Biosimilars 2017 Year in Review

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It was a busy year for biosimilar drug manufacturers, with 2017 being the most active year to date in the U.S. biosimilar space since the approval of the Biologics Price Competition and Innovation Act (BPCIA) in 2010. In 2017, five biosimilar drugs were approved, Renflexis® (a biosimilar of Remicade®) was launched, 11 new district court litigations were filed, and over 85 IPR petitions were submitted. This year also brought additional guidance on the bounds of the BPCIA, including from the Supreme Court and Federal Circuit. Moreover, in January 2017, the FDA provided much anticipated draft guidance on biosimilar interchangeability.

Increase in FDA approval for biologics and biosimilars

Biologics and biosimilars are a growing industry in the U.S., as evidenced by the increasing number of applications approved by the FDA each year. For example, in 2017, the FDA approved more than 20 biologics license applications (BLAs), up from the 15 approved in 2016 and the 13 approved in 2015. Several of these recently approved applications were from the England-based Alba Bioscience. Roche, GlaxoSmithKline, Novartis and Merck also each a BLA approved.

Similarly, 2017 saw an increase in the number of FDA-approved abbreviated biologics license applications (aBLAs) for biosimilars. The FDA approved five new biosimilars this year: Cyltezo® (adalimumab-adbm), Mvasi® (bevacizumab-awwb), Ogivri® (trastuzumab-dkst), Renflexis® (infliximab-abda), and Ixifi® (infliximab-qbtx). Two of the five, Ogivri® and Mvasi®, biosimilars of Herceptin® and Avastin®, respectively, are the first biosimilars approved for cancer indications.

On January 17, 2017, the FDA released its long-awaited draft guidance on biosimilar interchangeability. The guidance recommends that interchangeable applicants perform switching studies to show that patients can alternate safely between the biologic and interchangeable. The comment period closed on May 19, with 53 filed comments by brand companies, biosimilar companies, healthcare providers, insurers, and other interested organizations. As of now, the FDA has not committed on when or if it will finalize this guidance, but has committed to provide draft guidance related to post-approval manufacturing changes by March 31, 2019 and to publish revised draft guidance applicable to biosimilars and interchangeables on “Good Review Management Principles and Practices for PDUFA Products” by the end of fiscal year 2018. Despite the FDA’s draft guidance—and the fact that nine companies have publicly disclosed a total of 14 interchangeable applications—no interchangeable has yet been approved by the FDA.

The following charts summarize publicly available information regarding approved and pending aBLAs, and illustrate additional trends in the biosimilar space. For example, the data shows that the average time from aBLA acceptance to approval has been decreasing: 9.8 months in 2017 versus more than 12 months in previous years.

Table 1. Approved Biosimilars

Biosimilar Drug	Biologic Drug	Biosimilar Code Name	FDA Approval Date	Time from aBLA Acceptance to Approval	Commercial Launch Date	Price Discount
Ixifi® (Pfizer)	Remicade® (Johnson & Johnson)	Infliximab-qbtx	December 13, 2017	8 months	No U.S. launch intended	
Ogivri® (Mylan)	Herceptin® (Genentech & Roche)	Trastuzumab-dkst	December 1, 2017	11 months	Confidential under license agreement	
Mvasi ® (Amgen & Allergan)	Avastin® (Roche)	Bevacizumab-awwb	September 14, 2017	10 months		
Cyltezo® (Boehringer Ingelheim)	Humira® (AbbVie)	Adalimumab-adbm	August 25, 2017	7 months		
Renflexis® (Samsung Bioepis/ Merck)	Remicade® (Johnson & Johnson)	Infliximab-abda	April 21, 2017	13 months	July 2017	35%
Amjevita® (Amgen)	Humira® (AbbVie)	Adalimumab-atto	September 23, 2016	8 months or less	Will not launch until 2023 per settlement	
Erelzi® (Sandoz)	Enbrel® (Amgen)	Etanercept-szzs	August 30, 2016	13 months		
Inflectra® (Pfizer/ Celltrion)	Remicade® (Johnson & Johnson)	Infliximab-dyyb	April 5, 2016	20 months	November 2016	15%
Zarxio® (Sandoz)	Neupogen® (Amgen)	Filgrastim-sndz	March 6, 2015	10 months	September 2015	15%

Table 2. aBLA Applications Pending as of January 2018

Biosimilar Drug	Biologic Drug	Biosimilar Code Name	Date of FDA Acceptance	Notes
Retacrit® (Pfizer/ Hospira)	Epogen®/ Procrit® (Amgen/ Johnson & Johnson)	Epoetin alfa	January 2015	• Rejected in 2015 • Resubmitted in December 2016 • In June 2017, the FDA issued a complete response letter (CRL) regarding concerns about immunogenicity assays and the manufacturing process
LA-EP2006 (Sandoz)	Neulasta® (Amgen)	Pegfilgrastim	November 2015	• Rejected in 2016 • US resubmission planned for 2019
Adello Biologics	Neupogen® (Amgen)	Filgrastim	September 2017	
CHS-1701 (Coherus)	Neulasta® (Amgen)	Pegfilgrastim	October 2016	• CRL response letter issued in June 2017 that "request[ed] a reanalysis of a subset of subject samples with a revised immunogenicity assay and additional information on the manufacturing process."
Rixathon® (Sandoz)	Rituxan® (Genentech)	Rituximab	September 2017	
CT-P10 (Celltrion/ Teva)	Rituxan® (Genentech)	Rituximab	June 2017	
CT-P6 (Celltrion/ Teva)	Herceptin® (Genentech & Roche)	Trastuzumab	July 2017	
ABP 980 (Amgen/ Allergan)	Herceptin® (Genentech & Roche)	Trastuzumab	Pending acceptance	• aBLA submitted in July 2017
PF-05280014 (Pfizer)	Herceptin® (Genentech & Roche)	Trastuzumab	August 2017	
SB3 (Samsung Bioepis/ Merck)	Herceptin® (Genentech & Roche)	Trastuzumab	December 2017	
GP2017 (Sandoz)	Humira® (AbbVie)	Adalimumab	January 2018	• Sandoz announced that a 51-week clinical study confirms that its proposed biosimilar for adalimumab matches

				Humira®'s safety and efficacy profile
GP1111 (Sandoz)	Remicade® (Johnson & Johnson)	Infliximab	May 2017	
MYL-1401H (Mylan/ Biocon)	Neulasta® (Amgen)	Pegfilgrastim	February 2017	• CRL response letter issued in October 2017, but Biocon stated that it does not expect the CRL to affect commercial launch
Lapelga® (Apotex)	Neulasta® (Amgen)	Pegfilgrastim	December 2014	
Grastofil® (Apotex)	Neupogen® (Amgen)	Filgrastim	February 2015	

Increased Guidance from the Judiciary

In 2017, the judiciary was actively involved in interpreting and defining the contours of the BPCIA. For the first time, the Supreme Court weighed in on the BPCIA, deciding *Amgen v. Sandoz*, a case involving a biosimilar of Amgen's Neupogen® (filgrastim). The Supreme Court unanimously held that a biosimilar applicant could provide notice of commercial marketing to the reference product sponsors before the FDA's approval of the biosimilar. The court also held that biosimilar applicants cannot be forced through a federal injunction to participate in the BPCIA's "patent dance" disclosure provisions (requiring biosimilar applicants to provide copies of their aBLAs to reference product sponsors). The Court did not, however, decide whether the BPCIA pre-empted any state law remedies and remanded that issue back to the Federal Circuit. Six months later, the Federal Circuit held that the BPCIA preempted all state remedies when a biosimilar applicant opts out of the "patent dance."

This year, the Federal Circuit provided further guidance regarding the BPCIA. In *Amgen v. Hospira*, a case involving Hospira's biosimilar to Amgen's Epogen® (epoetin alfa), the Federal Circuit held that even if a biosimilar applicant fails to disclose information under the BPCIA, the biologic manufacturer still has a reasonable basis to list potentially infringed patents on its "patent dance" list and thereafter assert claims of patent infringement so long as it has a good-faith belief, which could be based on an applicant's withholding of information. In doing so, the court denied Amgen's motion to compel discovery to produce other manufacturing information—unrelated to the patents-in-suit—to identify other infringed patents.

Additionally, in *Amgen v. Apotex*, the Federal Circuit held that information in the pre-litigation letters exchanged under the BPCIA's disclosure provisions are party admissions and must be considered in an infringement analysis, but they are not binding and may be overcome by contrary evidence. In a suit involving Neulasta® (pegfilgrastim) and Neupogen® (filgrastim) biosimilars, Amgen argued that the district court below refused to give weight to pre-litigation admissions made by Apotex in its aBLAs and during the disclosures required under the BPCIA. Amgen further argued that Apotex's representations were party admissions and thus should have been considered in the court's infringement analysis. The Federal Circuit agreed with Amgen in holding that "statements in the pre-litigation letters are party admissions and have some

probative weight," but held that the court below properly considered the letters and did not err in finding the letters were outweighed by other evidence.

The federal district courts have also had a busy year, with 11 biosimilar cases filed, up from six filed in 2016. The new district court litigations are summarized in the chart below. A majority of the cases were filed in the District of Delaware. The most active biosimilar litigants in 2017 were Amgen and Genentech, each named as a party in five complaints.

Note that each new case does not correspond to a separate, new biosimilar. For example, four cases filed this year related to Amgen's Mvasi® biosimilar of Genentech's Avastin®. Further, the recently filed *Janssen v. Celltrion* case is the third in a series of cases ongoing since 2015 involving the same patent (US 7,598,083) and the same biosimilar of Remicade®.

Table 3. BPCIA Cases Filed in 2017

Case Name	Court	Filing Date	Drug at Issue	Number of Patents
Genentech, Inc. v. Amgen Inc. (1:17-cv-00165)	D. Del	2/15/2017	Avastin®/Mvasi® (bevacizumab)	0 (alleged violations of BPCIA)
Amgen Inc. et al v. Coherus Biosciences, Inc. (1:17-cv-00546)	D. Del.	5/10/2017	Neulasta®/CHS-1701 (pegfilgrastim)	1
Janssen Biotech, Inc. v. Samsung Bioepis Co., Ltd. (2:17-cv-03524)	D. N.J.	5/17/2017	Remicade®/ Renflexis® (infliximab)	3
Janssen Biotech, Inc. v. Celltrion Healthcare Co., Ltd. et al (1:17-cv-11008)	D. Mass.	5/31/2017	Remicade®/Inflectra® (infliximab)	1
AbbVie Inc. et al v. Boehringer Ingelheim Int'l GmbH et al (1:17-cv-01065)	D. Del.	8/2/2017	Humira®/Cyltezo® (adalimumab)	8

Amgen Inc. et al v. Mylan Inc. et al (2:17-cv-01235)	W.D. Pa.	9/22/2017	Neulasta®/MYL-140H (pegfilgrastim)	2
Amgen Inc. v. Genentech, Inc. et al (2:17-cv-07349)	C.D. Cal.	10/6/2017	Avastin®/Mvasi® (bevacizumab)	27
Genentech, Inc. et al v. Amgen Inc. (1:17-cv-01407)	D. Del.	10/6/2017	Avastin®/Mvasi® (bevacizumab)	25
Genentech, Inc. et al v. Amgen, Inc. (1:17-cv-01471)	D. Del.	10/18/2017	Avastin®/Mvasi® (bevacizumab)	25
Genentech, Inc. et al v. Pfizer, Inc. (1:17-cv-01672)	D. Del.	11/17/2017	Herceptin®/PF-05280014 (trastuzumab)	40
Genentech, Inc. et al v. Sandoz, Inc. et al (2:17-cv-13507)	D. N.J.	12/21/2017	Rituxan®/Rixathon® (rituximab)	24

As a preferred venue, it is not surprising that the District of Delaware saw the first damages award in BPCIA litigation. In September 2017, the jury in *Amgen v. Hospira* awarded $70 million in reasonable royalty damages to Amgen. This case concerned Pfizer's infringement of a now expired patent covering Amgen's biologic Epogen®. The jury found that some of Pfizer's biosimilar batches were not solely related to Hospira's aBLA application and thus were not exempted by the safe harbor of 35 U.S.C. § 271(e)(1). Further, the jury decided to award damages even though Hospira's aBLA had not yet been approved and no biosimilar sales had been made in the U.S.

Increase in Post-Grant Practice

Along with the increase in district court litigation, the total number of IPR petitions in the biologics space reached an all-time high this year, with 88 petitions filed. This is almost six times the number of petitions that were filed in 2016 (15 petitions total).

Of the 52 petitions that reached an institution decision, 28 were instituted. Of the 28 petitions instituted, two petitions were terminated following a settlement and only six final decisions were issued. Five of these final written decisions found three of AbbVie's Humira® patents unpatentable. The remaining final written decision upheld the validity of claims covering Orencia® (abatacept).

Pfizer was the most active entity challenging biologic patents in 2017, filing 23 petitions. The biosimilar manufacturers Celltrion and Sandoz were also active challengers, filing 13 and 10 petitions, respectively. Genentech's Herceptin® patent portfolio was the most challenged at the patent office, with 31 petitions. Biogen Idec / Genentech's Rituxan® came in second (with 19 petitions) and AbbVie's Humira® came in third (with 14 petitions). Method of treatment patents and formulation patents remained the most commonly challenged patents in the biologic space.

The large increase in IPR petitions in the biologics space may be attributed to a "freedom to operate" strategy aiming to clear patents in the early stages of biosimilar development so that they do not become impediments when a biosimilar application is filed. Additionally, IPRs may be useful for chipping away at a large biologic patent portfolio. Consistent with this, a majority of biologic petitions (56) have taken aim at three biologic drugs with large patent portfolios: Herceptin®, Humira® and Rituxan®.

Some petitioners have been fairly successful at the PTAB. For example, Coherus and Boehringer Ingelheim successfully petitioned to institute review of three of AbbVie's Humira® patents. The PTAB invalidated all claims in all three patents. On May 16, 2017, the PTAB invalidated all five claims of AbbVie's cornerstone method patent, US 8,889,135, marking the first time that any Humira® patent was invalidated in the U.S. On June 9, 2017, the PTAB also invalidated all claims of two other Humira® method of treatment patents—US 9,017,680 and US 9,073,987.

It is unclear if this uptick in biologics IPR petitions will continue in 2018. First, on November 20, 2017, the U.S. Patent and Trademark Office issued a rule adjusting IPR fees. The petitioning fee for challenging up to 20 claims will increase by $6,500, potentially dissuading some petitioners. IPR post-institution fees will also increase, but only by $1,000. Along with the rising costs, IPR lawyers and petitioners alike are awaiting the Supreme Court's decision in *Oil States*, which will decide whether post-grant patent practice, including the institution of IPRs, is unconstitutional. The Supreme Court's opinion is expected in early or mid-2018.

Conclusion

Seven years after the enactment of the BPCIA, the U.S. biosimilar market is continuing to grow, with three biosimilar drugs on the market, six others approved, and a pipeline of biosimilar applications under review at the FDA. Looking forward to 2018, we anticipate continued litigation in both the district court and at the PTAB, pending the outcome of *Oil States*. This year brought clarity in the form of Supreme Court and Federal Circuit decisions, and more is sure to come.

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