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Update on Biosimilar Approvals and Pending Applications in Europe and the U.S.

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Approvals of biosimilar products in Europe continue to outpace those in the United States. Currently, 28 biosimilars are approved in Europe and five in the U.S. In 2017, the European Medicines Agency (EMA) has approved six biosimilar applications, including applications for biosimilars to two of the best-selling complex biologics, Humira (adalimumab) and MabThera (rituximab). The EMA is likely to approve seven more biosimilar applications in the coming months. The U.S. Food and Drug Administration in turn has approved one biosimilar this year, and an agency advisory committee in late May recommended approval of Pfizer's proposed biosimilar of Amgen's EPO (epoetin alfa), which the agency previously rejected. Proposed biosimilars of complex biologics in a number of new classes are pending before both agencies at the same time.

2017 Biosimilar Approvals in Europe

The six biosimilar applications approved by the EMA so far this year fall into four classes. In January, the EMA approved STADA Arzneimittel and Gedeon Richter's biosimilars of the Eli Lilly osteoporosis drug Forsteo (teriparatide, sold under the trade name Forteo in the U.S.), a recombinant 1-34 N-terminal fragment of human parathyroid hormone. These approvals were followed in February by approval of Celltrion's Truxima, a biosimilar of Roche's monoclonal antibody MabThera (rituximab), which is marketed as Rituxan in the U.S. In March, the EMA approved Amgen's application for its biosimilar of AbbVie's Humira (adalimumab). Finally, in April, the EMA approved Merck's biosimilar of Sanofi's Lantus (insulin glargine), the second such biosimilar to receive approval in the EU. Other than for Merck's biosimilar of insulin glargine, all the other products approved this year fall into new categories of biosimilars for the European market.

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CHMP Issues Positive Opinions for Seven More Applications

In April and May 2017, the EMA's Committee for Medicinal Products for Human Use (CHMP) issued seven positive opinions on biosimilar applications. In April, the CHMP recommended approval of Sandoz's Erelzi (etanercept), a biosimilar of Amgen's Enbrel that is already approved in the U.S., as well as Sandoz's Rixathon and Riximyo, a biosimilar of Roche's MabThera/Rituxan (rituximab). On May 18, 2017, the CHMP recommended approval of Celltrion's Blitzima/Tuxella/Ritemvia rituximab biosimilar applications and Sanofi's application for a biosimilar of Eli Lilly's Humalog (insulin lispro). The positive opinions from the CHMP mean that the EMA is likely to approve these additional applications in the coming months.

Pending Biosimilar Applications in Europe and a Recent Withdrawal

Eleven additional biosimilar applications are under evaluation by the EMA as of May 2017: two applications for biosimilars of AbbVie's Humira (adalimumab), one application for a biosimilar of Sanofi's Lantus (insulin glargine), two applications for biosimilars of Amgen's Neulasta (pegfilgrastim), four applications for biosimilars of Genentech's Herceptin (trastuzumab), and two applications for biosimilars of Genentech's Avastin (bevacizumab). Eight of the pending applications seek to introduce biosimilars for products without biosimilars on the European market, i.e., biosimilars of pegfilgrastim, trastuzumab, and bevacizumab.

Sandoz recently withdrew its proposed biosimilar of Amgen's Neulasta (pegfilgrastim) after the EMA required additional data on a timetable that Sandoz could not meet. Sandoz's application is the third application for a biosimilar of pegfilgrastim that has been recently withdrawn. The two pegfilgrastim biosimilar applications currently under review by EMA are from Coherus and Mylan/Biocon.

Five Biosimilars Approved In the U.S.

The FDA has approved another biosimilar this year, Samsung Bioepis' Renflexis (infliximab-abda), for a total of five approved biosimilar medicines. Renflexis, the second biosimilar of infliximab, was the first biosimilar to be approved in the U.S. without a public advisory committee meeting. The FDA has said that it does not plan to hold public advisory committee meetings after the first biosimilar of a product is approved.

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BIOSIMILARS APPROVED IN EUROPE AS OF MAY 2017[1]

Biosimilar Trade Name	Marketer	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[2]	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[3]	Apotex	filgrastim	Neupogen	2013
Nivestim	Hospira	filgrastim	Neupogen	2010
Ratiograstim	Ratiopharm	filgrastim	Neupogen	2008
Tevagrastim	Teva	filgrastim	Neupogen	2008
Zarzio[4]	Sandoz	filgrastim	Neupogen	2009
Follitropins				
Bemfola	Finox	follitropin alfa	GONAL-f	2014
Ovaleap	Teva	follitropin alfa	GONAL-f	2013
Growth Hormones				
Omnitrope[5]	Sandoz	somatropin	Genotropin	2006
Insulins[6]				
Abasaglar[7]	Eli Lilly	insulin glargine	Lantus	2014
Lusduna	Merck	insulin glargine	Lantus	2017
Low-Molecular Weight Heparins				
Inhixa	Techdow Europe AB	enoxaparin sodium	Clexane	2016
Thorinane	Pharmathen S.A.	enoxaparin sodium	Clexane	2016

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Monoclonal Antibodies				
Amgevita[8]	Amgen	adalimumab	Humira	2017
Solymbic[8]	Amgen	adalimumab	Humira	2017
Flixabi[9]	Samsung Bioepis	infliximab	Remicade	2016
Inflectra[10]	Hospira	infliximab	Remicade	2013
Remsima[10]	Celltrion	infliximab	Remicade	2013
Truxima[11]	Celltrion	rituximab	MabThera	2017
Parathyroid Hormone Fragment				
Movymia	STADA Arzneimittel	teriparatide	Forsteo	2017
Terrosa	Gedeon Richter	teriparatide	Forsteo	2017
Fusion Proteins				
Benepali[12]	Samsung Bioepis	etanercept	Enbrel	2016

[1] Three additional biosimilars were approved by the EMA but subsequently had their authorizations withdrawn.

[2] An FDA advisory committee on May 25, 2017, recommended approval of Hospira's U.S. biosimilar application.

[3] Biosimilar application to market in the United States was accepted for review by the FDA but has not been approved.

[4] Approved in the United States as a biosimilar under the Biologics Price Competition and Innovation Act of 2009 (BPCIA) with the trade name Zarxio.

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

[6] Sanofi's application for a biosimilar of Eli Lilly's Humalog (insulin lispro) received a favorable opinion from the EMA's Committee for Medicinal Products for Human Use (CHMP) in May 2017 and may soon be approved in Europe.

[7] 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.

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

[9] Approved in the United States in April 2017 under trade name Renflexis.

[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.

[11] Other applications for biosimilars of MabThera/Rituxan, Sandoz's Rixathon/Riximyo and Celltrion's Blitzima/Tuxella/Ritemvia, received favorable opinions from CHMP in April and May 2017 and may soon be approved in Europe.

[12] A different biosimilar of Amgen's Enbrel, Sandoz's Erelzi, has been approved in the United States as a biosimilar under the BPCIA. Erelzi received a favorable opinion from CHMP in April 2017 and may soon be approved in Europe.

Source: Patterson Belknap Webb & Tyler LLP

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Although the U.S. was first to approve a biosimilar of AbbVie's Humira (adalimumab), with the EMA's March 2017 approval of Amgen's Amgevita (Amjevita in the U.S.), every reference product with an approved biosimilar in the U.S. also has an approved biosimilar in Europe. If the EMA approves Sandoz's application for its biosimilar of Amgen's Enbrel, as expected from the favorable CHMP recommendation, each of the biosimilars approved in the U.S. will also be approved for marketing in Europe.

Pending Biosimilar Applications in the U.S.

Many of the biosimilar applications that are currently pending before the EMA are also under review by the FDA. Just as in Europe, Coherus and Mylan/Biocon have pending applications in the U.S. for a biosimilar of Amgen's Neulasta (pegfilgrastim). No biosimilars of pegfilgrastim have been approved in the U.S. or Europe. Apotex was the first to file a proposed biosimilar application for pegfilgrastim. It did so in 2014 but experienced hurdles with its proposed biosimilar. With ap-

U.S. APPROVED BIOSIMILARS AS OF MAY 2017			
Biosimilar Trade Name	**Marketer**	**Reference Drug**	**Approval Date**
Zarxio (filgrastim-sndz)	Sandoz	Neupogen	March 6, 2015
Inflectra (infliximab-dyyb)	Celltrion/Hospira	Remicade	April 5, 2016
Erelzi (etanercept-szzs)	Sandoz	Enbrel	Aug. 30, 2016
Amjevita (adalimumab-atto)	Amgen	Humira	Sept. 23, 2016
Renflexis (infliximab-abda)	Samsung Bioepis	Remicade	April 21, 2017

Source: Patterson Belknap Webb & Tyler LLP

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plications now pending before the FDA from two competitors, in a recent citizen petition Apotex has asked the FDA to require biosimilar applicants that are trying to obtain approval of a pegfilgastim biosimilar to conduct appropriate clinical studies for this complex biologic. Apotex also noted that Coherus apparently has not conducted the necessary studies. Although the status of Apotex's own proposed pegfilgrastim biosimilar is unclear, Apotex still hopes to have the first pegfilgrastim biosimilar on the U.S. market.

In addition to the applications for biosimilars of pegfilgrastim, a number of other applications are being reviewed by both the FDA and the EMA. Mylan and Biocon have an application for a biosimilar of Genentech's Herceptin (trastuzumab) under review by the FDA and the EMA. Amgen and Allergan have a proposed biosimilar of Genentech's Avastin (bevacizumab) under review by the FDA and the EMA. Boehringer Ingelheim has a pending application for a proposed biosimilar of AbbVie's Humira (adalimumab) before the FDA and the EMA.

The FDA appears to have completed its review of a biosimilar of Amgen's EPO (epoetin alfa). Although biosimilars of EPO have been on the European market for many years, there is no biosimilar EPO on the U.S. market. Pfizer (Hospira) encountered difficulties in obtaining approval of an EPO biosimilar in the U.S. The FDA's Oncological Drugs Advisory Committee on May 25, 2017, recommended approval of Hospira's application for its biosimilar of Amgen's EPO. With the Advisory Committee's favorable recommendation, the FDA will most likely approve Hospira's application this summer.

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Although the European biosimilars market continues to outpace the U.S., the FDA and the EMA are currently reviewing the same applications for complex biologics. Biosimilar products that would be new to both markets are under review. 2017 is likely to see an expansion of product classes of biosimilars in both markets with guidance from both regulatory agencies as to what is needed to obtain approval of biosimilars in these classes.

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