Repurposing and Enforcement during Patent Term Extensions for Pharma Products

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Imagine your client is developing a new use for the active ingredient in an existing pharmaceutical product. The active ingredient is a patented small molecule, formulated for oral delivery in treating gout. It has been approved by the FDA and on the market for years. Your client believes the same active ingredient, if formulated for topical ophthalmic use, would be useful in treating glaucoma. And because the active ingredient is already well characterized, she believes it would take her just a few years to develop the topical ophthalmic formulation and obtain approval for the new use. The patent for the active ingredient expires a few years from now, but it also received a patent term extension of five years. Your client asks you whether the extended-term patent will be enforceable against her repurposed use for the active ingredient once she has filed for FDA approval. She has read the statute and believes that a patent term extension of a compound patent is only enforceable against the same or similar products for the existing use because 35 U.S.C. § 156(b)(1) essentially says enforcement rights of such an extended patent are “limited to any use approved for the product.” However, the statute does not give clear guidance on patent enforcement during the extended period, creating uncertainty in the law. This article will briefly review the litigation history and evolution of § 156 as it pertains to eligibility for patent term extension and patent enforcement during the extension period.

Background
In 1984, the Hatch-Waxman Act opened the door to a healthy and now-dominant generic drug market in the United States. In exchange for allowing generic pharmaceutical companies to perform the required testing while a patent is still in force (so they can sell the generic drug the day the patent expires), the innovator companies can get the term of their patents covering that drug extended to make up for some of the patent time lost due to the required regulatory testing for approval before commercialization of the patented product is allowed. Because typical development time for a new drug may be 10 or more years—half or more of the 20-year life of a U.S. patent—patent term extension is an important aspect of encouraging innovation and investment in new drugs.
Patents covering pharmaceuticals or medical devices\(^1\) can have their term extended up to five years in the United States (officially called “patent term restoration” in the United States and “supplementary protection certificate” in Europe).\(^2\) Similar patent term extensions are available in other major countries, including Australia and Japan, though not Canada due to its policy of favoring generics over innovative drugs.

Pharma patent term extensions in the United States are calculated by taking half the time between (1) a company’s initial FDA filing for approval to test the drug in humans (“investigational new drug,” or “IND,” application), and (2) its filing with the FDA—after extensive testing in humans—for approval of the drug (“new drug application,” or “NDA”) or biologic (“biologics license application,” or “BLA”), plus (3) all the time taken by the FDA to approve the drug after the NDA or BLA filing, up to a total of five years.\(^3\) This extension adds to any patent term *adjustment* provided for specified delays by the U.S. Patent and Trademark Office (USPTO) during prosecution of the patent.\(^4\)

There are a number of substantive and procedural requirements for obtaining patent term extension. Important substantive requirements include that the patent to be extended must be in force when the application for extension is filed and cannot have previously been extended, and the approval must be the *first* commercial approval of the drug.\(^5\) In other words, if the drug’s active ingredient has previously been approved as a small molecule or biologic, a patent covering a completely different use or formulation of the same active ingredient is *not* entitled to an extension.

Another important enforcement limitation for patent term extensions in the United States is that the extension applies only if “the product has been subject to a regulatory review period before its commercial marketing or use.”\(^6\) As a result, patent term extensions do not extend the patent term for all purposes. Instead, the patent term is extended *only* for FDA-approved products that were subject to a regulatory review period before commercial marketing or use. The scope of this limitation and its effect on repurposing will be explored in more detail later on in this article.

The FDA takes the position that any subsequently approved drug product containing the same “active moiety”\(^7\) as the approved drug product is also entitled to the same patent term extension, which the FDA lists in its Orange Book.\(^8\)

Thus, patent term extensions for pharma patents in the United States are allowed only for those patents that cover the first approval of a drug product. In addition, an application for the extension must be filed within 60 days of the approval date.\(^9\) If you miss that date by even one day, only a private act by Congress can help. As a result, only one patent may be extended for an approved drug product (including biologics), and the remaining patent life after extension cannot exceed 14 years.\(^10\)

There is an exception for veterinary drugs. A patent for a new veterinary drug may be extended even if the same drug was previously approved for human use.\(^11\) U.S. courts have also expanded the scope of patent term extensions, e.g., by confirming eligibility for patent term extensions for new patents covering new approved drug products containing esters or isomers of drug compounds that have already been approved.\(^12\)
In Europe, there are similar rules for obtaining pharma patent term extensions, but in addition, under the recent 2012 *Neurim* European Court case, one can now obtain a patent term extension for a patent covering a new use of an old, previously approved drug. However, that type of patent term extension is not permitted under current U.S. law.

A related, perhaps unanswered, question is whether a patent covering a new drug that has had a patent term extension for a specified approved use may be enforced against a third-party approval of a completely different *new use* of that same new drug. That is, can the patent owner of an extended-term patent covering an active compound that has been approved for a specific use enforce that patent during the patent term extension against a third party that has obtained an approval of the *same* active compound for an entirely *new* use?

This is an important issue for the current wave of repurposed drug products employing the strategy of taking older, approved active compounds and finding new therapeutic uses for them. Because these active compounds have been tested in humans and detailed pharmacology and toxicity information is available about them, it is much easier and faster to obtain marketing approvals for new uses.

**Eligibility for Patent Term Extension**

Since enactment of the Hatch-Waxman Act, courts have been called upon to interpret what products are eligible for patent term extension under § 156. Initially, courts interpreted the term “approved products” under § 156 to only include pharmaceutical products. Subsequently, courts expanded their interpretations to include class II and class III medical devices. More recently, courts have interpreted approved products on an ingredient-by-ingredient basis, concluding that a product comprised of more than one active ingredient would be eligible for patent term extension only if at least one of the active ingredients has never been previously approved for marketing under the relevant provision of the Food Drug and Cosmetic Act (FDCA). For example, a new approved product having two or more active compounds where both active compounds have previously been subject to regulatory review under the FDCA and approved for marketing is not eligible for patent term extension under § 156.

Courts have also been called upon to decide what the term “claims” means in the preamble of § 156, which states in part:

> The term of a patent which *claims a product*, a method of using a product, or a method of manufacturing a product shall be extended in accordance with this section from the original expiration date of the patent, which shall include any patent term adjustment granted under section 154(b).]

In *Hoechst-Roussel Pharmaceuticals, Inc. v. Lehman*, Hoechst sought to extend a patent that claimed a metabolite of its approved product Cognex® but not the approved product itself. Hoechst argued that its patent would be infringed by a person using the approved product because once inside the body it is metabolized into the active ingredient claimed in its patent. The Federal Circuit, in upholding the USPTO’s patent term extension denial, ruled that the word *claims* in § 156 does not mean *infringed* and thus the patent did not claim or “cover” the approved product.
The courts have also construed the term “active moiety” versus “active ingredient.” Under the “active moiety” construction, a patent claiming the acid, salt, or ester of an approved product could only be extended under § 156 if it were the first approved use of the “active moiety.” For example, in *Glaxo Operations UK Ltd. v. Quigg*, the USPTO decided that the previously approved and marketed cefuroxime salts barred extending a patent claiming the new Glaxo approved product Ceftin, which was made using the ester form of the drug cefuroxime axetil. Thus, the USPTO interpreted “active ingredient” to mean active chemical moiety. However, the Federal Circuit did not agree and ruled that the plain meaning of the statute defines “product” as the “active ingredient” and any “salt” or “ester” of the “active ingredient.” That is, “active ingredient” means the actual active ingredient, not the active moiety, and the previously approved products were salts, not esters, of cefuroxime.

The Federal Court addressed the issue of “active ingredient” versus “active moiety” claim construction when determining eligibility for patent term extension again in *PhotoCure ASA v. Dudas*. In *PhotoCure*, the USPTO had refused to extend PhotoCure’s patent claiming methyl aminolevulinate hydrochloride (MAL HCL) in view of the prior approval of the parent acid aminolevulinic acid (ALA). The USPTO decided that both compounds shared the same “active moiety” and thus MAL HCL was a previously approved active ingredient that was ineligible for patent term extension. The lower court overturned the USPTO, and the Federal Circuit affirmed the lower court, stating that the USPTO’s “active moiety” interpretation of the term product was legally incorrect and that the plain meaning of “active ingredient” should be used to assess eligibility for patent term extension.

The final case to be considered when construing claims for patent extension eligibility is *Ortho-McNeil Pharmaceutical, Inc. v. Lupin Pharmaceuticals, Inc.* In *Ortho-McNeil*, the USPTO granted a patent term extension for levofloxacin, an enantiomer of a previously approved racemic mixture ofloxacin. Lupin challenged the patent term extension in federal court arguing that grant was improper based on the FDA’s prior approval of the active ingredient which is found in the racemic mixture ofloxacin. The lower court and Federal Circuit ruled that there is a longstanding practice of considering an enantiomer distinct from its racemic mixture and held that the enantiomer was the “product” for purposes of § 156.

**Patent Enforcement in a Litigation Setting**

Up to this point, we have addressed how the USPTO and federal courts construe claims when determining eligibility for patent term extension. While this background case law is informative and provides a lens from which to view how claims may be construed during litigation, it is not dispositive.

The first case to actually deal squarely with patent enforcement in the post-extension period is *Pfizer, Inc. v. Dr. Reddy’s Laboratories, Ltd.* In *Pfizer*, the Federal Circuit ruled contrary to the holding in *Glaxo* when it applied the “active moiety” interpretation of “active ingredient” in finding that the Pfizer patent claiming amlodipine besylate was infringed by Dr. Reddy’s amlodipine maleate product because the therapeutically active agent was amlodipine in vivo regardless of what salt was administered.

The *Pfizer* court was construing the claim in a litigation setting and was asked to determine whether Dr. Reddy’s product (amlodipine maleate) infringed the Pfizer patent during the extended period (the Pfizer patent was extended based on the approval of amlodipine besylate). The originally granted claims of
the Pfizer patent were broad enough to read on any amlodipine acid addition salt. Therefore, the Federal Circuit construed the claims of the Pfizer patent during the extended period to read with the same breadth the claims would be given in the pre-extended period. Thus, the Pfizer case is an example of the Federal Circuit merely construing a claim in the post-extension period exactly as the claim would have been construed during the same patent’s natural life span.

The Pfizer decision is consistent, at least in part, with the court’s ruling in Edwards Lifesciences AG v. CoreValve, Inc. In Edwards, the court considered the issue of a claimed use versus a claimed product.

Edwards was the assignee of U.S. Patent No. 5,411,552 (‘552 patent), which discloses techniques for “implanting prosthetic valves into patients’ aortic annuluses by means of a catheter.” The ‘552 patent expired in 2012, but the USPTO subsequently extended its term to 2014.

In 2008 (during the natural life of the ‘552 patent), Edwards sued CoreValve Inc. and Medtronic CoreValve LLC (collectively, Medtronic) for infringement of various patents, including the ‘552 patent. The jury returned a verdict in favor of Edwards for literal infringement of the ‘552 patent. After the verdict, Edwards brought a motion for a preliminary injunction to enjoin Medtronic from continuing to infringe the ‘552 patent. In disputing Edwards’s claims for meeting the preliminary injunction criteria, Medtronic argued that “Edwards’ rights are limited to copies of the [Edwards device] and do not cover any devices . . . that are not copies of the [Edwards device].” The district court disagreed.

The court held that under § 156, “the language of the statute makes clear that the rights secured by the extension of the ‘552 patent are limited by the use of the [Edwards device], not just copies of the [Edwards device].” In supporting its position, the court cited Ortho-McNeil, stating that rights under § 156(b) “apply to uses of the product,” and Boehringer Ingelheim International GmbH v. Barr Laboratories, Inc., stating “that the plaintiff had the right to exclude the use then under regulatory review.”

Ultimately, the court held “[s]ince Edwards has outright prevailed in the litigation regarding the ‘552 patent and the appeals process is over, the court concludes that Edwards has more than demonstrated a likelihood of success on the merits.” The district court granted the preliminary injunction in part.

The Edwards case demonstrates that the courts will not limit the claim of a patent extended under § 156 to exact copies, or generic versions, of the product. It appears that the Edwards decision stands for claim construction as to the “product” being broader than just mere generic copies. However, the courts may limit the enforcement of a patent to the approved use as they did in Genetics Institute, LLC v. Novartis Vaccines and Diagnostics, Inc.

In Genetics, the court was asked to consider whether a patent term extension under § 156 applied to the patent as a whole or only specific claims during the extension period. The patent in suit was U.S. Patent No. 4,868,112 (‘112 patent), which claims various compositions and methods involving the Factor VIII peptide. The ‘112 patent was set to expire in 2006 but received a patent term extension to 2010.
Genetics filed suit against Novartis Vaccines and Diagnostics Inc. in 2008 (after the original expiration date of the '112 patent) to determine priority between the '112 patent and patents where Novartis was the assignee. In an appeal before the Federal Circuit, Novartis argued, in part, that the district court did not have jurisdiction for the interference proceeding because the patent term extension only applied to certain claims identified in the patent term extension application, and that the nonidentified claims had expired as of the original patent expiration date.

The Federal Circuit disagreed. The court held that patent term extension under § 156 applies to the patent as a whole and not to specific claims. Particularly, the court found the “plain language” of § 156 refutes patent term extension on a claim-by-claim basis; this statutory language includes § 156(a), which specifies “[t]he term of a patent,” and § 156(b), which includes rights “derived from any patent the term of which is extended under this section.” As such, “for patents that claim a product, the rights in the extended term are ‘limited to any use approved for the product.’”

The court further held that § 156(a) and (b) “set forth the legal effect of the patent term extension itself.” The court supported its interpretation that patent term extensions under § 156 have limitations in their effect by citing congressional intent from a 1982 House Report: “[I]f a chemical is subjected to regulatory review for new drugs uses, but also marketed for other commercial uses, the patent term extension would apply only to the new drug uses for which regulatory review was required.” Thus, the court held “[a] patent as a whole is extended even though its effect may be limited to certain of its claims.” This holding clearly suggests that the Federal Circuit believes that there was congressional intent to limit patent enforcement during the § 156 extension period to approved uses for the product (the active ingredient) and not all uses.

**Conclusion and Discussion**

At the outset, we presented the perhaps unanswered question as to whether a compound patent covering a new drug that has had a patent term extension for a specified approved use may be enforced against a third party approval of a completely different new use of that same new drug. That is, can the patent owner of an extended patent covering a compound that has been approved for a specific use enforce the patent during the patent term extension against a third party that has obtained an approval of the same compound for an entirely new use?

We have examined two aspects of claim construction related to patent term extensions under § 156 in an effort to answer this question. First we reviewed administrative claim construction when determining patent term extension eligibility. Over the years, the courts and the USPTO have expanded the type of patents eligible for § 156 extension from pharmaceuticals to include medical devices. The first approved use limitation has moved from the more limiting “active moiety” standard the USPTO initially employed to a broader “active ingredient” standard. Now patents claiming the salts, acids, or esters of a pharmaceutical compound are each separately extendable, and previously approved racemic mixtures no longer restrict extending a patent claiming the purified enantiomers.
In the litigation context, courts have ruled that medical device patents extended by § 156 are not limited to exact copies of the approved device. Patent enforceability must focus on the approved use. This “approved use limitation” has also found itself into the pharmaceutical patent arena as well in Genetics, in which the Federal Circuit also found support for the use limitation in the legislative history of the Hatch-Waxman Act.

In conclusion, while it is far from crystal clear, and we look forward to more definitive court decisions on point, it is reasonable to infer from the plain meaning of the statute and the legal history discussed herein that the courts are more likely to limit claims in a patent extended under § 156 based on “approved use” than structure of the device or active ingredient. That is, in the future the courts are more likely than not to rule that repurposing an old drug for a new use would not be covered during the extension period by a compound patent approved for a different use.

Endnotes

1. For patent term extensions for medical devices, see Michelle A. Sherwood, Medical Devices and Patent Term Extension under the Hatch-Waxman Act, 2 LANDSLIDE, no. 6, July/Aug. 2010, at 38.
2. 35 U.S.C. § 156.
3. Id. § 156(a)(3).
4. Id. § 154(b).
5. Id. § 156(a)(1), (2), (5).
6. Id. § 156(a)(4).
7. “Active moiety” refers to the portion of the drug molecule that is biologically active. Different salts, esters, and hydrates of the same active drug contain the same active moiety.
8. The FDA Orange Book is the FDA publication Approved Drug Products with Therapeutic Equivalence Evaluations, available online at http://www.fda.gov/cder/ob.
10. Id. § 156(c)(3).
11. Id. § 156(a)(5).
12. See Ortho-McNeil Pharm., Inc. v. Lupin Pharm., Inc., 603 F.3d 1377 (Fed. Cir. 2010); PhotoCure ASA v. Kappos, 603 F.3d 1372 (Fed. Cir. 2010).
17. 35 U.S.C. § 156(a) (emphasis added).
18. 109 F.3d 756 (Fed. Cir. 1997).
19. Id. at 758–59.
20. 894 F.2d 392 (Fed. Cir. 1990).
21. Id. at 395 (quoting 35 U.S.C. § 156(f)(2)).
23. 603 F.3d 1377 (Fed. Cir. 2010).
24. 359 F.3d 1361 (Fed. Cir. 2004).
27. Id. at *4–5.
28. Edwards anticipated the patent term would be extended again to March 22, 2016. Id. at *5.
29. Id. at *1–2.
30. Id. at *9.
31. Id. at *10.
32. 592 F.3d 1340, 1349 (Fed. Cir. 2010).
34. Id. at *11.
35. Id. at *42.
36. 655 F.3d 1291 (Fed. Cir. 2011).
37. Id. at 1295.
38. Id. at 1297.
39. Id. at 1300–01.
40. Id. at 1301 (emphasis added).
41. Id.
43. Genetics, 655 F.3d at 1301 (emphasis added).