Brief

IP Strategies in the Emerging Biosimilar Market

U.S. Patent Strategies in the Biosimilars Space

Biosimilar Litigation Landscape

Decision Points and Strategies for the Patent Dance
Biosimilars are fundamentally different from generic versions of chemical drugs. Traditional generic pharmaceuticals share the same chemical structure as the reference branded pharmaceutical, so a patent that covers the branded drug will normally encompass within its scope the corresponding generic. This is not the case, however, for biosimilars. As defined by the BPCIA, a biosimilar is a biological product that is highly similar to an approved biological reference product (RP), notwithstanding minor differences in clinically inactive components, and for which there are no clinically meaningful differences in terms of safety, purity and potency. 42 U.S.C. § 262(i)(2). Even an interchangeable biosimilar product may differ in its structure from the RP so long as it is expected to produce the same clinical result. 42 U.S.C. § 262(i)(3).

The goal of the biosimilar applicant in developing its biological product is thus to design around patent claims of the RP sponsor without generating a molecule that is no longer biosimilar within the contours of the BPCIA. The patent strategy of the RP sponsor, on the other hand, is to craft claims that capture not only the reference product itself but the entire biosimilar landscape. Secondary patents, including those that cover variations in product, manufacturing processes, expression systems, diagnostic and pharmacologic assays, and underlying research tools and platform technologies accordingly have acquired added significance in the context of biosimilars.

To accomplish its goal of erecting a fence around the biosimilar landscape, the RP sponsor must consider the kinds of modifications that can be introduced into the reference product and the product’s method of manufacture that will result in a highly similar product. For example, the RP sponsor should consider nucleic acid or amino acid sequence changes that can be introduced that yield a product that is highly similar to the RP. Consideration also should be given to different expression systems, culture conditions and downstream processes for the separation, purification and refinement of the biologic that yield a highly similar product. Each modification that results in a highly similar product should be taken into account by the innovator in developing its patent strategy.

The patent strategy developed around the reference product and the biosimilar landscape must be further informed by recent developments in patent law, including, for example, current interpretation of 35 U.S.C. §§ 101, 102, 103 and 112. Strategies for patenting biologics that incorporate natural products, for example, should be contemplated. In addition, data supporting the effects of modifications to the reference product and to its method of manufacture should be considered for inclusion in the innovator’s patent filings. This breadth of disclosure may accomplish the goal of the RP sponsor by enabling some forms of functional claiming that encompass both the RP and the biosimilar product while still defining over the relevant prior art.

In short, it is imperative that innovators develop a comprehensive plan to protect or increase market share in the biologics space. Patent strategy is at the core of this plan. Implementation of the suggested prelitigation strategies will facilitate quick and decisive action by the innovator if and when a biosimilar application under the FDA’s abbreviated licensure pathway is filed.

Felicity Groth is a partner in BakerHostetler’s Intellectual Property Group. She focuses her practice on the life sciences arena, with a specific focus on diagnostic and therapeutic biologics.

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Recent litigations about the BPCIA have focused on four major issues: whether a (k) applicant 1) may elect not to disclose its abbreviated BLA or the manufacturing information under 42 U.S.C. § 262(l)(2)(A) and bypass the “patent dance”; 2) may cut short the “patent dance” after it has begun; 3) may give notice of commercial marketing under 42 U.S.C. § 262(l)(8)(A) before the FDA licensure of its product; and 4) is even required to provide the 180-day notice of commercial marketing.

The chart below summarizes the actions and the positions taken by the parties in these litigations and, where applicable, the court’s holdings.

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<table>
<thead>
<tr>
<th>Product</th>
<th>RPS</th>
<th>Applicant</th>
<th>Court</th>
<th>Patent Dance</th>
<th>(k) appl’n provided?</th>
<th>Mfg info. provided?</th>
<th>180-day notice of commercial marketing provided?</th>
<th>Notes</th>
</tr>
</thead>
<tbody>
<tr>
<td>Neupogen®</td>
<td>Amgen</td>
<td>Sandoz</td>
<td>N.D. Cal.</td>
<td>CAFC</td>
<td>No</td>
<td>No</td>
<td>No</td>
<td>CAFC held BPCIA not violated by applicant’s failure to provide (k) application and manufacturing information, but ruled that 180-day notice before licensure was ineffective. CAFC further ruled that the 180-day notice is mandatory at least in the situation where the applicant has fully complied with the BPCIA. Sandoz filed cert. petition. Amgen filed conditional cross-petition.</td>
</tr>
<tr>
<td>Neulasta®</td>
<td>Amgen</td>
<td>Apotex</td>
<td>S.D. Fla.</td>
<td>Yes</td>
<td>Yes</td>
<td>Yes</td>
<td>Will not</td>
<td>Apotex said it was not required to provide 180-day notice after licensure because it complied with BPCIA. Court ruled that 180-day notice was mandatory and this requirement was not conditioned on whether applicant complied with BPCIA. Apotex appealed to CAFC.</td>
</tr>
<tr>
<td>Neupogen®</td>
<td>Amgen</td>
<td>Apotex</td>
<td>S.D. Fla.</td>
<td>Yes</td>
<td>Yes</td>
<td>Yes</td>
<td>Will not</td>
<td>Apotex said it was not required to provide 180-day notice after licensure because it complied with BPCIA. Case consolidated with Neulasta® case.</td>
</tr>
<tr>
<td>Enbrel®</td>
<td>Amgen</td>
<td>Sandoz</td>
<td>D.N.J.</td>
<td>Cut short according to Amgen</td>
<td>Yes</td>
<td>Yes</td>
<td>Not yet</td>
<td>Sandoz said it agreed with the (l)(3)(A) list and waived its right to receive (l)(3)(C) statement; it declared negotiations per (l)(4) and (5) unnecessary. Amgen brought infringement action under 271(e)(2)(A) and brought DJ action of infringement under 262(l)(8).</td>
</tr>
<tr>
<td>Remicade®</td>
<td>Janssen</td>
<td>Celltrion</td>
<td>D. Mass</td>
<td>Yes</td>
<td>Yes</td>
<td>Janssen says no</td>
<td>Before licensure (and notice post-licensure conditioned on outcome of Amgen v. Apotex appeal)</td>
<td>Janssen seeks 1) DJ that notice was ineffective and an order requiring Celltrion to comply with BPCIA; 2) injunction that Celltrion cannot market until 180 days after an effective notice; and 3) infringement. FDA approved Celltrion’s product on April 5, 2016. Parties entered into a stipulation whereby Celltrion agreed not to sell its biosimilar product before June 30, 2016. Court denied PI without prejudice. Parties will confer after CAFC’s ruling in Amgen v. Apotex re any renewed PI motion by Janssen.</td>
</tr>
<tr>
<td>Epogen®</td>
<td>Amgen</td>
<td>Hospira</td>
<td>D. Del</td>
<td>Cut short according to Amgen</td>
<td>Yes</td>
<td>Amgen says no</td>
<td>First, before licensure and then said it will not provide notice</td>
<td>After Amgen provided its (l)(3)(C) statement, Hospira said it agreed with the (l)(3)(A) list. Amgen seeks 1) DJ that notice is ineffective and injunction requiring Hospira to provide effective notice; and 2) infringement of three patents. Hospira filed motion to dismiss count 1 on the ground that BPCIA did not confer private right of action.</td>
</tr>
<tr>
<td>Neulasta®</td>
<td>Amgen</td>
<td>Sandoz</td>
<td>D.N.J.</td>
<td>Cut short according to Amgen</td>
<td>Yes</td>
<td>Yes</td>
<td>Not yet</td>
<td>Sandoz said it agreed with the (l)(3)(A) list and waived its right to receive statement pursuant to (l)(3)(C); it declared negotiations per (l)(4) and (5) unnecessary and asserted that Amgen must file infringement suit under § 262(l)(8) by March 4, 2016, or such suit would be untimely and Amgen’s damages would be limited to reasonable royalty under 35 U.S.C. § 271(e)(2)(B). Amgen brought suit seeking compliance with BPCIA, but did not bring infringement suit. Sandoz filed motion to dismiss for lack of standing.</td>
</tr>
<tr>
<td>Neulasta®</td>
<td>Amgen</td>
<td>Sandoz</td>
<td>N.D. Cal.</td>
<td>Yes</td>
<td>Yes</td>
<td>Yes</td>
<td>Not yet</td>
<td>According to Amgen’s complaint, the parties completed the “patent dance” and agreed to the two patents being asserted by Amgen.</td>
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Decision Points and Strategies for the Patent Dance

By Gary H. Levin and Henrik D. Parker

The Biologics Price Competition and Innovation Act (the BPCIA) contains a complicated set of litigation provisions centered around what has come to be called “the patent dance,” as well as other provisions dealing with an applicant’s providing a sponsor of a reference product a 180-day advance notice of intended commercial marketing. These provisions allow certain litigation proceedings while precluding others, presenting options to both the Reference Product Sponsor (RPS) and the applicant for a biosimilar license. Those varied options come with pluses and minuses that require a close examination before choosing a path. While an abbreviated biologics license application (aBLA) applicant does not have many options for bringing its own suit, its decisions establish the options the RPS will have.

The aBLA Applicant’s First Decision: To Provide the Application or Not

The first decision for an aBLA applicant is whether to engage in the patent dance at all, a step that would require it to provide its biosimilar application and related information to the RPS. As recently determined in the Federal Circuit’s Amgen decision, an aBLA applicant is not required to engage in the dance to be entitled to have its application processed by FDA, and therefore is not required to provide its aBLA or any other information to the RPS.1 Such an “opt-out” by the applicant opens up a distinct, parallel set of litigation possibilities that leaves the RPS with less knowledge about the biosimilar but potentially a quicker route to resolution.

If the aBLA applicant opts out of the dance, the RPS may immediately declare a declaratory judgment action for infringement, validity or enforceability of any of its patents that the RPS believes to cover the biosimilar product or its use, while the aBLA applicant is explicitly precluded from bringing any action. 42 U.S.C. § 262(l)(9)(C). Although this section of the BPCIA seemingly omits process patents from the RPS’s arsenal at this point, the Federal Circuit has specifically pointed out that the RPS can also file suit under 35 U.S.C. § 271(e)(2)(C)(ii), which makes the filing of an aBLA an act of infringement as to any patent that could have been identified during the BPCIA’s patent dance – thus allowing for the assertion of process patents as well. Amgen, 794 F.3d at 1356 n.3. An opting-out applicant, by precluding itself from any declaratory action, may subject itself to an at-risk launch if the RPS decides not to file until the biosimilar license is granted and there is actual infringement. While the RPS has the right to immediately file suit, it may have little knowledge of the structure of the biosimilar or how it is manufactured because it has not received the aBLA. Thus, the RPS may have difficulty determining which of its patents apply. It would not be surprising that the RPS would be unable to assert its patent(s) before the actual launch of the biosimilar.

The aBLA Applicant’s Second Decision: To Finish the Dance or Not

If the aBLA applicant starts the patent dance by providing its aBLA and other required information to the RPS, the RPS must then specify an original list of patents that the RPS believes would be infringed by the proposed biosimilar. This sets up another series of back-and-forth exchanges between the applicant and RPS as to what patents should be litigated. The applicant can quit the dance at any point during this period by, for example, not providing responses on the patents, or even by failing to provide the 180-day notice of commercial marketing. If the applicant does quit the discussions, or fails to provide proper marketing notice, the RPS may immediately seek a declaration of infringement, validity or enforcement, while the applicant – again – is specifically precluded from bringing any action. 42 U.S.C. § 262(l)(9)(B).

Some applicants may find it advantageous to pull out of the dance as soon as the RPS’s original patent list is received. The applicant may realize, especially if it has done its homework earlier, that the listed patents are not a major impediment for it and may choose to pull out of the process at that point, hoping to accelerate a declaratory challenge by the RPS or knowing what patents to target in an inter partes review (IPR). Having at least started the dance, the applicant may see an advantage, in addition to accelerating resolution of the patent issues, in possibly being exempted from having to provide the 180-day advance marketing notice. (The issue of whether notice is required for an applicant that at least starts the dance was left open in the Federal Circuit’s Amgen case. One district court has already ruled that the notice is always required.)

An applicant’s entering the patent dance places an extra duty on the RPS. The RPS must properly analyze the aBLA and include all possibly relevant patents on its original list. Significantly, failing to include any otherwise applicable patent on this list precludes the RPS from filing any infringement action against the biosimilar product on the omitted patent. 35 U.S.C. § 271(e)(2)(C). Although future court decisions may hold differently, there is nothing in the statute that expressly lifts this restriction even if the applicant pulls out of the dance.

An aBLA applicant is not required to engage in the patent dance to be entitled to have its application processed by FDA, and therefore is not required to provide any information to the Reference Product Sponsor.

The aBLA Applicant’s Third Decision: Notice or No Notice

Separate and, at least arguably, distinct from the patent dance and its related litigation procedures is the BPCIA requirement that an aBLA applicant “shall provide notice to the [RPS] not later than 180 days before the date of the first commercial marketing of the biological product licensed.” 42 U.S.C. § 262(l)(9)(A). The Federal Circuit has held that this notice: (a) is mandatory, at least where the aBLA applicant has chosen to totally opt out of the patent dance; and (b) is not legally effective unless given after the FDA approves the biosimilar application. Amgen, 794 F.3d at 1358-60. If the aBLA applicant that has fully engaged in the patent dance chooses to give the 180-day notice, at least a couple of litigation options arise as to the category of patents that were on the RPS’s original list but were not part of the agreed list for earlier suit.

1 Amgen, Inc. v. Sandoz, Inc., 794 F.3d 1347 (Fed. Cir. 2015).


The BPCIA contemplates that an applicant may choose not to give the notice, even when required to do so. (The pending Federal Circuit case will decide the extent of this requirement.) In that case, the RPS, but not the aBLA applicant, may bring an action for declaration of infringement, validity or enforceability of any patent on the RPS’s original patent list. 42 U.S.C. § 262(l)(9)(B). So, even if some suits were commenced as part of the patent dance earlier, the RPS can initiate suit on any remaining patents from its original list. Even with this remedy, the RPS could seek to enforce the 180-day notice provision.3

On the other hand, as illustrated in Amgen v. Sandofz, if the aBLA applicant opts out of the patent dance initially and fails to give the 180-day notice of commercial marketing, then the RPS can seek to compel compliance with the proper giving of the 180-day notice because notice in such a situation is mandatory. Indeed, with no patent dance and no notice, an RPS may have sufficient information about the biosimilar until after it launches, at which point the RPS could seek, at a minimum, a 180-day TRO.

The marketing notice is not effective, and therefore not practically due, until the biosimilar is approved, but an applicant who chooses not to provide notice could slip under the radar; an RPS would be advised to monitor the purple book for biosimilar approvals.

Open Issue

Among other open issues that will affect strategy is the question of when the 180-day clock for provision of notice begins to run when approval occurs and notice is given during the 12-year period of exclusivity. The BPCIA provides that a biosimilar application may not be approved by FDA until 12 years after the reference product was first licensed, giving the RPS 12 years of exclusivity regardless of patent rights or the status of the FDA’s review.4

3 This provision provides certain litigation remedies against a non-notifying approved applicant, and it remains an open question whether those remedies, such as seeking a contributory infringement or inducement, if an RPS could seek a declaratory judgment action and seek to enforce the 180-day patent in the same declaratory judgment suit, is constructive.

4 This provision provides certain litigation remedies against a non-notifying approved applicant, and it remains an open question whether those remedies, such as seeking a contributory infringement or inducement, if an RPS could seek a declaratory judgment action and seek to enforce the 180-day patent in the same declaratory judgment suit, is constructive.
of an aBLA application. In all cases to date, including the Federal Circuit’s Amgen decision, the application was not submitted until well after the RPS’s 12-year period had passed. But in future cases involving more recently licensed biologics, biosimilar applicants may submit their applications while the reference biologic is still within its 12-year exclusivity period, hoping to gain approval and start the 180-day clock running so as to be free to launch as soon as the 12-year period expires.

The Amgen panel recognized that Amgen received an “extra 180 days” precisely because Sandoz’s application was filed only after Amgen’s 12-year period on its Neupogen® biologic had ended. The panel majority further opined that this extra 180 days of exclusivity “will not likely be the usual case, as biosimilar applications will often be filed during the 12-year exclusivity period for other products.” But although that comment indicates how those two majority judges might rule when the issue is actually before them, it is not binding on other panels. So the question remains as to the effect of having a biosimilar application approved within the 12-year exclusivity period: Can the approved applicant give effective notice at that time, so that the 180 days runs and expires within that period and the applicant can launch as soon as the 12th year is up? Or, since the law states that an approval “may not be made effective” until the 12 years are up, does the legal effectiveness of notice not ripen, and the running of the 180 days not begin, until then?

Conclusion

In most situations, engaging in the patent dance and the subsequent litigation under the BPCIA will provide benefits to both parties. In particular, both sides can figure out what patents are in dispute and can resolve those disputes prelaunch. With the parameters of the dispute more defined, potential license discussions can take place. From the RPS’s viewpoint, there is the prospect of obtaining an injunction if its infringement claims are successful. From the applicant’s viewpoint, if the RPS has a robust patent portfolio, the applicant may prefer to participate in the patent dance to narrow the scope (and cost) of the dispute. Of course, if the RPS has few applicable patents, the applicant may prefer to skip the patent dance, make an at-risk launch sooner than it might otherwise and take its chances in a standard infringement action. And even though the Act precludes a nonparticipating applicant from filing any declaratory actions of its own, an applicant can consider instituting an IPR against the RPS’s patents even before it makes its biosimilar application to the FDA.

The bottom line for now is that the applicant will largely control the manner in which any dispute will play out under the BPCIA by choosing whether or not to participate and continue in the Act’s regimens. Those choices will vary depending on the relative risks based on the specific facts of the situation. In all events, the savvy biologic manufacturer will fully consider all possible paths before making a decision as to where to take its chances and about which patents.

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