generic fluoxetine. The direct economic impact to Lilly can be easily calculated from the fact that the "549" patent was scheduled to expire in December of 2003. On the other hand, from Barr's point of view, it could have filed their ANDA at the end of April 1994, when the 4 018 895 patent issued to Lilly, which claimed the use of fluoxetine to treat depression, expired.

This author speculates that had Lilly recognized the inherent weaknesses of their later patents it might have pursued other patent extension strategies such as developing newer formulations. It appears that the patent team did not fully appreciate the subtleties of the term "patentably distinct." The 2 "method of use claims," though apparently different on paper (claim 1 of the "213" patent is to treat anxiety and claim 7 of the "549" patent is to block serotonin uptake), are essentially the same. It is interesting to consider the following hypothetical situation. Assume that serotonin reuptake could be quantified in humans and each therapeutic indication (eg, anxiety, depression) requires a specific degree of reuptake inhibition (ie, dose–response data). Patent claims then could have been written with different doses for treating anxiety and depression by fluoxetine. Most likely, such claims would be "patentably distinct."

Formulation Issues - The Prilosec Case: Designing Around Patents

In simple terms, patent law allows one to evade infringement by a designing a product that has fewer components (elements) than the patented product. This case provides insights into how a formulation scientist can play a more active role in patent protection

This infringement arose when several generic companies, namely, Andrx Pharmaceutical Inc ("Andrx"), Genpharm Inc ("Genpharm"), Cheminor Drugs Ltd, Reddy-Cheminor Inc, and Scheien Pharmaceuticals Inc (collectively "Cheminor") and Kremers Urban Development Co and Schwarz Pharma Inc (collectively "KUDCo") submitted ANDAs to market generic versions of the highly successful Prilosec (active ingredient: omeprazole) marketed by the Astra Aktiebolag, Aktiebolahet Hassle, KBI Inc, Astrazeneca LP, Astra Pharmaceuticals LP, Astra Merck Enterprises Inc, and Astra Merck Inc (collectively Astra).[13,14] These companies also provided paragraph IV (Hatch-Waxman Act) certification that each of their generic versions would not infringe the 2 patents listed by Astra, namely, patents 4 786 505 (the "505" patent) and 4 853 230 (the "230" patent). The trial court[13] found, that except for KUDCo, all other parties had infringed the Astra patents. This discussion will focus on the KUDCo portion of the decision because it is more related to the objectives of this article.

The central question for the trial court[13] was "whether the KUDCo formulations contain an ARC [Alkaline Reacting Compound]."[13] Note that omeprazole is an acid labile drug, and Astra used a buffer (ARC) to protect it from gastric acidity. The pertinent "505" patent claims (modified for simplicity) read as follows:

Claim 1: An oral pharmaceutical preparation comprising

1. 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 alkaline omeprazole salt alone,
2. an inert subcoating, which is soluble or rapidly disintegrating in water disposed on said core-region, said subcoating comprising one or more layers of materials selected from among tablet excipients and polymeric film-form compounds, and
3. an outer layer disposed on said subcoating comprising an enteric coating.

Like the Prilosec product, the KUDCo tablet had 3 components: (A) a core, (B) a subcoat, and (C) an enteric coat. The court concluded that the subcoat and the enteric coat of the KUDCo microtablet did not differ from the "505" patent, which appears reasonable even on the limited details presented here. So, the case turned to a comparison of the "core" in the 2 products.

The word "comprising" in claim 1 has legal significance; such claims are called "open-ended." In pertinent part, it means the holder (patentee) of such a claim (eg, with 3 elements A, B, and C) is protected from products containing the same (or additional) elements. It does not however protect the patentee from a product with a combination containing any 2 of the claimed elements (eg, A and B, or A and C). Applying this rule, a product containing omeprazole without an alkaline-reacting compound will not infringe claim 1. The core of the KUDCo tablet contained micronized and unmicronized omeprazole, hydroxymethyl methylcellulose, crospovidone, and glycerol behenate. The important point is that there was no ARC; such a product would not infringe Prilosec, as the court ruled. On appeal, the court upheld the trial court decision commenting that

"Astra would infer an ARC in the core [of the KUDCo product]. This court disagrees because the claims plainly require an ARC (emphasis added)."[14]

Proactive patent protection strategies could have been developed for Prilosec based on the fundamental right of a patentee to prevent others from "practicing your invention" (ie, copying your formulation, in this situation). The technology that went into creation of the "230" and "505" patents was relatively old, since they were issued in April 1989, and November 1988, respectively. So, one formulation strategy would have been to patent new formulations using newer or different technologies. The need for ARC in Prilosec was to prevent/minimize gastric degradation; KUDCo solved that problem without the use of an ARC. In this connection, patent holders, such as Astra in this case, will usually have an advantage over generic companies, since patentees have greater knowledge of the chemistry and pharmacology of the drug and often have greater resources. The developmental costs associated with patent protection of this commercially successful product should be cost-effective since United States sales of Prilosec were $4 billion in 2000.[15] The negative economic effect of this court decision can be easily calculated by noting that the earliest the "230" and "505" patents would have expired was in 2006 and 2005.

Teachers of drug delivery and formulation courses are urged to study the discussion of scientific and technical issues presented in this lengthy (~200 pages) decision[13] and include them in their courses; the assistance of an attorney familiar with patent law is recommended. This additional education will enable scientists to develop a clear understanding of technical issues as seen through the prism of a courtroom, where the precise meaning of words are often the bone of contention in patent infringement cases. For example, the court learns the meaning of terms important in this case such as "core," "core region," "alkaline-reacting compound," "effective amount," "subcoating," "inert," "pH-buffering," and "micro-environment," unless clearly defined in the specification, through the testimony of scientists, dictionaries, and prosecution history. For the "scientist" side of this author, this discussion emphasized the need to clearly understand the inherent assumptions and "unknowns" of various scientific terms used in a patent. For example, the lengthy discussion of the precise meaning of "subcoat," a common word in pharmaceutical technology, is quite fascinating and educational.[13]

Active Metabolite and Prodrug Issues: The Buspar Case

The facts of this infringement case[16] are as follows: Bristol Myers Squibb Co (BMS) had listed 2 patents with respect to their anti-anxiolytic drug buspirone (Buspar) NDA. Patent number 4 182 763 (the "763" patent), in which BMS claimed buspirone as an antianxiety drug, expired on July 21, 2000. In anticipation, 3 companies, Danbury Pharmacol Inc and Watson Pharmaceuticals Inc (collectively "Watson"), and Mylan Pharmaceuticals Inc, Mylan Laboratories Inc, and Mylan Technologies Inc (collectively "Mylan") had obtained tentative FDA approval to market generic buspirone on July 22, 2000, the day after the expiration of the "763" patent. However, BMS obtained a second patent (the "365" patent), which involved an active metabolite of buspirone, on July 21,2000, 11 hours before the expiration of the "763" patent (patent processing by the USPTO can be expedited by making the application "special"); BMS then hand-delivered copies of this patent to the FDA and requested that it be listed in the "Orange Book" with a declaration that the new patent covers, among other things, a method of using buspirone for all approved uses. As required by law, the FDA then informed Watson and Mylan that their ANDAs were incomplete and needed certification that their generic versions of buspirone will not infringe upon the "365" patent. These companies responded by making the required (paragraph IV) certification under the Hatch-Waxman Act; BMS then brought an infringement suit against them.

The "365" patent had only one claim:

A process for ameliorating an undesirable anxiety state in a mammal comprising systemic administration to the mammal of an effective but nontoxic anxiolytic dose of 6-hydroxy-8-[4-[-(2-pyrimidinyl)-piperazinyl]-butyl]-8-azaspiro[4,5]-7,9-dione or a pharmaceutically acceptable acid addition salt or hydrate thereof (emphasis added).[16]

In addition, the following statement can be found in the description section of the "365" patent:

Systemic administration may also be realized by a second method of achieving effective anxiolytic blood levels of the [6-hydroxy metabolite] which is to be orally administered by a precursor form of the [6-hydroxy] metabolite].[16]

The later ("365") patent was based on the discovery that one of the metabolites of buspirone (the 6-hydroxy metabolite) had pharmacological activity. Based on its relatively high blood concentrations and activity data, the anxiolytic activity of buspirone was attributed to the 6-hydroxy metabolite. One central issue in this case was the meaning of the term "systemic." It is instructive to note that patent law allows a patentee to be his own "lexicographer" and use special definitions of words, as long as they are clearly stated in the "patent specification or file history."[15] In the absence of such special definitions, as in this case, words are "presumed to be used and to be intended to be understood, as they would be by persons experienced in the field of the invention." This is commonly accomplished through expert testimony and/or referring to appropriate dictionaries. The court used Stedman's Medical Dictionary (26th edition), which defines "systemic" as "relating to a system; specifically somatic, relating to the entire organism as distinguished from any of its individual parts."[16]

While agreeing that the term "systemic" has a common and well-defined meaning, BMS argued that the term "systemic administration" in the claim in the "365" patent means systemic administration of either buspirone or the 6-hydroxy metabolite. The court also reviews patent prosecution (ie, process of getting a patent) history of the "365" patent. Based on statements made by BMS, the court stated that "the prosecution history leaves no doubt that the "365" patent does not cover the use of buspirone."[16]

The meaning of the term "dose" also came under scrutiny. The court correctly stated that "the idea of a 'dose' as a quantity that is 'taken at one time' has a clear meaning in reference to an externally-measured amount of a substance that is to be ingested or administered in the body all at once, but would have no precise meaning if used to refer to *in vivo* levels in the blood stream . . ." Since quantitative metabolism data were included in the "365" patent ("[the 6-OH metabolite] is the second-most abundant metabolite. . . in human urine) in their patent application, it would be interesting to know if attempts were made during trial to estimate the "dose" of the 6-OH metabolite based on quantitative metabolite data. No such information was found in the case details.[16]

Pharmaceutical scientists, especially pharmacokineticists, recognize that in-vivo kinetics of the 6-hydroxy metabolite resulting from oral administration of buspirone are different from that following oral dosing of the metabolite. Close scrutiny of the claims by a pharmacokineticist with an understanding of patent claims is likely to have resulted in the inclusion of more precise meanings for the 2 terms, namely, "systemic administration" and "dose" in the patent specification. However, this is a "balancing" act since clear definitions preclude the introduction of other meanings at a later date.

Economic issues, as with any industry, will clearly dominate the debate in the patent litigation area. For example, Prilosec had worldwide sales of $6.26 billion in 2000.[15] It was reported that "AstraZenexa will receive an extra $5.6 million from Prilosec sales every day it can prolong this trial."[17] In addition, more than half of today's blockbuster drugs (annual sales of at least $1 billion) are expected to lose patent protection by 2008,[18] and the entry of new drug entities into the market has slowed down in recent years.[4] The patent battles are therefore likely to intensify. Consumers and their "friends" support policies that improve availability of low-cost pharmaceuticals that prolong life and improve quality of life here in the United States and abroad. But, many times, in the heat of emotion, an obvious and simple fact is forgotten: no "generics" are possible without first having "brand-name" (almost always patented) drugs. An economic analysis, examining the consequences of removing all patent protection, concluded that every $1 saved today by providing easy access to generics will in the future cost the consumer $3 in enhanced health-care costs owing to lack of incentives for pharmaceutical companies to get into the high-risk, high-cost business of drug discovery and development.[19] The daunting task of all stakeholders is the continued development of patent policies that fairly balance the interests of competing interests of generic and brand-name companies. The Hatch-Waxman Act was a small step in that direction.[20] Pharmaceutical scientists knowledgeable of intellectual property issues can play a key role in hastening the development of such policies.

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