Biosimilars and the Biologics Price Competition and Innovation Act (BPCIA)

A Practical Guidance® Practice Note by
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This practice note discusses biosimilars, the litigation process set up by the Biologics Price Competition and Innovation Act (BPCIA) to facilitate resolution of patent disputes between reference product sponsors and biosimilar manufacturers. This note also touches on related trends, such as the potential use of inter partes review proceedings by biosimilar manufacturers as an alternative or in addition to litigation. The BPCIA provides an abbreviated pathway for companies to bring biologic drugs to market that are "biosimilar" to previously approved branded reference products by relying on clinical studies that were performed by the reference product sponsor (RPS).

Background

Three out of the five top-selling prescription drugs in 2020 were biologics. Conventional drugs, like Tylenol® (acetaminophen), Nexium® (esomeprazole magnesium), and Advair® (fluticasone propionate), sometimes referred to as "small molecule" drugs, generally have fully characterized chemical structures, and are assembled through a sequence of chemical reaction and purification steps. Biologics, or "large molecule" drugs, in contrast, tend to be complex mixtures of much larger proteins, polysaccharides, or nucleic acids that may not be fully structurally characterized, and are produced by biotechnology methods that can result in important variation between lots. Examples include:

- Antibodies (proteins that target (e.g., proteins expressed by cancer cells to trigger the body's immune response)) such as Herceptin® (trastuzumab)
- Growth factors (proteins that affect the growth of a cell) such as Regranex® (becaplermin)
- Enzymes (proteins that speed up biochemical reactions) such as Fabrazyme® (agalsidase beta)
- Immunomodulators (agents that affect immune response) such as Orencia® (abatacept) –and–
- Vaccines (biological preparations that provide active immunity to a particular infectious disease) such as Shingrix for shingles

In 1984, Congress modified the Food Drug, and Cosmetic Act and the Patent Act to permit generic manufacturers of conventional drugs to apply for marketing approval through an abbreviated process by relying on clinical studies performed by the sponsor of the reference brand name drug. See Hatch-Waxman Act Fundamentals. The BPCIA was signed into law as part of the Affordable Care Act on March 23, 2010, and created an abbreviated pathway for companies to bring biologic drugs to market that

are biosimilar to previously approved branded reference products by relying on clinical studies that were performed by the RPS.

Over a decade later, there are now more than 25 FDA-approved biosimilars in the United States, and the Food and Drug Administration (FDA) is working to facilitate further biosimilar development and market access. The number of biosimilars is expected to increase in coming years as companies become more familiar with the legal framework and major biologics begin to lose patent protection and marketing exclusivity.

What Are Biosimilars?

Biologics

Section 351(i) of the Public Health Service Act (PHS) defines a "biological product" as a "virus, therapeutic serum, toxin, antitoxin, vaccine, blood, blood component or derivative, allergenic product, protein (except any chemically synthesized polypeptide), or analogous product, or arsphenamine or derivative of arsphenamine (or any other trivalent organic arsenic compound), applicable to the prevention, treatment, or cure of a disease or condition of human beings." 42 U.S.C. § 262(i)(1). Marketing of a new biologic product requires filing a biologics license application (BLA) pursuant to Section 351(a) of the PHS. 42 U.S.C. § 262(a).

Abbreviated Biologics License Applications: Demonstration of Biosimilarity and Interchangeability to the Reference Product

The BPCIA modified Section 351(k) of the PHS to allow for licensure of biosimilar products through an abbreviated BLA (aBLA).

Biosimilars are drug products that are intended to be clinically similar to, or "interchangeable" with, an existing biologic product. Under the BPCIA, a biologic product can be licensed as "biosimilar" to an already-approved biologic by showing that the product is "highly similar to the reference product notwithstanding minor differences in clinically inactive components," and has "no clinically meaningful differences" from the reference product in terms of "safety, purity, and potency." 42 U.S.C. § 262(i)(2). Biosimilarity is based on analytical studies; animal studies, including toxicity assessments; and a clinical study or studies, including assessments of immunogenicity and pharmacokinetics or pharmacodynamics. 42 U.S.C. § 262(k)(2)(A)(i)(I). The biosimilar must have the same dosage form, strength, mechanism of action, and conditions of use as the approved reference product. 42 U.S.C. § 262(k)(2)(A)(i)(II)–(IV).

An "interchangeable" is a biosimilar for which it has been further demonstrated that the proposed product is "expected to produce the same clinical result as the reference product in any given patient," and that the risk of alternating between the proposed interchangeable and the reference product "is not greater than the risk of using the reference product without such alteration or switch." 42 U.S.C. § 262(k)(4). As the name suggests, the demonstration of interchangeability means that FDA has concluded that it may be substituted for the reference product without consulting the prescriber. 42 U.S.C. § 262(i)(3). Whether a product may be automatically substituted, or consent must be sought from the patient or prescriber, is governed at the state level. As of the start of 2021, forty-five states and Puerto Rico have enacted laws that permit or require pharmacists to dispense an interchangeable biological product in certain situations. The states that have not yet passed legislation on the topic are Alabama, Arkansas, Maine, Mississippi, Oklahoma, and the District of Columbia. See NCSL - State Laws and Legislation Related to Biologic Medications and Substitution of Biosimilars. In addition, **the first interchangeable product, but not the first biosimilar**, is entitled to up to one year of market exclusivity as against other interchangeable products. 42 U.S.C. § 262(k)(6).

Regulatory Exclusivities

No 351(k) application for a biosimilar can be filed for four years after the date the reference product was first licensed for approval. 42 U.S.C. § 262(k)(7)(B). Reference products also have 12 years of marketing exclusivity before approval of a biosimilar can be made effective. 42 U.S.C. § 262(k)(7)(A). These periods of exclusivity can be extended an additional six months for pediatric exclusivity if the RPS completes FDA-requested pediatric studies within the allotted time frame, and the FDA completes its review and accepts the study report more than nine months before the original exclusivity would expire. 42 U.S.C. § 262(m). Reference products may be separately entitled to a seven-year period of "orphan drug" exclusivity for an approved indication for treating a condition affecting fewer than 200,000 in the U.S. (or more but with no hope of recovering costs). 21 U.S.C. §§ 360bb, 360cc.

Biosimilar vs. Generic Version of Conventional

Drug

While biosimilars are sometimes described as "generic" versions of biologics, there are important distinctions to be made between biosimilars and generic versions of small molecule drugs. Because of the complexity and biosynthetic preparation, biosimilars are not exact copies of the reference product and require additional testing to demonstrate similarity than for conventional generic drugs. See April 2015 FDA Guidance for Industry on demonstrating biosimilarity; January 2017 FDA Draft Guidance for Industry on demonstrating interchangeability; May 2019 FDA Considerations in Demonstrating Interchangeability With A Reference Product Guidance for Industry. As a result, biosimilars are significantly more expensive and time-consuming to develop than generic small molecule drugs. See here (estimated at $100 million over five to nine years for development of a biosimilar versus $1–2 million over two years for a conventional generic drug); Erwin A. Blackstone & P. Fuhr Joseph, *The Economics of Biosimilars*, 6(8) AMER. HEALTH & DRUG BENEFITS 469–78, 470–71 (2013). Marketing costs are also higher for biosimilar products than small-module generics, at least for those that are not granted the "interchangeable" stamp.

In addition, unlike for generic drugs, biosimilars have their own proprietary and nonproprietary names. The FDA has issued guidances requiring the nonproprietary name to be a combination of the core name of the reference product and a four lowercase-letter suffix that is devoid of meaning. See January 2017 Nonproprietary Naming of Biological Products Guidance for Industry.

Biologics also tend to be protected by larger patent portfolios than small molecules. These portfolios may include patents covering the active component itself, variations thereof, manufacturing processes, formulations, and methods of treatment. Unlike with conventional drugs, for which the reference product sponsor has the opportunity to identify patents covering a product or an approved method of use by way of FDA Form 3542, which the FDA then publishes in the FDA's "Orange Book," there is no equivalent listing mechanism for biologics. Instead, the BPCIA envisions optional steps to aid the RPS and 351(k) applicant in identifying assertable patents.

Biosimilar Litigation

The BPCIA contains a framework that contemplates various exchanges of information between the RPS and 351(k) applicant and two rounds of patent litigation, often referred to as the "patent dance." The Supreme Court confirmed that this patent dance is not required, and the 351(k) applicant can choose to opt out of the various exchanges. Sandoz Inc. v. Amgen Inc., 137 S. Ct. 1664, 1669, 1673–74 (2017). This gives the 351(k) applicant control over how and when litigation transpires.

Patent Dance: Phase I

35 U.S.C. § 271(e)(1) excludes from patent infringement liability certain actions taken in connection with seeking approval from the FDA to market a new drug or biologic. As discussed below, additional provisions of 35 U.S.C. § 271(e) set forth conditions of constructive patent infringement following submission of an aBLA. Prior to satisfaction of conditions set forth in such sections of § 271(e); however, no case or controversy may exist supporting a declaratory judgment action. See Sandoz Inc. v. Amgen Inc., 773 F.3d 1274, 1278–80 (Fed. Cir. 2014).

351(k) Applicant Provides aBLA

The first phase of litigation may be initiated when, within 20 days of the aBLA being accepted for review, the 351(k) applicant "shall provide" the aBLA to the RPS and "such other information that describes the process or processes used to manufacture" the proposed biosimilar or interchangeable. 42 U.S.C. § 262(l)(2). Disclosure of the aBLA is limited to designated outside counsel and one in-house attorney that do not engage in patent prosecution "relevant or related to the reference product." 42 U.S.C. § 262(l)(1)(B). If the aBLA is timely provided, neither the RPS nor the 351(k) applicant may file a declaratory judgment action until the 351(k) applicant provides notice of commercial marketing (see Patent Dance: Phase II, below). 42 U.S.C. § 262(l)(9)(A).

RPS Provides Patent List

Within 60 days of receipt of the aBLA, the RPS provides to the 351(k) applicant a list of patents for which the RPS believes a claim of patent infringement could reasonably be asserted "if a person not licensed by the reference product sponsor engaged in the making, using, offering to sell, selling, or importing into the United States of the biological" product that is the subject of the 351(k) application as well as a list of such patents that the RPS "would be prepared to license." 42 U.S.C. § 262(l)(3)(A). Failure to timely list a patent by the RPS means the RPS cannot sue the 351(k) applicant on that patent under 35 U.S.C. § 271(e), meaning the RPS may not be able to sue on that patent until the 351(k) applicant commercially markets. 35 U.S.C. § 271(e)(6)(C). Given the relatively short notice, to the extent possible, the RPS should be prepared with its patent lists in advance of the four-year date on which an aBLA may be submitted.

Likewise, the RPS should also include patents that could potentially be infringed; the Federal Circuit found no Rule 11 (Fed. R. Civ. P. 11) problem listing patents for which additional discovery might be needed beyond the aBLA to determine potential infringement. Amgen Inc. v. Hospira, Inc., 866 F.3d 1355, 1362–63 (Fed. Cir. 2017).

351(k) Applicant Provides Counter-List and Detailed Statement

Within 60 days of receiving the patent lists, the 351(k) applicant "may" provide to the RPS a list of patents that the 351(k) applicant believes could be reasonably asserted by the RPS pursuant to § 262(l)(3)(A), and "shall" provide (1) for each of the patents identified by the RPS and the 351(k) applicant, a detailed statement on a claim-by-claim basis of the factual and legal bases for any assertion of invalidity, unenforceability, and noninfringement; and (2) a response regarding each patent identified by the RPS for potential licensing. 42 U.S.C. § 262(l)(3)(B). Within 60 days of receiving these materials from the 351(k) applicant, the RPS provides a detailed statement on a claim-by-claim basis of the factual and legal bases for allegations of infringement and responses to the assertions of validity and unenforceability. 42 U.S.C. § 262(l)(3)(C). Statements in these letters may be party admissions, and therefore great care should be taken in drafting. See Amgen Inc. v. Apotex Inc., 712 Fed.Appx. 985 (Fed. Cir. 2017).

The Parties Negotiate

After the exchange of patent lists and detailed statements, the parties then negotiate which patents should be the subject of immediate infringement litigation. 42 U.S.C. § 262(l)(4). If the parties cannot reach an agreement within 15 days, the 351(k) applicant tells the RPS the number of patents that the applicant will provide, and the parties subsequently exchange respective lists with that number of patents for immediate litigation. 42 U.S.C. § 262(l)(5). This gives the 351(k) applicant significant control over the scope of phase I litigation. If the 351(k) applicant lists no patents, the RPS is still permitted to list a single patent. 42 U.S.C. § 262(l)(5)(B)(ii)(II). Given the relatively short time frame for negotiation, both parties should be prepared as early as practicable with strategies regarding which patents to litigate at this stage.

RPS Brings Suit

Within 30 days of agreeing to a list of patents for immediate resolution or within 30 days after the exchange of lists when no agreement can be reached, the RPS shall bring an action for patent infringement with respect to each implicated patent. 42 U.S.C. § 262(l)(6). 35 U.S.C. § 271(e)(2)(C)(i) makes the filing of the 351(k) application an artificial act of infringement of these patents. Phase I litigation may result in injunctive relief or damages due to any commercial manufacture, use, offer for sale, or sale within the United States not protected by the safe harbor provision of 35 U.S.C. § 271(e)(1). 35 U.S.C. § 271(e)(4). For example, a jury in the District of Delaware recently awarded $70 million in damages for patent infringement even though the biosimilar had not yet been approved by the FDA because the jury found the manufacture of the product was not "solely for uses reasonably related to" seeking FDA approval. Amgen Inc. v. Hospira, Inc., No. 1:15-cv-00839, ECF No. 326 at 3–4 (2017). At the time of writing, motions for judgment as a matter of law were pending. 351(k) applicants that manufacture product or store product in the United States should be ready to demonstrate a nexus to FDA approval.

Injunctive relief is granted ("the court shall order a permanent injunction") for any patents on which the RPS is successful during phase I litigation where the reference product has time remaining in the 12-year period of market exclusivity. 35 U.S.C. § 271(e)(4)(D). Failure to file an infringement suit within the applicable 30-day window (see above) limits a successful RPS to a reasonable royalty; no injunctive relief will be available. 35 U.S.C. § 271(e)(6)(B).

For patents that issue or are exclusively licensed after the first exchange of lists, the RPS has 30 days to provide a supplemental list with these patents to the 351(k) applicant. 42 U.S.C. § 262(l)(7). These later issued patents will be included in second phase of litigation. Id.

Patent Dance: Phase II

The second phase of litigation is initiated when the 351(k) applicant provides notice of intended commercial marketing, which must occur at least 180 days before marketing first occurs. 42 U.S.C. § 262(l)(8). This notice can be provided even prior to FDA approval. Sandoz Inc., 137 S. Ct. at 1677; Amgen Inc. v. Apotex Inc., 827 F.3d 1052, 1054–55 (Fed. Cir. 2016). After receiving that notice, the RPS "may seek a preliminary injunction prohibiting the subsection (k) applicant from engaging in the commercial manufacture or sale of such biological product until the court decides the issue of patent validity, enforcement, and infringement" of any patent included in the lists of patents provided by the RPS and 351(k) applicant in the previous exchanges that were not the subject of phase I litigation. 42 U.S.C. § 262(l)(8)(B). Because the 351(k) applicant is not statutorily required to notify the RPS of the actual launch date, the RPS has little choice but to make best use of the 180-day window post-notice to file any infringement action and seek injunctive relief.

No Patent Dance

The 351(k) applicant is not required to provide the aBLA to the RPS, and the RPS cannot compel its production. Sandoz Inc., 137 S. Ct. at 1674–77; Amgen Inc. v. Sandoz Inc., 877 F.3d 1315, 1327–30 (Fed. Cir. 2017). If the aBLA is not provided, 35 U.S.C. § 271(e)(2)(c) makes the filing of the 351(k) application an artificial act of infringement "for a patent that could be identified" by the RPS in phase I of the patent dance, and 42 U.S.C. § 262(l)(9)(C) permits declaratory judgment claims "of infringement, validity, or enforceability of any patent that claims the biological product or a use of the biological product." If the 351(k) applicant initiates phase I by providing the aBLA but then fails to take an action required in phase I of the patent dance or to provide notice of commercial marketing, the RPS but not the 351(k) applicant "may bring" an action for declaratory judgment "of infringement, validity, or enforceability of any patent" included on the RPS's initial list of patents. 42 U.S.C. § 262(l)(9)(B). Thus, if the 351(k) applicant fails to comply with the patent dance procedure, the RPS gains significant control over the scope and timing of litigation.

Biosimilars and Inter Partes Review

The America Invents Act (AIA) created the inter partes review (IPR) as a quicker and less expensive avenue for third parties to challenge the validity of patents on 35 U.S.C. §§ 102 or 103 grounds based on prior art patents or printed publications in a trial proceeding conducted before a panel of administrative patent law judges. 35 U.S.C. §§ 311–319. The AIA also created procedurally similar post-grant review proceedings (PGR) that allow third parties to challenge patents issuing under the new first-to-file system (effective priority date on or after March 16, 2013) within nine months of issuance, which can include additional grounds of invalidity not available in IPRs such as lack of written description or enablement. 35 U.S.C. §§ 321–329. IPRs are generally completed within 18 months of initial petition, with a six-month period for the Patent Trial and Appeal Board (PTAB) to decide whether to institute a trial if the patent owner files a preliminary response to the petition and a one-year period to issue a final written decision. 35 U.S.C. § 314(b); 42 C.F.R. § 42.100(c).

Patent challengers can only file an IPR if they have not already filed a declaratory judgment action challenging the validity of the patent. 35 U.S.C. § 315(a). However, if the patent owner sues the patent challenger for patent infringement, there is a one-year window for the challenger to file an IPR. 35 U.S.C. § 315(b). 351(k) applicants should consider early whether it is preferable to file an IPR instead of seeking a declaration of invalidity.

In an IPR, the patent is not presumed valid, and accordingly, the challenger has the burden of proving unpatentability by a mere preponderance of the evidence, instead of the clear and convincing evidence standard of district court litigation. 35 U.S.C. §§ 282(a), 316(e). When this note was first written, in contrast to the *Phillips* claim construction standards that apply in district court litigation, the PTAB applied the broadest reasonable interpretation in light of the specification to unexpired patents. 37 C.F.R. § 42.100(b); Phillips v. AWH Corp., 415 F.3d 1303 (Fed. Cir. 2005) (en banc); see also Immunex Corporation v. Sanofi-Aventis U.S. LLC, 977 F.3d 1212 (Fed. Cir. 2020). However, the PTAB replaced the broadest reasonable interpretation standard with the Phillips standard effective November 13, 2018. See 83 Fed. Reg. 197, 51340 (October 11, 2018).

In further contrast to litigation, the patent owner in an IPR has an opportunity to amend the challenged claims by canceling them or proposing substitute claims. 35 U.S.C. § 316(d). Even for these substitute claims, the persuasive burden remains on the challenger to prove unpatentability. Aqua Products v. Matal, 872 F.3d 1290, 1296, 1327–28 (Fed. Cir. 2017).

It has been common for multiple IPRs to be filed against single patents covering biologics. See here. The PTAB, however, has warned petitioners against filing serial or follow-on petitions challenging patents that have already been challenged in a previously unsuccessful IPR. See, e.g., *General Plastic Indus. Co. v. Canon Kabushiki Kaisha*, IPR2016-01357, Paper 19 at 16–19 (P.T.A.B. Sept. 6, 2017) (precedential). Such petitions may be denied institution under 35 U.S.C. §§ 314(a), 325(d), and 37 C.F.R. § 42.108(a) to prevent petitioners from waiting to file the best challenges until they receive guidance from the PTAB and/or the patent owner's preliminary response. It is therefore a risk to file a single IPR, wait to see if it is instituted, and then file a subsequent IPR on the same patent with different art without having an explanation as to why the subsequent IPR could not have been brought sooner.

Unlike Article III court litigation, there is no standing requirement to bring an IPR challenge. See, e.g., 35 U.S.C. § 311(a). Accordingly, companies have used IPRs early in an attempt to knock-out patents before there would be declaratory judgment jurisdiction.

While IPRs appear to be a convenient and easier way to invalidate a patent, there are risks for the petitioner. If unsuccessful at the final written decision stage, the

petitioner is estopped from making further arguments in the USPTO or ITC or a district court proceeding on "any ground that the petitioner raised or reasonably could have raised during that inter partes review." 35 U.S.C. § 315(e).

Before the Supreme Court's decision in SAS Institute, Inc. v. Iancu, 138 S.Ct. 1348 (2018), the Federal Circuit had determined that estoppel did not apply to grounds that were petitioned but not instituted, Shaw Industries Group, Inc. v. Automated Creel Systems, Inc., 817 F.3d 1293 (Fed. Cir. 2016), and district courts split on whether estoppel applied to grounds that were not included in the petition. See Biscotti Inc. v. Microsoft Corp., No. 2:13-cv-0105, 2017 U.S. Dist. LEXIS 144164, at *15–21 (E.D. Tex. May 11, 2017) (recognizing differing interpretations by district courts). After SAS required any institution to include all claims and grounds, courts have consistently applied estoppel even to grounds that were not raised, but reasonably could have been raised, in the petition. See, e.g., WiLan Inc. v. LG Electronics Inc., 2019 U.S. Dist. LEXIS 191173, at *19 (S.D. Cal. Nov. 4, 2019) (collecting cases).

An unsuccessful patent owner also faces estoppel from taking action inconsistent with an adverse judgment, including seeking a patent claim that is "not patentably distinct" from a finally refused or canceled claim. 37 C.F.R. § 42.73(d). Further, to seek review of a PTAB decision upholding a patent claim on appeal to the Federal Circuit, Article III standing must be demonstrated. Phigenix, Inc. v. Immunogen, Inc., 845 F.3d 1168, 1172–76 (Fed. Cir. 2017). As an example from the biosimilars context, Momenta Pharmaceuticals lacked standing to invoke federal appellant jurisdiction, and the appeal was mooted, over an IPR decision upholding claims that would have been assertable against Momenta's planned biosimilar to Bristol-Myers Squibb's Orencia® product after Momenta's 351(k) product had failed clinical testing and been withdrawn from FDA review. Momenta Pharmaceuticals, Inc. v. Bristol-Myers Squibb Co., 915 F.3d 764 (Fed. Cir. 2019).

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Michael Furrow is a former medicinal chemist who counsels pharmaceutical and biotech innovators on all aspects of patent and related regulatory strategy from the early development stages through product launch and eventual high-stakes patent disputes. He has counseled on products covering dozens of therapeutic areas and has handled actions in federal courts and before the U.S. Patent and Trademark Office. Mike's background as a chemist affords him an intimate understanding of the challenges innate to the discovery of new medicines, and clients value his resulting drive to help them explore creative ways to maximize market exclusivities.

Combining his science background with his legal prowess, Mike is known for exhaustively exploring the facts and pushing the envelope on merits strategy. He engages with the technology at a level that permits him to develop strong relationships with inventors, scientific officers, and technical experts, and typically takes the lead on critical issues of patent infringement and validity throughout a matter, including trial. Mike has protected and defended innovation in all aspects of drug discovery, including new chemical entities, salt forms, prodrugs, solid-state forms, dosage forms, combination products, therapeutic methods, methods of manufacture, REMS programs, DNA polymerization, genetically modified organisms, and laboratory techniques and tools.

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April Abele Isaacson has 25 years of experience as a trial lawyer and is a registered United States patent attorney. Her practice focuses on pharmaceutical, biotechnology, and chemical patent litigation, particularly Hatch-Waxman cases on behalf of drug innovators. April has tried cases in several federal district courts throughout the United States, as well as appeals before the Federal Circuit, representing both plaintiffs and defendants. April also provides counseling on patent and related regulatory issues faced by the biopharma industry, including patent portfolio strategy, litigation preparation and strategy, licensing, patent term extension strategy, and Orange Book patent listing and Use Code strategy, and provides opinions on issues of patentability/validity, freedom-to-operate, and loss of exclusivity.

April previously served for nearly five years as in-house counsel at a public specialty pharmaceutical company where she provided broad intellectual property and regulatory strategic counseling during all stages of product development and managed numerous Hatch-Waxman litigations. She also served as a partner at a major international law firm and at a predecessor firm to Kilpatrick Townsend.

April began her legal career as a U.S. Navy JAG Corps prosecutor where she won several high profile jury cases and earned multiple achievement medals and letters of commendation for superior service and leadership. Prior to attending law school, she was an HIV/AIDS research scientist at Boston Children's Hospital.