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The Long and Winding Road for BIOSIMILARS: Charting a Pathway through Patent, FDA, Antitrust, Prescription Filling, Reimbursement and Liability Law





By Chiemi Suzuki, Deborah Yellin, Barbara Ryland, Lauren Patterson and John Fuson

The Biologics Price Competition and Innovation Act (BPCIA), signed into law in March 2010 as part of the Patient Protection and Affordable Care Act, amended the Public Health Service Act and created a new abbreviated licensure pathway for ''generic'' biological products. The BPCIA opens the door for such lower cost copies of expensive biologics by allowing the U.S. Food and Drug Administration (FDA) to approve biologics that are biosimilar to or interchangeable with a single previously approved reference biological product.

Chiemi Suzuki (csuzuki@crowell.com) is a counsel with Crowell & Moring LLP in New York. Deborah Yellin (dyellin@crowell.com) is a counsel with the firm in Washington, D.C. Barbara Ryland (bryland@crowell.com) is a senior counsel with the firm in Washington, D.C. Lauren Patterson (lpatterson@crowell.com) is a counsel with the firm in Washington, D.C. John Fuson (jfuson@crowell.com) is a partner with the firm in Washington, D.C. The views, opinions, and statements expressed in this article are those of the authors and do not represent the views of Crowell & Moring LLP or its clients. This article is for general information purposes and is not intended to be and should not be taken as legal advice.

Five years after this pathway was opened, the era of generic competition in the U.S. biologics market seems finally to have arrived. In March 2015, FDA approved Zarxio, the first biosimilar product licensed under the BPCIA's abbreviated pathway. Based on that approval and other applications in the pipeline, stakeholders, from drug companies and insurers to individual patients, may soon begin to see whether the BPCIA's promises of faster approvals, greater choice, and lower costs will come to fruition in a biologics market that has been forecasted to reach $250 billion globally by 2020.[1]

Guiding expectations for the opportunities and issues that are likely to accompany the arrival of biosimilars are the lessons learned over the thirty years since the Hatch-Waxman Amendments to the Federal Food, Drug, and Cosmetic Act created a framework for expediting approval of generic drugs. Even with that experience, this new approval pathway for biosimilars raises a host of new questions in the regulatory, patent, antitrust, health insurance and liability fields. For example:

- How will FDA determine biosimilarity and what will it take for companies to secure licensure?
- Once licensure is secured, what are the implications for reimbursement by government and private health benefit programs for both the biosimilar and the reference product?

[1] Sarah Rickwood & Stefano Di Biase, *Searching for Terra Firma in the Biosimilars and Non-Original Biologics Market: Insights for the Coming Decade of Change* (IMS Health, London, Eng. 2013), at 3.

- What rules will govern whether pharmacies can fill a prescription using the brand name of a drug with a now available biosimilar drug?
- How will patent disputes be adjudicated, and how will the biosimilar approval pathway affect patent owner strategy and patent estate management?
- And what are the antitrust implications as these new products compete for space in the marketplace?

Manufacturers, providers, and payers for health services must consider the likely answers to all these questions as they prepare strategies for navigating this brand new marketplace.

I. A New Expedited Approval Pathway

Biological products (or biologics) are medical products derived from a living organism, in many cases by means of recombinant DNA and/or controlled gene expression methods.[2] These products include polypeptides, vaccines, cell or gene therapies, therapeutic protein hormones, cytokines and tissue growth factors, monoclonal antibodies, and nucleic acids. The molecular characteristics of biologics are more complex than the traditional small molecule compounds produced by chemical means that are typically reviewed under FDA's new drug and abbreviated new drug application processes. Unlike generic drug products, where the active ingredients are identical to their branded counterparts, biosimilars are unlikely to be identical to the original product. Indeed, biosimilars made by different manufacturers may differ from both the original product and from each other.

FDA's Center for Biologics Evaluation and Research (CBER) reviews applications for biologics (called biologics license applications or BLAs). If a biologic described in a BLA meets standards of safety and efficacy, FDA may grant a license to market the product in accordance with section 351 of the Public Health Service Act. Under the BPCIA, FDA may likewise review applications for biosimilars. BLAs for biosimilars compare the proposed product to a single, previously-licensed reference product. A biologic product is biosimilar to a reference product if data demonstrates that the two products are ''highly similar'' to each other, notwithstanding ''minor differences in clinically inactive components'' and that ''there are no clinically meaningful differences between the biological product and the reference product in terms of the safety, purity, and potency of the product.''[3]

Applications for biosimilars may rely on publicly available information about FDA's prior determination that the reference product is safe, pure, and potent.[4] They must, however, show that the biosimilar and the reference product use ''the same mechanism or mechanisms of action for the condition or conditions of use prescribed'' as well as the same route of administration, dosage form, and strength.[5] If a reference product is approved for multiple indications and multiple routes of administration, biosimilar applications may choose to obtain licensure for a subset of those indications or routes.

Applications for biosimilars may also show that the product is interchangeable with the reference product.[6] A biosimilar is interchangeable if it ''can be expected to produce the same clinical result as the reference product in any given patient.''[7] Further, to be deemed interchangeable, the BLA must demonstrate that the biosimilar, if administered more than once to an individual, poses no greater risk ''in terms of safety or diminished efficacy of alternating or switching between the use of the [biosimilar] and the reference product.''[8] If FDA determines that a biosimilar is interchangeable, a pharmacist may substitute the product for the reference product without the intervention of the health care provider who prescribed the reference product.[9]

II. Covering the Costs of Biosimilars

A. State Substitution Laws

State restrictions on the substitution of biosimilars for reference products, even when they are deemed interchangeable, will pose a challenge to their market entry. Typically, states permit pharmacies to automatically substitute a therapeutically equivalent generic for a branded drug, but these laws do not apply to biosimilars. The BPCIA provides for automatic substitution of interchangeable biosimilars,[10] but several state legislatures have enacted bills limiting a pharmacist's ability to substitute any biosimilar, including those deemed interchangeable. As of August 2015, 23 states had considered legislation to establish standards regarding the substitution of biosimilars.[11] While statutes generally permit substitution of interchangeable biosimilars, they impose conditions not found in the generic context, such as requiring notice to prescribers and patients, requiring pharmacists to maintain records regarding the substitution, and permitting prescribers and patients to prohibit or refuse the substitution. Proponents of the legislation note that biologics are more complex, are not exact duplicates, and therefore raise safety and efficacy concerns. Opponents believe that safety concerns are addressed by the FDA standards for interchangeability and biosimilarity, and argue that additional legislation will prevent or hinder biosimilar use.

B. Prescription Drug Coverage and Formulary Development

Commercial and government health plan prescription drug coverage now incorporate management tech-

[2] ''Biological product'' is defined 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).

[3] 42 U.S.C. § 262(k)(2)(A)(i)(I)(aa).

[4] 42 U.S.C. § 262(k)(2)(A)(i)(I)(cc).

[5] 42 U.S.C. § 262(k)(2)(A)(i)(II)-(IV).

[6] 42 U.S.C. § 262(k)(3).

[7] 42 U.S.C. § 262(k)(4)(A)(ii).

[8] 42 U.S.C. § 262(k)(4)(B).

[9] 42 U.S.C. § 262(i)(3).

[10] *Id*.

[11] Richard Cauchi, *State Laws and Legislation Related to Biologic Medications and Substitution of Biosimilars*, National Conference of State Legislatures, http://www.ncsl.org/research/health/state-laws-and-legislation-related-to-biologic-medications-and-substitution-of-biosimilars.aspx (last visited Sept. 9, 2015).

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niques that have become familiar to both purchasers and regulators. These typically are based on prescription drug formularies, or lists of approved drugs in nearly every drug category, where consumer cost-sharing varies based on which ''tier'' a drug is placed in. The ''lowest'' tier is usually comprised of generic drugs, and depending on the formulary, it is fairly common for a ''brand'' product to have non-formulary status if there is a generic equivalent for that product.[12]

In addition to establishing multi-tier formularies, prescription drug management can include such common techniques as step therapy, prior authorization, or quantity limits. More recently, formularies have begun including a ''specialty tier,'' in which high cost specialty drugs are placed in a single tier with specific cost-sharing for drugs within that tier.[13]

The paradigm underlying formulary development and management posits either a brand with a chemically identical generic product, or multiple branded products within a single ''class'' or ''category'' of products. In addition to whatever state law policies are enacted to govern the substitution of a biosimilar to the original branded product, formulary development and management will need to address how biosimilars fit into this paradigm, or whether new or modified techniques are necessary to encourage the use of less expensive biosimilars without unduly foreclosing access to the original product.

At this point, the application of prescription drug management and formulary development raises a host of questions without any obvious answers. While the more obvious paradigm is for a biosimilar to be treated as a ''generic,'' such that the branded product would be in the ''highest'' tier of the formulary, or off-formulary altogether, this might not be the most desirable outcome.

First, no matter how ''similar'' the two drugs are in therapeutic action, they do not have the same one to one correspondence in their active ''chemical'' ingredients. For the foreseeable future, at least, plans should expect a higher level of resistance from physicians and patients (even if not medically justified) in treating a biosimilar as a true equivalent of the original branded product. Second, many biosimilar products, while likely less expensive than their branded counterparts, may nonetheless still be costly enough that a plan could see utility in managing biosimilar products using similar techniques that they use for expensive specialty products, rather than automatically designating a biosimilar as a ''generic'' that could fall into a much lower cost-sharing tier.

On the other hand, adoption of a ''brand to brand'' paradigm, in which the plan chooses one of the products over the other as a preferred product, could generate a different set of problems. For one thing, plans might not be able to take advantage of more liberal state substitution laws in creating or modifying formularies, so that the less expensive biosimilar becomes covered and preferred—in whatever fashion—as a matter of course (as most formularies are set up to do). This approach might also be disfavored or simply disallowed by the Centers for Medicare & Medicaid Services (CMS) in its regulation of Part D plans, because CMS can be expected to adhere to FDA's view on the substitutability of biosimilars for the original branded product. To the extent that management techniques are still considered important in limiting utilization of specific products, a plan might have to engage in more costly (and more intrusive) intervention, such as prior authorization or step therapy.

While regulatory issues governing formulary development and design are being worked out, plans should try to be as transparent as possible about the decisions they make in coverage and cost sharing decisions for biosimilar products and their original branded counterparts. The drip-drip evolution of acceptable prescription drug management practices resulted in a gradual adoption of best practices, but also resulted in highly visible and expensive enforcement actions under unfair and deceptive trade practice and other consumer protection statutes, as well as, later, federal fraud and abuse statutes and the False Claims Act.

III. Patent Protection and Exclusivity for Biosimilars

A. Patent Protection for Biologics

Even after FDA establishes similarity between a proposed biosimilar and a reference product, and payors are prepared to cover their costs, there remain other barriers to market entry. Chief among those are patents covering the original reference product. Manufacturers of biosimilars will need to have identified a course around those patents or have prepared a strategy for challenging them.

There are many ways to claim the active ingredient of a biologic product in a patent. The subject matter of such patents may include claims to molecules, nucleic acid and amino acid sequences, antibodies, and cells lines. Patents directed to methods of manufacture, formulations, and methods of use may also be reasonably asserted against a biosimilar applicant. Moreover, claims that include elements directed to molecule function, potency, purity, immunogenicity, safety, pharmacokinetic profiles, and other characteristics of a biologic may also be reasonably asserted. Often when a patent application is filed, the subject biologic ingredient is not yet fully characterized, but the function is understood. Where that has occurred, applicants may find it useful to pursue ''product by process'' claims, which recite functional language.

Biosimilar compounds may vary from the molecule or sequence claimed in the patent, so determining infringement of patents covering biologics may be far more complicated than with small molecule drug patents. Because there may be structural differences between a biosimilar and its reference product, the biosimilar may not fall within the scope of a claim cover-

[12] *See e.g.*, CTR. FOR MEDICARE & MEDICAID SERVS., MEDICARE PRESCRIPTION DRUG BENEFIT MANUAL, Ch. 6 – Part D Drugs and Formulary Development, § 30 *et seq*.

[13] For instance, 42 C.F.R. § 423.578(a)(7) allows Part D sponsors to exempt from tiered cost-sharing exceptions a formulary tier in which the sponsor places very high cost and unique items. In order to avoid discouraging enrollment by patients who rely on these medications, CMS will only approve specialty tiers within formularies and benefit designs that comply with standards specified in Section 30.2.4 of the Medicare Prescription Drug Benefit Manual, Chapter 6 – Part D Drugs and Formulary Development.

ing the reference product.[14] For example, a small change such as an amino acid substitution in a protein may prevent a biosimilar from infringing a claim reciting a specific amino acid sequence found in the reference product. However, by pursuing claims that are too broad, a patent holder may leave their patent vulnerable to a written description or an obviousness attack at litigation or post-grant proceeding before the U.S. Patent and Trademark Office. Given that biosimilars manufactured by one company may differ structurally from biosimilars manufactured by a second company, it may be difficult to draft a claim which would block any potential biosimilar product.

When a biosimilar does not literally infringe a claim, the patent holder will have to rely on the doctrine of equivalents to show infringement. A product infringes under the doctrine of equivalents if it performs the same function in substantially the same way and accomplishes substantially the same result, even if it differs in name, form or shape.[15] To this end, a biosimilar is a product which will at least perform the same function and produce substantially the same result as the reference product. However, the biosimilar may not perform the same function in the same way.

The patent owner will also have to carefully balance its infringement and validity arguments. On one hand, this may require arguing for patent infringement purposes that even where there is a small change in a biosimilar compared to the originator product, the biosimilar still reads on each and every element of the asserted patent claims. On the other hand, this may also require arguing that small changes in its own compound compared to prior art are significant enough to make the invention patentable over the prior art.

B. Exclusivity

The BPCIA provides additional protections to licensed biologics that are separate from what is available through patents. For example, FDA may not license any new biosimilar as interchangeable until twelve years after the reference product was first licensed, and it will not even accept applications for biosimilars until four years after the reference product was licensed. FDA likewise may not license a second biosimilar for one year after the first commercial marketing of the first interchangeable biosimilar to a reference product. Thus, even in the absence of patents, licensed biologics enjoy a certain period of market protection.

IV. Challenging and Enforcing Patents Claiming Biosimilars

When there are patents claiming reference products, biosimilar applicants have several options for clearing a pathway to market. Stakeholders in the health care and life sciences industries are likely already familiar with the procedures for patent litigation under the Hatch-Waxman framework, and while there are similarities under the BPCIA, patent litigation involving biosimilars will differ in several important ways. For example, while patents covering drug products appear in FDA's *Approved Drug Products with Therapeutic Equivalence Evaluations* (commonly known as the ''Orange Book''), there is no similar list for patents covering reference biological products. Moreover, the initiation of litigation under the provisions of the BPCIA does not provide an automatic stay of FDA approval of the underlying application for a biosimilar.

Despite differences in the approval processes for generic drugs and biosimilars, those with experience with the Hatch-Waxman Act will find that the dynamic interplay between FDA regulatory processes and related patent litigation remains for litigation under the BPCIA. We are now in only the nascent stages of litigating disputes arising from the biosimilar approval processes. The earliest jurisprudence in this area highlights the stakes involved for reference sponsors and biosimilar applicants, as well as the strategic considerations for each side that come with each step in the process.

The BPCIA, as interpreted by the Federal Circuit, puts the biosimilar applicant in the driver's seat at the earliest stages, empowering the applicant to make a choice of whether or not to provide a reference sponsor with a copy of the biosimilar application.[16] The applicant's decision—to provide the application or not—largely determines the scope and pace of the patent litigation that may follow. The sections below summarize the litigation consequences of this early choice, first detailing the situation where the applicant provides the reference sponsor with the biosimilar application, and next detailing the situation where the applicant elects not to provide the application.

A. An Applicant's Disclosure of Its Biosimilar Application Leads to a Patent Dance

Where an applicant elects to provide its application to the reference sponsor, what follows is patent litigation under the guidelines of a ''comprehensive, integrated litigation management system,''[17] as outlined by the various provisions of the BPCIA. The BPCIA provides that no later than twenty days after receiving notice from FDA that an application for licensure of a biosimilar[18] has been accepted for review, the applicant shall provide on a confidential basis[19] a copy of the application to the sponsor of the reference product, including ''such other information that describes the process or processes used to manufacture the biological product that is the subject of such application. . . .''[20] The reference sponsor's use of the confidential information in the application is limited, and to this end, the statute provides that the application

> shall be used for the sole and exclusive purpose of determining . . . whether a claim of patent infringement could reasonably be asserted if the . . . applicant engaged in the manufacture, use, offering for sale, sale, or importation into the United States of the [proposed biosimilar].[21]

From here, a series of disclosures and negotiations begins, a process that many have termed a ''patent dance.''

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[14] *See generally* Janet Freilich, *Patent Infringement in the Context of Follow-on Biologics*, 16 Stan. Tech. L. Rev. 9 (2012).

[15] *Warner-Jenkinson Co., Inc. v. Hilton Davis Chem. Co.*, 520 U.S. 17, 40 (1997).

[16] *See generally Amgen Inc. v. Sandoz Inc.*, No. 2015-1499, 2015 BL 231910, at *5-7 (Fed. Cir. July 21, 2015).

[17] *Id.* at *20 (Chen, J., dissenting-in-part).

[18] 42 U.S.C. § 262(k). The BPCIA refers to this application as the ''subsection (k) application.''

[19] 42 U.S.C. § 262(l).

[20] 42 U.S.C. § 262(l)(2)(A).

[21] 42 U.S.C. § 262(l)(1)(D).

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1. **Dance Step One – Reference Sponsor's List of Patents**

Within sixty days of receipt of a copy of an application accepted by FDA for review, the reference sponsor must provide the biosimilar applicant with

> (i) a list of patents for which the reference product sponsor believes a claim of patent infringement could reasonably be asserted by the reference product sponsor, . . . and
>
> (ii) an identification of the patents on such list that the reference product sponsor would be prepared to license to the [biosimilar applicant].[22]

A reference sponsor who fails to include a patent on this list may not bring an action for infringement of that patent based solely on the filing of the biosimilar application.[23]

2. **Dance Step Two – Biosimilar Applicant's Response**

Within sixty days after the biosimilar applicant receives the patent list from the reference sponsor, the applicant must provide, for each patent listed by the reference sponsor,

> (I) a detailed statement that describes, on a claim by claim basis, the factual and legal basis of the opinion of the [biosimilar applicant] that such patent is invalid, unenforceable, or will not be infringed by the commercial marketing of the [proposed biosimilar]; or
>
> (II) a statement that the [biosimilar] applicant does not intend to begin commercial marketing of the biological product before the date that such patent expires. . . .[24]

Within the same timeframe, the biosimilar applicant must also provide a response regarding any patent the reference sponsor has offered to license.[25] The biosimilar applicant may also provide the reference sponsor with a list of patents for which the applicant believes

> a claim of patent infringement could reasonably be asserted by the reference product sponsor 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 [proposed biosimilar]. . . .[26]

3. **Dance Step Three – Reference Sponsor's Response**

Within sixty days after receipt of the detailed statement and any list of patents from the biosimilar applicant, the reference sponsor must provide

> a detailed statement that describes . . . on a claim by claim basis, the factual and legal basis of the opinion of the reference product sponsor that such patent will be infringed by the commercial marketing of the [proposed biosimilar] and a response to the statement concerning validity and enforceability. . . .[27]

4. **Dance Step Four – Good Faith Negotiations and Litigation**

Beginning fifteen days after receipt of the detailed statement from the reference sponsor, the biosimilar applicant must ''engage in good faith negotiations to agree on which, if any, patents listed . . . by the [biosimilar applicant] or the reference product sponsor shall be the subject of an action for patent infringement. . . .''[28] In the event the reference sponsor and biosimilar applicant agree on the patents, not later than thirty days after such agreement, the reference sponsor shall bring an action for patent infringement with respect to each of those agreed upon patents.[29]

But where the reference sponsor and biosimilar applicant cannot agree on which patents to include on the list, the biosimilar applicant notifies the reference sponsor of the *number of patents* it will provide on a list to the reference sponsor.[30] Then, within five days, the reference sponsor and the biosimilar applicant simultaneously exchange

> (I) the list of patents that the [biosimilar applicant] believes should be the subject of an action for patent infringement . . . and
>
> (II) the list of patents . . . that the reference product sponsor believes should be the subject of an action for patent infringement. . . .[31]

In this simultaneous exchange, the reference sponsor may not list more than the number of patents identified five days earlier by the biosimilar applicant,[32] unless the biosimilar applicant identified that it would provide zero patents in the exchange, in which case the reference sponsor may list one patent.[33] Within thirty days after the exchange of these lists, ''the reference product sponsor shall bring an action for patent infringement with respect to each patent that is included on such lists.''[34]

Where the reference sponsor initiates a suit more than thirty days after either agreement on the list of patents to be litigated,[35] or exchange of the lists in the event the parties do not agree on the patent list,[36] or the suit was timely brought within the thirty day time period but was dismissed without prejudice or was not prosecuted to judgment in good faith, the sole and exclusive remedy that may be granted by the court for a finding of infringement is a reasonable royalty.[37]

Where a reference sponsor initiates and prevails a patent infringement suit under the BPCIA, it is entitled to a permanent injunction prohibiting ''any infringement of the patent by the biological product involved in the infringement until a date which is not earlier than the date of the expiration of the patent that has been infringed,''[38] provided that (1) the patent is the subject of a ''final decision of a court from which no appeal (other than a petition to the U.S. Supreme Court for a writ of

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[22] 42 U.S.C. § 262(l)(3)(A).
[23] 35 U.S.C. § 271(e)(6)(C).
[24] 42 U.S.C. § 262(l)(3)(B)(ii).
[25] 42 U.S.C. § 262(l)(3)(B)(iii).
[26] 42 U.S.C. § 262(l)(3)(B)(i).
[27] 42 U.S.C. § 262(l)(3)(C).
[28] 42 U.S.C. § 262(l)(4)(A).
[29] 42 U.S.C. § 262(l)(6)(A).
[30] 42 U.S.C. § 262(l)(5)(A).
[31] 42 U.S.C. § 262(l)(5)(B).
[32] 42 U.S.C. § 262(l)(5)(B)(ii)(I).
[33] 42 U.S.C. § 262(l)(5)(B)(ii)(II).
[34] 42 U.S.C. § 262(l)(6)(B).
[35] 42 U.S.C. § 262(l)(6)(A).
[36] 42 U.S.C. § 262(l)(6)(B).
[37] 35 U.S.C. § 271(e)(6)(B).
[38] 35 U.S.C. § 271(e)(4)(D).

certiorari) has been or can be taken,''[39] and (2) FDA has not yet approved the biosimilar because the reference product maintains its twelve-year market exclusivity.[40]

B. An Applicant May Elect Not To Disclose Its Biosimilar Application

While the BPCIA provides that the applicant ''*shall provide* to the reference product sponsor a copy of the [biosimilar] application,''[41] the U.S. Court of Appeals for the Federal Circuit recently clarified that an applicant does not violate the BPCIA by failing to disclose its application and the manufacturing information by the statutory deadline.[42] As the Federal Circuit recognized, the BPCIA expressly contemplates an applicant's failure to disclose its biosimilar application.[43]

> If a subsection (k) applicant *fails to provide the application and information required under paragraph (2)(A)*, the reference product sponsor, but not the subsection (k) applicant, may bring an action under section 2201 of Title 28, for a declaration of *infringement, validity, or enforceability of any patent* that claims the biological product or a use of the biological product.[44]

Additionally, 35 U.S.C. § 271(e)(2)(C)(ii) states:

> It shall be an act of infringement to submit . . . if the applicant for the application [seeking approval of a biological product*] fails to provide the application and information required* under section 351(l)(2)(A) of such Act, an application seeking approval of a biological product for a patent that could be identified pursuant to section 351(l)(3)(A)(i) of such Act, if the purpose of such submission is to obtain approval under such Act to engage in the commercial manufacture, use, or sale of a . . . biological product, or biological product claimed in a patent or the use of which is claimed in a patent before the expiration of such patent.[45]

The remedies provided under 35 U.S.C. § 271(e)(4)(D) are the ''only remedies'' a court may grant for the act of infringement described in 35 U.S.C. § 271(e)(2)(C)(ii).[46]

Where an applicant elects not to disclose its application, any patent litigation brought by the reference sponsor proceeds without the negotiation requirements and patent number limits detailed in the BPCIA.[47] And the reference sponsor would expect to gain access to the application and manufacturing information through discovery.[48]

C. The BPCIA's Notice of Commercial Marketing Requirement

The BPCIA provides that a biosimilar applicant ''shall provide notice to the reference product sponsor not later than 180 days before the date of first commercial marketing of the [proposed biosimilar].''[49] Effective notice of commercial marketing requires that FDA has licensed an applicant's product.[50] This timing ''ensures the existence of a fully crystallized controversy regarding the need for injunctive relief.''[51] It also gives the reference sponsor adequate time to determine whether, and on which patents, to seek a preliminary injunction, and it gives the parties and court time to assess the parties' rights prior to commercial launch of the product at issue.[52]

Where the applicant disclosed its application and the parties proceeded according to the BPCIA's litigation management scheme, the reference sponsor may seek a preliminary injunction with respect to any patent that was included on the reference sponsor's original list of patents it provided after first receipt of the biosimilar application,[53] but that was ultimately excluded on the list of patents to be litigated during the good faith negotiation.[54]

Importantly, the notice provision is mandatory for applicants that have elected not to provide their applications.[55] Judge Chen, dissenting-in-part in the Federal Circuit's *Amgen v. Sandoz* opinion noted that the practical consequence of requiring these applicants to provide notice of marketing is the reference sponsor's ''inherent right to an automatic 180-day injunction,'' without a need to show any likelihood of success on the merits.[56] Judge Chen pointed out that nothing in the majority opinion suggested that this automatic injunction would be available where an applicant had provided its application to the reference sponsor during the statutory period.[57] Moreover, his opinion points out a ''peculiar outcome.''[58] Where an applicant refuses to provide its application during the statutory period, the applicant cannot refuse to provide notice because the BPCIA authorizes an automatic entitlement to a 180-day injunction.[59] Yet where an applicant complies with the BPCIA's requirements, the applicant may refuse to comply with the 180-day notice provision.[60] In that situation, there would not be an automatic 180-day injunction because 42 U.S.C. § 262(l)(9)(B) allows the reference sponsor to immediately file suit on any patent it earlier listed during the patent negotiation process.[61]

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[39] 42 U.S.C. § 262(k)(6); 35 U.S.C. § 271(e)(4)(D).
[40] 35 U.S.C. § 271(e)(4)(D).
[41] 42 U.S.C. § 262(l)(2)(A) (emphasis added).
[42] *Amgen*, 2015 BL 231910, at *7-8.
[43] *Id.* at *5.
[44] 42 U.S.C. § 262(l)(9)(C) (emphasis added).
[45] 35 U.S.C. § 271(e)(2)(C)(ii) (emphasis added).
[46] *See Amgen*, 2015 BL 231910, at *7.
[47] *Id.* at *18 (Chen, J., dissenting-in-part) (explaining that the reference sponsor's course of action is ''clearly defined in [42 U.S.C. § 262](l)(9) and § 271(e)(2)(C)(ii): the unfettered right to immediately pursue patent infringement litigation unconstrained by any of the timing controls or limits on the number of patents it may assert that would result from the [42 U.S.C. § 262] (l)(2)-(l) (8) process'').
[48] *Id.* at *7.
[49] 42 U.S.C. § 262(l)(8)(A).
[50] *Amgen*, 2015 BL 231910, at *8-9.
[51] *Id.* at *9 (explaining that before licensure, the product, its therapeutic uses, and manufacturing processes may not be fixed, and marketing is not imminent).
[52] *Id.*; *see id.* at *11 (''The purpose of paragraph (l)(8)A) is clear: requiring notice of commercial marketing be given to allow the RPS [reference product sponsor] a period of time to assess and act upon its patent rights.'').
[53] 42 U.S.C. § 262(l)(3)(A).
[54] 42 U.S.C. § 262(l)(8)(B).
[55] *Amgen*, 2015 BL 231910, at *11.
[56] *Id.* at *22 (Chen, J., dissenting-in-part).
[57] *Id.*
[58] *Id.* at *22.
[59] *Id.*
[60] *Id.*
[61] *Id.*

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D. Initial Cases Involving Biosimilars Have Focused on Interpretations of the BPCIA and Its Procedures for Resolving Patent Disputes

Litigation under the BPCIA began just recently with a pair of lawsuits between Amgen Inc. (''Amgen'') and Sandoz Inc. (''Sandoz'') that have propelled interpretation of various aspects of the statute to the forefront. These early cases concern key statutory interpretations and nuances in the BPCIA, and are developing the playbook of strategies that litigants and counsel will need to consider when disputes arise.

1. The Case or Controversy Requirement for Jurisdiction of Declaratory Judgment Claims Brought by a Biosimilar Applicant

In *Sandoz v. Amgen*, Sandoz sought a declaration that its biologic product containing etanercept—on which it had not yet filed an FDA application for licensure as biosimilar to Amgen's Enbrel®—did not infringe any claim of U.S. Patent Nos. 8,063,182 and 8,163,522, and that the patents are invalid and unenforceable.[62] Sandoz had begun Phase III clinical trials on its proposed etanercept product on the day it filed the complaint, and while Sandoz intended to file an application with FDA for licensure of its product as biosimilar to Enbrel, it had not done so yet.[63] Neither Sandoz nor Amgen had even begun the statutory exchanges of information under the BPCIA.[64] Even so, Sandoz contended that its declaratory judgment action was proper under the notice of first commercial marketing provisions of the Act, as Sandoz had given notice in this instance.[65]

On two separate grounds, the district court dismissed Sandoz's complaint. First, the U.S. District Court for the Northern District of California focused on the BPCIA's requirement that the notice must be given no later than 180 days ''before the date of the first commercial marketing *of the* [*proposed biosimilar*].''[66] The court concluded that as a matter of law Sandoz could not have provided notice because its etanercept product is not licensed under the BPCIA.[67] The district court also concluded that even after an applicant provides notice, it cannot bring a declaratory judgment action until—at minimum—it has provided the reference sponsor with a copy of the biosimilar application and other information the describes the process or processes used to manufacture the proposed biosimilar.[68]

Second, the district court determined that Sandoz had not yet met the ''case or controversy'' requirement required for jurisdiction.[69] Sandoz lacked any ''immediate threat'' of injury or future injury caused by Amgen.[70] Moreover, Sandoz's allegation that it intended to file an application with FDA in the future was insufficient to create a case or controversy.[71] The district court dismissed Sandoz's complaint without prejudice and without leave to amend.[72]

On appeal, the U.S. Court of Appeals for the Federal Circuit affirmed the district court's conclusion that ''Sandoz did not allege an injury of sufficient immediacy and reality to create subject matter jurisdiction,'' but the appeals court did not address the district court's interpretation of the BPCIA.[73] Turning to the case or controversy requirements for justiciability, the Federal Circuit pointed out that Amgen

> has not suggested that anything Sandoz is currently doing exposes it to infringement liability, and there is no dispute that Sandoz cannot engage in the only liability-exposing conduct at issue without FDA approval of an application precisely defining the products it may market. Sandoz has not even filed such an application.[74]

In particular, the Federal Circuit highlighted contingencies that may lead to delay of Sandoz's plans to file an application with FDA. The Federal Circuit noted that Sandoz could not ''simply assum[e] that the Phase III trial will wholly succeed.''[75] The appeals court also noted that, even if the Phase III trial is successful, the biosimilarity approval standard was brand new and not yet applied or interpreted by FDA.[76] In short, the Federal Circuit determined that ''[a]ny dispute about patent infringement is at present subject to significant uncertainties,'' and the precise product—not yet fixed or fully known—would frame any patent dispute. [77] The court explained:

> In the pre-application context presented here, we conclude that the events exposing Sandoz to infringement liability ''may not occur as anticipated, or indeed may not occur at all,'' . . . and that ''further factual development would significantly advance'' a court's ability to identify and define the issues for resolution. . . .[78]

Accordingly, due to the present uncertainties, the appeals court affirmed the judgment of the district court.[79]

2. The Choice to Engage in the Disclosure and Negotiation Process Outlined in the BPCIA and the 180-Day Notice Provision

A second lawsuit involving the same parties, *Amgen v. Sandoz* concerning Amgen's Neupogen® (filgrastim) product, followed just three months later. Sandoz filed an application to receive biosimilar status for its filgrastim product and on July 7, 2014 it received notice that FDA had accepted the application for review.[80] The

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[62] *Sandoz Inc. v. Amgen Inc.*, No. 13-cv-2904, 2013 BL 312978, at *1 (N.D. Cal. Nov. 12, 2013).

[63] *Id.*; *Sandoz, Inc. v. Amgen Inc.*, 773 F.3d 1274, 1276 (Fed. Cir. 2014).

[64] *See Sandoz*, 2013 BL 312978 at *2.

[65] *Id.*

[66] 42 U.S.C. § 282(l)(8)(A).

[67] *Sandoz*, 2013 BL 312978, at *2 (citing 42 U.S.C. § 282(l)(8)(A)).

[68] *Id.* (citing 42 U.S.C. § 282(l)(2)(A)).

[69] *Id.*

[70] *Id.* (explaining that Amgen never advised that they intended to sue Sandoz; that Sandoz did not demonstrate that Amgen had subjected Sandoz to any immediate threat of injury; and that Amgen's own statements that the patents cover etanercept and that Amgen defends its patents do not suffice to show an ''immediate threat'').

[71] *Id.* at *2-3.

[72] *Id.* at *3.

[73] *Sandoz*, 773 F.3d at 1265.

[74] *Id.* at 1279.

[75] *Id.* at 1279-80.

[76] *Id.* at 1280.

[77] *Id.* at 1280.

[78] *Id.* at 1281 (citations omitted).

[79] *Id.* at 1282.

[80] *Amgen Inc. v. Sandoz Inc.*, No. 14-cv-04741, 2015 BL 75537, at *4 (N.D. Cal. Mar. 19, 2015).

next day, on July 8, 2014, Sandoz offered to share its application with Amgen under a proposed Offer of Confidential Access.[81] In the same letter, Sandoz informed Amgen that it expected to receive FDA approval during the first or second quarter of 2015 and stated its intent to market its biosimilar product immediately thereafter.[82]

On July 25, 2014, Sandoz wrote Amgen another letter, again offering confidential access to its application, but also asserting that the BPCIA entitled it to opt out of the statutory procedures for resolving patent disputes, and that Amgen could instead procure information regarding Sandoz's proposed product and application through an infringement action.[83] Amgen apparently declined both offers of access to the application, and on October 24, 2014 Amgen sued in the U.S. District Court for the Northern District of California asserting claims of (1) state law unlawful competition based on Sandoz's alleged violation of the BPCIA for failure to comply with the disclosure and negotiation procedures and for Sandoz's interpretation of the 180-day notice provision; (2) conversion for Sandoz's use of Amgen's FDA license for Neupogen® in its application without abiding by the procedures under the BPCIA; and (3) infringement of Amgen's U.S. Patent No. 6,162,427 (''the '427 patent'').[84] Amgen alleged that Sandoz violated the BPCIA by failing to disclose its application and manufacturing information, and by giving premature, ineffective notice of commercial marketing before FDA approved its product.[85] As to the disclosure process under the BPCIA, the district court recognized that compliance offers benefits to biosimilar applicants because it

> allows the applicant to preview which patents the reference product sponsor believes are valid and infringed, assess related factual and legal support, and exercise some control over which patents are litigated and when. An applicant with a high (or unknown) risk of liability for infringement could benefit considerably from this process: it would be able to undergo the information exchange while protected by the statute's safe harbor from litigation, and if necessary, delay its product launch to protect the investment it made in developing its biosimilar.[86]

Yet the court also recognized the time commitment to proceeding under these procedures, noting that it could take up to 230 days just to commence a patent litigation, which some applicants could consider to introduce ''needless communications and delay.''[87] As to Sandoz's choice to forego the disclosure and negotiation process, the court observed that Sandoz ''traded in the chance to narrow the scope of potential litigation with Amgen through [the BPCIA's] steps, in exchange for the expediency of an immediate lawsuit,'' a process supported by the statute's plain language and overall statutory scheme.[88]

Under the district court's interpretation of the statute, Sandoz did not violate the BPCIA and committed no unlawful predicate act to support Amgen's state law unfair competition and conversion claims.[89] The court thus dismissed Amgen's claims with prejudice.[90] As to Sandoz's counterclaims for a declaratory judgment of noninfringement and invalidity of the '427 patent, Amgen argued that the counterclaims should be barred because Sandoz did not provide its application and manufacturing process to the sponsor.[91] The district court concluded that the counterclaims were not barred by the BPCIA.[92] Finally, the court denied Amgen's motion for a preliminary injunction. It found that the harms alleged by Amgen were ''at best highly speculative,'' and that since the twelve-year exclusivity period for Neupogen® had already expired, there was ''no basis on which Amgen is entitled to injunctive relief or other remedies for disadvantages it may suffer due to market competition from Sandoz.''[93] The parties jointly moved for entry of final judgment as to Amgen's unfair competition and conversion claims, and as to Sandoz's BPCIA counterclaims.[94] Amgen appealed to the Federal Circuit from the final judgment and the district court's denial of the preliminary injunction.[95]

The Federal Circuit held that the disclosure and negotiation procedures under the BPCIA are permissive, and tied the notice of commercial marketing provision to FDA licensure.[96] The appeals court held that the district court did not err in concluding that a biosimilar applicant may elect not to disclose its application and manufacturing information.[97] Consequently, it held that because Sandoz ''took a path expressly contemplated'' by the statute, it did not violate the BPCIA by not disclosing its application and manufacturing information to Amgen by the statutory deadline.[98]

As to the notice requirement, the court concluded that under 42 U.S.C. § 262(l)(8)(A), operative notice of commercial marketing requires that the applicant already have FDA licensure of its product.[99] Sandoz gave notice in July 2014, the day after FDA accepted its application for review.[100] Because FDA had yet to approve the underlying product, that notice was premature and ineffective.[101] On March 6, 2015, FDA approved Sandoz's product, Zarxio, the first biosimilar licensed under the BPCIA.[102] Sandoz gave Amgen ''further'' notice of commercial marketing that same day, and only that notice serves as the operative and effective notice under the BPCIA.[103] Additionally, the court concluded that where an applicant fails to provide its application and manufacturing information by the statutory deadline under the BPCIA, the notice of commercial marketing

[81] *Id.*
[82] *Id.*
[83] *Amgen*, 2015 BL 75537, at *4; *Amgen*, 2015 BL 231910, at *3-4.
[84] *Amgen*, 2015 BL 75537, at *3-4.
[85] *See Amgen*, 2015 BL 231910, at *4.
[86] *Sandoz*, 2013 BL 312978, at *6
[87] *Id.* at *7.
[88] *Id.*
[89] *Id.*
[90] *Id.* at *9.
[91] *Id.*
[92] *Id.*
[93] *Id.* at *10.
[94] *Amgen*, 2015 BL 231910, at *5.
[95] *Id.*
[96] *Id.* at *8-9.
[97] *Id.* at *5-8.
[98] *Id.* at *7-8.
[99] *Id.* at *9.
[100] *Id.* at *10.
[101] *Id.*
[102] *Id.*; Press Release, FDA, FDA approves first biosimilar product Zarxio (Mar. 6, 2015), http://www.fda.gov/NewsEvents/Newsroom/PressAnnouncements/ucm436648.htm (last visited May 7, 2015).
[103] *Amgen*, 2015 BL 231910, at *10.

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requirement is mandatory.[104] Accordingly, Sandoz is prohibited from marketing its Zarxio product until September 2, 2015, 180 days from its notice to Amgen on March 6, 2015.[105] On September 2, 2015, the Federal Circuit rejected Amgen's request for a new injunction pending Amgen's petition for en banc rehearing that would have continued to block Sandoz's sales of Zarxio. [106]

Zarxio became the first U.S. biosimilar the next day when Sandoz began U.S. sales offering a 15 percent discount to Neupogen. [107]

V. Antitrust Hazards under the BPCIA

When the Hatch-Waxman framework for expediting approval of generic drugs became law, the Federal Trade Commission (FTC) lauded the prospect of ''substantially reduced prescription drug prices and overall prescription drug expenditure, increased access to therapeutic drugs for more Americans, and [a] hastened . . . pace of innovation.''[108] FTC was similarly supportive of the BPCIA's expedited pathway for approving biosimilars, although, because of the greater complexities involved in the development and manufacturing of all biologics—including biosimilars—its optimism has been more muted.

In a 2009 report, the FTC examined whether introducing biosimilars into the marketplace could reduce the price of reference biologic products.[109] The report recognized important differences between biosimilars and generic drugs including the high cost of both manufacturing biologics and securing FDA approval for biosimilars, as well as the lack of automatic substitution between a biosimilar and its reference biological product if FDA did not deem the biosimilar interchangeable. Because of these and other differences, the FTC concluded that competition between biosimilars and referenced biologic products was more likely to resemble branded-branded drug competition than branded-generic competition.[110]

Nonetheless, the FTC report concluded that competition from biosimilars would lead to some price discounts and, like Hatch-Waxman, would expand consumer access to biologics. Like Hatch-Waxman, the BPCIA balances encouragement of innovation and patent protection with provisions to promote accessibility through competition. The FTC observed that many of the threats to competition that arose under Hatch-Waxman are likely to present themselves as new applications for biosimilars make their way through FDA.

A. Reverse Payment Settlements

One major threat to competition that emerged under the Hatch-Waxman statutory scheme is reverse payment settlements, in which a branded drug manufacturer pays a generic manufacturer to settle patent challenges, and the generic agrees not to bring its product to market for a period of time.[111] Manufacturers of reference biological products may likewise seek to use reverse-settlement payments to resolve infringement litigation with biosimilar makers.

The Supreme Court examined these types of settlements in *FTC v. Actavis*, holding that ''large and unjustified'' reverse payment settlement agreements may violate the antitrust laws and should be reviewed under the rule of reason.[112] Yet the *Actavis* decision did not mention biologics, leaving open whether and to what extent the decision applies to patent settlements involving such products.

In *Actavis*, Solvay Pharmaceuticals filed for and received a patent for the brand name drug AndroGel®. Two companies, Actavis and Paddock, each filed abbreviated new drug applications (ANDAs) to market generic versions of AndroGel® and certified under paragraph IV of the Hatch Waxman Act that they would not infringe Solvay's patent and that the patent was invalid, which prompted Solvay to sue the companies for patent infringement. In 2006, the parties reached a settlement under which the defendants agreed not to market a generic version of AndroGel® until August 2015 and agreed to promote AndroGel® to doctors. In exchange, Solvay agreed to pay the companies millions, including an estimated $19-30 million annually for nine years to Actavis.[113]

The FTC filed suit against the settling companies under Section 5 of the FTC Act, alleging that the generic manufacturers unlawfully agreed to abandon their patent challenges and refrain from launching their generics. The District Court dismissed the complaint and the Eleventh Circuit affirmed. The Supreme Court reversed, in an opinion that focused heavily on the size and impact of the disputed settlement terms as evidence of anticompetitive behavior. The court examined its past precedent and determined that ''patent-related settlement agreements can sometimes violate the antitrust laws,'' in contrast to the Eleventh Circuit's decision, which permitted settlements that were within the scope of the patent.[114] The Court characterized the settlement at issue as an ''unusual'' agreement ''to pay the defendants millions to say out of [plaintiff's] market, even though the defendants had no monetary claim against the plaintiff.''[115] The effect, said the Court, would be that ''the consumer loses,'' because the settlement ''keeps prices at patentee-set levels . . . while dividing that [monopoly] return between the challenged patentee and patent challenger.[116] Therefore, ''a court,

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[104] *Id.*

[105] *Id.* at *11.

[106] Order, *Amgen Inc. v. Sandoz Inc.*, No. 2015-1499 (Fed. Cir. Sept. 2, 2015).

[107] Press Release, Novartis, Sandoz launches ZarxioTM (filgrastim-sndz), the first biosimilar in the United States (Sept. 3, 2015); Ben Hirschler & Michael Shields, *Novartis launches first U.S. 'biosimilar' drug at 15 percent discount*, REUTERS, Sept. 3, 2015, available at http://tinyurl.com/oelnjsg.

[108] Federal Trade Commission, ''Emerging Health Care Issues: Follow-On Biologic Drug Competition'' (June 2009), *available at* https://www.ftc.gov/sites/default/files/documents/reports/emerging-health-care-issues-follow-biologic-drug-competition-federal-trade-commission-report/p083901biologicsreport.pdf (hereafter 2009 FTC Biologic Report).

[109] *Id.*

[110] *Id.* at Executive Summary.

[111] *See generally FTC v. Actavis, Inc.*, 133 S. Ct. 2223, 2227 (2013).

[112] *Id.* at 2237.

[113] *Id.* at 2229.

[114] *Id.* at 2232.

[115] *Id.* at 2225. The Court repeated the characterization of the payment as one to stay out of a market no fewer than four times throughout the opinion. *Id.* at 2225, 2226, 2233, 2234-5.

[116] *Id.* at 2226, 2234-35.

by examining the size of the payment, may well be able to assess its likely anticompetitive effects along with its potential justifications without litigating the validity of the patent.[117]''

Though the Court granted certiorari in *Actavis* to determine ''the application of the antitrust laws *to Hatch-Waxman-related patent settlements*,''[118] the overall thrust of the opinion will likely have broader application to any unusually large settlements that could provide evidence of an anticompetitive agreement to keep a competitor out of the market.[119] The *Actavis* decision itself does not limit its definition of ''reverse payment'' to Hatch-Waxman, nor even to the generic/branded context. Rather, it simply defines the term as a settlement that requires the patentee to pay the infringer money in exchange for the infringer's agreement not to produce the patented product for a period of time.[120] Further, the Court's summary of its own holding does not mention Hatch-Waxman.[121]

The applicability of *Actavis* to biologics was addressed recently at the 2015 ABA Antitrust Spring Meeting. Markus H. Meier, Assistant Director of the Health Care Division of the Bureau of Competition at the FTC, speaking on his own behalf, observed that the agency likely will seek to use *Actavis* in the biologics context. According to Meier, as long as competitors could come together and divide monopoly profits at the expense of consumers, *Actavis* would be relevant. Others on the panel agreed, noting that the BPCIA was loosely patterned after Hatch-Waxman, and the statute contemplates pre-approval patent litigation to expedite market entry.

Given the similarities between branded-generic drug competition and biologic-biosimilar competition, the overall frame of analysis will most likely be comparable, and the FTC will scrutinize any agreements between biosimilar applicants and the reference product sponsor that would delay marketing of the product in return for payments in a manner similar to the *Actavis* ''pay for delay'' agreements. Arguments similar to those adopted in many circuit courts prior to *Actavis*, which upheld settlements that were within the scope of the patent, will most likely be rejected.

B. Efforts to Prevent or Delay Generic Entry

1. **''Product Hopping''**

Biologics and biosimilars will likely have to contend with an issue receiving an increasingly significant amount of attention in the branded-generic context. On May 28, 2015, the Second Circuit handed down the first appellate decision to consider the legal limits of ''product hopping,'' a term used to describe efforts by a drug manufacturer to shift patients from a drug that is nearing expiration of its patent protection to a successor drug with more patent life remaining. According to the FTC, product hopping occurs when the drug manufacturer ''makes minor non-therapeutic changes to the brand product, such as dosage or form change,'' then removes the original product from the market (directly or indirectly) before generic rivals can enter.[122] Using this strategy, the brand name manufacturer continues its monopoly and prevents consumers from recognizing cost savings from generics.

In *New York v. Actavis*, the Second Circuit Court of Appeals affirmed the district court's grant of preliminary injunction, holding that Actavis and its wholly owned subsidiary Forest Laboratories likely violated Section 2 of the Sherman Act by using a ''hard switch'': to avoid impending generic competition, defendants withdrew virtually all of their popular Alzheimer drug Namenda IR when it neared the end of its patent exclusivity period in order to force patients to switch to new version, Namenda XR, which had patents extending until 2029.[123] The court observed that Namenda IR and Namenda XR had ''the same active ingredient and the same therapeutic effect,'' such that ''[t]he relevant medical difference between the two is that IR, which is released immediately into the bloodstream, is taken twice a day while XR, which is released gradually, is taken once a day.''[124]

Under state drug substitution laws, the generic IR versions preparing to enter the market were therapeutically equivalent only to Namenda IR, meaning that pharmacists could not substitute the generic IR for Namenda XR in most states.[125] The court stated that ''product redesign is anticompetitive when it coerces consumers and impedes competition,'' and found that defendants' hard switch was both coercive—because it ''forced Alzheimer's patients who depend on memantine [drug] therapy to switch to XR'' and ''would likely impede generic competition by precluding generic substitution through state substitution laws.''[126] The court summarily rejected Defendants' procompetitive justifications for withdrawing IR as pretextual, finding instead that the record held substantial evidence that Defendants acted as they did to block generic competition.[127]

Product entry is not identical under the BPCIA context, but it is likely that companies will seek ways to extend their patent protection as long as possible. There are two key differences under the BPCIA. First, the lack of state substitution laws may reduce the incentive for a reference product manufacturer to make minor changes, since pharmacists cannot automatically substitute biosimilars. Second, the BPCIA excludes from the twelve year and four year reference product exclusivity periods subsequent applications by the same manufacturer or sponsor for minor changes such as ''new indication, route of administration, dosing schedule, dosage form, delivery system, delivery device, or strength'' or ''a modification to the structure of the biologic product that does not result in a change in safety, purity, or potency.''[128] The BPCIA list is not comprehensive, however, and the complexity of biologics lends itself to other avenues of change, such as new formula-

[117] *Id.* at 2237.
[118] *Id.* at 2230 (emphasis added).
[119] *Id.* at 2225.
[120] *Id.* at 2227.
[121] *Id.* at 2237.

[122] Brief for FTC as Amicus Curiae at 8, *Mylan Pharm., Inc. v. Warner Chilcott Pub. Co.,* No. 12-3824 (E.D. Pa. Nov. 21, 2012).
[123] *New York v. Actavis,* No. 14-4626, 2015 WL 3405461, at *1 (2nd Cir. May 22, 2015).
[124] *Id.* at *4.
[125] *Id.*
[126] *Id.* at *10.
[127] *Id.* at *13.
[128] 42 U.S.C. § 262(k)(7).

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tions or manufacturing processes, which reference manufacturers may exploit to preserve exclusivity.

It remains to be seen how the BPCIA provisions will impact efforts to avoid competition from biosimilars. Plaintiffs may still raise concerns if a reference product manufacturer makes changes to the biologic and tries to switch consumers to the new product when a biosimilar is about to enter the market. As with the reverse payments context, it is highly likely that courts would apply the same framework of analysis to biologic makers who attempt to delay competition.

2. **Abuse of Risk Evaluation and Mitigation Strategies**

A third potential antitrust issue surrounds the responsibilities of a branded drug manufacturer—and likely a reference product manufacturer—to provide product samples to potential competitors. FDA requires drug and biologics manufacturers to develop risk evaluation and mitigation strategies (REMS) programs when approving a drug that may pose a health and safety risk. Manufacturers may implement distribution restrictions as part of their FDA-approved REMS program. When generic drug manufacturers submit ANDAs to FDA, they must demonstrate bioequivalence between the proposed generic drug and a previously approved reference listed drug (RLD). In order to make this showing, the generic drug manufacturer must acquire samples of the RLD.

The FTC has alleged that some branded manufacturers improperly have taken advantage of the distribution restrictions in their REMS program to impede generic competition by refusing to provide samples of RLDs that would allow generic manufacturers to run tests.[129] The FTC has described this practice as a ''troubling phenomenon: the possibility that procedures intended to ensure the safe distribution of certain prescription drugs may be exploited by brand drug companies to thwart generic competition.''[130] According to the FTC, ''[i]f a brand firm can effectively block generic firms from accessing brand product for bioequivalence testing, it may be able to continue to prevent generic competition even after its patents on these products expire.''[131]

In an ongoing court case, Mylan Pharmaceuticals (''Mylan'') has alleged, among other things, that branded drug manufacturer Celgene Corporation (''Celgene'') abused its REMS program in precisely this way, creating an unlawful monopoly under § 2 of the Sherman Act.[132] Mylan's Section 2 claims survived a motion to dismiss[133] when the court found it alleged facts that ''may plausibly give rise to a duty to deal'' with competitors on the part of Celgene. The court further observed that the complaint properly alleged that there was no legitimate business reason for Celgene's actions; and that Celgene sold samples at retail and to research organizations, but refused to sell to Mylan because of its anticompetitive goals.[134] In its amicus brief in the case, the FTC urged this result, stating that Mylan's allegation—''that Celgene is willing to provide access to noncompetitors, despite its distribution restrictions, but refuses to provide access to its potential competitors, even if compensated at full retail price—supports a viable theory of exclusionary conduct under existing precedent.''[135]

Because FDA can also require REMS for biologics,[136] similar disputes may arise between the manufacturers of biosimilars and the referenced biologic products. Over a dozen biologics are marketed under REMS, some of which have restrictions on distribution.[137] As with the generic drug approval process, a company submitting an application for licensure of a follow-on biologic must demonstrate that the product is ''highly similar'' to the reference product and utilizes the same mechanisms of action, among other requirements.[138] To make the necessary showing, developers of biosimilars need samples of the reference product for testing, thus creating an opportunity for an abuse of REMS allegation similar to what the FTC alleges has occurred in the generic drug market. Given the similarities with the branded-generic context, the FTC is likely to apply the same analysis.

C. Patent Information Exchange and Collusion

As described above, the BPCIA requires a reference sponsor to provide biosimilar applicants with a list of patents the reference sponsor may assert.[139] In response, the biosimilar applicant is to provide, for each patent listed by the reference sponsor, a detailed statement of the factual and legal basis for its assertion that the patent is invalid, unenforceable, or will not be infringed by the follow-on biologic.[140] The FTC has expressed concern that this process could encourage collusion, including agreements to delay entry, allocate markets, or fix prices, since the detailed information that the follow-on applicant must provide will likely include competitively sensitive information, such as information about the timing and content of the follow-on's application, manufacturing processes, or product improvements.[141] This information exchange process differs from the Hatch-Waxman context, so there is not a precise analogue for analysis, though the FTC has likened such conduct to the pay-for-delay settlements discussed above.[142]

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[129] FTC Press Release, FTC Amicus Brief: Improper Use of Restricted Drug Distribution Programs May Impede Generic Competition (June 19, 2014), *available at* https://www.ftc.gov/news-events/press-releases/2014/06/ftc-amicus-brief-improper-use-restricted-drug-distribution.

[130] Brief for FTC as Amicus Curiae at 1, *Mylan Pharm., Inc. v. Celgene Corp.,* No. 2:14-cv-02094-ES (D.N.J Apr. 3, 2014).

[131] *Id.* at 19.

[132] Complaint, *Mylan Pharms., Inc. v. Celgene Corp.*, No. 2:14-cv-02094-ES (D.N.J Apr. 3, 2014).

[133] Order, *Mylan Pharms., Inc. v. Celgene Corp.*, No. 2:14-0294-ES (D.N.J. Dec. 23, 2014).

[134] Oral opinion of Hon. Esther Salas in the case of *Mylan Pharmaceuticals v. Celgene Corporation*, No. 2:14-02094-ES (Dec. 22, 2014).

[135] Brief for FTC as Amicus Curiae at 41, *Mylan Pharm., Inc. v. Celgene Corp.,* No. 2:14-cv-02094-ES (D.N.J Apr. 3, 2014).

[136] 21 U.S.C. § 355-1 (as amended by Pub. L. No. 110-85, § 505-1, 121 Stat. 823, 926 (2007).

[137] *See* FDA, Approved Risk Evaluation and Mitigation Strategies (REMS), *available at* http://www.fda.gov/Drugs/DrugSafety/PostmarketDrugSafetyInformationforPatientsandProviders/ucm111350.htm (last visited April 27, 2015).

[138] 42 U.S.C. § 262(k)(2)(i).

[139] 42 U.S.C. § 262 (l)(3)(A).

[140] 42 U.S.C. § 262 (l)(3)(B)(ii).

[141] 2009 FTC Biologic Report, at 58.

[142] *Id.*

Many of the competitive issues that surround biologics have an analogue in the pharmaceutical context, which helps provide insight into the way companies, agencies, and courts may analyze and resolve such concerns. At the same time, biologics have unique features that may impact the competitive landscape. As more biologics are developed and approved, it remains to be seen whether they truly hold the competitive promise the FTC predicted.

VI. Conclusion

FDA has established the basic parameters for approving licenses for biosimilars. As these new products begin making their way to the marketplace, we can also start to glean how providers and payors will make space for them in their portfolios. While much work remains, the framework for resolving patent disputes involving biosimilars is coming into sharper relief. And though key differences make this a treacherous and uncertain space, the patent framework shares many qualities with well-established procedures under Hatch-Waxman. In short, the guideposts for navigating the road to bringing biosimilars to market are emerging. Those brave enough to take the tentative first steps, however, need a comprehensive strategy that addresses the myriad of risks lying before them.

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