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EXPERT ANALYSIS

Biologics and the Right to Exclude During the Patent Term Extension Period

By Eric Steffe, Esq., and Marsha Rose Gillentine, Ph.D., *Sterne, Kessler, Goldstein & Fox,* and Helene Carlson, Esq., *Meso Scale Diagnostics*

Although the Biologics Price Competition and Innovation Act of 2009 provides 12 years of market exclusivity for a reference biological product, patents can provide an additional barrier to entry for a biosimilar product. Therefore, PTE applications remain important in the BPCIA era.

But the scope of the right to exclude during the PTE period as applied to a biological product is unclear.

There is potential for confusion in the current statutory and regulatory framework as applied to biological products.

The U.S. Supreme Court's Jan. 13 decision to resolve the biological drug dispute in two consolidated cases brings this issue to the forefront. *Amgen Inc. v. Sandoz Inc.,* No. 15-1195, *cert. granted,* 2017 WL 125662; *Sandoz Inc. v. Amgen Inc.,* No. 15-1039, *cert. granted,* 2017 WL 125661 (U.S. Jan. 13, 2017).

WHY PTES ARE IMPORTANT FOR BIOLOGICAL DRUG PRODUCTS

The 20-year-from-filing patent term for U.S. patents would seemingly provide additional exclusivity beyond the BPCIA-provided 12 years. But in practice, developing a patent portfolio around a biological product requires significant strategic forethought and coordination.

Initial patent filings directed to a newly discovered biologic, which may be the easiest to obtain and the most resistant to an invalidity attack, are often submitted well before clinical trials begin.

Clinical trials can be time-intensive to complete. Without a PTE, the 20-year term of a composition patent might not provide additional exclusivity beyond the 12 years provided by the BPCIA. Obtaining certain patent rights might take more than eight years from the initial filing.

Additionally, obtaining these "clinical trial patents" with significantly longer patent terms can be difficult due to several legal developments over the last 10 years.

Evolving law pertaining to obviousness,[1] written description,[2] obviousness-type double patenting[3] and statutory subject matter[4] has created barriers to patenting these types of inventions.[5]

Often, an additional obstacle to generating a strong patent portfolio for a biological product is "self-generated prior art" — public disclosures made by the biological drug sponsor itself, such as news releases, poster presentations, peer-reviewed publications and patent applications.

While each successfully met milestone in a clinical trial provides an opportunity to publish the results, a rush to do so can result in premature patent filings that may not adequately protect the ultimate commercial product.

Attracting investors and collaborators through such public disclosures, while at the same time obtaining valuable downstream patents, is a difficult balancing act even for the most sophisticated company.

Often, an additional obstacle to generating a strong patent portfolio for a biological product is "self-generated prior art" — public disclosures made by the biological drug sponsor itself.

The PTE provides a significant benefit that counters the practical difficulties associated with developing a comprehensive patent portfolio around a biological product.

A patent-holding company may obtain a PTE of up to five years provided the period does not exceed 14 years following approval of the biological product by the Food and Drug Administration, pursuant to Section 156(c)(3) of the Patent Act, 35 U.S.C.A. § 156(c)(3).

For certain products, if not for the PTE period, very little of a patent's term would exist beyond the 12-year data exclusivity period.

OVERVIEW OF THE PTE PROVISION

Congress instituted the PTE benefit for new drug and medicinal products to restore a portion of patent term lost to the premarket federal regulatory approval process.[6]

Under the PTE provision, the patentee may extend the term of one patent with at least one claim encompassing an FDA-approved active ingredient based on regulatory delay.

Congress' purpose in implementing this provision was to incentivize pharmaceutical companies to develop and market products requiring a lengthy premarket approval process, including biological products.

But the patent is deemed to encompass only approved uses of the approved active ingredient during the extended term.

So even if the claims encompass a broad genus of active ingredients, the patent is construed during the extended period to encompass only the approved product's active ingredient and only approved uses of that active ingredient, according to Section 156(b)(1) of the Patent Act, 35 U.S.C.A. § 156(b)(1), which says:

> [T]he rights derived from any patent the term of which is extended under this section shall during the period during which the term of the patent is extended — in the case of a patent which claims a product, be limited to any use approved for the product.

The statute defines "product" as a "drug product," which is "the active ingredient of a new drug, antibiotic drug, or human biological product ... including any salt or ester of the active ingredient."

Therefore, Congress contemplated the extended patent to be enforceable against a generic drug product containing some statutorily defined structural differences.

Because a PTE can be applied only to one patent, a patentee must carefully consider which patent to extend.

For example, any extension to which the patent owner is entitled for FDA regulatory delay is added to the patent expiration date, including any patent term adjustment, so the 14-years-from-approval cap must be considered.

Additionally, the PTE applies even if a terminal disclaimer must be filed to obviate an obviousness-type double patenting challenge, but any necessary statutory disclaimer must be filed before the reference patent expires.[7]

Further, due to the way the PTE is calculated, a patent owner may receive even more additional term if the terminal disclaimer is filed before the PTE application.

Therefore, when determining which patent to extend, the patent owner must carefully assess every patent in a biological product's portfolio and not just the patent with the earliest expiration date.

PTE PROVISION AND BIOLOGICAL PRODUCTS

In the context of small-molecule products, an extended patent is enforceable against proposed generic products containing the same active ingredient as the approved product or salts or esters of that active ingredient.

The FDA has interpreted the term "active ingredient" as "active moiety," which the agency has defined as "the molecule or ion, excluding those appended portions of the molecule that cause the drug to be an ester, salt ... responsible for the physiological or pharmacological action of the drug substance."[8]

In other words, the extended patent will be considered to cover "minor" structural variants of the approved product's active ingredient during the extended term, so long as the allegedly infringing product contains the same active moiety.

However, the PTE statute does not include language governing what constitutes minor structural variations in the context of a biological product.

And in enacting the BPCIA, Congress did not amend the PTE statute to clarify whether the right to exclude extends to so-called minor structural variants of an approved biological product's active ingredient during the extension period.

Biological products are much more complicated than small molecules.

It is unlikely a biosimilar product will be completely identical structurally to the reference biological product.

For example, a biosimilar product may differ in primary amino acid sequence; modification to amino acids, e.g., glycosylation and phosphorylation; and higher order structure, e.g., protein folding and protein-protein interactions.

In fact, FDA guidance on establishing biosimilarity to a reference biological product allows for minor structural differences as long as those differences are not clinically meaningful.

For example, the FDA stated in its "guidance for industry" that while "[i]t is expected that the expression construct for a proposed product will encode the same primary amino acid sequence as its reference product ... minor modifications such as N- or C-terminal truncations that are not expected to change the product performance may be justified and should be explained by the sponsor."

Further, as the market and technology advance, the FDA may be willing to approve a biosimilar product containing minor amino acid substitutions as compared to the biological product, so long as the biosimilar applicant is able to prove the biosimilar product is "highly similar."

Because the PTE statute is silent as to what so-called minor modifications fall within the right to exclude during the extension period in the context of a biological product, it is possible a court will apply the active moiety test derived from the small molecule arena.

But what is the active moiety of a biological product? Is the active moiety the primary amino acid sequence?

If it is, a biosimilar applicant may be able to argue it is not subject to the extended patent term if its biosimilar product has a different primary amino acid sequence even though its biosimilar product is otherwise "highly similar" to the reference biological product both in terms of higher order structure and function.

Indeed, two biological products having identical primary amino acid sequences could nonetheless have different safety/efficacy profiles due to differences in higher order structure.

Also, two biological products having different primary amino acid sequences could have the same safety or efficacy profile because they have the same higher order structures.

Thus, rather than the primary amino acid sequence, should the active moiety instead be considered a biological product's higher order structure?

While analytical techniques may allow the higher order structure of some biological products to be characterized, the higher order structure of other biological products may be difficult to determine.

Because a patent term extension can be applied only to one patent, a patentee must carefully consider which patent to extend.

Biological products are much more complicated than small molecules.

Additionally, the FDA acknowledges "current analytical methodology may not be able to detect all relevant structural and functional differences between two products."

Therefore, if the two biosimilar products must have the same higher order structure as the reference biological product, technology limitations may make it difficult for a court to determine whether a biosimilar product is the same active moiety subject to the PTE provision.

An alternative to looking at the primary amino acid sequence or higher order structure is to apply the same "totality of the evidence" approach the FDA uses in determining whether a proposed biosimilar product is "highly similar."

The FDA's totality-of-the-evidence approach considers structural and functional characterization as well as clinical trial results.

However, because the PTE provision is silent as to whether an active ingredient's activity should be considered, it is unclear whether this interpretation would be consistent with the statute.[9]

The first four biosimilar products the FDA approved have amino acid sequences identical to the reference biological product.[10]

To our knowledge, the scope of the right to exclude during the PTE period has not been an issue in any of these instances.

But given the number of biosimilar products in development, it is likely only a matter of time until this issue arises.

Absent congressional action to address the ambiguity in the provision, courts will bear the onus of interpreting the PTE provision in the context of a biological product based on a statute that was written — and cases that were decided — with small molecules in mind.

NOTES

[1] *See, e.g., KSR Int'l Co. v. Teleflex Inc.,* 550 U.S. 398 (2007).

[2] *See, e.g., AbbVie Deutschland GmbH & Co. v. Janssen Biotech Inc.,* 759 F.3d 1285, 1299 (Fed. Cir. 2014); *Ariad Pharm. Inc. v. Eli Lilly & Co.,* 598 F.3d 1336, 1352-54 (Fed. Cir. 2010) (en banc).

[3] *See, e.g., Gilead Scis. Inc. v. Natco Pharma Ltd.,* 753 F.3d 1208 (Fed. Cir. 2014); *AbbVie Inc. v. Mathilda & Terence Kennedy Inst. of Rheumatology Trust,* 764 F.3d 1366, 1374 (Fed. Cir. 2014). The Federal Circuit has held that a patent issuing after, but expiring before, an earlier-filed patent can qualify as a double patenting reference against the later-expiring patent. This holding particularly impacts the pharmaceutical industry, where it is common to prosecute multiple applications in the same family and/or related families. The Federal Circuit has not yet addressed whether a later-filed, but earlier-expiring continuation application can serve as a reference patent against the claims of a parent patent that expires later than the child continuation patent due to a patent term adjustment to which the parent patent is entitled.

[4] *See, e.g., Mayo Collaborative Servs. v Prometheus Labs.,* 132 S. Ct. 1289 (2012); *Ass'n for Molecular Pathology v. Myriad Genetics,* 133 S. Ct. 2107, 2109 (2013). The Supreme Court has held that claims to "naturally occurring" subject matter, even if isolated from its natural environment, are not patent eligible.

[5] Inventions that arise out of clinical trials include but are not limited to manufacturing processes, dosing, dosing regimens, formulations, new indications, combinations and biomarkers.

[6] *Pfizer Inc. v. Dr. Reddy's Labs. Ltd.,* 359 F.3d 1361, 1364 (Fed. Cir. 2004).

[7] *Merck & Co. v. Hi-Tech Pharmacal Co.,* 482 F.3d 1317 (Fed. Cir. 2007); *Boehringer Ingelheim Int'l GmbH v. Barr Labs. Inc.,* 592 F.3d 1340, 1347 (Fed. Cir. 2010).

[8] *Pfizer*, 359 F.3d at 1366 (citing Abbreviated New Drug Application Regulations: Patent and Exclusivity Provisions, 59 Fed. Reg. 50,338, 50,358 (Oct. 3, 1994) (quoting 21 C.F.R. § 314.108(a) (alterations in original).

[9] U.S. Dep't of Health & Human Servs. et al., Scientific Considerations in Demonstrating Biosimilarity to a Reference Product: Guidance for Industry 5-9 (April 2015) ("guidance for industry"), http://bit.ly/1CS6kPj.

[10] *See* Sandoz Inc., FDA Oncologic Drugs Advisory Committee Meeting 29 (Jan. 7, 2015), http://bit.ly/1xBJx6L; Ctr. for Drug Evaluation & Research, Pharmacology Review(s) 7 (July 13, 2016), http://bit.ly/2kjMRnd; Food & Drug Admin., FDA Briefing Document, Arthritis Advisory Committee Meeting (July 13, 2016), http://bit.ly/29xVDLF; Ctr. for Drug Evaluation & Research, Summary Review 7 (Aug. 29, 2016), http://bit.ly/2kKZSXT; Ctr. for Drug Evaluation & Research, Summary Review 7 (Sept. 23, 2016), http://bit.ly/2kjZK13.



Eric Steffe (L), director at the intellectual property law firm **Sterne, Kessler, Goldstein & Fox** in Washington, is a leader of the firm's biotechnology and chemical group. He can be reached at esteffe@skgf.com. **Marsha Rose Gillentine** (C), a director in the biotechnology and chemical group at the firm, provides patent litigation strategic counseling to innovator and generic pharmaceutical companies. She can be reached at mgillentine@skgf.com. **Helene C. Carlson** (R), senior IP counsel at the biotech firm **Meso Scale Diagnostics** in Rockville, Maryland, provides strategic and patent prosecution counseling, having served as back-up counsel in inter partes review proceedings. She can be reached at heleneccarlson@gmail.com. The opinions expressed are the authors' own and are not to be attributed to any author's company, firm or client.