Bloomberg BNA

Life Sciences Law & Industry Report™

Patents

Impact of Post-Grant Proceedings on Biologics and Biosimilars

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Biologics, primarily therapeutic antibodies and recombinant proteins, represent a growing share of the drug market and are projected to achieve worldwide sales of approximately $278 billion by 2020, partly due to their relatively high cost. Indeed, the therapeutic antibody Humira® is currently the top-selling drug in the world by sales, but not even in the top 50 by the number of monthly prescriptions. While the process for marketing generic versions of small molecules under the Hatch-Waxman Act is well understood, the process for marketing generic versions of biologics, referred to as ''biosimilars,'' under the Biologics Price Competition and Innovation Act (BPCIA) is still being established and presents many unresolved questions. What is clear is that it involves a very complex patent litigation procedure that potentially discourages biosimilar development, particularly while the courts are still determining many issues left unresolved by Congress and the Food and Drug Administration (FDA). As an alternative, or supplement, to patent litigation, biosimilar developers are beginning to make use of post-grant proceedings, such as inter partes review (IPR), at the U.S. Patent and Trademark Office (USPTO) to challenge blocking patents. This article discusses strategic considerations for the use of post-grant proceedings to try to bring greater certainty to biosimilar development, including analysis of those that have been filed to date.

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Resolving Patent Disputes Under the BPCIA

Up until 2010, there was no mechanism in the U.S. for marketing biosimilars. A growing recognition of the need to provide incentives for developing new biologics, while also permitting competition from generics, led to implementation of the BPCIA in March 2010. The first biosimilar—Zarxio® (filgrastim-sndz), marketed by Sandoz—achieved approval under this pathway in 2015.[1]

Similarly to Hatch-Waxman, the BPCIA provides an abbreviated pathway for obtaining FDA approval by allowing a biosimilar applicant to rely on clinical data associated with an earlier-approved product (''reference product''). The biosimilar must be ''highly similar to the reference product notwithstanding minor differences in clinically inactive components'' with ''no clinically meaningful differences between the biological product and the reference product in terms of the safety, purity, and potency of the product.''[2] Notably, a biosimilar applicant can obtain approval for less than all of the indications, routes of administration, or delivery devices for which the reference product obtained approval,[3] allow-

[1] http://www.fda.gov/Drugs/InformationOnDrugs/ApprovedDrugs/ucm436953.htm.

[2] FDA Guidance for Industry, ''Biosimilars: Questions and Answers Regarding Implementation of the Biologics Price Competition and Innovation Act of 2009,'' April 2015, pages 3-4, citing § 351(i)(2) of the Public Health Service (PHS) Act (42 U.S.C. § 262(i)(2)).

[3] *Id.* at 7-8.

 ISSN 1935-7257

ing a ''carve-out'' scenario in which the biosimilar applicant can avoid specific patent protection surrounding the reference product. The BPCIA provides the innovator reference product with 12 years of regulatory exclusivity, including four years in which the FDA will not accept a biosimilar application, and eight years in which the FDA will accept an application but will not grant approval.[4]

Also similarly to Hatch-Waxman, the BPCIA provides a mechanism for resolving patent disputes between the biosimilar applicant and the reference product sponsor (RPS); however, there are significant differences between the two pathways.[5] Under Hatch-Waxman, the New Drug Application (NDA) holder provides a list of all patents that would reasonably be infringed by a generic, which are published in the Orange Book.[6] A generic manufacturer can challenge those patents prior to marketing by filing a paragraph IV certification accompanying an Abbreviated New Drug Application (ANDA), asserting that the patents are invalid or not infringed.[7] The NDA holder can then sue the generic manufacturer and obtain a 30-month stay, during which the FDA will not approve the generic's ANDA application.[8]

The BPCIA pathway does not involve an Orange Book listing, a paragraph IV certification, or a 30-month stay. Instead it contemplates a complex back-and-forth between the parties to establish patents to be litigated, referred to as a ''patent dance,'' followed by two waves of patent litigation. The process starts when the FDA accepts the biosimilar application, which provides a 20-day window for the applicant to provide a copy of its application, including manufacturing information, to the RPS.[9] Next, over a six-month period, the two parties exchange patent lists, including opinions on validity, enforceability and infringement, negotiating which patents will be included in the ''first wave'' of litigation.[10] The biosimilar applicant is also required to provide notice to the RPS within 180 days of commercial marketing, which provokes the ''second wave'' of patent litigation, allowing the RPS to seek a preliminary injunction based on patents that were not litigated in the first wave.[11]

Challenges to the BPCIA

Early litigation challenges to the BPCIA are shaping our understanding of the complex statutory requirements. Not surprisingly, it is clear so far that biosimilar applicants would like to avoid the ''patent dance,'' at least in part because of its stringent and time-sensitive requirements for information disclosure, including information about the biosimilar itself, and about the biosimilar applicant's invalidity/infringement contentions. As a result, litigation challenges to the BPCIA so far have focused on whether the patent dance is really a requirement.

Several cases have addressed the question of whether a biosimilar applicant can instigate a declaratory judgment action before filing a biosimilar application, which would bypass the need for the patent dance.[12,13,14,15] However, this approach does not appear to be viable for circumventing the patent dance because in each case the courts have found a lack of case or controversy, leading to dismissal.

In 2015, the U.S. Court of Appeals for the Federal Circuit addressed the question of what would happen if a biosimilar applicant refused to partake in the patent dance following submission of a biosimilar application.[16] Sandoz had applied to the FDA in May 2014 for approval of a biosimilar of filgrastim (marketed by Amgen as Neupogen®).[17] While Sandoz informed Amgen that its application had been accepted by the FDA, it did not provide Amgen with a copy of its application or manufacturing information under 42 U.S.C. § 262(l)(2)(A); instead, Sandoz informed Amgen that it was entitled to sue under 42 U.S.C. § 262(l)(9)(C).[18] The Federal Circuit found that Sandoz had acted within its rights under the BPCIA, holding that a biosimilar applicant is not required to disclose its biosimilar application to the RPS, and that the failure to do so represents an act of infringement, allowing the RPS to bring a declaratory judgment action under 42 U.S.C. § 262(l)(9)(C) and 35 U.S.C. § 271(e)(2)(C)(ii).[19] Thus, the BPCIA appears to provide a mechanism for the biosimilar applicant to avoid the patent dance by allowing the RPS to bring a declaratory judgment action.

Other significant questions not yet resolved relate to whether it is mandatory under the BPCIA for the biosimilar applicant to provide a 180-day notice before commercial marketing and, if so, whether the biosimilar applicant can provide this notice before receiving FDA approval of the biosimilar. In *Amgen Inc. v. Sandoz Inc.*, the Federal Circuit held that, at least in a scenario where the biosimilar applicant chooses not to partake in the patent dance, the 180-day notice is required and can only be given after FDA approval of the biosimilar.[20] Sandoz has recently petitioned the Supreme Court to consider the question of whether the biosimilar applicant can provide the requisite notice before obtaining FDA approval.[21] Whether the 180-day notice is also required for biosimilar applicants who do comply with the patent dance is currently under consideration by the Federal Circuit.[22]

It remains to be seen whether any biosimilar applicants will choose to partake in the patent dance, if it is

[4] *Id.* at 4.
[5] Reviewed by Kowalchyk and Crowley-Weber, ''Biosimilars: impact of differences with Hatch-Waxman,'' *Pharm. Pat. Analyst* (2013) 2(1):29-37.
[6] 21 U.S.C. § 355(b)(1).
[7] 21 U.S.C. § 355(j)(2)(A)(vii)(IV).
[8] 21 U.S.C. § 355(j)(5)(B)(iiii).
[9] 42 U.S.C. §§ 262(l)(1)-(2).
[10] 42 U.S.C. §§ 262(l)(3)-(5).
[11] 42 U.S.C. § 262(l)(8).
[12] *Sandoz Inc. v. Amgen Inc.* (N.D. Cal. Nov. 12, 2013).
[13] *Celltrion Healthcare Co., Ltd. v. Kennedy Trust for Rheumatology Research* (S.D.N.Y. Dec. 1, 2014).
[14] *Hospira Inc. v. Janssen Biotech Inc.* (S.D.N.Y. Dec. 1, 2014).
[15] *Sandoz Inc. v. Amgen Inc.*, No. 2014-1693, slip op. (Fed. Cir. Dec. 5, 2014).
[16] *Amgen Inc. v. Sandoz Inc.*, No. 2015-1499, slip op. (Fed. Cir. July 21, 2015).
[17] *Id.* at 6-7.
[18] *Id.* at 7.
[19] *Id.* at 12-15.
[20] *Id.* at 16-21.
[21] ''Sandoz Asks High Court to Review Biosimilar Case,'' Life Sciences Law & Industry Report, Feb. 19, 2016.
[22] ''Amgen, Apotex Debate When Neulasta Biosimilar Can Be Released,'' Life Sciences Law & Industry Report, April 6, 2016.

   ISSN 1935-7257

truly an optional process. Resolving the questions surrounding the requirement for providing 180-day notice of commercial marketing will also be significant because mandating that such notice be given only *after* biosimilar approval can lead to a de facto additional six months of exclusivity for the RPS.

Advantages of Post-Grant Proceedings Relative to BPCIA for Biosimilar Developers

The America Invents Act (AIA), implemented in 2012, shifted the patent litigation landscape by creating mechanisms for resolving patent disputes at the U.S. Patent Trial and Appeal Board (PTAB) as an alternative or supplement to litigation. As of Feb. 29, 2016, 4,181 IPR petitions had been filed.[23] In addition to IPR, post-grant proceedings include Post Grant Review (PGR), and Covered Business Method Patent Review (CBM). However, the majority filed to date that are relevant for biopharma are IPRs, since PGRs can only be used to challenge post-AIA patents, and CBMs are only applicable to patents covering business methods.

For biosimilars, post-grant proceedings offer many advantages relative to litigation and should be considered as part of any biosimilar development program. A comparison of patent litigation under the BPCIA relative to IPR and PGR proceedings is provided in Table 1. From a procedural perspective, a notable difference is that while only the biosimilar applicant can challenge a patent under the BPCIA, and only within the strict guidelines of the BPCIA, in post-grant proceedings any party (other than the patent owner) can initiate a challenge, and the challenge is not tied to the biosimilar approval process. Accordingly, filing a post-grant proceeding can allow a biosimilar developer to potentially clear blocking patents—or at least determine the strength of patent protection covering the reference product—earlier in the biosimilar development pathway, before making a major investment in developing a biologic.

Additionally, post-grant proceedings are generally faster and less expensive than litigation, partly because post-grant proceedings have a set timeline, and also because the scope of discovery is extremely reduced relative to litigation. Moreover, because of the strict timeline, courts will frequently stay any concurrent litigation until the post-grant proceeding is decided.

Post-grant proceedings also offer several significant substantive advantages relative to litigation for the party challenging a patent, including a lower standard of proof (''preponderance of the evidence'' instead of ''clear and convincing evidence''), a broader standard for claim construction (''broadest reasonable interpretation'' instead of ordinary and customary meaning in light of the claims, specification and prosecution history) and a different judge and jury (an Administrative Patent Judge used to finding patents to be unpatentable while performing both functions, instead of a district court judge and jury who are not so experienced at splitting those functions). All these differences serve to shift the scale toward the challenger at the PTAB, making this an attractive forum for biosimilar developers. While there were initial concerns that patent owners could amend their claims and potentially strengthen their patents, these fears have proved largely unfounded in IPR proceedings. Very few patent owners have been able to make such amendments, at least in part because the patent owner is required to demonstrate patentability of any amended claims.

Initially, biopharma represented a small percentage of post-grant proceedings, partly because these proceedings are often filed concurrently with ongoing litigation and so are most common in highly litigious areas of technology such as electronics. In biopharma, where the time frame for bringing a product to market is lengthy, a post-grant filing is more likely to be part of a long-term business strategy. Additionally, the majority of post-grant proceedings filed so far have been IPRs, which are limited to prior art grounds, whereas challenges under 35 U.S.C. §§ 112 and 101 have tended to play an important role in litigation of biopharma patents. PGRs, which are just starting to become available, will help to level that aspect of the playing field since they can be based on any statutory ground other than best mode.

Recent statistics reveal that biopharma post-grant proceedings are increasing. In particular, generic and biosimilar manufacturers are recognizing advantages of this pathway. The high success rates achieved so far are also compelling. For IPR petitions that have reached a final disposition as of Feb. 29, 2016, out of 1,359 IPR trials that have been instituted (including all areas of technology), 53 percent have resulted in some or all instituted claims being cancelled (corresponding to 87 percent of trials that reach the final written decision stage).[24] For biosimilar developers, since many of the composition-of-matter patents covering brand-name biologics are close to expiry, post-grant proceedings represent a particularly promising strategy for attacking follow-on patents, such as those covering formulations or specific dosing regimens.

Insight from Early IPRs Challenging Patents Covering Biologics

IPRs challenging patents covering brand-name biologics (recombinantly produced proteins including antibodies) have been filed both by biosimilar developers directly (Table 2) and also by other entities (Table 3). The first such IPRs to reach a final written decision were initiated by BioMarin Pharmaceutical Inc. challenging patents covering Myozyme® and Lumizyme®, marketed by Genzyme.[25] The challenged claims in those cases were broad method-of-treatment claims reciting mechanistic limitations and dosing limitations. The PTAB found all challenged claims to be unpatentable based on obviousness, stating that ''the claimed subject matter was a product of routine clinical trial processes.''[26] The PTAB was unconvinced by the patent owner's arguments related to secondary considerations, finding an insufficient nexus between the evidence and the claim features.[27] While BioMarin's motivation was to clear a path for a competing biologic, rather than a biosimilar, the decisions nevertheless have relevance for potential biosimilar developers since the result could allow earlier market entry for biosimilars.

[23] http://www.uspto.gov/patents-application-process/appealing-patent-decisions/statistics/aia-trial-statistics.

[24] *Id.*

[25] IPR2013-00534, IPR2013-00535 and IPR2013-00537.

[26] IPR2013-00537, slip op. at 15 (Feb. 23, 2015)(Paper 79).

[27] *Id.* at 22.

In a proceeding initiated by Phigenix, Inc., challenging a patent covering Genentech's Kadcyla®, the PTAB reached the opposite outcome, upholding all of the challenged claims.[28] Notably, the claims in this case were composition-of-matter claims. The PTAB agreed with the patent owner that one of ordinary skill in the art would not have been motivated to combine the cited references, nor have had a reasonable expectation of success.[29] Interestingly, while the PTAB has generally not placed much emphasis on secondary considerations, in the analysis of picture claims covering Kadcyla®, the PTAB found convincing evidence of long-felt need, unexpected results and commercial success, and found a sufficient nexus between the evidence and the claims.[30] This finding may not be broadly applicable to challenges by biosimilar developers since establishing a nexus for composition-of-matter claims covering a product is understandably easier than establishing a nexus for claims in other patents, such as follow-on patents likely to be the subject of most challenges.

In the first example of a petition filed directly by a biosimilar developer challenging a patent covering a reference product, Hospira, which was developing a biosimilar of EPO (marketed by Janssen as Procrit® and by Amgen as Epogen®), filed an IPR petition challenging claims covering methods of administration of EPO.[31] The patent owner chose to disclaim all challenged claims, terminating the proceeding. This favorable result for Hospira provided it with increased certainty at an early stage of its biosimilar development, before even submitting its application to the FDA.[32]

Several biosimilar developers have filed IPR petitions challenging patents covering Rituxan®, a blockbuster therapeutic monoclonal antibody marketed in the U.S. by Genentech USA, Inc., and Biogen Idec Inc. Out of three petitions filed by Boehringer Ingelheim Pharmaceuticals, Inc. (BI), two were instituted, while a third was denied institution.[33] Following institution of the BI petitions, Celltrion, Inc. filed IPR petitions challenging the same patents as BI and sought joinder with BI's proceedings.[34,35] These proceedings were later terminated when BI halted its Rituxan® biosimilar development.[36,37] While it remains to be seen whether IPR challenges to Rituxan® will continue, the PTAB's two institution decisions reveal vulnerability in the challenged patents.

Not surprisingly, given the sales figures for Humira®, multiple parties have filed IPR petitions challenging patents covering Humira®. Two petitions filed by Amgen Inc. challenging formulation claims were denied institution,[38] while additional petitions filed by BI and Coherus BioSciences Inc., challenging claims directed to methods of treatment, are still awaiting a decision on institution.

Future Directions

Biosimilar developers are making increased use of post-grant proceedings. So far, it appears that broad mechanistic claims, as well as follow-on patent claims, such as those covering methods of treating specific patient populations, specific dosing regimens and formulations, will be vulnerable to obviousness challenges at the PTAB, at least based on institution decisions and a small number of final written decisions. A recent rule change allowing patent owners to submit expert declaration evidence prior to the decision on institution could serve to reduce the high rates of institution by strengthening the patent owner's position pre-institution. A potential rule change requiring petitioners to have standing, in an attempt to crack down on filings by non-practicing entities such as the Coalition for Affordable Drugs, could limit one source of biologic IPRs. Irrespective of potential rule changes, considering the high overall success rate in IPRs, and the increased certainty that can be attained by clearing blocking patents early, post-grant proceedings will likely be incorporated into most, if not all, biosimilar development strategies.

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[28] IPR2014-00676.

[29] *Id.*, slip op. at 21, 23 (Oct. 27, 2015)(Paper 39).

[30] *Id.* at 24-26.

[31] IPR2013-00365.

[32] http://www.biologicsblog.com/blog/biosimilar-makers-turn-to-iprs-before-litigation-under-bpcia/.

[33] IPR2015-00415 and IPR2015-00417 were instituted while IPR2015-00418 was not instituted. Biogen Idec Inc. and Boehringer Ingelheim Pharmaceuticals, Inc., are Wolf Greenfield clients, though the firm did not represent either company in these IPRs.

[34] IPR2015-01733 and IPR2015-01744.

[35] http://www.ptabwatch.com/2015/10/ptab-dismisses-biosimilar-companys-ipr-petition-without-prejudice-when-petitioner-loses-its-expert/.

[36] http://www.gabionline.net/Biosimilars/News/Boehringer-Ingelheim-stops-biosimilar-rituximab-development.

[37] http://www.ptabwatch.com/2015/10/ptab-dismisses-biosimilar-companys-ipr-petition-without-prejudice-when-petitioner-loses-its-expert/.

[38] IPR2015-01514 and IPR2015-01517.

  LSLR ISSN 1935-7257

Table 1: Comparison of BPCIA vs Post-Grant Proceedings

	BPCIA—District Court Litigation	IPR	PGR
Who can challenge a patent under the proceedings?	▪ Entity seeking FDA approval of biosimilar under BPCIA	▪ Anyone other than patent owner ▪ Petitioner does not need to be seeking FDA approval of biosimilar ▪ Petitioner does not need Declaratory Judgment ("DJ") jurisdiction	▪ Anyone other than patent owner ▪ Petitioner does not need to be seeking FDA approval of biosimilar ▪ Petitioner does not need Declaratory Judgment ("DJ") jurisdiction
When can the proceedings be initiated?	▪ If the parties participate in the patent dance, then FDA acceptance of biosimilar application, followed by patent dance, initiates first wave of litigation ▪ 180-day notice of commercial marketing triggers second wave of litigation	▪ For pre-AIA patents, anytime, except that if an infringement suit has been filed against the petitioner, then the petitioner has to initiate the proceeding within one year of the infringement suit ▪ For post-AIA patents, from the later of: (i) 9 months of patent issuance; or (ii) the date of termination of any PGR ▪ The petitioner cannot have already filed a DJ action challenging the patent	▪ Within 9 months of patent issuance ▪ The petitioner cannot have already filed a DJ action challenging the patent
What is the expected time frame for the proceedings?	▪ No set time frame ▪ Predicted time frame 2-4 years	▪ Petition filing to final decision in 24 months ▪ Typically 18 months	▪ Petition filing to final decision in 24 months ▪ Typically 18 months
Who decides the proceedings?	▪ District court judge and/or jury	▪ Technically trained administrative patent judges ("APJs") within the PTAB at the USPTO	▪ Technically trained administrative patent judges ("APJs") within the PTAB at the USPTO
Which patents can be challenged?	▪ Primarily the patents that are included in the patent dance (if the parties participate in the patent dance)	▪ Any patents	▪ Post-AIA patents
What grounds can be relied upon?	▪ Any patentability ground: 35 U.S.C. §§ 101, 102, 103, 112 (except for best mode), and double patenting	▪ Anticipation (35 U.S.C. § 102) or obviousness (35 U.S.C. § 103), relying on patents or printed publications	▪ Any patentability ground: 35 U.S.C. §§ 101, 102, 103, 112 (except for best mode), and double patenting
What is the standard of proof?	▪ Presumption of validity applies ▪ Clear and convincing evidence standard for proving invalidity	▪ Presumption of validity does not apply ▪ Preponderance of the evidence standard for proving invalidity	▪ Presumption of validity does not apply ▪ Preponderance of the evidence standard for proving invalidity
What is the standard for claim construction?	▪ Ordinary and customary meaning (*Phillips v. AWH Corp.*)	▪ Broadest reasonable interpretation	▪ Broadest reasonable interpretation
Does estoppel apply?	▪ Estopped from re-litigating the same issue	▪ Estoppel only applies if a final written decision is issued ▪ Petitioner is estopped from raising before the USPTO or in a litigation any ground raised or that reasonably could have been raised in the IPR ▪ If a claim is cancelled, patent owner is estopped from taking action inconsistent with the adverse judgment	▪ Estoppel only applies if a final written decision is issued ▪ Petitioner is estopped from raising before the USPTO or in a litigation any ground raised or that reasonably could have been raised in the PGR ▪ If a claim is cancelled, patent owner is estopped from taking action inconsistent with the adverse judgment

Table 2: Summary of IPR Challenges by Biosimilar Developers

Biologic	Patent Owner	Patent No.	IPR No.	Petitioner	Status of Proceeding
▪ Procrit® ▪ Epogen®	▪ Janssen Pharmaceuticals, Inc.	▪ 6,747,002 ▪ Claims directed to methods of administration	▪ IPR2013-00365	▪ Hospira, Inc.	▪ Not instituted ▪ Patent owner disclaimed all challenged claims before institution decision
▪ Rituxan®	▪ Biogen IDEC, Inc. ▪ Genentech, Inc.	▪ 7,820,161 ▪ Claims directed to methods of treatment involving combination therapy	▪ IPR2015-00415	▪ Boehringer Ingelheim International GmbH ▪ Boehringer Ingelheim Pharmaceuticals, Inc.	▪ Instituted ▪ Proceeding terminated by petitioner following institution
▪ Rituxan®	▪ Genentech, Inc.	▪ 7,976,838 ▪ Claims directed to methods of treatment, reciting specific patient population and specific dose	▪ IPR2015-00417	▪ Boehringer Ingelheim International GmbH ▪ Boehringer Ingelheim Pharmaceuticals, Inc.	▪ Instituted ▪ Proceeding terminated by petitioner following institution
▪ Rituxan®	▪ Biogen Inc.	▪ 8,329,172 ▪ Claim directed to methods of administration, including specific dose	▪ IPR2015-00418	▪ Boehringer Ingelheim International GmbH ▪ Boehringer Ingelheim Pharmaceuticals, Inc.	▪ Not instituted ▪ Denied by PTAB
▪ Humira®	▪ AbbVie Biotechnology Ltd.	▪ 8,916,157 ▪ Claims directed to formulations	▪ IPR2015-01514	▪ Amgen Inc	▪ Not instituted ▪ Denied by PTAB
▪ Humira®	▪ AbbVie Biotechnology Ltd.	▪ 8,916,158 ▪ Claims directed to formulations	▪ IPR2015-01517	▪ Amgen Inc	▪ Not instituted ▪ Denied by PTAB
▪ Orencia®	▪ Bristol-Myers Squibb Company	▪ 8,476,239 ▪ Claims directed to formulations	▪ IPR2015-01537	▪ Momenta Pharmaceuticals, Inc.	▪ Instituted ▪ Proceeding is pending
▪ Rituxan®	▪ Genentech, Inc.	▪ 7,976,838 ▪ Claims directed to methods of treatment, reciting specific patient population and specific dose	▪ IPR2015-01733	▪ Celltrion, Inc.	▪ Not instituted ▪ Petitioner sought joinder with IPR2015-00417 ▪ Following termination of IPR2015-00417, petitioner terminated proceeding
▪ Rituxan®	▪ Biogen IDEC, Inc. ▪ Genentech, Inc.	▪ 7,820,161 ▪ Claims directed to methods of treatment involving combination therapy	▪ IPR2015-01744	▪ Celltrion, Inc.	▪ Not instituted ▪ Petitioner sought joinder with IPR2015-00415 ▪ Following termination of IPR2015-00415, petitioner terminated proceeding
▪ Humira®	▪ AbbVie Biotechnology Ltd.	▪ 8,889,135 ▪ Claims directed to methods of treatment including dose regimen	▪ IPR2016-00172	▪ Coherus BioSciences Inc.	▪ Pending, prior to institution decision
▪ Humira®	▪ AbbVie Biotechnology Ltd.	▪ 9,017,680 ▪ Claims directed to methods of treatment, reciting combination therapy and dosing regimen	▪ IPR2016-00188	▪ Coherus BioSciences Inc.	▪ Pending, prior to institution decision
▪ Humira®	▪ AbbVie Biotechnology Ltd.	▪ 9,073,987 ▪ Claims directed to methods of treatment, reciting a dosing regimen	▪ IPR2016-00189	▪ Coherus BioSciences Inc.	▪ Pending, prior to institution decision
▪ Humira®	▪ AbbVie Biotechnology Ltd.	▪ 8,889,135 ▪ Claims directed to methods of treatment including dose regimen	▪ IPR2016-00408	▪ Boehringer Ingelheim International GmbH ▪ Boehringer Ingelheim Pharmaceuticals, Inc.	▪ Pending, prior to institution decision
▪ Humira®	▪ AbbVie Biotechnology Ltd.	▪ 8,889,135 ▪ Claims directed to methods of treatment including dose regimen	▪ IPR2016-00409	▪ Boehringer Ingelheim International GmbH ▪ Boehringer Ingelheim Pharmaceuticals, Inc.	▪ Pending, prior to institution decision

   ISSN 1935-7257

Table 3: Additional IPRs Challenging Brand-Name Biologics

Biologic	Patent Owner	Patent No.	IPR No.	Petitioner	Status of Proceeding
▪ Myozyme® ▪ Lumizyme®	▪ Genzyme Therapeutic Products Limited Partnership	▪ 7,351,410 ▪ Claims directed to methods of treatment	▪ IPR2013-00534	▪ BioMarin Pharmaceutical Inc.	▪ Final written decision ▪ PTAB found every challenged claim unpatentable
▪ Myozyme® ▪ Lumizyme®	▪ Duke University	▪ 7,056,712 ▪ Claims directed to methods of treatment	▪ IPR2013-00535	▪ BioMarin Pharmaceutical Inc.	▪ Final written decision ▪ PTAB found every challenged claim unpatentable
▪ Myozyme® ▪ Lumizyme®	▪ Genzyme Therapeutic Products Limited Partnership	▪ 7,655,226 ▪ Claims directed to methods of treatment	▪ IPR2013-00537	▪ BioMarin Pharmaceutical Inc.	▪ Final written decision ▪ PTAB found every challenged claim unpatentable
▪ Kadcyla®	▪ ImmunoGen, Inc.	▪ 8,337,856 ▪ Claims directed to immunoconjugates	▪ IPR2014-00676	▪ Phigenix, Inc.	▪ Final written decision ▪ All challenged claims upheld by PTAB
▪ Kadcyla®	▪ Genentech, Inc. ▪ ImmunoGen, Inc.	▪ 7,575,748 ▪ Claims directed to methods of treatment using an immunoconjugate, including a diagnostic step	▪ IPR2014-00842	▪ Phigenix, Inc.	▪ Not instituted ▪ Denied by PTAB
▪ CroFab®	▪ BTG International Inc.	▪ 8,048,414 ▪ Claims directed to antivenom pharmaceutical compositions comprising Fab fragments	▪ IPR2014-01269	▪ Laboratorios Silanes, S.A. de C.V. ▪ Instituto Bioclon, S.A. de C.V. ▪ Rare Disease Therapeutics, Inc.	▪ Not instituted ▪ Joint motion to terminate proceedings filed by petitioner and patent owner
▪ CroFab®	▪ BTG International Inc.	▪ 8,048,414 ▪ Claims directed to antivenom pharmaceutical compositions comprising Fab fragments	▪ IPR2015-01305	▪ Bioactive Laboratories	▪ Not instituted ▪ Denied by PTAB
▪ Enbrel®	▪ Hoffmann-La Roche Inc.	▪ 8,163,522 ▪ Claims directed to method of production	▪ IPR2015-01792	▪ Coalition for Affordable Drugs V LLC	▪ Not instituted ▪ Denied by PTAB