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U.S., European Biosimilar Approval Activity in 2017

BY IRENA ROYZMAN AND JACOB F. SIEGEL

U.S. Biosimilar Approvals Soar

Marketing approval for U.S. biosimilars took off in 2017. The FDA approved five biosimilar products in 2017, increasing the number of approved biosimilars from four to nine. In addition to new biosimilars of AbbVie's Humira and Janssen's Remicade, the FDA has approved the first two biosimilars for the treatment of cancer. All five of the products approved last year are biosimilars of complex blockbuster therapeutic antibodies.

Five Biosimilars Approved In the U.S.

The FDA approved five biosimilars in 2017, more than doubling the number of approved biosimilar medicines in the U.S. The biosimilars approved in 2017 include the first two biosimilars approved for cancer treatment, Mylan and Biocon's Ogivri, a biosimilar of Genentech's Herceptin, and Amgen and Allergan's Mvasi, a biosimilar of Genentech's Avastin.

The most recently approved biosimilar in the U.S. is Pfizer's Ixifi (infliximab-qbtx), the third biosimilar of Remicade approved by the FDA. Ixifi is Pfizer's second approved Remicade biosimilar; Pfizer also distributes Celltrion and Hospira's Inflectra (infliximab-dyyb) in the U.S. After the announcement of the FDA's approval of Ixifi, Pfizer reported that it has no current plans to commercialize Ixifi in the U.S. and is considering its "strategic options." The approval of Ixifi follows the April 2016 approval of Inflectra and the April 2017 approval of Samsung Bioepis's Remicade biosimilar, Renflexis (infliximab-abda).

Also approved in 2017 was Boehringer Ingelheim's Cyltezo (adalimumab-adbm), a biosimilar of AbbVie's Humira. Cyltezo, which received FDA approval in August, is the second Humira biosimilar approved in the U.S. The FDA approved Amgen's Amjevita

(adalimumab-atto), the first biosimilar of Humira, in September 2016.

Of the nine FDA-approved biosimilars, three are on the U.S. market: Sandoz's biosimilar of Neupogen and Pfizer's and Samsung Bioepis's biosimilars of Remicade. As to the other six, the launch dates for two, Mylan/Biocon's Ogivri and Amgen's Amjevita, are subject to settlement agreements, Pfizer has no current plans to market Ifixi and the biosimilar makers for the other four products have not launched at risk to date and some are awaiting resolution of patent litigation.

Pending U.S. Biosimilar Applications

A number of biosimilar applications are currently pending before the FDA. Mylan's Ogivri, the first U.S. biosimilar of Genentech's Herceptin (trastuzumab) was approved by FDA on December 1, but at least four other applications for Herceptin biosimilars have been submitted to FDA in recent months. Amgen and Allergan's application for a biosimilar of Herceptin was submitted for review in July 2017, Celltrion and Teva's application was accepted for review in July 2017, Pfizer's application was accepted for review in August 2017, and Samsung Bioepis's application was accepted for review in December 2017. The FDA has also accepted for review two applications for biosimilars of Biogen and Genentech's Rituxan (rituximab). The FDA accepted Celltrion and Teva's application for review in June 2017, and Sandoz's application in September 2017. Both of these proposed biosimilars have been previously approved by the EMA for marketing in Europe. The FDA is also reviewing Adello Biologics's proposed biosimilar of Neupogen (filgrastim). The FDA accepted Adello's application for review in September 2017. If Adello's application is approved, it may be the second filgrastim biosimilar approved in the U.S., after Sandoz's Zarxio, the first U.S. biosimilar approved and the first U.S. biosimilar to launch commercially. The FDA accepted Apotex's application for a proposed Neupogen biosimilar for review in 2015 but the product has not been approved to date.

Rejected U.S. Biosimilar Applications

Neulasta (pegfilgrastim) biosimilars have faced a number of hurdles in both the U.S. and Europe, and no biosimilars of Neulasta, a pegylated version of Neupogen, have been approved by the FDA or the EMA to

Irena Royzman is co-chair of Patterson Belknap's Biotechnology Practice, where she focuses her work on biotech and pharmaceutical litigation. Jacob F. Siegel is an associate in Patterson Belknap's litigation department.

U.S. Approved Biosimilars as of December 2017

Biosimilar Trade Name	Applicant	Reference Drug	Approval Date	Status
Zarxio (filgrastim-sndz)	Sandoz	Neupogen	Mar. 6, 2015	Launched in US September 2015; ongoing patent litigation
Inflixtra (infliximab-dyyb)	Celltrion/Hospira	Remicade	Apr. 5, 2016	Launched in US November 2016; ongoing patent litigation
Erelzi (etanercept-szsz)	Sandoz	Enbrel	Aug. 30, 2016	No launch until 2018 at earliest pending outcome of litigation
Amjevita (adalimumab-atto)	Amgen	Humira	Sept. 23, 2016	Launch in US on Jan. 31, 2023, pursuant to global settlement agreement
Renflexis (infliximab-abda)	Samsung Bioepis	Remicade	Apr. 21, 2017	Launched in US July 2017
Cyltezo (adalimumab-adbm)	Boehringer Ingelheim	Humira	Aug. 25, 2017	No launch date announced; litigation pending
Mvasi (bevacizumab-awwb)	Amgen/Allergan	Avastin	Sept. 14, 2017	No launch date announced; litigation pending
Orivri (trastuzumab-dkst)	Mylan/Biocon	Herceptin	Dec. 1, 2017	Launch date undisclosed under settlement agreement
Ixifi (infliximab-qbtx)	Pfizer	Remicade	Dec. 13, 2017	No current plans for US launch

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date. In the past six months, the FDA rejected two pending pegfilgrastim biosimilar applications. The FDA rejected Coherus's application in June 2017, although Coherus reports that it hopes to resubmit its application "mid-first quarter of 2018 subject to a meeting with the FDA." Mylan/Biocon's application for a Neulasta biosimilar was rejected in October 2017. Biocon has stated that it does not expect the rejection to impact the timing of the commercial launch of its product. Sandoz reported this year that it intends to resubmit its pegfilgrastim biosimilar application to the FDA in 2019. The FDA rejected Sandoz's application in 2016.

The pegfilgrastim applications were not the only biosimilar applications that the FDA rejected in 2017. In June, the FDA rejected for a second time Hospira's application for a biosimilar of Amgen's EPO (epoetin alfa). Although a number of biosimilars of EPO have been on the European market for a decade, the FDA has not approved an EPO biosimilar for the U.S. market. Hospira's biosimilar received a favorable recommendation from the Oncological Drugs Advisory Committee in May 2017 but the FDA rejected the application. Pfizer, Hospira's parent company, announced that the FDA's rejection related to issues uncovered during a February 2017 FDA inspection of the proposed manufacturing facility for the biosimilar.

2017 Biosimilar Approvals in Europe

The European biosimilar market expanded at a record pace in 2017. The EMA approved marketing of 16 biosimilar products referencing seven different innovator biologic products. For five of the innovator products – AbbVie's Humira, Biogen/Genentech's Rituxan, Ge-

nentech's Herceptin, Eli Lilly's Humalog, and Eli Lilly's Forsteo – no biosimilar was previously approved in Europe.

CHMP Issues Positive Opinions

Two additional biosimilars, Amgen/Allergan's Mvasi and Celltrion's Herzuma, received favorable opinions from EMA's Committee on Medicinal Products for Human Use (CHMP) in 2017 and may soon be approved in Europe. Mvasi, a biosimilar of Genentech's Avastin (bevacizumab), received a favorable recommendation from CHMP on Nov. 9, 2017. Mvasi was approved as a biosimilar in the U.S. in September 2017. Celltrion's Herzuma, a biosimilar of Genentech's Herceptin (trastuzumab), received a positive opinion from CHMP on December 14, 2017. If, as anticipated, the European Commission follows the recommendation of CHMP, Mvasi and Herzuma likely will be approved in Europe in the coming months.

Pending Biosimilar Applications in Europe

Eleven additional biosimilar applications were under evaluation by the EMA as of December 2017: three applications for biosimilars of AbbVie's (adalimumab), one application for a biosimilar of Sanofi's Lantus (insulin glargine), six applications for biosimilars of Amgen's Neulasta (pegfilgrastim), one application for a biosimilar of Janssen's Remicade (infliximab) and four applications for biosimilars of Genentech's Herceptin (trastuzumab). (The Lantus biosimilar, Mylan/Biocon's Semglee, received a positive CHMP opinion in January 2018.)

The six pending applications for biosimilars of Amgen's

Biosimilars Approved in Europe as of December 2017*

Biosimilar Trade Name	Marketers	Active Substance	Reference Drug	Year of Approval
Epoetins				
Abseamed	Medice	epoetin alfa	Eprex/Erypo	2007
Binocrit	Sandoz	epoetin alfa	Eprex/Erypo	2007
Epoetin Alfa Hexal	Hexal	epoetin alfa	Eprex/Erypo	2007
Retacrit (1)	Hospira	epoetin zeta	Eprex/Erypo	2007
Silapo	Stada	epoetin zeta	Eprex/Erypo	2007
Filgrastims				
Accofil	Accord	filgrastim	Neupogen	2014
Filgrastim Hexal	Hexal	filgrastim	Neupogen	2009
Grastofil (2)	Apotex	filgrastim	Neupogen	2013
Nivestim	Hospira	filgrastim	Neupogen	2010
Ratiograstim	Ratiopharm	filgrastim	Neupogen	2008
Tevagrastim	Teva	filgrastim	Neupogen	2008
Zarzio (3)	Sandoz	filgrastim	Neupogen	2009
Follitropins				
Bemfola	Finox	follitropin alfa	GONAL-f	2014
Ovaleap	Teva	follitropin alfa	GONAL-f	2013
Growth Hormones				
Omnitrope (4)	Sandoz	somatropin	Genotropin	2006
Insulins				
Abasaglar (5)	Eli Lilly	insulin glargine	Lantus	2014
Lusduna (6)	Merck	insulin glargine	Lantus	2017
Insulin lispro Sanofi	Sanofi	insulin lispro	Humalog	2017

Biosimilar Trade Name	Marketers	Active Substance	Reference Drug	Year of Approval
Low-Molecular Weight Heparins				
Inhixa	Techdow Europe AB	enoxaparin sodium	Clexane	2016
Thorinane	Pharmathen S.A.	enoxaparin sodium	Clexane	2016
Monoclonal Antibodies				
Amgevita/Solymbic (7)	Amgen	adalimumab	Humira	2017
Cyltezo (8)	Boehringer Ingelheim	adalimumab	Humira	2017
Imraldi	Samsung Bioepis	adalimumab	Humira	2017
Flixabi (9)	Samsung Bioepis	infliximab	Remicade	2016
Inflectra (10)	Hospira	infliximab	Remicade	2013
Remsima (10)	Celltrion	infliximab	Remicade	2013
Rixathon/Riximyo (11)	Sandoz	rituximab	MabThera	2017
Truxima/Blitzima/Ritemvia/Rituzena (12)	Celltrion	rituximab	MabThera	2017
Ontruzant (13)	Samsung Bioepis	trastuzumab	Herceptin	2017
Parathyroid Hormone Fragment				
Movymia	STADA Arzneimittel	teriparatide	Forsteo	2017
Terrosa	Gedeon Richter	teriparatide	Forsteo	2017
Fusion Proteins				
Benepali	Samsung Bioepis	etanercept	Enbrel	2016
Erelzi (14)	Sandoz	etanercept	Enbrel	2017

*Three additional biosimilars were approved by the EMA but subsequently had their authorizations withdrawn.

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Retacrit (1)

An FDA advisory committee recommended approval of Hospira's U.S. biosimilar application in May 2017, but the application was rejected by the FDA in June 2017.

Grastofil (2)

A biosimilar application to market in the United States was accepted for review by the FDA but has not been approved.

Zarzio (3)

Approved in the United States as a biosimilar under the Biosimilar Price Competition and Innovation Act of 2009 (BPCIA) with the trade name Zarzio.

Omnitrope (4)

Approved in the United States under the 505(b)(2) pathway.

Abasaglar (5)

Original EU trade name was Abasria; it was approved in the United States under the 505(b)(2) pathway with the trade name Basaglar and launched in the United States in December 2016.

Lusduna (6)

In July 2017, Lusduna received tentative approval in the United States under the 505(b)(2) pathway.

Amgevita/Solymbic (7)

Approved in the United States in September 2016 with trade name Amgevita. Amgevita and Solymbic are different trade names for the same monoclonal antibody.

Cyltezo (8)

Approved in the United States in August 2017 as a biosimilar under the BPCIA.

Flixabi (9)

Approved in the United States in April 2017 as a biosimilar under the BPCIA under trade name Renflexis.

Inflectra/Remsima (10)

Inflectra has been approved in the United States as a biosimilar under the BPCIA. Inflectra and Remsima are different trade names for the same monoclonal antibody.

Rixathon/Riximyo (11)

Rixathon and Riximyo are different trade names for the same monoclonal antibody. A biosimilar application to market in the United States has been accepted by the FDA.

Truxima/Blitzima/Ritemvia/Rituzena (12)

Celltrion's MabThera biosimilar was first approved in Europe in February 2017 under the name Truxima. Additional marketing authorizations under the trade names Blitzima, Ritemvia, and Rituzena (previously Tuxella) were granted in July 2017. A biosimilar application to market in the United States has been accepted by FDA.

Ontruzant (13)

Samsung Bioepis announced in November that it had received marketing authorization in Europe.

Erelzi (14)

Approved in the United States as a biosimilar under the BPCIA.

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Neulasta (pegfilgrastim) are particularly notable. EMA has rejected a number of the previous applications for pegfilgrastim biosimilars and no pegfilgrastim biosimi-

lars have been approved to date. Indeed, two of the currently pending applications for pegfilgrastim biosimilars are resubmissions of rejected applications. San-

doz's resubmitted application was accepted for review in October 2017, while Mylan/Biocon's resubmitted application was accepted for review in November 2017. Other pending applications include applications from Coherus, Spain's Cinfa, and Indian pharmaceutical manufacturer USV.

EMA is also reviewing Mylan/Biocon's application for Ogivri, a biosimilar of Genentech's Herceptin (trastuzumab). Ogivri was approved as a biosimilar in the United States on December 1, 2017. However, Mylan/Biocon's application for marketing approval for Ogivri in Europe, like its application for its pegfilgrastim biosimilar, ran into problems last summer after a European inspection of Biocon's manufacturing facility. Like the pegfilgrastim application, the Ogivri applica-

tion was withdrawn in August 2017 but resubmitted in November.

2017 was a record-setting year for biosimilar approvals in the U.S. and Europe. In the U.S., five complex antibody products were approved, two of which are in new therapeutic areas for U.S. biosimilars. In Europe, 16 biosimilars were approved. The number of approved biosimilars in Europe has doubled in the past two years. These approvals have expanded European biosimilars into new therapeutic areas and new classes of biologics. In both markets, biosimilars of pegylated biologic products, such as pegfilgrastim, continue to pose challenges for biosimilar makers.