Panacea or Poison Pill? Making Sense of the New Biosimilars Law

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I. INTRODUCTION

A fter more than a decade of debate and mounting demand for lower-cost “generic” versions of biotechnology products, Congress on March 21 passed the Biologics Price Competition and Innovation Act (the Biosimilar Act), which is included as Title VII of the Patient Protection and Affordable Care Act (the Healthcare Reform Act). The Biosimilar Act creates what is intended to be a streamlined development and FDA approval pathway for competing versions of already-marketed biologic drug products1, with the goal of lowering prices through increased competition in the fastest growing and arguably most important segment of the health care industry. However, the new law already has been subject to criticism from longtime biosimilar advocates for both its complexity and its perceived bias toward innovator biologics manufacturers.

The act is indisputably complex, and many important details are left undefined or open-ended. FDA and the courts will be forced to take on significant burdens in interpreting and implementing the new law. It likely will be several years before even the basic elements of the law are elucidated, and if experience under the Hatch-Waxman amendments to the Federal Food,

1 Such products are variously referred to as “biosimilars,” “follow-on biologics,” or (less commonly) “biogenerics.” Follow-on products that may prove to be superior to the original brand name product are referred to a “bio-betters” or “bio-superiors.”
Drug, and Cosmetic Act (FDCA) is any guide, specific disputes under the new law likely will continue to arise for decades.

This article provides a brief overview of the history leading up to passage of the Biosimilar Act, discusses in detail both the FDA regulatory and patent litigation provisions of the act (with comparisons and contrasts to the Hatch-Waxman scheme), probes potential interpretations of key provisions, and offers practical strategic considerations both for companies seeking to pursue product approvals under the new law, and for companies whose products now may face increased competition from follow-on products.

II. BACKGROUND

A. Biologics are Different. Under the Public Health Service Act (PHSA), biologics are defined to include articles composed of “a virus, therapeutic serum, toxin, antitoxin, vaccine, blood, blood component or derivative, allergenic product, or analogous product ... applicable to the prevention, treatment, or cure of a disease or condition of human beings.” 2 FDA defines the term “analogous” broadly3 such that the term “biologic” also includes, among other things, therapeutic protein products, monoclonal antibodies, and immunoglobulin products. As the term suggests, biologics typically are derived from living organisms, and they are much larger and more complex than traditional chemical pharmaceuticals. As a result, it often is difficult if not impossible to precisely “characterize” or replicate the structure and composition of the biologic molecule. 4

Like pharmaceuticals, FDA approval of an innovator biologic product requires extensive clinical studies, along with a validated and consistent manufacturing process, to prove the safety and efficacy of the product. 5 For traditional drugs, Hatch-Waxman allows approval of a generic version based on the relatively simple showings that the proposed generic version uses the same active molecule in the same strength, dosage form, and route of administration, and that the generic version is “bioequivalent” 6 to the original product. However, Hatch-Waxman only applies to drugs that were originally approved pursuant to a new drug application (NDA) under section 505(b) of the FDCA. Because biologics are approved pursuant to biologics license applications (BLA) under the PHSA, prior to the enactment of the Biosimilar Act, no abbreviated pathway existed for the approval of “generic” versions of biologics.

B. The Legislative Pathway to a Biosimilar Approval Process. The drive for a biosimilar approval pathway gained momentum with a flourish of legislative activity in Congress in 2007-2008. Numerous versions of bills with competing approaches to critical issues were proposed in the House and the Senate. Significant debates centered on potential data and market exclusivity for innovator biologics and the concept of biosimilarity versus interchangeability. At one point it appeared that a compromise deal had been reached, but the effort eventually stalled due to friction between key members of Congress and declining support from the generic industry which hoped for a better bill under a potential Democratic administration after the 2008 elections.

The window for biosimilar legislation reopened with the election of President Obama and the push for health care reform legislation. The president and congressional Democrats sought to include biosimilars legislation in the health care reform bill to help subsidize the significant costs associated with health care reform. 7 However, the biosimilar provisions ultimately included in the health care reform bill tracked the approach advocated by Rep. Anna Eshoo (D-Calif.) whose Silicon Valley district includes many biotechnology companies. In many key respects this version was seen as far less favorable to the generic industry than the compromise version nearly passed prior to the 2008 elections. The Biosimilar Act became law on March 23, when the president signed the health care reform act (P.L. 390, 3/26/10).

The Biosimilar Act has two main sections dealing with (i) the regulatory standards and procedures for approval of follow-on biologic products, including regulatory exclusivity periods for innovator and follow-on biologic products, and (ii) complex rules and procedures for identifying and resolving patent disputes involving proposed follow-on products. These two interrelated sets of issues are addressed in the following sections.

III. OPPORTUNITIES AND OBSTACLES ON THE REGULATORY PATHWAY

A. Biosimilarity and Interchangeability

The Biosimilar Act creates a regulatory scheme for two types of generic biologics: “biosimilars” and interchangeable biologic products. Under the act, a generic product can be approved as “biosimilar” to a reference (brand name) biologic product if it is shown to be “highly similar to the reference product notwithstanding minor differences in clinically inactive components” and “there are no clinically meaningful differences between the [biosimilar] biological product and the reference product in terms of safety, purity, and potency of the product.” 8 A biosimilar biological product can be deemed “interchangeable” if “the biological product may be substituted for the reference product without the intervention of the health care provider who prescribed the reference product.”

1. “Biosimilar”— Approval Lite? To meet the baseline criteria for approval of a follow-on biologic, a company

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2 42 U.S.C. § 262(i).
3 21 C.F.R. § 600.3(h).
4 For this reason, the term “generic biologic,” with its connotations of exact product duplication, has fallen into relative disuse, even among proponents of a follow-on biologic approval pathway.
5 Under the PHSA, biologics must be shown to be “potent” rather than “effective,” but the two terms are, in regulatory practice, essentially synonymous. See 21 C.F.R. § 600.3(s) (defining “potency”).
6 “Bioequivalence” is defined as “the absence of a significant difference in the rate and extent to which the active ingredient or active moiety in pharmaceutical equivalents or pharmaceutical alternatives becomes available at the site of drug action when administered at the same molar dose under similar conditions in an appropriately designed study.” 21 C.F.R. § 320.1.
8 The cost savings potential of the bill was vigorously debated, with the Congressional Budget Office estimating $6 billion to $7 billion in savings over 10 years, and the generic industry arguing that the savings could be twice as great.
9 42 U.S.C. § 262(i)(2).
10 42 U.S.C. § 262(i)(3).
must submit an application demonstrating that the biological product is biosimilar to the reference product based upon data derived from analytical, animal, and clinical studies. Additionally, the applicant must demonstrate that: (i) the follow-on biological product and reference product "utilize the same mechanism or mechanisms of action for the conditions or conditions of use prescribed" (to the extent the mechanism of action is known), (ii) "that the conditions or conditions of use have been previously approved for the reference product," (iii) that the route of administration, (iv) the dosage form, and (v) the strength of the biological product are the same as those of the reference product, and (vi) that "the facility in which the biological product is manufactured . . . meets standards designed to assure that the biological product continues to be safe, pure, and potent."11 The assumption, which has yet to be proven, is that the quantum of data necessary for a biosimilar approval will be substantially less than that originally required in support of approval of the reference product.

This baseline "biosimilar" approval option is enough to get a product to market, but it may not be enough to allow for the same level of competitiveness and cost savings as is seen with the approval of generic versions of traditional pharmaceuticals. Without an FDA endorsement of interchangeability (reflected in the generic drug context by an "A" rating in FDA's Orange Book), pharmacists or hospitals may not automatically substitute a "biosimilar" follow-on product when presented with a prescription or order for the original brand name product. Thus, to gain market acceptance and market share, a biosimilar product sponsor will need to brand its product and engage in costly marketing efforts to encourage prescribers to use its product as an alternative to the original innovator product.

The greater the marketing costs, the costlier the product will be to patients and the lower the savings to the health care system. Indeed, this scenario has played out with existing versions of similar biologics such as erythropoietin (Procrit and Epogen), and botulinum toxin (Botox, Dysport, and Myobloc), each of which was approved under a full BLA but which are not deemed interchangeable for each other.12 Approval as a "biosimilar" under the Biosimilar Act thus might save sponsors some time and money in the development and approval process, but may not move the needle much in terms of overall cost savings to patients and the health care system.

2. Interchangeability—Oasis or Mirage? The Biosimilar Act contemplates the potential additional approval of a biosimilar biologic as interchangeable with the relevant innovator product. Before further approving a biosimilar biologic as interchangeable, FDA also must conclude that the follow-on product "can be expected to produce the same clinical result as the reference product in any given patient."13 More specifically, FDA must find that "the risk in terms of safety or diminished efficacy of alternating or switching between use of the biological product and the reference product is not greater than the risk of using the reference product without such alternation or switch."14

The standards outlined in the law, as they will likely be interpreted by FDA, may be difficult to meet. As key FDA officials suggested in a 2007 article:

To establish that two protein products would be substitutable, the sponsor of a follow-on product would need to demonstrate through additional clinical data that repeated switches from the follow-on product to the referenced product (and vice versa) would have no negative effect on the safety and/or effectiveness of the products as a result of immunogenicity. For many follow-on protein products—and in particular, the more complex proteins—there is a significant potential for repeated switches between products to have a negative impact on the safety and/or effectiveness. Therefore, the ability to make determinations of substitutability for follow-on protein products may be limited.15

Thus, establishing interchangeability for a biosimilar product rarely may be achieved. Nevertheless, in an emerging era of health care austerity, and with the potential rise of comparative effectiveness research as a basis for therapeutic reimbursement decision making, the market for "mere" biosimilar (noninterchangeable) products may follow a significant growth curve and contribute meaningfully to reduced health care expenditures.

3. FDA's Role in Determining Biosimilarity and Interchangeability. The Biosimilar Act specifically carves out a prominent role for FDA in determining the relevant standards for interchangeability and biosimilarity. In particular, the act provides that FDA may issue general or specific guidances with respect to biological products after a period for public comment.16 Moreover, the act specifically permits FDA to issue a guidance indicating that, in light of "science and experience," certain products or product classes will not receive approval. Notably, the act provides that if FDA does issue a class-specific guidance, it must include the criteria that FDA will use to determine interchangeability and biosimilarity. Given the time and effort needed to develop complex scientific guidelines, initial determinations likely will be made on a case-by-case basis.

B. Data and Market Exclusivity

1. Exclusivity for Reference Product

Perhaps the most hotly debated issue during the legislative process was the length of regulatory "data exclusivity" and "market exclusivity" to be granted for innovator biologic products. Data exclusivity prevents competitors from relying on clinical data developed by the original product sponsor in support of FDA approval of a competing version of the product. Market exclusivity operates to delay FDA approval of an appli-
cation that relies upon a prior product’s safety and efficacy data. Under the Hatch-Waxman amendments there is a five-year data exclusivity barrier to the submission of abbreviated new drug applications (ANDAs) for generic versions of a “new chemical entity” drug product. In addition, under Hatch-Waxman, clinically backed changes to innovator drug products may qualify for an additional three-year marketing exclusivity.

Prior proposed versions of the Biosimilar Act included innovator biologic exclusivity periods ranging from 14 years (as advocated by the Biotechnology Industry Organization (BIO)) to no exclusivity at all (as proposed at one point by Rep. Henry Waxman (D-Calif.)). The law as enacted provides for four years of data exclusivity during which time FDA cannot accept the submission of a biosimilar application, and a total of 12 years of market exclusivity during which time FDA may not approve such a biosimilar application.

The Biosimilar Act does not permit exclusivity for supplements to approved BLAs (along the lines of the Hatch-Waxman three-year exclusivity) and also seeks to restrict exclusivity for new applications submitted by an original sponsor for a new version of its biologic product. Specifically, new BLAs that result in new indications, routes of administration, dosing schedules, dosage forms, delivery system, delivery device, or strength, generally are not eligible for exclusivity. However, this limitation comes with a critical caveat. A new BLA may obtain exclusivity if the change involves a “modification to the structure” of the product and the structural change results in a change in safety, purity, or potency of the product.

Despite efforts to limit the Biosimilar Act’s exclusivity provisions, critics argue that the system nevertheless will be subject to “evergreening” strategies by sponsors of innovator biologics. For example, although exclusivity does not apply to a “modification to the structure of the biological product that does not result in a change in safety, purity, or potency” of the product, given the complex nature of biologics and the potential for even seemingly minor changes (in formulation or even complex nature of biologics and the potential for even this question.

Moreover, because the Biosimilar Act provides that a biosimilar application “may not be evaluated against more than one reference product,” if FDA were to determine that a structural change to a reference product creates a new reference product, an applicant with a pending biosimilar application might be required to go back to square one and resubmit an application that only references the modified version of the reference product. In such circumstances, some fear, the biosimilar applicant might be forced to wait for the expiration of a second or even third 12-year exclusivity period.

In addition to the 12-year exclusivity, the Biosimilar Act provides for an additional six months of pediatric exclusivity for a reference product if FDA determines that the product may produce health benefits in the pediatric population and the sponsor completes and submits requested pediatric studies of its product. The six month pediatric exclusivity period is available for both new and already-marketeted biological products.

2. Market Exclusivity for First Interchangeable Biosimilar Products

Under the Hatch-Waxman system, the first applicant to submit an ANDA that contains a “Paragraph IV” certification challenging a reference drug’s Orange Book listed patent as invalid, unenforceable, or not infringed is eligible for a 180-day exclusivity period against the approval of subsequently filed Paragraph IV ANDAs.

The Biosimilar Act provides a modified type of biosimilar exclusivity that temporarily prevents the FDA from making an interchangeability determination for a biosimilar product in circumstances where a prior biosimilar already has been deemed to be interchangeable with the same reference product.

The length of this exclusivity period depends on the circumstances involving the marketing of the first interchangeable product and the status of any patent litigation involving the first interchangeable product sponsor. Specifically, after the first product has received a determination of interchangeability, FDA cannot make an interchangeability determination for a second product until the earlier of: (i) one year after the first commercial marketing of the first interchangeable product; (ii) 18 months after a final court decision in favor of the applicant with respect to all patents in suit (or the dismissal of the complaint with or without prejudice); (iii) 42 months after approval of the first interchangeable product if patent litigation is still ongoing; or (iv) 18 months after approval of the first interchangeable product if the first interchangeable applicant has not been sued.

Significantly, this exclusivity only bars FDA from making a subsequent determination of interchangeability, and does not bar immediate approval of a second product as biosimilar without a determination of interchangeability. Given the expected difficulty of obtaining an interchangeability determination, as described

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17 Both data and market exclusivity operate independently of any patent protections.
18 See 42 U.S.C. § 262(k)(7). This exclusivity does not bar the submission of an ANDA, but does delay approval of generic versions that include the change protected by the exclusivity.
22 See 42 U.S.C. § 262(k)(5)(F)(iii). This exclusivity does not bar the submission of an ANDA, but does delay approval of generic versions that include the change protected by the exclusivity.
26 See Natrex Review, supra (FDA discusses safety and potency effects of manufacturing and structural changes for Avenox (interferon beta-1a) and Eprex (erythropoietin-alfa)).
above, and in light of the cumbersome patent litigation procedures applicable to biosimilar products, as described below, it is doubtful that the interchangeable product exclusivity provisions will ever have the broad commercial and legal impact that the Hatch-Waxman generic exclusivity period has had for the generic pharmaceutical industry. With the resource constraints FDA faces, the complexity of the biosimilar scheme in general, and the exclusivity provisions in particular, it is unlikely that the agency will give high priority to developing guidance or regulations for this exclusivity system unless and until it faces a specific situation in which an exclusivity decision must be made.

IV. THE KABUKI THEATER OF BIOLOGICS PATENT LITIGATION

As complex as traditional Hatch-Waxman patent litigation can be, after 25 years that system has acquired a familiarity to sponsors, attorneys, and judges which allows for a relative degree of efficiency and a reasonably manageable and predictable set of procedural expectations. Rather than adopting a comparable litigation process for follow-on biologics, however, Congress, in the Biosimilar Act, has created an even more complex and process-bound system for resolving patent disputes involving biosimilar products. Thus, resolving biosimilar patent disputes will impose a significant new learning curve for companies, counsel, and courts.

The Biosimilar Act requires significantly more pre-litigation interaction between the reference product sponsor and the biosimilar applicant. This includes (i) immediate full disclosure of the biosimilar application to the reference product sponsor, (ii) identification of the patents each party believes are relevant to the reference and biosimilar products, (iii) an exchange of substantive briefings on the validity and potential infringement of the identified patents, (iv) a (rather artificial) negotiation process regarding which patents will actually be litigated, and (v) a simultaneous double-blind exchange of patents designated for litigation, in the event prior agreement has not been reached.

Moreover, the law imposes potentially significant limitations on the patent rights of innovator biologics sponsors by giving the biosimilar applicant unilateral power to limit the number of patents that may initially be asserted by the reference product sponsor, limiting patent infringement remedies, in some circumstances, to a reasonable royalty, and by not providing an automatic stay of approval of the biosimilar application as is available under Hatch-Waxman. These issues are discussed in more detail below.

A. Burden-Shifting Informational Advantages for Reference Product Sponsors

The Biosimilar Act gives reference product sponsors two strong informational advantages that NDA holders do not enjoy under Hatch-Waxman.

First, unlike under Hatch-Waxman, the Biosimilar Act does not provide for the publication by FDA of a list of approved biologic products and the patents which the reference sponsor claims cover such products. Thus, biosimilar applicants are on their own, when developing a biosimilar product, in determining which patents must be avoided or challenged.

While companies sophisticated enough to pursue biosimilar applications likely are also knowledgeable about patent searching and analysis, the lack of a definitive innovator-generated patent list does impose a resource burden as well as a risk of under-inclusion in the biosimilar applicant’s patent due diligence. For example, the scientific nomenclature for antibodies and other types of biologics is not always as standardized as for small molecule drugs, especially in the early stages of their development. Moreover, small molecule patents can be searched based on molecular structure, whereas this is more difficult for large-molecule biologics. In addition, unlike under Hatch-Waxman, under the Biosimilar Act manufacturing or process patents are subject to the biosimilar litigation process, but these types of patents can also be more difficult to search.

Second, under Hatch-Waxman, generic applicants have four procedural options by which they can obtain approval without disclosing in advance that they have filed a generic application; these are the Paragraph I, II, and III certifications, and the “section (vii)” labeling carve-out statement.32 Only when a generic applicant seeks approval prior to expiration of an Orange Book-listed patent must the applicant notify the reference drug sponsor that an application has been filed.33 In contrast, there is no choice of patent certification options for biosimilar applicants. Rather, the Biosimilar Act requires the disclosure of a complete copy of every biosimilar application to the reference product sponsor, even if the applicant does not intend to market its product prior to the expiration of applicable patents.34 Some companies hoping to pursue biosimilar applications are strongly critical of this requirement, fearing that it will allow reference sponsors to pursue strategic blocking strategies with the information contained in the biosimilar application.35

B. Exchange of Application and Patent Information

1. Disclosure of Biosimilar Application to the Reference Product Sponsor

The biosimilar applicant must disclose its application within 20 days of FDA’s acceptance of the application. The applicant also must include “such other information that describes the process or processes used to manufacture the biological product.”36 This starts the multi-step procedure leading up to patent litigation. However, the requirements may leave some patent owners in the dark regarding a potential competitive threat to their patents.

Specifically, unlike a Hatch-Waxman Paragraph IV notification, which must be provided to both the NDA sponsor and the owner of the listed patent (if the NDA sponsor does not own the listed patent),37 the biosimilar application disclosure is only sent to the sponsor of the reference product BLA. The act appears to allow a reference product sponsor to share the biosimilar application with third-party owners of patents which are exclusively licensed to the reference product sponsor, but only if the patent owner agrees in writing to be subject to the statutory confidentiality rules governing the use of the application information.38

34 42 U.S.C. § 262(l)(1)-(2).
35 Indeed, some companies have publicly stated that they will pursue full BLAs rather than biosimilar applications, specifically to avoid this disclosure requirement.
product sponsor is not required to notify third-party patentees, and such patentees are not required to participate in the confidential disclosure process. Thus, third-party owners of patents that may be infringed by a biosimilar product might not become aware of the filing of a potentially infringing biosimilar application, or may strategically decline to participate in the pre-litigation process with respect to their patents.

2. Reference Sponsor’s Comprehensive Patent List. After a reference product sponsor has received the application and other information from the biosimilar applicant, the sponsor must, within 60 days, provide a list of patents which it believes cover the biological product. The list shall include any patent that would be infringed by “someone engaged in the making, using, offering to sell, selling or importing into United States of the biological product.” This is broader than Hatch-Waxman because the relevant patents under the Biosimilar Act include process patents (any patent that would be infringed by “someone engaged in the making” of a product), whereas under Hatch-Waxman, reference drug sponsors may only list, and generic applicants need only certify to, patents that claim the drug or a use of the drug. The reference product sponsor may identify patents owned by third parties for which it is the exclusive licensee, apparently without regard to whether the third-party patentee has agreed to receive the biosimilar application under the statutory confidentiality rules.

3. Biosimilar Applicant’s Comprehensive Patent List and the Exchange of Detailed Statements. Within 60 days of receipt of the reference sponsor’s comprehensive patent list, the biosimilar applicant may, but is not required to, reciprocate with its own patent list identifying those patents for which the biosimilar applicant believes an infringement claim could reasonably be asserted by the reference sponsor.

In all cases, however, the biosimilar applicant must substantively respond to the sponsor’s list of patents. The response either may identify reasons that the patents identified by the reference sponsor (and any other patents identified by the biosimilar applicant) are invalid, unenforceable, or would not be infringed by the commercial marketing of the biosimilar product, or state that the applicant “does not intend to begin commercial marketing of the biological product before the date that such patent expires.” This “detailed statement” requirement is analogous to the Paragraph IV notification process under Hatch-Waxman, and companies who have filed ANDAs may take a similar approach here.

After this stage, the biosimilar scheme departs more dramatically from the Hatch-Waxman process. Under Hatch-Waxman, once the generic company provides its detailed statement and Paragraph IV Notification, the innovator company is free to assert the challenged patents in district court. In contrast, under the Biosimilar Act, after the biosimilar applicant supplies its detailed statement(s), the reference product sponsor must, within 60 days, provide a detailed counter-statement setting forth on a patent-by-patent and 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 [biosimilar] product . . . and a response to the [biosimilar applicant’s] statement concerning the validity and enforceability” of the patent.

Thus, the Biosimilar Act seems to contemplate that the parties will extensively brief their legal and factual positions in such a way that litigation might be avoided for many of the patents at issue, and be streamlined for patents that go to trial. However, the act does not specify how much information and analysis are required for a detailed statement to be deemed sufficiently “detailed.” In the Hatch-Waxman context FDA has steadfastly refused to engage in adjudicating the sufficiency of Paragraph IV detailed statements.

Given the tight deadline for a responsive “detailed statement” by the reference product sponsor, the potentially large number of patents for which a response may be required, and the potentially binding effect of such statements in future litigation, reference product sponsors may have strong incentives to provide minimalistic detailed statements at this stage of the dispute process. Similar incentives may influence biosimilar applicants’ detailed statement strategies as well, so rather than reducing patent litigation the act may well result both in more patent litigation and more efforts to seek judicial redress in cases where allegedly insufficient detailed statements have been provided by biosimilar applicants or reference product sponsors.

C. Teeing Up the Initial Litigation

1. Patent Resolution Negotiations. The preceding exchange sets in motion what the act calls the “Patent Resolution Negotiation.” Under this provision, the reference sponsor and biosimilar applicant “shall engage in good faith negotiations to agree on which, if any patents” on the lists previously exchanged by the parties should be litigated. The parties have 15 days to reach agreement. If the parties agree on which patents should be litigated, then the reference product sponsor shall bring an action for patent infringement with respect to the patents so identified.

spect to each such patent within 30 days of such agree-
ment.  

2. Designation of Patents for Litigation. If the parties do
not reach agreement on which patents to litigate, the
parties exchange additional lists. First, the biosimilar
applicant informs the reference sponsor how many pat-
ents it believes should be litigated. This is a prelude to
the final exchange in which each party identifies the
specific patents it seeks to litigate. The preliminary
notice by the biosimilar applicant of the number of pat-
ents it will designate for litigation is important because
the act provides that the reference product sponsor may
not designate a greater number of patents than the bio-
similar applicant (unless the applicant designates no patents in which case the reference sponsor may design-
ate one patent).

Although the biosimilar applicant controls how many
patents will be litigated at this initial stage of the dis-
pute by controlling how many patents may be design-
ated by each party for litigation, the total number of
patents potentially eligible for litigation actually is twice
the number of patents designated by the applicant. For
example, if the applicant chooses to designate three
patents for litigation, the reference sponsor also may
designate three patents, but these will not necessarily be
the same three patents designated by the applicant.
The designated patent lists must be exchanged simulta-
eously, so neither party can strategically select patents
based on the other party’s designations. After the litiga-
tion lists are exchanged, the reference sponsor “shall bring” an infringement action with respect to “each patent that is included on such lists”—i.e., all patents on
the applicant’s list and all patents on the sponsor’s list.
Congress’s use of the mandatory “shall bring” appears to
leave the reference sponsor no discretion at this stage to decline to litigate a designated patent, and in fact the sponsor may lose substantial rights if it fails to bring a timely lawsuit. Once the complaint is
filed, the biosimilar applicant must notify FDA, which
then must publish a notice of the lawsuit in the Federal
Register.

Importantly, unlike under Hatch-Waxman, there is
no automatic regulatory stay of approval of the biosim-
lar application during the course of the litigation, al-
though, as described in the following section, there is
an opportunity to seek judicial injunction in the period
just prior to the biosimilar market launch.

D. The Second Stage of Litigation

The procedures described above establish, and poten-
tially limit, the universe of patents that will be liti-
gated in the initial phase of the lawsuit. However, a ref-
ence product sponsor has a chance to “call in the res-
serves” by bringing a preliminary injunction motion
with respect to patents that are not included in the ini-
tial litigation. Specifically, the act requires the biosimi-
lar applicant to give 180 days notice in advance of its
first commercial marketing of its proposed biosimilar
product. After receiving this notice, the reference
sponsor may seek a preliminary injunction against the
commercial manufacture or sale of the biosimilar prod-
uct based on alleged infringement of any patent that is
not the subject of the initial litigation phase, but was ini-
tially listed by either party as potentially applicable to
the proposed biosimilar product.

E. Strategic Considerations

1. Designating Patents for Litigation. As discussed
above, much of the complexity of the Biosimilar Act’s
patent related provisions arises from the process for
identifying which patents actually will be subject to a
lawsuit in the initial litigation phase. These provisions
pose significant strategic challenges in uncharted terri-
tory for both reference product sponsors and biosimilar
applicants. One key question for both is whether to be
over-inclusive or under-inclusive in seeking to define
the initial scope of litigation. In answering this question,
companies will want to predict as accurately as possible
what type of strategy the other party will adopt, as well
as which specific patents they likely will designate for
trial. The answers to these questions are neither obvi-
ous nor simple.

The Kitchen Sink Approach? . . . For reference spon-
sors, there may be a temptation to throw as many pat-
ents as possible in the pathway of a biosimilar competi-
tor in order to maximize the chances that at least one
patent will prevail, and as a secondary effect, deplete
the competitor’s financial and operational resources in
a complex multi-patent lawsuit. However, Congress has
limited this strategic approach by allowing the biosimi-
lar applicant to decide unilaterally the maximum num-
ber of patents that may be subject to the initial litiga-
tion. Nevertheless, this limitation may be irrelevant in
some cases, because biosimilar applicants themselves
may prefer to litigate numerous patents to minimize the
legal uncertainty about their freedom to market without
fear of patent liability, or even to attempt to impose re-
source burdens on the reference sponsor (which may in
fact be a smaller company than the biosimilar appli-
cant).

...Or a Game of “Chicken”? Alternatively, reference
sponsors might seek to challenge biosimilar applicants
to a game of “chicken” by holding back certain patents
from the initial litigation, with the implicit threat that
such patents may be interjected via a preliminary in-
junction motion in the six months prior to the appli-

54 It is an interesting question whether this mandatory law-
suit provision would trump Federal Rule of Civil Procedure 11
and its attorney sanction provisions in the event a biosimilar
applicant designates a patent for which the reference sponsor
believes it has an objectively reasonable basis to bring suit.
55 See infra section IV.F.
58 42 U.S.C. § 262(I)(8)(B). The statutory provision here is
not a model of drafting precision. Patents eligible for the
phase-2 PI motion must be (i) included in either the applicant’s or
the reference sponsor’s comprehensive patent lists and (ii)
“not included, as applicable, on—(I) the list of patents de-
scribed in paragraph (4); or (II) the list of patents described in
paragraph (5) (B)” 42 U.S.C. § 262(I)(8)(B)(i) (emphasis added). Paragraph (5)(B) clearly covers all patents on the par-
tial litigation designation lists, which are included in the first
(ongoing) phase of litigation, but paragraph (4) only directly
describes “the initial comprehensive lists under paragraph
(3), some of which patents by necessity would be included in
the designation lists and the initial litigation. The intent in
paragraph (4) appears to be simply to describe the agreed list
of patents for litigating against the reference sponsors, as opposed to the dual designa-
tion lists covered by paragraph (5)(B) when an agreed litiga-
tion list was not achieved.
cant’s announced commercial launch date. But biosimilar applicants can play this game too, in the hope that the reference product sponsor will not be able to convince a court to issue a PI on the eve of the biosimilar launch. In such circumstances, the coercive power of a threatened “launch at risk” may provide enough leverage for the biosimilar applicant to obtain a favorable settlement with the reference sponsor.

Other factors to consider include whether to designate third-party patents, or particular types of patents (e.g., process or manufacturing patents) for initial litigation or to hold those patents for potential PI motions. The perceived strength, and the expiration dates of relevant patents also will play a role in deciding whether and how to litigate.

**2. Can Biosimilar Applicants Avoid Litigating Process Patents?**

As noted above, process patents can be listed by reference sponsors in their initial disclosure lists and such patents appear to be fair game for litigation under the Biosimilar Act. However, there is arguably a loophole in the act that may give biosimilar applicants a way to avoid being enjoined from using a patented manufacturing process. Specifically, FDA is not explicitly required or authorized to deny approval based on a failure to disclose the biosimilar application.59 Rather, the only express remedy if the biosimilar applicant does not disclose its application, is that the reference product sponsor (but not the biosimilar applicant) may bring a declaratory judgment action for infringement and seek injunctive relief.60 Curiously, this DJ option applies to declaratory judgment action for infringement and seeks or manufacturing patent. In contrast, if the biosimilar applicant discloses its application upon FDA acceptance and the parties exchange patent lists, manufacturing or process patents may be so listed and are subject to either the initial phase of litigation, or to phase-2 PI litigation.61 Thus, the application disclosure “requirement” may not be as mandatory as it would seem, and there may be situations in which it would be strategically advantageous for an applicant to not provide the application to the reference product sponsor. It will be interesting to see if FDA (or the courts) interpret and implement these statutory provisions in a way that confirms, or closes, this strategic approach.

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59 Under Hatch-Waxman, the failure of a generic applicant to certify to all Orange Book-listed patents for FDA to refuse to approve the application, 21 U.S.C. § 355(j)(4)(J). In the biosimilar context, FDA might nevertheless establish by regulation that failure to disclose the application bars its approval. See 42 U.S.C. § 262(a)(2)(A) (FDA “shall establish, by regulation, requirements for the approval, suspension, and revocation of biologics licenses”). But cf., 21 C.F.R. § 601.4(b) (FDA may deny approval of a BLA if “the establishment or product does not meet the requirements established in this chapter.” (emphasis added). However, procedural rule of the applicant to disclose the application is not a failure of “the establishment or product” to meet a substantive requirement of the regulations.


61 See 42 U.S.C. § 262(b)(3)(A)(i) (allowing reference product sponsor to identify all patents that may be infringed by the “making, using, offering to sell, selling, or importing”).

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**F. Does the Act Strike the Right Balance With Respect to Patent Rights?**

Given the complexity of the patent dispute provisions of the Biosimilar Act, it will likely take several years and numerous litigated cases before it will be possible to draw firm conclusions about whether the law has struck an appropriate balance between the rights of patent owners and the interests of biosimilar applicants. A key question to be resolved is whether the act prevents, or actually facilitates, serial litigation beyond the scope of proceedings contemplated in the law. To be sure, the act appears to be designed, in part, to limit litigation, including by way of several restrictions on patent rights, but those provisions will ultimately require interpretation by the courts and the emerging judicial gloss will be critical in evaluating the success or failure of the Act in this regard.

For example, the Biosimilar Act seeks to incentivize prompt and fully resolved litigation on the patents designated by the parties. It does so by restricting patent infringement remedies to a “reasonable royalty” in cases where an action is brought after the expiration of the 30-day lawsuit filing window, and in cases where litigation is timely brought but the case is dismissed without prejudice or is “not prosecuted to judgment in good faith.”62 Moreover, the act provides for permanent injunctions against infringing biosimilar products, but only if the biosimilar product has not yet been approved and there is a final, nonappealable court decision of infringement.63

In addition, if any patent that “should have been included” in the reference sponsor’s initial comprehensive patent list “was not timely included,” the owner of the patent (even if it is a third party unrelated to the reference sponsor) may not bring an infringement action against the biosimilar applicant under section 271 (e).64 Thus, if a reference sponsor fails to list a third-party patent and thereby prevents the patentee from asserting its patent, the patent owner may well seek to challenge this restriction on various procedural, statutory, or even constitutional grounds.

It remains to be seen whether the system established by the Biosimilar Act succeeds in focusing and limiting patent litigation, or whether the attempt to specify numerous detailed procedures and limitations ultimately creates more loopholes than it closes.

**V. CONCLUSION**

Even though Congress, FDA, and industry have been debating and developing a biosimilars approval pathway for at least a decade, passage of the Biosimilar Act is in every meaningful sense just the beginning. Biosimilar product development research still is in its early stages, and there remain numerous scientific, regulatory and legal questions that must be resolved before we see approval of significant numbers of biosimilar product applications.

FDA will have its hands full interpreting and implementing the act, and there can be no doubt that litigation will flourish under the new law—including not only patent infringement actions, but also ancillary disputes over the pre-litigation process itself. Challenges to FDA
regulations and decisions involving product approvals, exclusivity, and the substantive standards (especially respecting interchangeability) applied to biosimilars also will likely proliferate. And finally, given the stakes involved, and the disappointment expressed by some as to the final provisions of the law, it is likely, if not probable, that Congress will face pressure in the coming years to revisit and amend the law. Anyone with an interest in this law will need to monitor its development closely for years to come.