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New Legal Pathway for Biosimilars Creates Opportunities and Challenges For Biological Manufacturers — A Guide To The Legislation

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On March 23, 2010, President Obama signed the *Patient Protection and Affordable Care Act*, known to most as the Health Care Reform bill. The Health Care Reform bill included the *Biologics Price Competition and Innovation Act of 2009*. The Act amended the Public Health Service Act (PHS Act) to create a new pathway for the approval of applications for biological products shown to be biosimilar to, or interchangeable with, a licensed reference product.

Biosimilar Products

The Act defines a biosimilar product to mean a biological product that is both "highly similar to the reference product notwithstanding minor differences in clinically inactive components" and for which "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."[1] Companies submitting biosimilar applications have the option to further demonstrate the interchangeability of the biosimilar product with a licensed reference product. An interchangeable biosimilar product is defined as a biological product that "may be substituted for the reference product without the intervention of the health care provider who prescribed the reference product."[2] An interchangeable product is required to be biosimilar to the reference product, expected to produce the same clinical result as the reference product in any given patient and if administered more than once to an individual, the risk in terms of safety or diminished efficacy of alternating or switching between use of the biosimilar product and the reference product is not greater than the risk of using the reference product without such alternation or switching.[3]

Scope of Biologics Covered

The Act permits the submission of a biosimilar application that references one (and only one) approved biologic license application (BLA) product.[4] Moreover, the Act modifies the definition of "biologic" to include a "protein (except any chemically synthesized polypeptide)."[5] Thus, the biologic definition now includes:

> a virus, therapeutic serum, toxin, antitoxin, blood, or blood component or derivative, allergenic product, protein (except any chemically synthesized polypeptide), or analogous product . . . applicable to the prevention, treatment, or cure of a disease or condition of human beings.

Exclusivity Provisions

The Act establishes a 12-year period of "market exclusivity" from the date of licensure for the licensed reference product, which may be extended by six months of pediatric exclusivity.[6] The first four years (or 4.5 years with pediatric exclusivity) is a period of so-called "data exclusivity" during which time an application for a biosimilar or interchangeable version of the reference licensed product may not be accepted for review by the Food & Drug Administration (FDA).[7] The 12 year "market exclusivity" operates only to block applications submitted via the biosimilar pathway, however. Thus, applicants who submit a full BLA will not be blocked by the 12 year exclusivity period.

The 12-year exclusivity period will not apply to the approval of a supplemental application or a subsequent application filed by the same sponsor for (a) a change resulting in a new indication, route of administration, dosing schedule, dosage form, delivery system, delivery device or strength, or (b) a structural modification that does not change safety, purity or potency.[8] This carve-out opens questions as to what FDA's position will be on the type of structural modifications that will be found to change a product's "safety, purity or potency", but it appears under the statute that such a product embodying such a change would be eligible for the 12 year exclusivity period.

Because biological products also are eligible for, and may obtain, orphan drug exclusivity, the Act specifically notes that the licensure of a biosimilar or interchangeable version of a reference product that was designated and approved as an orphan drug may only occur after expiration of the later of any applicable seven-year orphan drug exclusivity period or the 12-year market exclusivity period (or 7.5 years and 12.5 years with pediatric exclusivity).[9]

The first approved interchangeable biosimilar product is afforded its own period of market exclusivity, that expires on the earlier of: (1) one year after first commercial marketing of the interchangeable product; (2) 18 months after the resolution of patent litigation with the sponsor of the reference product; (3) 42 months after initial approval of the interchangeable product if patent infringement litigation is ongoing; or (4) 18 months after approval of the first interchangeable biosimilar if the biosimilar applicant has not been sued for patent infringement by the sponsor of the reference product.[10]

Requirements for Biosimilar Applications

A biosimilar application must contain information to demonstrate that the product is biosimilar based upon data derived from (1) analytical studies showing that the product is "highly similar" to a reference despite "differences in clinically inactive components;" (2) animal studies (including the assessment of toxicity); and (3)

clinical study(ies) sufficient to demonstrate "safety, purity and potency in 1 or more appropriate conditions for use" that parallel an approved use of the reference product.[11] Notably, however, the Act permits FDA to determine that any of the data outlined above may be unnecessary in any particular application.[12] Other requirements of the Act (that FDA cannot waive) include that (4) the application must contain the same mechanism of action as reference product (if known) for approved indication; (5) the label for the biosimilar must match an approved indication of the reference product; (6) the route of administration, dosage form, and strength must match the reference product; and (7) there must be an approved manufacturing facility (to assure the product continues to be safe, pure and potent).[13]

User Fees

While the Act authorizes user fees for biosimilar applications, they do not become effective until October 1, 2012. During this interim period FDA is responsible for evaluating the costs of review, accepting public comment and holding public meetings, and then reporting back to Congress on appropriate user fees. Therefore, although it appears that FDA may receive applications for biosimilar products immediately, there will be no user fees until October 2012.[14]

Guidance Documents

The Act authorizes, but does not require, FDA to issue guidance documents. The Act requires FDA to allow an opportunity for public comment prior to finalizing any guidance, but does not require any guidance to be finalized before FDA takes action on any biosimilar applications. Like much of the statute, the Act provides FDA with significant flexibility in the issuance of biosimilar guidance documents.[15]

Impact on Patent Litigation

The Act defines the submission of a biosimilar application as an act of patent infringement, and establishes a new and complex procedure for resolving resulting patent disputes. Notably, the biosimilar patent litigation procedure differs in significant ways from the corresponding patent dispute process under the Hatch-Waxman Act regarding abbreviated new drug applications (ANDAs). The differences and complexity of this new procedure will likely require time, FDA guidance, as well as court intervention, to establish exactly how this system will work going forward.

Details of the Patent Dispute Procedure Under the Act — Exchange of Biosimilar Manufacturing Process and First Patent Lists

The Act provides for several exchanges of information between the biosimilar applicant and BLA holder according to a strict schedule:

Within 20 days after the FDA has accepted its abbreviated application, a biosimilar applicant must provide the BLA holder: (i) a copy of the biosimilar application and (ii) other information describing the process(es) for manufacturing the biosimilar

product.[16] The BLA holder must keep the application and information confidential, and may only use such material to evaluate infringement.[17]

Within 60 days of receiving the above information, the BLA holder must provide the biosimilar applicant with a list (first BLA list) of all patents that the BLA holder reasonably believes are infringed, as could be asserted by either the BLA holder or a patent owner that has granted exclusive rights to the BLA holder.[18] The BLA holder also must identify any patents on the list that it is willing to license to the biosimilar applicant.[19]

Within 60 days of receiving the first BLA list, the biosimilar applicant *may* provide to the BLA holder a list (first biosimilar list) of patents that the biosimilar applicant believes could be subject to a claim of patent infringement.[20] The biosimilar applicant may choose to list no patents, a subset of patents listed in the first BLA list, or additional patents that it hopes to litigate.

Both Parties Provide Factual and Legal Basis

Within the same 60 days of receiving the first BLA list, regarding any patents listed in the first BLA list or the first biosimilar list, the biosimilar applicant *must* also provide: (I) a statement describing, on a claim by claim basis, a factual and legal basis for an opinion that a patent is invalid, unenforceable, or not infringed; or (II) a statement that the biosimilar applicant does not intend to market until the patent expires.[21] The biosimilar applicant must also provide a response to the BLA holder's offer to license patents.[22]

Within 60 days of receiving that material, the BLA holder must provide, regarding each patent discussed in (I) above, a reciprocal statement describing, on a claim by claim basis, a factual and legal basis for an opinion that a patent will be infringed as well as a response to any statement regarding validity and enforceability.[23]

Negotiations, Exchange of Second Patent Lists, and Patent Litigation

After this exchange of information, both parties must engage in good faith negotiations to identify which patents (if any) should be subject to patent infringement litigation.[24] Notably, the Act does not set out a deadline for commencing these negotiations, but does key other deadlines to the negotiation process.[25]

If the parties reach an agreement within 15 days during these negotiations, the BLA holder may sue the biosimilar applicant within 30 days of such an agreement.[26]

If the parties do not reach an agreement within 15 days of starting negotiations, the biosimilar applicant must notify the BLA holder of the number of patents it will provide in a second list, as discussed below.[27] Within five days of this notice, the parties must simultaneously exchange: (1) a list of patents that the biosimilar applicant believes should be subject to patent litigation (second biosimilar list); and (2) a list of patents that the BLA holder believes should be subject to patent litigation (second BLA list).[28] The number of patents in the second BLA list cannot exceed the

number of patents in the second biosimilar list, unless the second biosimilar list includes no patents, in which case the second BLA list may list *one* patent.[29] At this point, the BLA holder may sue the biosimilar applicant within 30 days of exchanging the two second lists.[30]

Thus, it appears that the biosimilar applicant determines the *number* of patents that may be litigated, but the BLA holder always has discretion to assert at least one patent. The biosimilar applicant does not necessarily control which patents are litigated, however. For example, if the biosimilar applicant notifies the BLA holder that its second list will contain two patents, the BLA holder potentially may be able sue with regard to four patents, i.e., two from each list. Specifically, four patents may be in play if it turns out that the biosimilar applicant and the BLA holder list entirely different patents during the simultaneous exchange of the second lists.

Within 30 days after a complaint is served, the biosimilar applicant must provide the FDA notice and a copy of the complaint.[31] The FDA will publish a notice of that complaint in the Federal Register.[32]

If a new patent issues or is exclusively licensed to the BLA holder after it has provided its first BLA list, the BLA holder has 30 days to provide a supplemental first list to the biosimilar applicant.[33] After receiving this supplemental first BLA list, the biosimilar applicant has 30 days to provide its statements (I) and/or (II) regarding the newly listed patent.[34] It is not clear that such patents are subject to the rest of the process described above, but the Act states that they are subject to the notice provisions described below.

180 Days Notice Before Biosimilar Marketing

No later than 180 days before going to market with a biosimilar product, the biosimilar applicant must provide notice to the BLA holder.[35] After receiving such notice, the BLA holder may seek a preliminary injunction prohibiting market entry until a court decides patent validity, enforcement, and infringement with regard to those patents listed in the first BLA or first biosimilar list, *but not including* those agreed upon for patent infringement litigation, or presented in second BLA and biosimilar lists.[36]

In other words, the BLA holder may only seek a preliminary injunction in a second litigation regarding patents not litigated in the first patent litigation (based on the list exchanges). Consequently, the preliminary injunction provision may influence the decision-making process behind the listing of patents. If a biosimilar applicant lists no patents in its second list, for example, it runs the risk of being subject to a preliminary junction regarding unlisted patents, which could further delay commercial marketing.

Comparing ANDA and Biosimilar Systems

As mentioned, the biosimilar patent dispute procedure under the Act differs from the corresponding process regarding ANDAs. One notable difference is the absence of a list of approved products with patent and exclusivity listings - the FDA's Approved

Drug Products with Therapeutic Equivalence Evaluations list (referred to as the FDA's "Orange Book") in the biosimilar regime. Under 35 U.S.C. § 271(e)(2)(A), (B), the submission of an ANDA is an act of infringement with respect to patents listed in the Orange Book. The new Act (via newly added § 271(e)(2)(C)) similarly defines the submission of a biosimilar application as infringement, but with regard to patents identified on the exchanged patents lists.[37]

Moreover, an NDA holder may not list patents directed to "methods of making" in the Orange Book, and therefore cannot assert such patents in an ANDA litigation.[38] By contrast, presumably because such patents are often the most relevant and viable IP protection for biologics, "methods of making" patents may be included in the exchanged patent lists, and therefore subject to biosimilar litigation.

Another notable difference relates to the exchange of a "factual and legal" basis regarding non-infringement/invalidity or infringement/validity of the patents. After submitting an ANDA with a Para. IV certification, an ANDA applicant must supply a factual and legal basis for its opinion that the Orange Book listed patent(s) are invalid, unenforceable or not infringed.[39] The NDA holder is not required to supply a reciprocal factual and legal basis, or otherwise respond to assertions in this regard.

Under the biosimilar regime, on the other hand, after a biosimilar applicant provides a factual and legal basis for its opinion that BLA listed patent(s) are invalid, unenforceable or not infringed, the BLA holder itself must provide a factual and legal basis regarding its opinion that patents are infringed, as well as a "response" to the biosimilar applicant's assertions regarding invalidity and unenforceability.[40] Thus, both biosimilar applicants and BLA holders may want to assess validity and possible infringement as early as possible in the process, to make sure they can exchange such information in a timely manner.

Regarding another difference, it is notable that there is no 30-month stay in the biosimilar procedure. Under the Hatch Waxman Act, if an NDA holder sues within 45 days of receiving notice of a Para. IV certification by an ANDA filer, the FDA cannot approve the ANDA until 30 months passes, or a court determines that the patent(s) at issue are invalid, not infringed or unenforceable, whichever happens first.[41] Because no 30-month stay exists in the biosimilar regime, presumably the FDA may grant approval as soon as it deems appropriate (subject to any market exclusivity period of the reference product, or for a second interchangeable biosimilar any exclusivity granted to a first approved interchangeable biosimilar product), thereby allowing biosimilar applicants to market "at risk."

As one last example of differences, in the Hatch Waxman regime, an ANDA filer may file a declaratory judgment (DJ) action if its ANDA includes a Para. IV certification and NDA holder has not sued within 45 days of receiving notice.[42] The NDA holder cannot bring a DJ action, however, except as normally available after the ANDA filer commercially markets. By contrast, if a biosimilar applicant meets its requirements, including supplying its application and manufacturing information to the BLA holder, neither party may sue for a DJ before the biosimilar applicant provides its 180-day notice of marketing.[43] If the biosimilar applicant fails to do any required actions, however, the BLA holder may bring a DJ action before the biosimilar applicant provides its 180-day notice.[44]

Other Considerations

BLA holders and biosimilar applicants already are studying the Act to assess its provisions and incentives, and identify any loop-holes. It remains to be seen how many biosimilar applicants will ultimately determine that the new system provides a sufficient "carrot" (or too much "stick") for them to bother with an "abbreviated" biosimilar application in the first place, rather than a full BLA application.

For example, in addition to having to wait out the 12-year exclusivity period granted to BLA holders, biosimilar applicants may be discouraged by the requirement to provide its biosimilar application and information about its manufacturing process to the BLA holder. While the Act sets limits on who can *see* such information (e.g., only one BLA holder in-house counsel who did not prosecute patents at issue), and what a BLA holder can do with the information,[45] biosimilar applicants may not be willing to trust BLA holders to follow these limitations.

Moreover, patent litigation in any context is expensive. Both BLA holders and biosimilar applicants will want to weigh the pros and cons of engaging in patent litigation at the pre-approval stage, versus later on after marketing, or at all. While patent litigation is worthwhile in some instances, it may be prohibitively expensive in others. For example, if it appears cheaper to file a full BLA application, as compared to filing a biosimilar application and following the patent litigation procedures, a potential applicant may choose to avoid the biosimilar process altogether. On the other hand, if a biosimilar applicant knows that patent litigation is imminent upon marketing anyway, the analysis may weigh in favor of a biosimilar patent litigation, so that patent issues are resolved before marketing.

Overall Implications

The new Act provides a long awaited pathway for obtaining FDA approval for biosimilar products. Notwithstanding details provided in the Act itself, many questions remain, however. For example, what will be the data requirements to establish that a product is highly similar to the reference product? How will applicants demonstrate 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? The complex procedure for resolving patent disputes after a biosimilar applicant files an application also will give rise to significant legal issues. While resolving such questions and issues may prove challenging and take time, having a pathway for biosimilar products is an important first step that opens the door for biosimilar products.

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[1] 42 U.S.C. § 262(i)(2)(A) & (B).
[2] 42 U.S.C. § 262(i)(3).
[3] 42 U.S.C. § 262(k)(4)(A) & (B).
[4] 42 U.S.C. § 262(k)(5).
[5] 42 U.S.C. § 262(i)(1).
[6] 42 U.S.C. § 262(k)(7); 42 U.S.C. § 262(m)(2) & (3).
[7] 42 U.S.C. § 262(k)(7)(B).
[8] 42 U.S.C. § 262(k)(7)(C).
[9] *See* Patient Protection and Affordable Care Act, Pub L. No. 111-148 (2010).
[10] 42 U.S.C. § 262(k)(6).
[11] 42 U.S.C. § 262(k)(2)(A)(i).
[12] 42 U.S.C. § 262(k)(2)(A)(ii).
[13] 42 U.S.C. § 262(k)(2)(A)(i).
[14] *See* Patient Protection and Affordable Care Act, Pub L. No. 111-148 (2010).
[15] 42 U.S.C. § 262(k)(8).
[16] 42 U.S.C. § 262(l)(1)(B)(i) & (2).
[17] 42 U.S.C. § 262(l)(1)(B)(ii)(II) & (C)-(H).
[18] 42 U.S.C. § 262(l)(3)(A)(i).
[19] 42 U.S.C. § 262(l)(3)(A)(ii).
[20] 42 U.S.C. § 262(l)(3)(B)(i).
[21] 42 U.S.C. § 262(l)(3)(B)(ii)(I) & (II).
[22] 42 U.S.C. § 262(l)(3)(B)(iii).
[23] 42 U.S.C. § 262(l)(3)(C).
[24] 42 U.S.C. § 262(l)(4).
[25] 42 U.S.C. § 262(l)(4)(A).
[26] 42 U.S.C. § 262(l)(6)(A).
[27] 42 U.S.C. § 262(l)(5)(A).
[28] 42 U.S.C. § 262(l)(5)(B)(i).
[29] 42 U.S.C. § 262(l)(5)(B)(ii).
[30] 42 U.S.C. § 262(l)(6)(B).
[31] 42 U.S.C. § 262(l)(6)(C)(i).
[32] 42 U.S.C. § 262(l)(6)(C)(ii).
[33] 42 U.S.C. § 262(l)(7)(A) & (B).
[34] 42 U.S.C. § 262(l)(7)(B).
[35] 42 U.S.C. § 262(l)(8)(A).
[36] 42 U.S.C. § 262(l)(8)(B).
[37] 35 U.S.C. § 271(e)(2)(C)(i) & (ii) (also stating that the submission is infringement with regard to patents that could have been listed in the first BLA list, if the biosimilar applicant fails to provide the biosimilar application and manufacturing information to the BLA holder).

[38] 21 U.S.C. § 355(b)(1).
[39] 21 U.S.C. § 355(j)(2)(B)(iv)(II).
[40] 42 U.S.C. § 262(l)(3)(B)(ii) & (C).
[41] 21 U.S.C. § 355(j)(5)(B)(iii).
[42] 21 U.S.C. § 355(j)(5)(C)(i)(I).
[43] 42 U.S.C. § 262(l)(9)(A).
[44] 42 U.S.C. § 262(l)(9)(B) & (C).
[45] 42 U.S.C. § 262(l)(1).