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Biosimilars: Looking Back and Looking Ahead



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It was a record year for biosimilars in the United States in 2016. The Food and Drug Administration (FDA) approved three new abbreviated Biologics License Applications (aBLAs) for biosimilar drugs and the second biosimilar therapeutic entered the U.S. commercial market. In addition, litigation involving biosimilar/biologic drugs is on the rise, and significant legal verdicts were handed down this year, which helped shape the bounds of the Biologics Price Competition and Innovation Act (BPCIA). Here are the highlights of the past year and predictions for biologic/biosimilar activity in 2017.

FDA Approves More Biosimilars and Second Biosimilar Enters the Market Prior to 2016, only one biologic product, ZARXIO® a biosimilar to Amgen's NEUPOGEN® (filgrastim) was approved by FDA and commercially available in the US.

This year, three new aBLAs were approved by FDA, ultimately leading to the commercial launch in December 2016 of INFLECTRA®. Approved in April 2016 as a biosimilar to Janssen's REMICADE® (infliximab), INFLECTRA is the second marketed biosimilar drug in the U.S., and the first monoclonal antibody biosimilar. The drug was approved for all of the clinical indications of the reference product including, among others, rheumatoid arthritis, Crohn's disease, ulcerative colitis and ankylosing spondylitis.

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The other two aBLAs approved in 2016 were ERELZI® and AMJEVITA®. ERELZI, a biosimilar of Amgen's ENBREL® (etanercept), was approved in August 2016. It is a fusion protein that interferes with TNF-α to treat autoimmune disease. Manufactured by Sandoz, a Novartis subsidiary, ERELZI was approved for all indications listed on the reference product's label, including rheumatoid arthritis, psoriatic arthritis, plaque psoriasis and ankylosing spondylitis.

AMJEVITA was approved in September 2016 as a biosimilar to AbbVie's HUMIRA® (adalimumab). AMJEVITA is a fully human monoclonal antibody that binds TNF-α. The therapeutic is manufactured by Amgen and was approved for all of HUMIRA's indications in the treatment of multiple inflammatory diseases. Approval of AMJEVITA affirms Amgen's identity as both a biologics innovator and a biosimilars developer.

Various other entities submitted aBLAs to FDA for review in 2016. In May 2016, partners Merck and Samsung Bioepis announced that FDA had agreed to review their proposed biosimilar to REMICADE. In October 2016, FDA accepted Coherus' aBLA for a NEULASTA® (pegfilgrastim) biosimilar candidate. November was also an active month for applications, beginning with partners Mylan and Biocon filing an aBLA for a HERCEPTIN® (trastuzumab) biosimilar. Amgen and Allergan together submitted an application for a bevacizumab biosimilar, referencing Genentech's AVASTIN®. Boehringer Ingelheim currently has two biosimilar monoclonal antibodies in late stage clinical develop-

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ment, an adalimumab biosimilar candidate to HUMIRA and its own bevacizumab biosimilar candidate to AVASTIN.

FDA also sent complete response letters to several applicants throughout 2016. In July 2016, Sandoz received a response letter for its pegfilgrastim application. According to press releases, Sandoz plans to initiate an additional study to address a data request with a potential new submission in 2018. Apotex continued to work with FDA in reviewing its applications for filgrastim and pegfilgrastim biosimilars. These aBLAs were originally accepted for review by FDA in December 2014 and February 2015, respectively. Hospira, a Pfizer subsidiary, continued to address a complete response letter it received from the FDA in 2015 for RETACRIT®, its biosimilar referencing Amgen's EPOGEN®. Table 1 below summarizes the current status of various biosimilar products before the FDA.

Federal Circuit Issues Second BPCIA Opinion; SCOTUS Grants Review In a 2015 case over Sandoz's biosimilar to NEUPOGEN (filgrastim), the Federal Circuit held in a case of first impression that the patent dance disclosures of Section 262(*l*)(2)(A) are not mandatory and notice of commercial marketing under the BPCIA was only effective after FDA approval. *Amgen v. Sandoz*, 794 F.3d 1347 (Fed. Cir. 2015).

The Federal Circuit issued its second opinion related to the BPCIA in 2016, weighing in on a dispute between Amgen and Apotex regarding Apotex's yet-to-be-approved pegfilgrastim biosimilar to NEULASTA. *Amgen v. Apotex*, 827 F.3d 1052 (Fed. Cir. 2016). The Federal Circuit held in July 2016 that the BPCIA's 180-day commercial marketing notice provision under Section 262(*l*)(8)(A) is mandatory for an applicant like Apotex, even when the parties have engaged in the patent dance. The court also ruled that the notice begins *post*-licensure.

In 2016, Amgen, Apotex and Sandoz separately petitioned the Supreme Court for *certiorari* to clarify the BPCIA provisions. Sandoz filed its petition, *Sandoz v. Amgen*, No. 15-1039 in February 2016 and the following month, Amgen opposed and filed a conditional cross-petition, *Amgen v. Sandoz*, 15-1195. In June 2016, the Court invited the Solicitor General to comment on several issues, which included whether notice of commercial marketing under Subsection (*l*)(8)(A) is legally effective if given *prior* to FDA approval, and if not, whether the notice requirement can be enforced by an injunction delaying market entry of the biosimilar by 180 days. Amgen's cross-petition separately asked whether an applicant's aBLA and related manufacturing information must be disclosed to the reference product sponsor in order to start the patent dance, and whether Subsection (*l*)(2)(A) of the BPCIA creates a binding obligation enforceable by injunction.

In September 2016, Apotex filed its own petition for review raising similar questions. On December 7, 2016, the Solicitor General weighed in with respect to the *Sandoz v. Amgen* petition and conditional cross-petition. Representing the interests of the U.S. government as *amicus curiae* to the Court, the Solicitor urged the Court to grant *certiorari* and to find the holding from *Amgen v. Apotex* incorrect. Specifically, the Solicitor argued that an injunction is not proper to enforce Section 262(*l*)(8)(A). Instead, a sponsor's sole recourse if a biosimilar applicant fails to provide information under (*l*)(8)(A) is commencement of a patent-infringement action. The Solicitor also made recommendations that aligned with Sandoz's positions, namely that the Court should find the Federal Circuit's holding incorrect with respect to the timing of the 180-day notice, arguing that notice is valid if given *pre*-licensure. With respect to the disclosure requirement in Subsection (*l*)(2)(A), the Solicitor recommended that the Court adopt the Federal Circuit's holding that a biosimilar manufacturer is not required to disclose its aBLA application and manufacturing process information and start the patent dance.

Five days later, on December 12, 2016, the Supreme Court denied Apotex's petition. On December 20, 2016, Amgen filed a supplemental brief in *Sandoz v. Amgen*, No. 15-1039. On January 13, 2017, the Court granted both the Amgen petition and the Sandoz petition, consolidating the cases for oral argument. The Court also granted a motion by Apotex to file a brief as amici curiae.

District Court Litigation Grew as Applicants Seek to Bring New Biosimilars to Market Throughout 2016, district courts continued to grapple with the provisions of the BPCIA as litigants tested the bounds of the patent dance provisions and the confidentiality exchanges set forth under the statute.

■ *Hospira's Biosimilar to EPOGEN and PROCRIT® (epoetin alfa)* – In *Amgen v. Hospira* (1:15-cv-839 D. Del.), the parties wrestled with a question relating to the scope of discovery. Specifically, Amgen and Hospira took opposite positions as to whether a reference product sponsor may obtain information that is not relevant to currently asserted claims, but which could be relevant to the sponsor's other patents. Amgen appealed to the Federal Circuit in August 2016 (Appeal No. 16-2179) to reverse an order given by the District of Delaware the same month. The order denied Amgen discovery of cell-culture manufacturing information used by biosimilar applicant Hospira to generate a biosimilar version of Amgen's EPOGEN. Resolution of the key issues in this case will shed light on the patents that a reference product sponsor must disclose during the patent dance, the scope of information that must be shared with the sponsor, and the extent of discovery available in a first wave of litigation under the BPCIA. As of January 2017, the parties had briefed their arguments regarding the BPCIA's limits on discovery and addressed jurisdictional issues before the Federal Circuit.

■ *Apotex's Biosimilar to NEUPOGEN (filgrastim)* – In August 2015, Amgen filed a BPCIA complaint against Apotex in the Southern District of Florida centered on its filgrastim product. (0:15-cv-61631 S.D. Fla.) After a bench trial in July 2016, the district court entered a judgment of non-infringement in favor of Apotex with respect to its yet-to-be approved filgrastim and pegfilgrastim biosimilars. Amgen appealed to the Federal Circuit (Appeal No. 16-1308) and filed an opening brief in December 2016.

■ *Celltrion's Biosimilar to INFLECTRA (infliximab)* – An ongoing lawsuit between Janssen and Celltrion relates to Celltrion's FDA-approved infliximab biosimilar, INFLECTRA. (1:15-cv-10698 D. Mass.) In August 2016, the District Court of Massachusetts granted Celltrion's motion for summary judgment that all claims of U.S.

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Patent No. 6,284,471 are invalid as obvious. Janssen's patent was set to expire in 2018.

In October 2016, Janssen appealed the invalidity ruling to the Federal Circuit. (Appeal No. 17-1120.) Janssen's opening brief on the merits is due by January 26, 2017. On November 14, 2016 the U.S. Patent Trial and Appeal Board (PTAB) affirmed the Examiner's final rejection of claims 1-7 of U.S. Patent No. 6,284,471 in an *ex parte* reexamination proceeding. Janssen filed a notice of appeal (Appeal No. 17-1257), to be combined for review before the same merits panel for oral argument before the Federal Circuit. Also in November, Celltrion's parent company, Pfizer, initiated shipments of INFLECTRA to wholesalers.

In addition to the pending litigation, six new district court litigations involving biosimilar drugs were initiated in 2016. In June 2016, Janssen filed two district court suits, one in Massachusetts (*Janssen v. Celltrion* (1:16-cv-11117 D. Mass.)) and the other in Utah (*Janssen v. Hyclone* (1:16-cv-00071 D. Utah)), to assert claims in U.S. Patent No. 7,598,083 covering its cell culture media for INFLECTRA. Four additional 2016 filings are outlined below.

■ *Sandoz's Biosimilar to ENBREL (etanercept)* – In February 2016, Immunex filed a BPCIA complaint against Sandoz regarding its FDA-approved ENBREL biosimilar. (2:16-cv-01118 D.N.J.) In August 2016, the District Court of New Jersey preliminarily enjoined Sandoz from making, using, importing, offering to sell, or selling its product pending trial in April 2018. As of December 2016, claim construction was underway.

■ *Sandoz's Biosimilar to NEULASTA (pegfilgrastim)* – In March 2016, Amgen sued Sandoz in the District of New Jersey for patent infringement based on Sandoz's biosimilar of Amgen's NEULASTA product. (2:16-cv-01276 D.N.J.) In July 2016, FDA rejected Sandoz's biosimilar application, and the case was dismissed with prejudice later that month. In May 2016, Amgen filed a patent infringement suit in the Northern District of California, also involving Sandoz's not-yet-approved pegfilgrastim biosimilar. (3:16-cv-02581 N.D. Cal.) The case was consolidated with the related *Amgen v. Sandoz* filgrastim matter (3:14-cv-04741 N.D. Cal.), which is scheduled for a jury trial in December 2017.

■ *Amgen's Biosimilar to HUMIRA (adalimumab)* – In August 2016, AbbVie filed a BPCIA complaint against Amgen in the District of Delaware regarding its FDA-approved adalimumab biosimilar, AMJEVITA®. (1:16-cv-00666 D. Del.) AbbVie asserted 10 patents as part of its first wave of litigation. Amgen listed 51 additional patents in the complaint for potential assertion in a second wave of litigation. A bench trial is scheduled to begin the first week of November 2019.

IPR Litigation Involving Biologics Increased in 2016 There was also an increase in *inter partes* review (IPR) proceedings of biologic drugs before the PTAB in 2016, with 17 new petitions filed challenging patents covering specific biologics. In 2015, there were only nine petitions challenging patents directed to particular biologics. The PTAB instituted trial on six of the biologic petitions filed in 2016, and on one other petition that was originally filed in 2015. Institution of IPR was denied in four of the 17 new filings, and seven are pending decision.

Various petitions challenging patents covering HUMIRA (adalimumab) were instituted, including two by Boehringer Ingelheim, IPR2016-00408 and IPR2016-00409. Three others were filed by Coherus Biosciences, IPR2016-00172, IPR2016-00188 and IPR2016-00189. Another petition, IPR2016-01018, was denied in November 2016 and petitioner Coherus filed a request for rehearing in December 2016. A patent covering a formulation of Bristol-Myers Squibb's OVENCIA® (abatacept) was challenged by Momenta Pharmaceuticals in 2015, resulting in trial being instituted this year and a decision issuing in December 2016. The PTAB did not invalidate any of the challenged claims.

In August 2016, several IPR petitions challenging an array of biologic patents were filed. Apotex filed IPR2016-01542 for review of U.S. Patent No. 8,952,138 directed to NEULASTA. A decision on institution is due by February 2017.

Mylan filed petitions IPR2016-01693 and IPR2016-01694, both challenging U.S. Patent No. 6,407,213 directed to formulations of Genentech's HERCEPTIN. Celltrion filed IPR2016-01614 and IPR2016-01667 for review of U.S. Patent Nos. 7,820,161 and 7,976,838 to RITUXAN® owned by Biogen and Genentech, respectively.

In September 2016, Hospira filed a petition for IPR (IPR2016-01771) challenging U.S. Patent No. 7,622,115, directed to Genentech's AVASTIN (bevacizumab). The same month, Hospira filed IPR2016-01837, seeking *inter partes* review of U.S. Patent No. 7,807,799, covering HERCEPTIN. Decisions regarding institution on the August-September filings remain pending.

Two cases initiated by the Coalition for Affordable Drugs were resolved in October 2016 in favor of the petitioner. These include IPR2015-00990 and IPR2015-01093, which challenged U.S. Patent No. 7,056,886 with claims covering GATTEX® (teduglutide). In its final written decision, the PTAB found all challenged claims unpatentable over the cited art.

Various biologic IPR petitions were terminated in 2016. In January 2016, the PTAB denied IPR2015-01514 and IPR2015-1517 in which Amgen had requested review of two AbbVie patents covering formulations of HUMIRA. In March 2016, the PTAB denied institution of IPR2015-01792, brought by hedge fund manager Kyle Bass and the Coalition for Affordable Drugs challenging U.S. Patent No. 8,163,522, with claims covering ENBREL. In October 2016, several petitions by Swiss Pharma International asking for review of patents covering Biogen's TYSABRI® (natalizumab) were denied. These included IPR2016-00912, IPR2016-00915 and IPR2016-00916 naming U.S. Patent Nos. 8,815,236, 8,349,321 and 8,900,577.

2017 Predictions As the U.S. biosimilar market continues to develop, additional aBLA filings are anticipated in 2017, as are decisions regarding FDA approval of other biosimilar drugs, such as Merck's proposed biosimilar to REMICADE, Coherus' proposed biosimilar to NEULASTA, Mylan's applied-for HERCEPTIN biosimilar, and Amgen's biosimilar candidate referencing AVASTIN. As more products are submitted for FDA approval, corresponding district court litigation is expected.

In addition, we anticipate the Supreme Court's industry-defining decision over the dispute between Amgen and Sandoz regarding the BPCIA provisions.

Briefing is expected to be completed this spring, and the Court may render its opinion this summer.

As discussed above, we also expect decisions from pending litigation that will continue to shape the bounds of the BPCIA provisions. The Federal Circuit should address the discovery dispute with respect to Hospira's biosimilar referencing EPOGEN, as well as Amgen's appeal of non-infringement concerning Apotex's NEUPOGEN biosimilar. The Federal Circuit may also come to a decision regarding the invalidity holding in the dispute centered around Celltrion's INFLECTRA biosimilar.

Finally, FDA released guidance in January 2017 on interchangeable biologic products. Interchangeable products can be substituted for the reference product by a pharmacist without the intervention of the prescribing health care provider. 42 U.S.C. § 262(i)(3). In order to meet the higher standard of interchangeability, a biosimilar applicant must demonstrate that the product can produce the same clinical result as the reference product in any given patient. To date, no approved biosimilar therapeutic has been deemed to be ''interchangeable,'' but the recent release of FDA guidance may help pave the way for the first interchangeable product. FDA states that applicants should submit data from switching studies to demonstrate the risk of switching between the reference product and the biosimilar. Several additional states, including Arizona, New Jersey, Oregon and Philadelphia passed biosimilar substitution laws in 2016. The laws allow pharmacists to automatically substitute a less expensive biosimilar product that has been deemed interchangeable by FDA for a brand name biological product.

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Brand Name	Innovator Company	Drug Class	Biosimilar	FDA Action/Status for Biosimilar
Avastin® (bevacizumab)	Genentech	Immunological Agent	Amgen/Allergan (ABP 215)	Amgen reported equivalence in a Phase III clinical trial 9/2015 Filed 11/2016
			Boehringer Ingelheim (BI 695502)	Boehringer Ingelheim reported equivalence in a Phase I clinical trial 11/2016
Enbrel® (etanercept)	Amgen	Anti-Inflammatory Tumor Necrosis Factor Inhibitor	Sandoz (Erelzi®)	Approved 8/30/2016
Epogen®/ Procrit® (epoetin alfa)	Amgen	Hematopoietic	Hospira (Retacrit®)	Filed 12/2014 Complete Response Letter 10/2015
Herceptin® (trastuzumab)	Genentech	Immunological Agent	Actavis/Amgen (ABP-980)	Amgen reported equivalence in a Phase III clinical trial 7/2016
			Mylan/Biocon (MYL-14010)	Filed 11/2016
			Pfizer (PF-05280014)	Pfizer reported equivalence in a Phase III clinical trial 11/2016
Humira® (adalimumab)	AbbVie	Antirheumatic	Amgen (Amjevita®)	Approved 9/23/2016
			Momenta (M923)	Momenta reported equivalence in a Phase III clinical trial 11/2016
			Boehringer Ingelheim (BI 695501)	Boehringer Ingelheim reported equivalence in a Phase III clinical trial 10/2016
Neulasta® (pegfilgrastim)	Amgen	Hematopoietic	Apotex	Accepted for review 12/2014
			Coherus BioSciences (CHS-1701)	Accepted for review 10/2016
			Sandoz/Novartis	Accepted for review 11/2015 CRL 7/2016
Neupogen® (filgrastim)	Amgen	Hematopoietic	Sandoz (Zarxio®)	Approved 3/6/2015 On the market
			Apotex (Grastofil®)	Accepted for review 2/2015
Orencia® (abatacept)	Bristol-Myers Squibb	Antirheumatic, Immune Modulator	Momenta (M834)	Phase I trial started 11/2016
Remicade® (infliximab)	Janssen	Gastrointestinal Agent, Immunological Agent	Celltrion (Inflectra®)	Approved 4/5/2016 On the market
			Merck/Samsung Bioepis (SB2)	Accepted for review 5/2016