Patent Strategy for Medical Products

By Tamsen Valoir and Linda J. Paradiso

Many medical products are regulated by the Food and Drug Administration (FDA) and cannot enter the marketplace without prior FDA approval. Similarly, a product may not be able to safely enter the marketplace if there are dominant patents covering that product. Therefore, both the FDA laws and the patent laws provide barriers to market entry. This article discusses FDA basics and gives the reader three issues to consider in designing a patent strategy that complements the FDA rules and provides the best market protection for medical products.

FDA Basics

The FDA provides significant barriers to market entry because drugs, biologics, and certain medical devices cannot be placed on the market without prior FDA approval, and they must be proven to be safe and effective before approval will be given. Furthermore, before a company can even begin human clinical trials, permission is also required in the form of an investigational new drug application (IND), which is usually supported by animal testing results. When the clinical trials are completed, a new drug application (NDA) is filed for a new small molecule drug, and the equivalent application for most biologics is the biologic license application (BLA). The NDA and BLA applications are voluminous, containing all of the manufacturing and stability testing data, proposed labeling, as well as all of the clinical and animal data establishing that the drug or biologic is both safe and effective for its proposed use.

Medical devices present a wide range of risk, ranging from little or no risk posed by bandages to a high degree of risk posed by pacemakers. Therefore, there are three levels of medical device regulation—Class I to III—and the regulations generally increase with the classification.

The pre-market notification application (PMA) is roughly analogous to the NDA or BLA and requires complete manufacturing information, proposed labeling, and all animal testing and clinical trial results. Further, an investigational device exception (IDE) is required before clinical trials can begin and is analogous to the IND.

The 501(k) application is for less risky devices, and the application needs only establish that the device is "substantially equivalent" to a predicate device. Clinical data may or may not be required to support a 510(k), depending on the device.

It is important to remember that PMA products are said to be "approved," whereas 501(k) products are "cleared." The FDA takes these distinctions seriously, and more than one company has received warning letters for using incorrect terminology.

Generally speaking, Class III devices are subject to PMA approval, Class II are subject to 510(k) clearance, and Class I devices are exempt from the approval requirements, although they are still regulated. However, there are many instances in which the classification and the type of approval process do not coincide because many Class III devices were already on the market when the law was enacted and thus are cleared under a 510(k) application.

In addition to the pre-market approval requirements for many healthcare products, there are certain instances when the FDA will withhold approval of certain drugs and biologics for a period of time, and to understand why we must first understand the 1984 amendments to our food and drug laws.

In 1984 Congress enacted the Drug Price Competition and Patent Term Restoration Act, more commonly known as the Hatch-Waxman Act.[1] The purpose of Hatch-Waxman was to strike a balance between brand-name and generic drug manufacturers by providing incentives to produce new drugs, while offering quick FDA approval for low-cost generic drugs.

Tamsen Valoir, PhD, is a partner in the Intellectual Property firm of Boulware & Valoir, practicing primarily in intellectual property and regulatory work in the area of life sciences. **Linda J. Paradiso**, DVM, MBA, is president and CEO of Linda Paradiso, Inc., a biopharmaceutical consulting firm. The authors may be contacted at *tvaloir@boulwarevaloir.com* and *linda_paradiso@yahoo.com*, respectively.

Prior to the Hatch-Waxman Act, generic drugs had to undergo the *same* rigorous safety and effectiveness testing that new drugs underwent. Hatch-Waxman created a faster approval process for generic drugs, allowing generic manufacturers to file an Abbreviated New Drug Application (ANDA) that is supported by showing only that the generic drug is "the same" as or "bioequivalent" to an already approved drug.[2] This process is somewhat analogous to the 510(k) clearance process, which was already in existence when the Hatch-Waxman Act was passed into law.

Hatch-Waxman also provides a safe harbor against patent infringement, expressly overruling the 1984 *Roche v. Bolar* decision holding that clinical tests conducted by generic manufacturers before patent expiration were infringing.[3] As a result of *Roche v. Bolar*, market exclusivity was extended beyond the patent term, because the generic manufacturer could not even *begin* FDA testing until the patent expired. Hatch-Waxman changed this, allowing bioequivalence testing to be performed *prior* to patent expiration. As a consequence, the FDA can now approve generic drug applications immediately on patent expiration, and generics can reach the market more quickly.

In exchange for allowing easier and faster generic drug approvals, the Hatch-Waxman Act establishes patent term restorations for innovator drugs.[4] Because new drug patents usually issue long before the drug receives FDA approval, part of the patent term is spent performing clinical trials and that portion of exclusive market time is lost. Patent term restorations are intended to offset the term used up during the approval process.

There are some limits to the restoration; it cannot exceed five years, nor can the period between product approval and patent expiration exceed 14 years.[5] The patentee must act with "due diligence" throughout the regulatory period. That is, the patentee must not delay FDA review, and anyone can challenge a restoration on that basis.[6]

The Hatch-Waxman Act also provides a dispute resolution procedure. The ANDA rules offer four routes for marketing of generic drugs.[7] Three routes–called Paragraph I, Paragraph II, and Paragraph III certifications–apply to ANDA filings that do not involve challenges to patents. Through these routes, multiple generics can enter the market at the same time, creating a very competitive market.

The fourth route is called a Paragraph IV certification.[8] It applies when patent protection has not yet expired and the generic drug maker claims *either* that the patent is invalid *or* that its product does not infringe the patent. Paragraph IV certifications are desirable, because the *first* to file one becomes eligible for six months of market exclusivity, during which time the FDA will not approve any other generic drug application. In this way, the Hatch-Waxman Act encourages challenges to patents, thus bringing cheaper generic drugs to the market even more quickly. However, the rules also provide that a Paragraph IV certification is an infringing act,[9] allowing the patentee to sue the generic manufacturer for patent infringement and obtaining an *automatic* 30-month stay on FDA approval.[10]

In exchange for allowing easier and faster generic drug approvals, the Hatch-Waxman Act establishes patent term restorations for innovator drugs.

In addition to the abbreviated generic drug approval procedures and Paragraph IV certification scheme, the FDA provides five years of data exclusivity when a new drug application is filed on a new chemical entity that has not been previously approved for any drug use. During the five-year period, the FDA will not approve a second application covering the same chemical entity unless the applicant provides its *own* safety and efficacy data. Since generating safety and efficacy data is so expensive, this has the practical effect of excluding generic applicants for the five years, even if there are no blocking patents.

There are also FDA exclusivities applicable for new uses or new formulations of a drug, pediatric studies, orphan drugs, and biologics, but there is no equivalent exclusivity period for medical devices. Table 1 lists these exclusivities.

The final piece of the FDA puzzle is the generic drug therapeutic equivalence rating system. Basically, any rating that starts with an "A" is either bioequivalent or the FDA considers bioequivalence to be irrelevant. "AB" means bioequivalence has been studied and demonstrated, and it is *not* a lower rating than "AA." The ratings AA, AN, AO, and AP do not require bioequivalence studies because the FDA believes them to be unnecessary.

Table 1: Summary of FDA exclusivity periods			
Type	**Requirements**	**Period**	**Cumulative**
New Chemical Entity	Chemical entities never previously approved by FDA either alone or in combination with other drugs. Bars 505(b)(2)[11] and ANDA applications for five years where applicant has not provided its own data or authorized data.[12] Can be reduced to four years if ANDA application contains a ¶ IV certification. 12 years data exclusivity and four year submission exclusivity for biologics.[13]	Five years 12 years for biologics	No
New or Modified Indication	Changes in an approved drug product that affect its active ingredient(s), strength, dosage form, route of administration, or conditions of use may be granted exclusivity if clinical investigations were essential to approval of the application containing those changes. Bars 505(b)(2) or ANDA applications where applicant has not provided own data or authorized data.[14] Not available for biologics.	Three years	No
Pediatric	FDA must request pediatric data, can be two pediatric term extensions, scope of protection same as that to which the six months is appended.[15]	Six months	Yes
Orphan Drug	For a rare disease affecting fewer than 200,000, bars any other FDA applications for that same active pharmaceutical ingredient (API) for treatment of the same disease for seven years, unless the holder cannot manufacture sufficient quantities to meet the needs or the holder gives consent.[16]	Seven years	No
First ANDA	First to file ANDA for generic drug with ¶ IV certification challenging a patent. Bars subsequent ANDA applications until six months after first marketing or favorable patent decision.[17] If patentee files infringement suit, first ANDA is stayed for 30 months.	Six months for ANDA applicant 30 months for patentee	No
Animal Product	Includes both new animal drugs and new uses.[18] Can be reduced to four years if ANDA application contains a ¶ IV certification.[19]	Five years for new animal drug; three years for new use	No

In contrast, drug products for which actual or potential bioequivalence problems have not been resolved begin with "B." Usually, the problem is with specific dosage forms or formulations, rather than with the active ingredients. These are designated BC, BD, BE, BN, BP, BR, BS, BT, BX, or B*. For example, an ointment would probably get a B rating if the name brand drug was formulated as a cream.

In order for a pharmacist to exchange a name brand drug with a generic, it must have an A rating; the pharmacist cannot automatically switch to a B rated drug in most states. Therefore, A ratings are highly desirable, and indeed, an A rated generic drug can take 50-80 percent of a name brand drug market within a year of market entry, whereas B rated generics usually gain much less market share.

Following is a discussion of a few of the issues to consider in formulating a patent strategy that complements these FDA principles.

Patent Term

Managing patent term is very important in the healthcare industry, where the patent term is

usually the most valuable in its last days. However, any product with a long market life should consider managing patent term as part of its strategy.

There are many methods of managing patent term, ranging from beginning with a provisional filing to patent term adjustments to patent term restoration to follow-on filings.

Provisional filings are very commonly used for medical products as a way of extending the term to 21 years, since the provisional year saves the priority date but does not count against term. The free year also gives the inventors additional time to develop the invention, and the application can be updated at the one-year date. This is the only time a patent application can be changed, except for minor typographical corrections and changes to the claims, so inventors should take this opportunity to update the application.

Patent term adjustments are awarded by the patent office to account for any lost term due to patent office delays that extend the period of obtaining a patent beyond three years. Checking the awarded patent term adjustment (PTA) should be standard practice, and it is advisable to petition for a longer PTA where warranted. Your patent counsel can elaborate on how to qualify for additional term adjustments.

Patent term restorations are available for *any* product for which market term was lost while awaiting FDA approval before marketing. Thus, drugs, biologics, medical devices, and combination products can *all* obtain an FDA term restoration. Applications are made to the FDA very shortly after the product is approved, and about half of the lost time can be awarded. Only a single patent can be extended, and the extension applies only to the actual FDA approved product, not the full scope of the patent claims.

Drug companies are very rigorous about applying for restorations within the required time period after approval. However, many medical device companies do not file for restorations and thus can be leaving valuable patent term on the table. Do not make this mistake, and consider filing for a restoration if the FDA delayed your product from entering the market.

Follow-on Patents

Most drug and medical device companies plan ahead and make judicious use of *follow-on*, but un-related patent filings to manage their patent term. These might also be called second-generation patents. "Un-related" in this context means that the follow-on application does *not* claim priority to the original filing. For example, a class of lead drug candidate molecules might be claimed in an initial patent application, but specific members can be claimed in later un-related applications as the pharmaceutical data for such members becomes available. Because the follow-on patent does not claim priority to the original foundational application, its term will run from the new filing date.

Most drug and medical device companies plan ahead and make judicious use of *follow-on*, but un-related patent filings to manage their patent term.

Follow-on patents can claim the ultimate product in a variety of ways. For example, different (and perhaps more efficacious) forms of a drug may be patented. As one example, the hemi-hydrate form of Paxil for treating depression is much more stable than the prior art anhydrate form, providing a significant commercial advantage. Similarly, a more convenient dosage form, such as once a day versus three times daily, can provide significant commercial advantage and is worth patenting. Another useful follow-on patent may be the process by which a patented molecule is made. This is particularly useful for biological products that are difficult to make by non-recombinant methods. A follow-on patent for a medical device might claim commercially significant features of a product or claim features of the final FDA approved or cleared prototype that were not disclosed or even thought of in the original application. For either drug or devices, follow-on patents can also include new indications for using the drug or medical device.

An important point to realize is that, because of the way that patent protection and FDA barriers intermesh, a follow-on patent can be quite narrow and *still* provide significant protection.

For example, a patent covering the method of formulating a very hydrophobic drug as a cream has great value as a market barrier for a few reasons. First, creams have more market appeal because ointments are greasy. Second, in order to obtain

an A rating, the generic competitor would have to formulate that drug as a cream. Third, because the formulation patent can validly be listed in the Orange Book, the generic competitor must wait until the patent expires if it wants an A rating (or successfully challenge the validity of the patent). Thus, the final cream formulation patent can be filed years after the drug was discovered and be quite narrow in scope, but because in most cases only A ratings are worth pursuing, the patent will effectively extend market exclusivity for the drug even though the formulation patent could easily be designed around. Similarly, narrow patents on particular dosage forms, conjugated forms of the drug, particular hydrates or isomers, and the like can all be quite valuable even though they too could easily be designed around.

Broad patent applications in the biotechnology industry also face significant hurdles to issuance because the industry is fairly new and the art is less predictable than, say, the mechanical engineering arts.

A variety of techniques are used to address the possibility of the first patent application being prior art to the second follow-on application. First, the follow-on application may be filed *before* publication of the first application—that is within 18 months of the first filing date. This removes the reference as prior art from most countries, and a statutory exemption can remove it as prior art in the United States.

Alternatively, researchers can plan ahead to collect head-to-head comparative data, showing that the new species or formulation has unexpected advantages over what was disclosed in the original application. Thus, a particular species of drug with a particular advantage might be patentable, even though the genus of compounds was disclosed earlier.

This is commonly done in the pharmaceutical industry where the foundational patent might claim a broad genus of chemicals that were identified as being lead candidates for drug development, but a follow-on patent claims the actual chemical species that was finally identified as having the optimal pharmacokinetic and toxicity profile. To obtain such a patent it is helpful to directly compare the pharmacokinetic and toxicity of the final drug against those members of the genus that were originally disclosed and to not disclose the final drug species in the original application.

We do not mean to suggest that the best material can be intentionally held back for follow-on filings, as this may present problems of patent unenforceability for failure to disclose the best mode. However, research and patents can be timed so that a patent application is filed without having best mode problems and yet without creating prior art problems for the follow-on applications.

Consider planning your research program to accommodate your patent strategy and draft each patent application with follow-on filings in mind.

Patent Scope

In the past, it was common practice to draft patent applications very broadly, trying to capture all possible applications and variations of a technology in the first application. Even if certain applications of the invention were inadequately described or enabled, one could always file a continuation-in-part (CIP) application (in the United States only) with additional data to support the less well described and enabled applications.

Claims were also drafted very broadly and then narrowed only when necessary to overcome the examiner's rejections. In a sense, patent practitioners tried for the broadest claim scope possible and let the search results determine the ultimate scope of the claims.

However, two changes in the law have made these broad drafting strategies less effective. First, in 1995 patent term was changed to 20 years from filing, rather than 17 years from issue. Thus, although patent applications can still be supplemented with CIP applications, patent term is all the while ticking away, and the CIP patent will issue with less patent term.[20] This is particularly detrimental in the pharmaceutical industry, where the last days of patent term can be worth one million dollars a day for a blockbuster drug.

Second, US law underwent a change in 2002 when the Supreme Court changed the doctrine of equivalents in *Festo Corp. v. Shoketsu Kinzoku Kogyo Kabushiki Co.*[21] The doctrine of equivalents imposes liability for patent infringement when the difference between the claims as written and the accused

product is so slight that it would be unfair not to impose liability. Thus, liability is found even though the claims are not literally infringed.

Since the *Festo* case, patent practitioners are reluctant to make narrowing changes to patent claims because the patentee is *presumed to have surrendered* all equivalents between the claims as originally presented to the PTO and the claims as finally allowed. Thus, it is more common post-*Festo* practice to draft an application with knowledge of the closest prior art and to draft the claims sufficiently narrowly so as to distinguish the invention over this art. In this way, the patent practitioner hopes the claims will be allowed as is, avoiding the detrimental application of any presumptions in later patent litigation.

In addition to these legal changes, broad patent applications in the biotechnology industry also face significant hurdles to issuance because the industry is fairly new and the art is less predictable than, say, the mechanical engineering arts. Thus, the patent office will typically reject the claims arguing that the broad scope of the claim is not fully enabled or described.

Furthermore, in the healthcare industry one should draft an application while cognizant of the follow-on patent plans. Drafting may intentionally be of narrower scope and both research and patents carefully timed to allow for such follow-on patents.

In summary, there are several reasons for drafting a patent application that is as broad as can reasonably be said to be enabled, but nonetheless does *not* read on the prior art *and* leaves room for planned follow-on patents.

Conclusion

These three issues are by no means the only issues to consider in formulating a patent strategy, but they do highlight those issues that are unique to medical products and illustrate that a patent strategy can differ for medical products, but together with FDA barriers, can still provide effective market protection.

Notes

1. Drug Price Competition and Patent Term Restoration Act of 1984 (hereinafter Hatch-Waxman Act), Pub. L. No. 98-417, 98 Stat. 1585 (1984) (codified as amended at 21 U.S.C. § 355 (2003) and 35 U.S.C. § 271(d)–(h) (2003)). *See also* FDA Generic Drugs Final Rule Questions and Answers summarizing the rule changes, found at *www.fda.gov/oc/initiatives/generics/qna.html.*
2. 21 U.S.C. § 355(j). The ANDA process is somewhat analogous to the 510(k) process. There is now also a follow-on process for biologics, but since biologics usually involve living organisms, the application is more complicated and both manufacturing data and clinical trials are still required. 42 U.S.C. § 262(i)(2)(A)-(B).
3. Roche Prods. v. Bolar Pharmaceutical Co., 733 F.2d 858 (Fed. Cir. 1984).
4. 35 U.S.C. § 156. Patent expiry dates for each drug are available in the Orange Book, which is searchable online at *http://www.accessdata.fda.gov/scripts/cder/ob/default.cfm.*
5. 35 U.S.C. § 156.
6. 35 U.S.C. § 156.
7. 21 U.S.C. § 355(j)(2)(A)(vii).
8. 21 U.S.C. § 355(j)(2)(A)(vii)(IV).
9. 35 U.S.C. § 271(e)(2).
10. 21 U.S.C. § 355 (j)(5)(B)(iii).
11. *See* 21 U.S.C. 355(b), commonly known as a 505(b)(2) application, named after the section numbers in the original act. A 505(b)(2) application is also known as a "new indication" application, allowing for a variation on an existing drug label.
12. 21 U.S.C. § 355.
13. 42 U.S.C. § 262(k)(7)(A)-(B).
14. 21 U.S.C. 355(c)(3)(E)(iii).
15. 21 U.S.C. 355(A).
16. 21 U.S.C. § 360AA-EE, especially 360CC. *See http://www.fda.gov/orphan/designat/index.htm* for additional details.
17. 21 U.S.C. § 355(j)(5)(B)(iv).
18. 21 U.S.C. § 360B. *See http://www.fda.gov/cvm/cvmm50.html* for additional details.
19. Referring to the Hatch-Waxman Act codified at 21 U.S.C. § 155, a ¶ IV certification is when the Abbreviated New Drug Application (ANDA) applicant certifies that either the patent is not infringed or it is invalid.
20. CIP applications are not even available in most countries outside the United States.
21. Festo Corp. v. Shoketsu Kinzoku Kogyo Kabushiki Co., 535 U.S. 722 (2002).