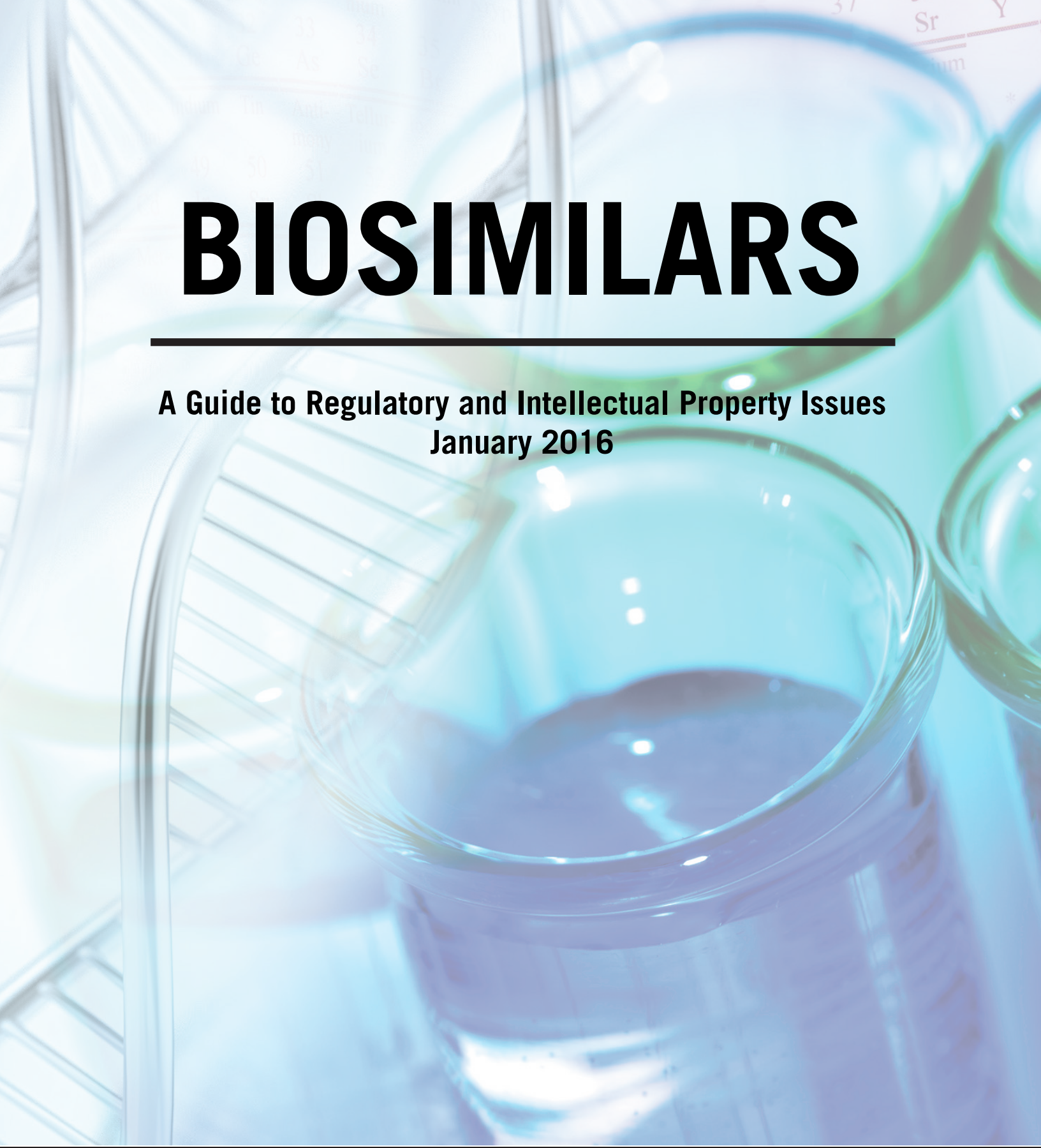

BIOSIMILARS

A Guide to Regulatory and Intellectual Property Issues
January 2016

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BIOSIMILARS

A Guide to Regulatory and Intellectual Property Issues

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INTRODUCTION

Biologic drug products have long promised to provide medical practitioners with new, highly-targeted and effective treatments for diseases that have not been sufficiently treatable, or treatable at all, with conventional small molecule drugs. That promise has become reality for a number of chronic and often fatal diseases such as Crohn's, rheumatoid arthritis, lupus erythematosus, psoriasis and various cancers.

The effectiveness of biologics has come at a price, however. Biologics are typically far more expensive than small molecule drugs, and their high cost has limited patient access. Many third-party payers, such as government health care funds and private insurance providers, are beginning to limit prescription drug benefits for biologics, and many patients without health insurance, particularly in developing nations, have little or no access to these important medications.

Thus, there is a global opportunity for lower cost "follow-on" biologic drug products. A follow-on biologic drug product is one that is intended to be clinically similar to, or interchangeable with, an already approved reference biologic product.

Taking a cue from the success of the Hatch-Waxman Act in the U.S., which created an abbreviated approval pathway for lower cost, generic versions of branded small molecule drug products, governments in the U.S., the EU, Japan, India, Korea, China and elsewhere have implemented abbreviated regulatory approval pathways and other incentives to facilitate the development of follow-on biologics.

Products approved via these abbreviated regulatory pathways are commonly called "biosimilars." The hope is that biosimilars, like small molecule generic drugs, will be less expensive than the branded products they are modeled after, and will thereby improve affordability and patient access.

Although biologic products can be technically challenging to develop, market prognosticators have long predicted that the market opportunities for companies capable of developing biosimilars, in particular the significant profit margins for biologics versus generic small molecule drugs, would draw a flood of new market entrants. As patents covering the first generation of biologics have expired or are near expiration, the market has eagerly awaited the launch of lower cost biosimilar versions of them.

While the flood has been slow to materialize, due in part to the relatively high cost of developing and marketing biosimilars, as well as the regulatory and market risks associated with being an early entrant in this developing field, many foreign regulatory agencies have approved a steady trickle of biosimilars. India, which has a robust and highly competitive domestic market for biologics and lower regulatory hurdles than some other jurisdictions, is one of the countries leading the way. Its Central Drugs Standard Control Organization has approved 20 biosimilars since 2012 (see Section 2, below). In more highly regulated markets, Europe leads the way. The European Medicines Agency (EMA) has approved 20 biosimilar products, principally versions of filgrastim and epoetin. In Japan, which is facing a rapid rise in healthcare costs stemming from an aging population, the Pharmaceuticals and Medical Devices Agency (PMDA) has approved seven biosimilars. Korea, which has become a notable global player in the biosimilars market, has five approved biosimilars on the market.

INTRODUCTION

While the U.S. has lagged far behind other nations in attracting and approving applications to market biosimilars, 2015 saw some dramatic changes. In March of last year, the U.S. Food and Drug Administration (FDA) approved Sandoz's Zarxio® (filgrastim-sndz), a biosimilar of Amgen's Neupogen® (filgrastim). FDA has also accepted biosimilar applications from Celltrion for infliximab (referencing Remicade), Hospira for epoetin zeta (referencing Epogen®), and Apotex and Sandoz for pegfilgrastim (referencing Neulasta). Other applicants appear to be not far behind.

These applications have also sparked the first wave of hotly contested patent infringement litigation under the complicated and often cumbersome statutory scheme for resolving such litigation in the U.S., known colloquially as "the patent dance." The Biologics Price Competition and Innovation Act (BPCIA), the statute governing biosimilars, was a compromise forged in the fires of unusually intense government lobbying and is not a model of clarity. The United States Court of Appeals for the Federal Circuit, which is charged with shepherding U.S. patent law, has gone so far as to dub the statute a "mystery inside an enigma." Nevertheless, courts have begun to clarify this mystery, and promise to make the biosimilar pathway much more predictable for brand and biosimilar manufacturers alike. Indeed, in its first crack at demystifying the BPCIA, the Federal Circuit has ruled that the patent dance is optional, and is only one pathway open to brand and biosimilar applicants seeking to resolve patent claims. This and future rulings may make biosimilars less risky, and thus more attractive, for drug manufacturers that have so far been watching and waiting from the sidelines.

Now that the first biosimilars have launched in various markets, it has become clear that biosimilars are not "generic" biologics. Biologics are far more complex than small molecule drugs, and developing, testing and manufacturing a biologic that is therapeutically highly similar to, or interchangeable with, an approved reference biologic is technically challenging. Regulatory authorities, which have a relative lack of experience with policing biosimilarity, have acted very cautiously and have subjected the first wave of biosimilar applications to careful scrutiny. The patent landscape for biologic products is also typically complex and multi-layered, and litigation may often be unavoidable. Once a biosimilar actually reaches the market, aggressive price competition by the reference brand sponsor, a lack of doctor and patient confidence in the degree of similarity with the reference brand product, and the absence of laws permitting automatic substitution for that brand product (in most circumstances) may limit market uptake. Unlike generic small molecule drugs, biosimilar manufacturers will have to engage in the sort of marketing typically employed for brand products.

Navigating these challenges requires careful planning. To assist, this guide presents an overview of the market challenges and opportunities for biosimilars and other "follow-on" biologics that are based in whole in or in part on approved reference products, such as improved "biobetter" versions. It includes an overview of the market and regulatory landscape in several important jurisdictions, as well as recent legal developments that could impact companies developing such products. A compendium of significant statutes, regulations, regulatory guidances, and legal case law is appended for easy reference.

Please visit Goodwin's Big Molecule Watch Blog (www.bigmoleculewatch.com) for updates and analyses on regulatory issues, litigation, legislation and other news in the ever-developing world of biosimilars.

MARKET DEVELOPMENTS FOR BIOSIMILARS

The Current Market for Biologics

The current global market for biologics is extremely robust, with sales of the top six products each exceeding $5 billion annually. Sales and market share of biologics as a fraction of the overall market for pharmaceuticals is expected to continue to grow rapidly, as market demand for such targeted "drugs of the future" remains robust, and as more manufacturers gain expertise with the development, manufacture and approval of such products.

Top Branded Biologic Products

Top Selling Biologics 2014[1]

Drug	Biologic	Innovator	2014 Global Sales*	Patent Expiration
Humira®	adalimumab	Abbvie Inc.	$12.8B	EU – 2018 U.S. - 2016
Remicade®	infliximab	Johnson & Johnson	$9.9B	EU – 2015 U.S. - 2018
Rituxan/Mabthera®	rituximab	Roche AG/Biogen Idec Inc.	$8.7B	EU - expired U.S. - 2018
Lantus®	insulin glargine	Sanofi SA	$8.3B	EU – expired U.S. - expired
Enbrel®	etanercept	Amgen Inc./Pfizer Inc.	$7.9B	EU – 2015 U.S. - 2029
Avastin®	rituximab	Genentech Inc.	$6.5B	EU – 2022 U.S. - 2019
Herceptin®	rituximab	Genentech Inc.	$6.3B	EU – 2014 U.S. - 2019
Neulasta®	pegfilgrastim	Amgen Inc.	$4.6B	EU – 2017 U.S. - 2015
Avonex/Rebif®	Interferon beta-1a	Biogen, Inc./Merck/Pfizer	$2.8B	EU – expired U.S. - 2015
Lovenox®	Enoxaparin sodium	Sanofi Inc.	$2.2B	EU – expired U.S. – expired

MARKET DEVELOPMENTS FOR BIOSIMILARS

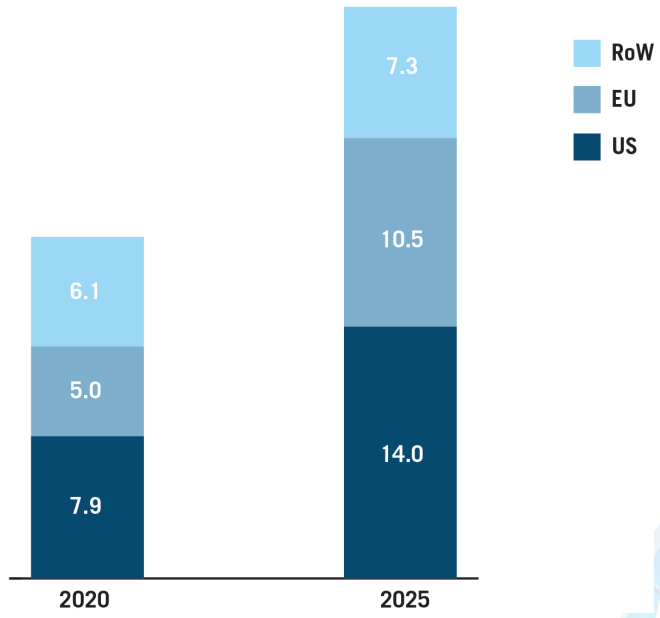
The high cost of branded biologics presents opportunities for pharmaceutical manufacturers with expertise in biologics to offer lower-cost biosimilars.

As biologics have become important disease-fighting tools, they have taken an increasing share of total spending on healthcare. This trend is expected to continue as drug companies increasingly focus on biologics as a means to bring innovative new therapies to the global market and to boost profitability. However, because of their cost, patient access to branded biologics is becoming increasingly restricted. Private third-party payers, such as health insurance plans and PBMs, and government third-party payers, such as national health care providers, are increasingly refusing to approve prescriptions of high-cost branded biologics, especially where the benefit to patients is incremental in comparison to alternative therapies. In developing countries, access to biologics is often substantially or completely restricted because of price, with many of the most effective biologics being out of the reach of sovereign heath care plans or private citizens.

Thus, there is a robust and growing global demand for biosimilars among third-party payers and national health agencies hoping to offer patients the benefits of biologics at lower and sustainable prices.

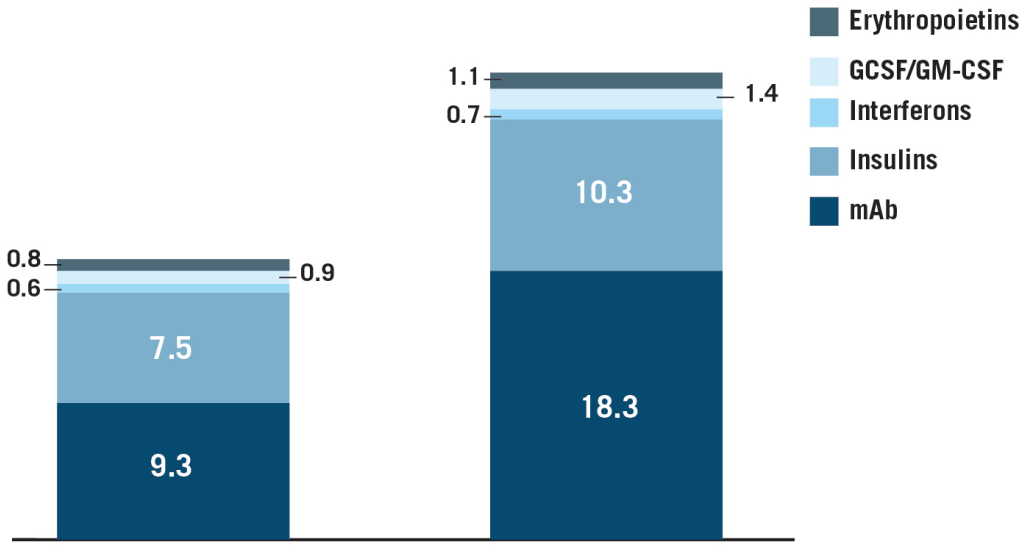
Although the global market for biosimilars is in its infancy, global demand for biosimilars is high, and the market is expected to continue to grow rapidly over the next decade. Forecasters predict global biosimilar sales will reach $19 billion in 2020 and $32 billion by 2025. Much of that growth is expected to come from the U.S. market:

Figure 14.1 Global Biosimilars Market Forecast: Distribution by Region, 2020 and 2025 (USD Billion)



Source: Global Biosimilars Market 2015-2025 from Roots Analysis

Figure 14.2 Global Biosimilars Market Forecast: Distribution by Product Category, 2020 and 2025 (USD Billion)



Source: Global Biosimilars Market 2015-2025 from Roots Analysis

U.S. Biosimilar Market: Zarxio® and New Biosimilar Applications to FDA

The U.S. has been a relative late comer to the biosimilar field. In March 2015, FDA approved Sandoz's "Zarxio®," the first biosimilar approved under section 262(k)[2] of the BPCIA.[3]

Zarxio® is a biosimilar of Amgen Inc.'s Neupogen® (filgrastim), which boosts white blood cell counts in cancer patients to help fight infections. Neupogen® was originally licensed in 1991 and generates $1.2 billion per year for Amgen, mostly in the United States.[4] U.S. sales of Zarxio® launched in September 2015. Sandoz initially priced Zarxio® at a 15% discount relative to Neupogen®, at the low end of the 15-30% range discount that is typical of biosimilars in Europe.[5]

As of November 2015, Zarxio® remains the only biosimilar that has been approved by FDA under section 262(k). FDA has accepted only a handful of additional publicly disclosed 262(k) applications. Celltrion's "Remsima" biosimilar application referencing Remicade (infliximab), and Apotex's biosimilar application referencing Amgen's Neulasta® (pegfilgrastim, a long acting version of Neupogen®) were both filed in 2014. Four new 262(k) applications were filed in 2015: Apotex's biosimilar application referencing Neupogen® (filgrastim)[6]; Hospira's Retacrit (epoetin zeta) referencing Amgen's Epogen® (epoetin alfa) and Janssen's Procrit® (epoetin alfa)[7]; Sandoz's biosimilar application referencing Amgen's Enbrel (etanercept)[8]; and Sandoz's biosimilar application referencing Neulasta®.[9] FDA rejected Hospira's Retacrit® application in October 2015, but the company and its parent, Pfizer, have indicated that they have additional evidence to support approval of the biosimilar and will likely amend the application.

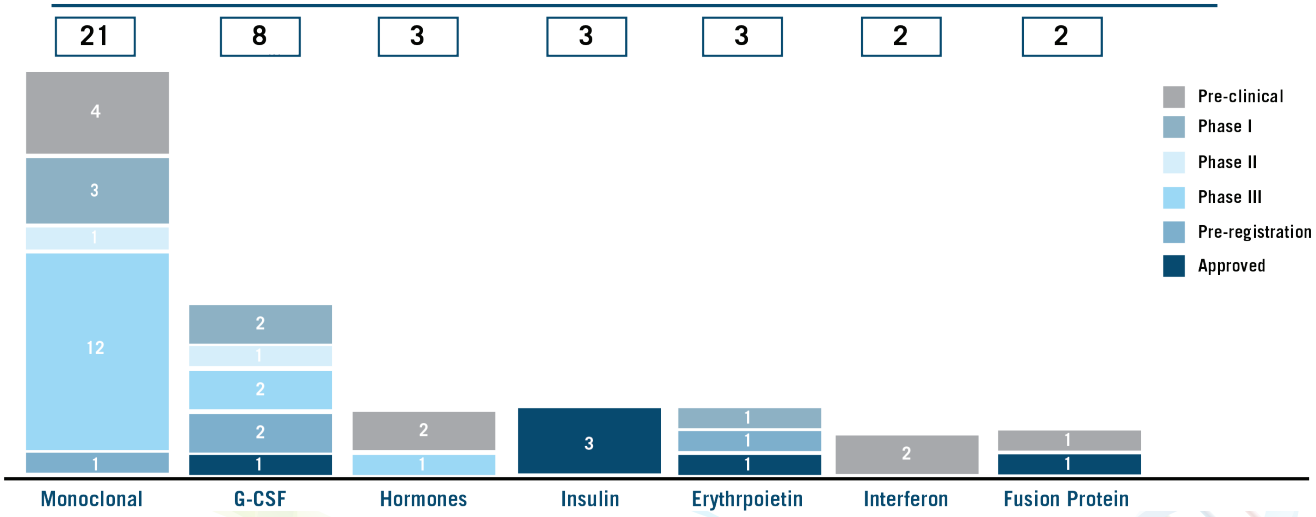
As of July 2015, 57 proposed biosimilar products referencing 16 different innovator products were enrolled in FDA's Biosimilar Product Development (BPD) Program.[10] As explained below, participation in this program is required in order to hold formal meetings between applicants and FDA staff to discuss development of a biosimilar. The Center for Drug Evaluation and Research (CDER) has reported that sponsors of an additional 27 proposed biosimilars have had Biosimilar Initial Advisory meetings with FDA, but have not yet joined the BPD program to pursue the development of their products.[11]

The U.S. Biosimilar Market: Distribution by Status of Development (as of July 2015)[12]

Status of Development	Number of Products	Share (%)
Approved	1	2
Pre-registration	4	9
Phase III	20	45
Phase II	4	9
Preclinical	14	31
NA	1	2

The U.S. Biosimilar Market: Distribution by Product Category (as of July 2015)[13]

Figure 14.4 the US Biosimilar Market: Distribution by Product Category



Global Biosimilars Market 2015-2025 from Roots Analysis

Likely Biosimilar Applications to FDA in 2016 and Beyond

Several companies have announced successful clinical trials, or expect to complete clinical trials soon, for biosimilar versions of AbbVie's Humira® (adalimumab), including Boehringer Ingelheim[14], Amgen[15], and Sandoz.[16] With remaining patent coverage expected to expire in 2016, applications for biosimilar versions of Humira® are also likely in the near future.

Basaglar, a biologic manufactured by Eli Lilly and Boehringer Ingelheim that is similar to Sanofi's Lantus (insulin glargine), received FDA approval in August 2014 via the 505(b)(2) pathway. It is now set to launch in the U.S. in December 2016 pursuant to a settlement with Sanofi.

Below is a chart of other targets that may attract biosimilar applications in the U.S. in the near term.

Name	Substance	Company	U.S. Patent Expiration	Global Sales	Developing Biosimilars for U.S.	Status
Humira®	adalimumab	AbbVie	2016	$12.8B	Boehringer Ingelheim	Phase III
					Amgen	Phase III
					Sandoz/Novartis	Phase III
					Coherus Biosciences	Phase I
					Pfizer	Phase I
Remicade®	infliximab	Johnson & Johnson	2018	$9.9B	Hospira/Celltrion	Pre-registration
					Pfizer	Phase III
Rituxan®	rituxamab	Biogen Idec Inc.	2018	$8.7B	Pfizer	Phase III
					Boehringer Ingelheim	Phase III
					Amgen/Actavis	Phase III
					Celltrion	Phase III
					iBio Inc.	Preclinical
Lantus®	insulin glargine	Sanofi SA	Expired	$8.3B	Samsung Bioepsis/ Merck	Phase III
					Eli Lilly	Pre-registration
Neulasta®	pegfilgrastim	Amgen, Inc.	2015	$4.6B	Coherus Biosciences	Phase I
					Pfenex/Agila Biotech	Pre-Clinical
					Sandoz	Pre-registration

MARKET DEVELOPMENTS FOR BIOSIMILARS

Name	Substance	Company	U.S. Patent Expiration	Global Sales	Developing Biosimilars for U.S.	Status
Neupogen®	filgrastim	Amgen, Inc.	Expired	$1.1B	Aequus BioPharma	Pre-Clinical
					Harvest Moon Pharmaceutical	Phase III
					Apotex	Pre-registration
Herceptin®	trastuzumab	Roche/Genentech	2019	$6.3B	Pfizer	Phase III
					STC Biologics	Phase I
					Actavis/Amgen	Phase III
Avonex®	interferon beta-1a	Biogen, Inc./ Merck/Pfizer	2015	$2.8B	Pfenex/Agila Biotech	Pre-Clinical

Looking further down the road, biosimilar manufacturers are likely scrutinizing products that were approved 8-12 years ago. Under the BPCIA, FDA is permitted to approve biosimilar applications after the reference product has been approved for 12 years, making these older products logical targets. This anticipated "second wave" of biosimilar applications may therefore involve the following products:

New Biologic Product Launches 2003-2007 [17]

Brand Name	Active Substance	Company	Indications	Date of Licensure
Erbitux®	cetuximab	Eli Lilly/Bristol-Myers Squibb	Colorectal cancer; head and neck cancer	2/12/2004
Avastin®	bevacizumab	Genentech	Metastatic colorectal cancer, non-squamous non-small cell lung cancer; glioblastoma; metastatic renal cell carcinoma; cervical cancer; ovarian cancer	2/26/2004
Tysabri®	natalizumab	Biogen Idec	Multiple sclerosis; Crohn's disease	11/23/2004
Kepivance®	palifermin	Amgen, Inc.	Oral mucositis in bone cancer patients	12/15/2004
Naglazyme®	galsulfase	Biomarin Pharmaceutical Inc.	Mucopolysaccharidosis VI	5/31/2005
Orencia®	abatacept	Bristol-Myers Squibb	Rheumatoid arthritis; juvenile idiopathic arthritis	12/23/2005
Myozyme®	alglucosidase alfa	Genzyme	Pompe disease	4/28/2006

Brand Name	Active Substance	Company	Indications	Date of Licensure
Lucentis®	ranibizumab	Genentech	Macular degeneration; macular edema; diabetic retinopathy	06/30/2006
Elaprase®	Idursulfase	Shire	Hunter syndrome (Mucopolysaccharidosis II)	7/24/2006
Vectibix®	panitumumab	Amgen	Metastatic colorectal cancer	09/27/2006
Soliris®	eculizumab	Alexion	Paroxysmal nocturnal hemoglobinuria; atypical hemolytic uremic syndrome	3/16/2007
Mircera®	methoxy polyethylene glycol-epoetin beta	Hoffmann-La Roche, Inc.	Anemia associated with chronic kidney disease	11/14/2007
Arcalyst®	rilonacept	Regeneron	Cryopyrin-associated periodic syndromes	2/27/2008
Cimzia®	certolizumab pegol	UCB	Crohn's disease; rheumatoid arthritis; psoriatic arthritis; ankylosing spondylitis	4/22/2008
Nplate®	romiplostim	Amgen	Thrombocytopenia in patients with chronic immune thrombocytopenia	8/22/2008
Cinryze®	C1 Esterase Inhibitor	Shire	Hereditary angioedema	10/10/2008

The Market Potential for Biosimilars: Insights From Europe and Asia

Outside of the U.S., regulatory authorities in some highly regulated markets including the EU, Japan, and Korea have acted early and effectively to facilitate the approval and market entry of new biosimilar products. Currently, 20 biosimilar products have been approved in the EU, seven have been approved in Japan, and five have been approved in Korea. In less regulated markets, India has been particularly successful in facilitating the entry of biosimilars, with 20 biosimilar products being approved since India's "similar biologics" guidelines came into effect on September 15, 2012. These approvals are summarized below:

Biosimilars Currently Approved in EU [18]

Product Name	Active Substance	Marketing Authorization Holder	Authorization Date
Abasaglar® (previously Abrasria)	insulin glargine	Eli Lilly Regional Operations GmbH.	September 9, 2014
Abseamed®	epoetin alfa	Medice Arzneimittel Pütter GmbH & Co. KG	August 28, 2007
Accofil®	filgrastim	Accord Healthcare Ltd	September 18, 2014

MARKET DEVELOPMENTS FOR BIOSIMILARS

Product Name	Active Substance	Marketing Authorization Holder	Authorization Date
Bemfola®	follitropin alfa	Finox Biotech AG	March 27, 2014
Binocrit®	epoetin alfa	Sandoz GmbH	August 28, 2007
Biograstim®	filgrastim	AbZ-Pharma GmbH	September 15, 2008
Epoetin alfa Hexal®	epoetin alfa	Hexal AG	August 28, 2007
Filgrastim Hexal®	filgrastim	Hexal AG	February 6, 2009
Grastofil®	filgrastim	Apotex Europe BV	October 18, 2013
Inflectra®	infliximab	Hospira UK Ltd.	September 10, 2013
Nivestim®	filgrastim	Hospira UK Ltd.	June 8, 2010
Omnitrope®	somatropin	Sandoz GmbH	April 12, 2006
Ovaleap®	follitropin alfa	Teva Pharma B.V.	September 27, 2013
Ratiograstim®	filgrastim	Ratiopharm GmbH	September 15, 2008
Remsima®	infliximab	Celltrion Healthcare Hungary Kft.	September 10, 2013
Retacrit®	epoetin zeta	Hospira UK Limited	December 18, 2007
Silapo®	epoetin zeta	Stada Arzneimittel AG	December 18, 2007
Somatropin®	somatropin	BioPartners	August 5, 2013
Tevagrastim®	filgrastim	Teva GmbH	September 15, 2008
Zarzio®	filgrastim	Sandoz GmbH	February 6, 2009

Biosimilars Currently Approved in Japan [19]

Japanese Accepted Name (JAN)	Active Substance	Manufacturer	Approved Year
Somatropin®	somatropin	Sandoz	2009
Epoetin Kappa® [Epoetin Alfa Biosimilar 1]	epoetin alfa	JCR Pharmaceuticals	2010
Filgrastim® [Filgrastim Biosimilar 1]	filgrastim	Fuji Pharma/Mochida Pharmaceutical	2012
Filgrastim® [Filgrastim Biosimilar 2]	filgrastim	NIPPON KAYAKU/Teva Pharma Japan	2013
Filgrastim® [Filgrastim Biosimilar 3]	filgrastim	Sandoz	2014

Japanese Accepted Name (JAN)	Active Substance	Manufacturer	Approved Year
Infliximab® [Infliximab Biosiilar 1]	infliximab	NIPPON KAYAKU/Celltrion	2014
Insulin Glargine® [Insulin Glargine Biosimilar 1]	insulin glargine	Eli Lilly Japan	2014

Biosimilars Currently Approved in Korea [20]

Product Name	Active Substance	Marketing Authorization Holder	Approved Year
Brenzys®	etanercept	Samsung Bioepsis/ Merck & Co.	2015
Davictrel®	etanercept	Hanwha Chemical	2014
Herzuma®	trastuzumab	Celltrion	2014
Omnitrope®	somatropin	Sandoz	2014
Remsima®	infliximab	Celltrion	2012

Approved Biosimilars in India Post-September 15, 2012 [21]

Product Name	Active Substance	Marketing Authorization Holder	Approved Year
AbcixiRel®	abciximab	Reliance Life Sciences	2013
Actorise®	darbepoetin alfa	Cipla/Hetero	2014
Alzumab®	itolizumab	Biocon	2012
CanMab®	trastuzumab	Biocon	2013
Darbatitor®	darbepoetin alfa	Torrent Pharmaceuticals	2014
Etacept®	etanercept	Cipla	2013
Exemptia®	adalimunab	Zydus Cadila	2014
Filgrastim®	filgrastim	Cadila Pharmaceutical	2013
Filgrastim®	filgrastim	Lupin	2013
Filgrastim®	filgrastim	USV	2013
Folisurge®	follitropin alfa	Intas Biopharmaceuticals	2013

MARKET DEVELOPMENTS FOR BIOSIMILARS

Product Name	Active Substance	Marketing Authorization Holder	Approved Year
Infimab®	infliximab	Epirus Biopharmaceuticals	2014
Intacept®	etanercept	Intas Pharmaceuticals	2015
Maball®	rituximab	Hetero Group	2015
MabTas®	rituximab	Intas Biopharmaceuticals	2013
Molgramostim®	recombinant human granulocyte macrophage colony stimulating factor	Zenotech Laboratories	2013
Peg-filgrastim®	peg-filgrastim	Lupin	2013
Peginterferon Alfa 2b®	pegylated recombinant human interferon alfa 2b	Intas Biopharmaceuticals	2013
Rituximab®	rituximab	Zenotech Laboratories	2013
Rituximab®	rituximab	Reliance Life Sciences	2015

Biosimilar Uptake in Europe

The uptake of biosimilars in the EU continues to be slower than initially expected. The EU experience makes clear that the market for biosimilars is different in many important respects from the market for generic small molecule drugs. While a branded small molecule drug may lose 70% or more of its market share to generics upon losing patent exclusivity, and the price of the generic may be 70% or less of the pre-generic brand price, similar price and market share erosion have not been observed with biosimilars.

Discounts for biosimilars have typically been 15-30% of the price for a branded product. For example, five biosimilars to EPO (Eprex) were approved in the EU in 2007, and discounting amounted to 20%. The upside of this is that revenues for early biosimilar products have been relatively high.

The downside is that market share accrual has been relatively slow. Sales volumes for almost all of the early biosimilars have been substantially lower than those of the reference biologics, as the brand manufacturers have matched the biosimilar price and maintained marketing support. Indeed, for most biosimilars, market share has been 25% or less of the reference product. However, biosimilar uptake within Europe varies widely between countries and type of biosimilar. For example, by the end of 2013, the range of biosimilar penetration for human growth hormone (somatropin) ranged from a low of 2% in Norway to a high of 99% in Poland. EPO biosimilar penetration also ranged widely, from 1% in Croatia to 62% in Bulgaria. And G-CSF biosimilar penetration ranged from 2% in Belgium to nearly 100% in Croatia, Czech Republic, Hungary and Romania.[22]

On average, market share for biosimilars was just 11% in Europe, with most of the conversion coming from alternative therapies instead of the reference biologic.

Market Breakup by Product Type in EU, Norway and Switzerland[23]

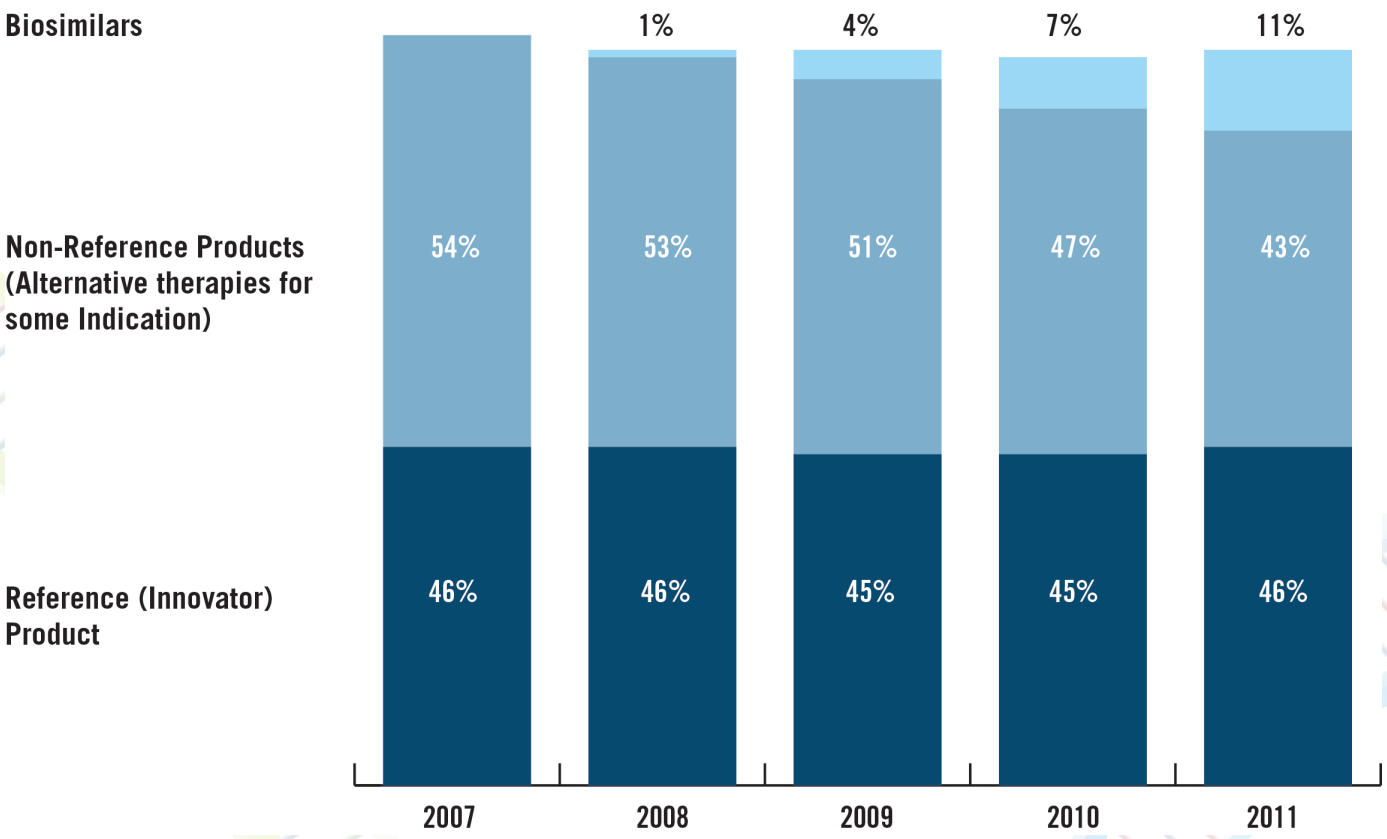


Figure 5: Market Breakup by Product Type in EU, Norway and Switzerland[24]

The primary reasons for this relatively slow uptake are (1) price matching by the brand and the absence of automatic substitution laws; and (2) the fact that there is no requirement in Europe for clinical data demonstrating interchangeability, which has caused some doctors to be skeptical about biosimilarity and reluctant to switch patients away from the branded product. The fact that co-payments have often been the same for the reference product and the biosimilar has also stifled patient demand. Third party payers have also refused to reimburse for biosimilars where they have deemed the discounts being offered to be insufficient.

The upshot is that biosimilar manufacturers have had to fight for market share by expending significant resources on educating patients and consumers about the availability, safety and efficacy of their products, and convincing third party payers to cover prescriptions.

Biosimilar Uptake in Asia

Asia is expected to be one of the fastest growing markets for biosimilars in the coming decade. Japan and Korea in particular have focused on developing strong regulatory pathways for biosimilar development. India, a country with a lower regulatory burden, has shown the greatest willingness among Asian countries to approve biosimilars and, given its large population, is likely to be a strong driver of biosimilar uptake globally.

APPROVAL PATHWAYS AND TIMELINES FOR FOLLOW-ON BIOLOGICS IN THE U.S.

A "follow-on" biologic drug product is one that is intended to be clinically similar to, or interchangeable with, an already-approved reference biologic product. Depending upon its composition, a follow-on biologic can be approved in the U.S. under one of three pathways. The first is as a "biosimilar" or "interchangeable" biosimilar under the relatively untested abbreviated regulatory pathway enacted in the U.S. in 2009. The second is as a new biologic drug product under the standard regulatory pathway that has governed the approval of new biologics in the U.S. for decades. The third, open only to a small number of less complex biologics that have been approved under the regulations governing small molecule drug products, is via the well-worn abbreviated regulatory pathway that has governed the approval of generic equivalents to small molecule drug products.

These three regulatory pathways are summarized below.

Biosimilar Application Under 262(k)

The Biologics Price Competition and Innovation Act (BPCIA) of 2009 was passed as part of the Affordable Care Act signed into law on March 23, 2010. It amended section 351 of the Public Health Service (PHS) Act to create an abbreviated licensure pathway for biological products shown to be "biosimilar" to, or "interchangeable" with, a reference product that has already been licensed by the U.S. Food & Drug Administration (FDA). Codified principally at 42 U.S.C. § 262(k) & (l), this new pathway, often referred to as the section 262(k) pathway, permits a biosimilar product to be licensed based on less than the full complement of preclinical and clinical test data normally required for a new biologic. The full text of section 262(k) appears in Appendix 1.

Definition of Key Terms

The BPCIA defines three key terms:

- **Biological product**: The term "biological product" means a virus, therapeutic serum, toxin, antitoxin, vaccine, blood, blood component or derivative, allergenic product, protein (except any chemically synthesized polypeptide), or analogous product, or arsphenamine or derivative of arsphenamine (or any other trivalent organic arsenic compound), applicable to the prevention, treatment, or cure of a disease or condition of human beings. 42 U.S.C. § 262(i)(1).

- **Biosimilarity**: The term "biosimilar" in reference to a biologic product that is the subject of an application under § 262(k), means "that the biological product is highly similar to the reference product notwithstanding minor differences in clinically inactive components" and that "there are no clinically meaningful differences between the biological product and the reference product in terms of the safety, purity and potency of the product." 42 U.S.C. § 262(i)(2).

- **Interchangeability**: "Interchangeability" is defined as a higher standard than biosimilarity because it allows the product to be substituted for the reference product without the healthcare provider's intervention. To be approved as an interchangeable product, the applicant must show that the biosimilar product can be expected to have the same clinical result as the reference product in any given patient, and that switching or alternating between the reference and biosimilar products does not increase risks to patients in terms of safety or diminished efficacy. 42 U.S.C. § 262(k)(4).

Contents of Application

A section 262(k) application must contain, among other things, information demonstrating biosimilarity based on data derived from:

- analytical studies showing that the biological product is "highly similar" to the reference product;
- animal studies, including the assessment of toxicity; and
- a clinical study or studies, including the assessment of immunogenicity and pharmacokinetic and pharmacodynamic data that are sufficient to show safety, purity, and potency in one or more appropriate conditions of use for which the reference product is licensed.

FDA has substantial flexibility in determining approval standards for biosimilars, including whether and what type of clinical studies will be required. Biosimilarity will be determined on a case-by-case basis, and FDA may determine, in its discretion, that certain studies are unnecessary for a particular product.

FDA has issued guidances, described in the "Biosimilars at FDA" section below and reproduced in Appendix 1, that frame in general terms various approaches to developing a biosimilar. In short, the goal of a section 262(k) application is to demonstrate biosimilarity between the proposed biosimilar and a reference product, including an assessment of the effects of any observed differences between the products. The application does not need to independently establish the safety and efficacy of the proposed biosimilar, as would be required for an entirely new biologic. FDA recommends a stepwise approach to developing the data and information needed to support a demonstration of biosimilarity. At each step, the biosimilar applicant should evaluate the extent to which there is residual uncertainty about the biosimilarity of the proposed product and identify steps to try to address that uncertainty. In evaluating an applicant's demonstration of biosimilarity, FDA will consider the totality of the data and information in the application.

Timing of Approval

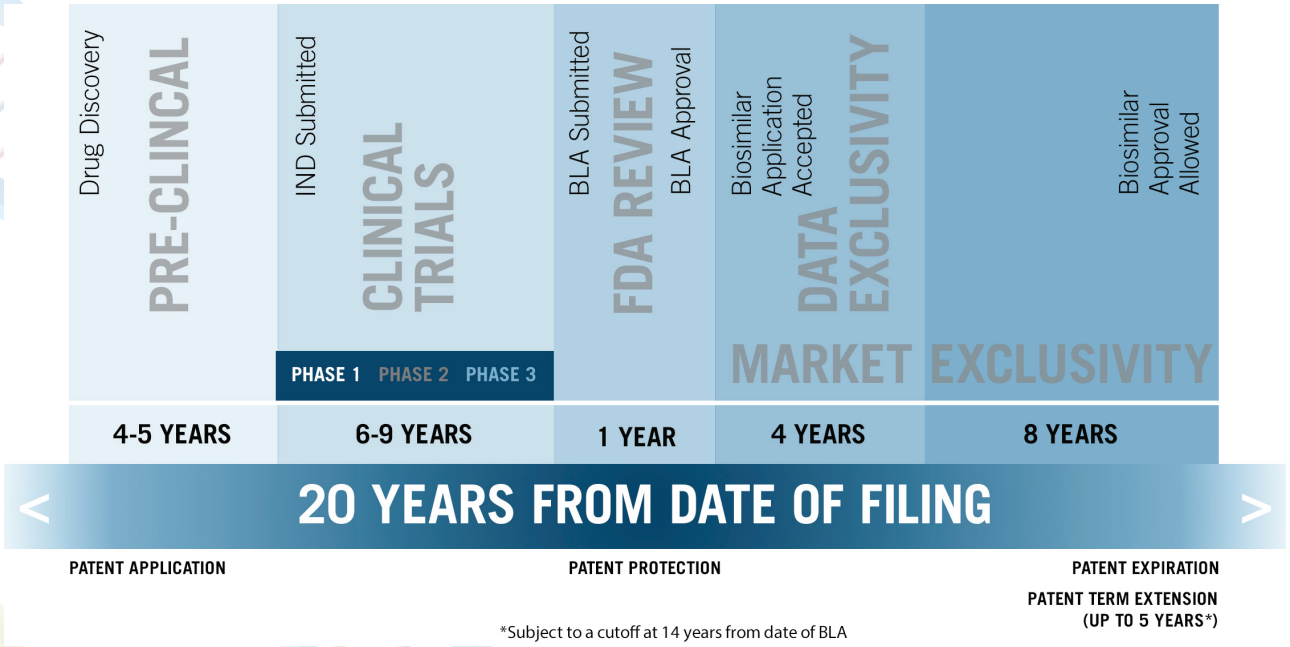
The filing and approval of a section 262(k) biosimilar application is governed in part by the BPCIA. A biosimilar application cannot be filed for four years after the reference product is approved, and the biosimilar product cannot be approved for 12 years after the reference product is approved.

While there is no set timeline for FDA review of biosimilar applications, some guideposts may be gleaned from FDA's Performance Goals, in which the agency set a goal to review and act on 85% of original biosimilar application submissions within 10 months of receipt in Fiscal Year 2016, with that number increasing to 90% of original biosimilar application submissions within 10 months of receipt in Fiscal Year 2017.[25]

APPROVAL PATHWAYS AND TIMELINES FOR FOLLOW-ON BIOLOGICS IN THE U.S.

The timeline for the first (and, as of the date of this publication, only) FDA approval of a biosimilar—Sandoz's Zarxio® biosimilar (referencing Amgen's Neupogen® product)—met FDA's target timeline of 10 months from receipt to approval of a biosimilar application: FDA accepted Sandoz's biosimilar application on July 7, 2014, and approved the application for licensure about eight months later, on March 6, 2015.

Section 262(K) Biosimilar Application Approval Timeline



Biologics License Application Under Section 262(a)

A follow-on biologic may also be the subject of a Biologics License Application (BLA), which is governed by section 262(a) of the PHS (reproduced in Appendix 1). A BLA is the application that must be filed in order to obtain FDA approval of an entirely new biologic drug product. It is the biologic equivalent to a New Drug Application (NDA) under the Food Drug and Cosmetic Act (FD&CA), and must contain sufficient pre-clinical and clinical test data to independently establish the safety and efficacy of the proposed product. A BLA license provides 12 years of marketing exclusivity for the product.

APPROVAL PATHWAYS AND TIMELINES FOR FOLLOW-ON BIOLOGICS IN THE U.S.

The regulatory framework for pre-clinical and clinical testing of biologics is similar to that for any new drug. Biologics must undergo laboratory and animal testing to define their pharmacologic and toxicologic effects before they can be studied in humans. If a BLA sponsor plans to perform clinical testing of a biologic in the U.S., it must first have an investigational new drug application (IND) in effect. The regulatory framework for clinical testing of biologics generally involves three phases:

- Phase 1: Phase 1 studies involve the introduction of the biologic into a small number of humans to assess the product's metabolism, pharmacology, and safety at escalating doses. Unlike phase 1 trials for nonbiologic drugs, phase 1 studies of biologics frequently involve administration to patients rather than healthy volunteers who will not derive benefit from them to ensure that the risk-benefit profile of the product is acceptable for ethical purposes.

- Phase 2: Phase 2 trials are controlled studies that evaluate short-term adverse events and effectiveness for a specific use in a larger group of patients than required by the phase 1 study.

- Phase 3: Phase 3 studies enroll patients and provide primary evidence for labeling claims and risk-benefit assessment.

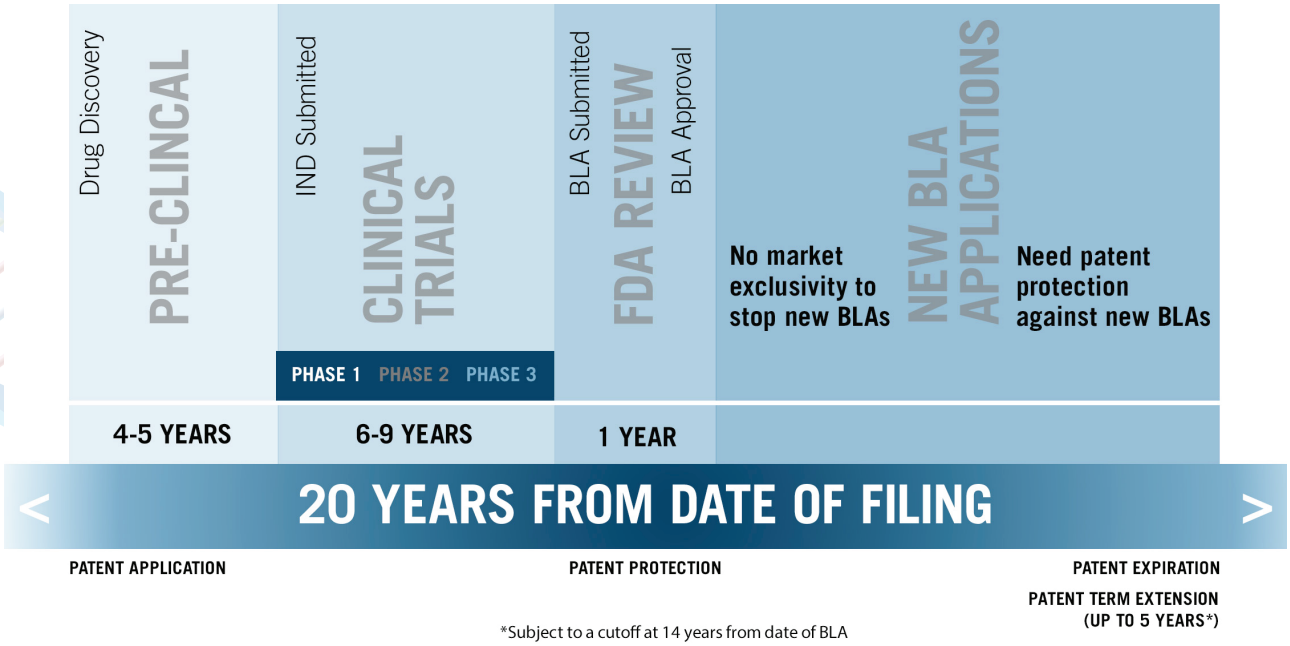
Under 21 C.F.R. § 601.2, a BLA must contain, among other things, non-clinical and clinical data showing the biologic's safety, purity and potency; a "full description of manufacturing methods" for the product; stability data substantiating the expiration date; product samples and a summary of test results for the lot from which they derived; proposed labeling, enclosures and containers; and the addresses of manufacturing facilities.

A BLA can be used to seek approval of a follow-on biologic. Unlike a biosimilar application, a BLA for a follow-on biologic under the traditional 262(a) pathway can be filed—and approved—at any time. A table below sets forth further differences between the 262(k) and 262(a) pathways.

In general, "biobetter" products may only be approved via the BLA route. Biobetters, unlike biosimilars, are not defined by the BPCIA and straddle the line between biosimilars and new biological molecules. Biobetters are based on an originator molecule, but biobetters include modifications to the originator molecule with the aim of enhancing one or more characteristics of the originator molecule. Indeed, biobetters are differentiated by unique characteristics that convey improved properties—such as reduced dose, extended half-life, more convenient dosage forms, increased safety, superior clinical efficacy, and cheaper and faster manufacturing. An applicant seeking approval of a biobetter must meet all of the BLA requirements to establish efficacy and safety. However, because FDA has often already approved a biologic from which the biobetter is derived, the non-clinical and clinical testing program may be somewhat streamlined. Moreover, approval does not require comparability studies designed to show biosimilarity to, or interchangeability with, a reference product.

APPROVAL PATHWAYS AND TIMELINES FOR FOLLOW-ON BIOLOGICS IN THE U.S.

BLA Approval Timeline



Abbreviated New Drug Application

Typically, an application for a follow-on biologic must be submitted under section 262(k) (for approval as a biosimilar product) or section 262(a) (as a new biologic product). There is one exception: an applicant may instead submit an Abbreviated New Drug Application (ANDA) under section 505(j) of the FD&CA, or "paper NDA" under section 505(b)(2), through March 23, 2020 if the application references an originator biologic product that FDA approved via an NDA under section 505(b)(1). FDA has approved three follow-on biologics as ANDAs and eight follow-on biologics as 505(b)(2) NDAs. For example, Sandoz, Amphastar and Teva have each obtained approval of ANDAs directed to Enoxaparin.

Comparison of Approval Pathways and Timelines

The table below sets forth the differences between the 262(k), 262(a), and ANDA/paper NDA pathways.

Comparison Between the BLA 262(a) Pathway and Biosimilar 262(k) Pathway

	262(a) Application	262(k) Application
Goal	The goal of "stand-alone" development is to demonstrate that the proposed product is safe and efficacious.	The goal is to demonstrate biosimilarity between the proposed product and the reference product.
Clinical studies	Clinical studies are required. Drug development starts with preclinical research, moves to Phase 1, 2 and culminates in Phase 3 "pivotal" trials to show safety and efficacy.	The goal is not independently to establish safety and effectiveness of the proposed product. Any comparative clinical study for a biosimilar development program should be designed to investigate whether there are clinically meaningful differences in terms of safety, purity and potency between the proposed product and the reference product. The nature and scope of the comparative clinical studies will depend on the extent of residual uncertainty about the biosimilarity of the proposed product and reference product after conducting structural and functional characterization and, if relevant, animal studies.
Timing of application	A 262(a) application can be filed and approved any time.	A 262(k) application cannot be filed for four years after the reference product is approved, and the biosimilar product cannot be approved for 12 years after that approval.
Advantages	Predictability.	Potential indication extrapolation and interchangeability designation.
Comparison to reference product	No need to be biosimilar to a reference product.	Must be biosimilar to a reference product.
Track record	FDA has approved follow-on biologics under the 262(a) pathway.	So far FDA has not approved any biosimilars under the 262(k) pathway.

APPROVAL PATHWAYS AND TIMELINES FOR FOLLOW-ON BIOLOGICS IN THE U.S.

Comparison Between the 262(a) Pathway and the ANDA Pathway

Provision	Hatch-Waxman Route (505(j) Application	Biosimilar Route (262(a) Application
Drug	Generic drug must be bioequivalent to an approved brand drug.	Biosimilar must be highly similar to the reference product notwithstanding differences in clinically inactive components and there can be no clinically meaningful differences between the biological product and the reference product in terms of the safety, purity, and potency of the product.
Regulatory law	Hatch-Waxman Act of 1984 of the Food, Drug, and Cosmetic Act.	Biologics Price Competition and Innovation Act of the Public Health Service Act of 2009.
Application	Abbreviated New Drug Application - 505(j) application.	262(k) application.
Timing of first application	ANDA can be filed four years after FDA approval of reference product if paragraph IV certification; otherwise, five years.	Biosimilar application can be filed four years after FDA approval of reference product.
Reference product exclusivity	• 5-year marketing exclusivity for new chemical entity • 6 months for pediatric exclusivity • 7 years for orphan drug exclusivity	• 12-year marketing exclusivity for new biologic • 6 months for pediatric exclusivity • 7 years for orphan drug exclusivity
Generic drug exclusivity	180 days if first to file and to certify under Paragraph IV challenging an Orange Book-listed patent.	Only if interchangeable – time is variable but intent is to give one year.
Orange Book	Orange Book listing of patents; certification by generic applicant.	No Orange Book; private exchange of patent information.[26]
Patent certifications	An ANDA applicant must make a certification addressing each patent listed in the Orange Book that claims the reference drug. The ANDA applicant must certify that (I) no such patent information has been submitted to FDA; (II) the patent has expired; (III) the patent is set to expire on a certain date; or (IV) the patent is invalid or will not be infringed by the manufacture, use, or sale of the new generic drug for which the ANDA is submitted. These are commonly referred to as paragraph I, II, III, and IV certifications.	A biosimilar applicant need not certify against any patents but may need to exchange with the BLA holder certain information on patents identified by the parties, and must negotiate in an attempt to agree on a list of patents to be included in the first phase of litigation. This complicated and controversial process is discussed in more detail in the following pages.
Stay upon filing of suit	Automatic 30-month stay.	No automatic stay.

Provision	Hatch-Waxman Route (505(j) Application	Biosimilar Route (262(a) Application
Exchange of contentions	NDA holders are required to list all patents that claim the drug or method of using the drug in the Orange Book, and a generic drug applicant seeking to enter the market before expiration are required to notify the NDA holder and provide a detailed analysis as to why it believes each challenged patent is invalid or will not be infringed. The NDA holder is not required to supply a reciprocal factual and legal basis, or otherwise respond to these assertions.	After a biosimilar applicant provides a factual and legal basis for its opinion that BLA-listed patent(s) are invalid, unenforceable or not infringed, the BLA holder itself must provide a factual and legal basis regarding its opinion that patents are infringed, as well as a response to the biosimilar applicant's assertions regarding invalidity and unenforceability.
Notice to launch	No.	180-day notice of intent to market biosimilar.
Option to opt out of statutory litigation scheme	No.	"Unless otherwise agreed to" in 42 U.S.C. § 262(l)(1)(A).

Mechanics of the Patent Dance Under the BPCIA

As shown above, the patent dance envisions two possible waves of litigation, each preceded by an exchange of information identifying the patents subject to litigation, and each constrained by a strict timeline for exchanges of information and subsequent initiation of litigation. These provisions are currently being litigated in the district courts and the Court of Appeals for the Federal Circuit, as discussed in detail below. One recent and critical decision from the Court of Appeals for the Federal Circuit is *Amgen Inc. v. Sandoz Inc.*, 794 F.3d 1347 (Fed. Cir. 2015).

i. First wave of litigation: 42 U.S.C. § 262(*l*)(2)-(6)

The first wave of litigation, the culmination of steps § 262(*l*)(2)-(6), is the primary wave, and can potentially cover the full realm of relevant patents that the reference product sponsor may assert regarding a proposed biosimilar product.

(*l*)(2)(A): Triggering event: Subsection (k) application information. The biosimilar applicant triggers the first step in the first wave of patent litigation when, within 20 days of being notified that FDA has accepted its biosimilar application for review, the applicant chooses to provide the reference product sponsor with a copy of its application and information about the manufacturing process to be used for the biosimilar product at issue. In *Amgen v. Sandoz*, the Court of Appeals for the Federal Circuit concluded that, although the patent dance provisions use the term "shall" to describe the exchanges of information under § 262(*l*), other provisions in the BPCIA and in conforming amendments to 35 U.S.C. § 271(e) provide clear consequences for an applicant's non-compliance with the patent dance steps, thus indicating that "the BPCIA explicitly contemplates that a subsection (k) applicant might fail to disclose the required information by the statutory deadline." The Federal Circuit further held that there is no "procedural right to compel compliance with the disclosure requirement of paragraph (*l*)(2)(A)," which triggers the patent dance, and if an applicant opts out of the disclosure requirements, the RPS's sole remedy is to bring an immediate action for infringement under other provisions of the BPCIA and its conforming amendments to 35 U.S.C. § 271(e).

Thus, under *Amgen v. Sandoz*, the patent dance information disclosure provisions are optional, in that biosimilar applicants can choose to either engage in the patent dance to delay litigation and narrow the patents asserted in any eventual litigation, or they can opt out of the patent dance and subject themselves to an immediate infringement action on any patents that the RPS could have identified had the parties engaged in the patent dance. Thus, biosimilar applicants can essentially choose the level of patent certainty they want before they launch their biosimilar products.

(*l*)(3)(A)-(C): Exchange of information: List of patents and detailed statements regarding each listed patent. Within 60 days of receiving the biosimilar application and manufacturing information from the applicant, the RPS must provide a ***list of patents*** that it believes could be reasonably asserted with regard to the proposed biosimilar product. (The RPS at this point also provides a list of any patents that it believes it could assert, but which it is willing to license to the applicant.) The applicant then has 60 days to respond to each of the patents identified in the sponsor's initial list with either (a) a ***detailed statement*** that describes the factual and legal basis of the applicant's opinion that such patent is invalid, unenforceable, or will not be infringed, or (b) a statement that the applicant does not intend to begin commercial marketing of its biosimilar product before the expiration of the listed patent. Upon receipt of the applicant's responses, the RPS then has 60 days to provide a responsive detailed statement of the validity, enforceability and infringement of each patent that the applicant has challenged.

(*l*)(4)(A): Negotiations on patents to be litigated. Following the exchange of detailed statements regarding the patents identified by the RPS, the parties then have 15 days to engage in good faith negotiations to agree on which of the patents identified in the RPS's original list shall be litigated in the first wave of litigation.

(*l*)(6)(A): Immediate patent infringement action where the parties agree on which patents shall be the subject of immediate litigation. If the parties agree on the set of patents that will be the subject of the first wave of litigation, then the RPS **"*shall*** bring an action for patent infringement ***with respect to each such [agreed-upon] patent," no later than 30 days*** after the parties agree on the list of patents to be litigated.

(*l*)(4)(B), (*l*)(5), (*l*)(6)(B): Immediate patent infringement action where the parties do not agree on which patents shall be the subject of immediate litigation. If, within 15 days of beginning negotiations, the parties fail to agree on a list of patents to be litigated in the first wave of litigation, then the parties engage in a simultaneous exchange of lists of patents that each side wants to litigate in an immediate infringement action. The number of patents each side can list for immediate action is determined by the applicant: before the simultaneous exchange, the applicant notifies the RPS of how many patents it will list for immediate litigation in the simultaneous exchange (without identifying *which* patents it will put on its list). The number of patents the applicant declares it will list limits the number of patents that the RPS can then list in the simultaneous exchange: the RPS may not list a greater number of patents than the applicant does (unless the applicant does not list any patents, in which case the RPS may list one patent for immediate litigation). Because the exchange of patent lists is simultaneous, the lists of patents identified for immediate action might not overlap, so the actual number of patents subject to immediate patent infringement action may be up to two times the number of patents the applicant declared it would list in the simultaneous exchange.

35 U.S.C. § 271(e)(6): Consequences of delayed action by the RPS. The BPCIA provides that the RPS shall bring an action for patent infringement with respect to each patent that is subject to immediate litigation "not later than 30 days" after the parties agree on the list of patents to be litigated, or in the case of no agreement, "not later than 30 days" after the parties simultaneously exchange the lists of patents each side has identified for immediate litigation. If the RPS fails to bring an action with regard to a listed patent within the 30-day period (or if an action was brought before the 30-day deadline but was dismissed without prejudice or not prosecuted to judgment in good faith), then the only form of relief to which the RPS may be entitled in a later infringement action on that patent is a ***reasonable royalty***.

35 U.S.C. § 271(e)(2)(ii), § 262(*l*)(9)(B)-(C): Consequences of non-compliance by the biosimilar applicant. As mentioned above, the Federal Circuit in *Amgen v. Sandoz* ruled that the only consequences for an applicant's failure to comply with any of these steps of the patent dance are laid out in 35 U.S.C. § 271(e)(2)(ii) and BPCIA § 262*(l)*(9)(B)-(C). Under those provisions, if a biosimilar applicant fails to provide its biosimilar application and manufacturing information under (*l*)(2)(A), or subsequently fails to follow through with the patent dance, it thereby enables the RPS to bring an immediate declaratory judgment action asserting patent infringement. The Federal Circuit Court of Appeals explained:

> Under 35 U.S.C. § 271(e)(2)(C)(ii), filing a subsection (k) application and failing to disclose the required information under paragraph (*l*)(2)(A) is an artificial "act of infringement" of "a patent that could be identified" pursuant to paragraph (*l*)(3)(A)(i). 42 U.S.C. § 262(*l*)(9)(C) further provides that "[i]f a subsection (k) applicant fails to provide the application and information required under paragraph (2)(A)," then the RPS, but not the subsection (k) applicant, may bring a declaratory judgment action on "any patent that claims the biological product or a use of the biological product." …Moreover, 35 U.S.C. § 271(e)(4) provides "the *only* remedies which may be granted by a court for an act of infringement described in paragraph (2)" (emphasis added).

Amgen Inc. v. Sandoz Inc., 794 F.3d 1347, 1356 (Fed. Cir. 2015)

ii. Second wave of litigation: 42 U.S.C. § 262(*l*)(7)-(8)

As set forth in more detail below, the BPCIA contemplates a second wave of litigation in which the RPS can assert any patents that it identified for litigation during the patent dance, but was not able to assert in the first wave due to lack of agreement with the applicant. This second wave of litigation is triggered under § 262(*l*)(8) when the biosimilar applicant notifies the RPS that it intends to begin commercial marketing of its biosimilar product in no less than 180 days. Upon receipt of this notice, and before the first commercial marketing of the product, the RPS may seek a preliminary injunction to prevent the launch of the biosimilar product until a court has reached a decision on the second wave of patent infringement claims.

(*l*)(7)(A)-(B): Newly issued or licensed patents. For any patent that is issued to, or exclusively licensed by, the RPS after it has provided its initial list of relevant patents to the applicant, the RPS can bring a second wave of litigation with regard to the biosimilar product at issue. To bring this second wave of litigation, the RPS must list the new patents in a supplement to the original patent list no later than ***30 days*** after the issuance or licensing of the additional patents. After the RPS provides the supplement list, the applicant has 30 days to provide a detailed statement responding to each of the additional patents. Thus, after the first wave of litigation, the only way the RPS can litigate other patents is if (a) it obtains patents or exclusive licenses to patents after it provides its original patent list to the applicant; or (b) some of the patents identified by the sponsor in its original list were not included on the list of patents eventually agreed upon for litigation by both parties under paragraph (*l*)(4).

35 U.S.C. § 271(e)(6)(C): Consequences to the RPS of failure to timely supplement the original patent list with newly issued or licensed patents. If the RPS fails to supplement its patent list within 30 days of the issuance or licensing of the additional patent under (*l*)(7), then the RPS is foreclosed from bringing an action for infringement of the new patent with respect to the biosimilar product.

(*l*)(8)(A)-(B): Litigation in connection with notice of commercial marketing and motion for preliminary injunction. Paragraph (8) of § 262(*l*) states that the applicant shall provide to the RPS a notice of commercial marketing no later than 180 days before the date of the first commercial marketing "of the biological product licensed under subsection (k)." After receipt of this notice, and before the date of the first commercial marketing, the RPS may seek a preliminary injunction prohibiting the applicant from launching its product until the court decides the issues of patent validity, enforcement and infringement with respect to any patents not subject to the first wave of litigation and any later issues or licensed patents identified on the RPS's supplemental list.

Use Of Post-Grant Patent Proceedings as a Tool in the Decision Making Process

Biosimilar applicants are also turning to post-grant proceedings before the United States Patent & Trademark Office's Patent Trial and Appeal Board (PTAB) to quickly and cost-effectively resolve patent disputes with the RPS. These proceedings include *inter partes* review (IPR) and post-grant review (PGR).

IPR is a mechanism for challenging the validity of issued patent claims based solely on the legal grounds of anticipation or obviousness using prior art patents and printed publications. Any party other than the patent owner can petition for the institution of an IPR, and the IPR may be instituted upon a showing that it is more likely than not that at least one claim challenged will be found unpatentable. PGR is a similar proceeding to IPR, except that it can only be used to challenge post-AIA patents within nine months of their issuance. The legal grounds that can be raised in PGR, though, are many more than in an IPR. A petition for PGR may be based on any statutory invalidity ground. There are various advantages and disadvantages to using these post-grant proceedings:

Advantages	Disadvantages
Biosimilar applicants need not wait until they have filed an FDA application to petition to invalidate a patent in an IPR or PGR.	An IPR petition cannot be filed more than one year after a patent infringement complaint is served against the challenger. A petition for IPR also cannot be filed after the challenger has filed a declaratory judgment action challenging the patent's validity.
An IPR or PGR decision can provide fast and early certainty with respect to the validity of patents blocking entry of a biosimilar.	Defenses such as lack of enablement and written description (which are often featured in patent litigation involving biologics) are not available in an IPR.
An IPR or PGR decision can provide early data for the decision on whether and when to file a biosimilar/BLA/biobetter application.	Though the PTAB has invalidated patents in all industries at a very high rate, challengers run the risk of strengthening or "gold-plating" the challenged patent if the PTAB ultimately upholds its validity.
An IPR or PGR decision can impact a patent owner's ability to obtain additional patents/applications covering the biosimilar. Under 37 CFR § 42.73(d)(3), a patent owner is estopped from taking action inconsistent with any adverse judgment, including obtaining a patent claim that is patentably indistinct from a finally refused or cancelled claim, or amending its specification or drawings in a way that was denied during the proceeding. The IPR or PGR decision can be used to challenge "evergreen" patents that do not contain claims that are patentably distinct from the claims found to be unpatentable in the IPR or PGR proceeding.	A final written decision will result in estoppel before the USPTO, district court, or ITC on any ground that the petitioner "raised or reasonably could have raised" during the IPR or PGR.

Some companies are already seeing the potential value in challenging patents protecting biologics in the PTAB. For example, on June 26, 2015, Amgen, Inc. filed IPR petitions (IPR2015-01514 and IPR2015-01517) against two Humira® (adalimumab) patents owned by AbbVie Inc., in an effort to clear the way for its Humira® biosimilar, ABP 501. U.S. Patent Nos. 8,916,157 and 8,916,158 are directed to improved formulations of Humira®, which Amgen argues are obvious because they merely combine adalimumab, a known antibody, with known antibody-containing liquid formulations. Amgen's Humira® biosimilar met the primary end-point of equivalence in treating moderate to severe rheumatoid arthritis in a Phase III clinical trial in February of 2015. Amgen has stated that it could launch ABP 501 in 2017, after patents covering the adalimumab molecule expire. The PTAB has not yet decided whether to institute these IPRs.

Also earlier this year, Boehringer Ingelheim (BI), a biosimilar maker, filed IPR petitions (IPR2015-00415, IPR2015-00417, and IPR2015-00418) against three patents covering the use of Rituxan® (rituximab), an antibody that binds to CD20, seeking to invalidate U.S. Patent Nos. 7,820,161, 7,976,838 and 8,329,172. The PTAB denied BI's petition against the '172 patent, but instituted IPR on the '161 and '838 patents. The challenged patents generally claim: (1) combination therapy using rituximab and methotrexate to treat rheumatoid arthritis, (2) treating rheumatoid arthritis in certain patients that do not respond to other therapy according to a specific dosing regimen, and (3) treating low grade B-cell non-Hodgkin's lymphoma using chemotherapy followed by administration of rituximab according to a specific regimen. Soon after the two IPRs were instituted, Celltrion, Inc. also filed petitions to join the IPRs on the '161 and '838 patents.

Since, pursuant to recent guidance from the courts, a biosimilar applicant can forgo the BPCIA's patent dance, we expect biosimilar applicants to increasingly consider the use of post-grant challenges at the USPTO to obtain greater certainty on the validity of patents likely to be asserted against them in future litigation.

More information on IPR proceedings, and considerations and strategies in litigating such proceedings on pharmaceutical patents can be found in Goodwin's *Pharmaceuticals at the Patent Trial and Appeal Board*, published in 2015.

RECENT LEGAL DEVELOPMENTS CONCERNING THE BPCIA

Overview: "Mystery Inside an Enigma"

On July 21, 2015, the Federal Circuit issued a split decision in *Amgen v. Sandoz,* the first case to test and interpret the provisions of the BPCIA patent dispute resolution procedures. In his opinion for the Court, Judge Lourie noted that the Court's split decision reflected the complexity of the statute, writing: "Winston Churchill once described Russia as 'a riddle wrapped in a mystery inside an enigma.' That is this statute. In these opinions, we do our best to unravel the riddle, solve the mystery, and comprehend the enigma." (Op. 3 n.1)

In its attempt to "unravel the riddle," the Court held that the patent dance is optional, that notice of commercial marketing can be given only after FDA has licensed an applicant's biosimilar product, and that such notice is mandatory when the biosimilar applicant has opted not to provide its biosimilar application and manufacturing information under the first step of the patent dance. Notwithstanding the elucidations of the three opinions in this pioneer case, several questions remain to prolong the mystery and sustain the enigma of the BPCIA.

<table>
<tr><td colspan="3">Amgen v. Sandoz
No. 14-CV-04741-RS, 2015 WL 1264756 (N.D. Cal. Mar. 19, 2015)
aff'd in part, vacated in part, remanded, 794 F.3d 1347 (Fed. Cir. 2015)
Products at issue: Neupogen® (filgrastim)</td></tr>
<tr><th>Case Status
(as of 12/21/15)</th><th>Patent Dance Posture</th><th>Notice of Commercial Marketing Issue(s)</th></tr>
<tr><td>Petitions for rehearing en banc on BPCIA issues denied. Patent infringement claims continuing in N.D. Cal.

Petitions for writ of certiorari, if any, due to the Supreme Court by January 14, 2016.</td><td><u>No dance</u>

Sandoz did not provide Amgen its (k) application or manufacturing information within 20 days of FDA's notification of acceptance.</td><td><u>Notice given before and after FDA approval</u>

Sandoz claimed to give notice of commercial marketing when it notified Amgen that FDA had accepted Sandoz's biosimilar application for review. After FDA approved Sandoz's biosimilar product, Sandoz gave Amgen another notice of commercial marketing.

The Federal Circuit held that Sandoz's pre-approval notice was ineffective under the BPCIA, and thus enjoined Sandoz from marketing its approved Zarxio® product until 180 days after the date of FDA approval, when Sandoz had given another notice of commercial marketing.</td></tr>
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Janssen v. Celltrion No. 15-cv-10698 (D. Mass., filed Mar. 6, 2015) Products at issue: Remicade® (infliximab)		
Case Status (as of 12/21/15)	**Patent Dance Posture**	**Notice of Commercial Marketing Issue(s)**
Pending cross-motions for summary judgment. Pending motion by Janssen to modify the protective order to permit filing of a new action Janssen filed a notice of supplemental authority, seeking to use the preliminary injunction order in *Amgen v. Apotex* as support for its motion for summary judgment.	***Some dance*** Celltrion produced its application, including manufacturing information (the completeness of which Janssen disputes), within the statutory 20-day window. Janssen served its patent list, Celltrion provided a detailed statement in response, and agreed that all of the patents identified by Janssen would be the subject of the first wave of litigation.	***Notice before FDA approval*** The defendants served a purported notice of commercial marketing on February 5, 2015. Janssen argues that this notice is ineffective under the BPCIA. Celltrion responds that under *Amgen v. Sandoz*, it is not required to provide notice of commercial marketing because it has engaged in the patent dance.
Amgen v. Apotex No. 15-cv-61631-JIC/BSS (S.D. Fla., filed Aug. 6, 2015) Products at issue: Neulasta® (pegfilgrastim)		
Case Status (as of 12/21/15)	**Patent Dance Posture**	**Notice of Commercial Marketing Issue(s)**
The district court granted Amgen's motion for preliminary injunction on December 9, 2015. Apotex appealed the order on December 10, 2015, and moved to expedite the schedule on appeal. Amgen has opposed the motion to expedite. Trial has been scheduled for July 11, 2016.	***Dance completed through first wave*** Amgen and Apotex reached agreement upon a list of patents that should be the subject of a first wave of patent litigation.	***Notice before FDA approval*** Apotex sent Amgen a purported notice of commercial marketing on April 17, 2015. Amgen seeks a declaratory judgment that Apotex can provide an effective 180-day notice of commercial marketing only after FDA licenses its proposed biosimilar product.

Amgen v. Hospira No. 15-cv-839-RGA (D. Del., filed Sept. 18, 2015) Products at issue: Epogen® (epoetin alfa)		
Case Status (as of 12/21/15)	**Patent Dance Posture**	**Notice of Commercial Marketing Issue(s)**
Hospira has moved to dismiss Amgen's BPCIA claims. After winning a preliminary injunction in *Amgen v. Apotex* on its claim that the BPCIA requires all biosimilar applicants to provide 180 days' notice prior to the first date of commercial marketing, Amgen filed a notice of supplemental authority hoping to capitalize on that win by using it to oppose Hospira's motion to dismiss.	***Some dance*** Hospira provided its biosimilar application to Amgen within the 20-day statutory window, but allegedly has not provided manufacturing information. Amgen provided a list of patents that could be asserted, and Hospira provided responses and agreed that every patent Amgen listed would be the subject of the first wave of litigation.	***Notice before FDA approval*** Hospira provided a purported notice of commercial marketing on April 8, 2015. Amgen argues that this notice is legally ineffective under the BPCIA. Hospira argues that it is not required to give any notice under the Federal Circuit's interpretation of the notice provision of the BPCIA.

Amgen v. Sandoz

On October 24, 2014, Amgen filed a complaint in the U.S. District Court for the Northern District of California alleging that Sandoz unlawfully refused to follow the BPCIA's patent resolution procedures set forth in § 262(*l*) (§ 351(*l*) of the Public Health Services Act), and sought declaratory and injunctive relief to compel Sandoz to comply with the patent dance provisions. In particular, Amgen alleged that once Sandoz received notice from FDA that it had accepted Sandoz's 262(k) application for a biosimilar version of Neupogen®, BPCIA § 262(*l*)(2) required that Sandoz then provide Amgen a copy of its accepted application, together with manufacturing information for its proposed biosimilar product, within 20 days. Sandoz did not provide its application or manufacturing information within 20 days of FDA's acceptance of its biosimilar application, and instead told Amgen that it did not intend to engage in the patent dance, and that it intended to launch its biosimilar product immediately upon FDA approval.

Amgen alleged that not only did Sandoz's refusal to provide its application and manufacturing information violate § 262(*l*)(2) of the BPCIA, but also that Sandoz's purported notice of commercial launch immediately upon FDA approval was legally insufficient under BPCIA § 262(*l*)(8). That provision requires biosimilar applicants to provide notice to the RPS "not later than 180 days before the date of the first commercial marketing" of its biosimilar product, which Amgen alleged meant that Sandoz could not provide effective notice until *after* FDA licensed its biosimilar product.

The district court ruled in favor of Sandoz on all counts, holding that the patent dance steps are not mandatory, and that biosimilar applicants do not have to wait for FDA approval before they can provide sufficient notice of commercial marketing under the BPCIA.

On appeal, the Federal Circuit agreed in a split decision that the information disclosure steps of the patent dance are not mandatory, but held that since Sandoz had not engaged in the patent dance at all, it was required to provide 180-days' notice of commercial marketing *after* FDA licensure. That decision is final for now, as the Federal Circuit denied the parties' petitions for rehearing *en banc* on October 16, 2015.

As described above, there were two main questions presented in *Amgen v. Sandoz*:

1. Whether a biosimilar applicant may opt out of the patent dance disclosure provisions, subject only to the consequences set forth in other provisions of the BPCIA (i.e., the possibility of an immediate action for patent infringement by the RPS);

2. Whether a biosimilar applicant "may satisfy its obligation to give notice of commercial marketing under 42 U.S.C. § 262(*l*)(8)(A) by doing so before FDA licenses its product," and whether such notice is "mandatory." Op. 15, 19.

Judge Lourie wrote the majority (2-1) opinion for the court in the Federal Circuit's July 21, 2015 decision in *Amgen v. Sandoz*. Judge Newman wrote an opinion concurring with the Court's opinion on the notice issue, and dissenting on the information disclosure question. Judge Chen wrote a separate opinion dissenting as to the Court's interpretation of the notice provision, and concurring with the decision on the information disclosure question.

Holding	Judge Newman	Judge Lourie	Judge Chen
1. Biosimilar applicants can choose not to disclose aBLA and manufacturing information, subject only to immediate suit for infringement by RPS.	✗	✓	✓
2. Notice of commercial marketing can be given only after FDA approval of the biosimilar product.	✓	✓	✗

Question 1

On the first question of whether an applicant must disclose its biosimilar application and manufacturing information within 20 days of FDA's notification of acceptance of the application, the Court concluded that although the "shall" provision in (*l*)(2)(A), on its own, "*appears* to mean that a subsection (k) applicant is required to disclose its aBLA and manufacturing information to the RPS by the deadline specified in the statute," (emphasis added), this provision "cannot be read in isolation": "In other provisions, the BPCIA explicitly contemplates that a subsection (k) applicant might fail to disclose the required information by the statutory deadline." *Amgen Inc.*, 794 F.3d at 1355. Thus, although the plain language of the "shall" provision itself might support Amgen's reading of the statute, the Court explained, other provisions in the BPCIA and in 35 U.S.C. § 271(e)(2)(C)(ii) "indicate that 'shall'…does not mean 'must.'" Op. 13.

The Court concluded that there is thus no "procedural right to compel compliance with the disclosure requirement of paragraph (*l*)(2)(A)," Op. 13, and that, as Sandoz argued, if an applicant "fails" to comply with the disclosure requirements, the BPCIA expressly provides the sole remedies to redress such failure: i.e., the RPS may bring an immediate action for infringement under (*l*)(9)(C) and 35 U.S.C. § 271(e)(2)(C)(ii). Amgen's position—that the BPCIA mandates compliance with the disclosure provisions—would render these other provisions "superfluous," contrary to established canons of statutory interpretation. Therefore, the Court concluded, "[b]ecause Sandoz took a path expressly contemplated by the BPCIA, ***it did not violate the BPCIA*** by not disclosing its aBLA and the manufacturing information by the statutory deadline." Op. 15.

Judge Newman dissented from this part of the opinion, writing that use of the word "shall" in § 262(*l*)(2) indicates that disclosure of the applicant's biosimilar application and manufacturing information is a statutory command that is mandatory upon the biosimilar applicant. As a matter of legislative sense, according to Judge Newman, the disclosure provision in (*l*)(2)(A) must be considered mandatory because it triggers the "designated exchange of information [that] is fundamental to the BPCIA purposes of efficient resolution of patent issues," Op. 5. The fact that subparagraph (*l*)(9)(C) provides a consequence for non-compliance does not render the plain "shall" language into a non-mandatory provision, she wrote, because that subparagraph provides only for declaratory action by an RPS on product and use claims; it does not enable action on manufacturing process patents, which are especially critical in biosimilars litigation.

In support of her position, Judge Newman also drew on legislative history to show that the balance struck by the drafters of the BPCIA requires compliance with the disclosure provisions in order to "avert and…expedite litigation." Op. 6. She wrote: "The balance established in the BPCIA requires the statutorily identified disclosures at the threshold, in order both to avert and to expedite litigation. This purpose pervades the legislative record," and the statute as a whole "requires judicial implementation that conforms to 'the design of the statute … and to its object and policy.'" Op. 8 (internal citation omitted).

The opinion for the Court, however, is clear: "when a subsection (k) applicant fails the disclosure requirement, 42 U.S.C. § 262(*l*)(9)(C) and 35 U.S.C. § 271(e) expressly provide the only remedies as those being based on a claim of patent infringement." If an applicant decides not to comply with the disclosure requirement, the RPS cannot go through the courts to compel compliance—its only remedy is to bring an immediate action for patent infringement under 42 U.S.C. § 262(*l*)(9)(C) and 35 U.S.C. § 271(e).

Question 2

On the second question of when a biosimilar applicant can provide effective notice of commercial marketing, the Court (2-1) sided with Amgen, and held that "a subsection (k) applicant may only give effective notice of commercial marketing ***after*** FDA has licensed its product." (Op. 16 (emphasis added)).

The Court adopted Amgen's reasoning from the language of the statute, giving determinative weight to Congress's use of the phrase "biological product ***licensed*** under subsection (k)," (emphasis added) in the notice provision instead of the phrase "the biological product that is the subject of" the biosimilar application, used elsewhere in the statute.

Judge Lourie's opinion for the Court reasoned that notice after licensure makes more legislative sense, because only after licensure is the scope of the approved license known, the manufacturing processes fixed, and the marketing of the biosimilar product imminent. Requiring notice of commercial marketing to be given *after* licensure, the majority opinion explains, "ensures the existence of a fully crystallized controversy regarding the need for injunctive relief." (Op. 17.) If the statute were interpreted otherwise to allow commercial marketing at any time before FDA licensure, the RPS might be unable to seek a preliminary injunction as contemplated by the statute: "the RPS would be left to guess the scope of the approved license and when commercial marketing would actually begin." (Op. 17.)

The Court also addressed the question of whether the "shall" language in the (*l*)(8)(A) notice provision renders that provision mandatory. Unlike the disclosure provision of (*l*)(2)(A), the Court concluded that "shall" in the notice provision was indeed mandatory for Sandoz. The critical difference, the Court explained, is that whereas the disclosure provision of (*l*)(2)(A) corresponds to other provisions that expressly specify the consequences for failure to comply with that disclosure step, the (*l*)(8)(A) notice provision lacks any corresponding provision that contemplates non-compliance with that step or provides any consequence for failure to provide notice. Although, as Sandoz noted, (*l*)(9)(B) provides that the RPS may bring a declaratory judgment action for failure to comply with certain patent dance steps including the notice provision, that provision applies *only after the applicant has already complied with the disclosure provisions of* (*l*)(2)(A); when an applicant opts out of the disclosure provisions "*completely*" (emphasis added), the Court held, it *must* provide notice of commercial marketing in accordance with (*l*)(8)(A).

In this case, therefore, Sandoz was required to provide notice of commercial marketing 180 days prior to launch, and only Sandoz's *post-licensure* notice of commercial marketing was effective under the BPCIA. The Court consequently enjoined Sandoz from launching its licensed biosimilar product until 180 days after the date it had provided notice post-FDA licensure of its product.

Judge Chen dissented from the Court's opinion on this issue, writing that just as the information disclosure provision in (*l*)(2)(A) cannot be read in isolation, neither should the notice provision of (*l*)(8)(A) be read as a standalone provision: (*l*)(8) should be read as simply another step in the rest of the patent dance, each step of which is contingent on the preceding step. This means that if the applicant fails to take the first step in (*l*)(2)(A), as Sandoz did here, the rest of the patent dance provisions "cease to matter." (Op. 2.) At that point, Judge Chen wrote, "the RPS's course of action is clearly defined in (*l*)(9) and § 271(e)(2)(C)(ii): the unfettered right to immediately pursue patent infringement litigation unconstrained by any of the timing controls or limits on the number of patents it may assert that would result from the (*l*)(2)– (*l*)(8) process." (Op. 2.) The notice provision, Judge Chen reasoned, "express[ly] assum[es]" that the parties have already engaged in the preceding patent dance steps: "the entirety of (*l*)(8), including (*l*)(8)(A)'s notice provision, serves to ensure that an RPS will be able to assert all relevant patents before the (k) applicant launches its biosimilar product." (Op. 6.) The "interwoven structure" of all the steps provided in subsection (*l*) of the BPCIA "indicates that Congress viewed the procedures of (*l*)(8) as inseverable from the preceding steps in (*l*)," (Op. 7): if the parties have not engaged in the steps prior to (*l*)(8), then (*l*)(8) is not even triggered.

The majority opinion's interpretation of the notice provision, Judge Chen added, erroneously grants Amgen "an extra-statutory exclusivity windfall," (Op. 2,) and in practice "provides an inherent right to an automatic 180-day injunction." (Op. 9.) This cannot be what Congress intended, Judge Chen reasoned, because "[i]f Congress intended to create a 180-day automatic stay it understood how to do so" by clearer means. (Op. 9.)

It should also be noted, Judge Chen added, that under the majority opinion, this "automatic stay" would apply only if the applicant does not comply with the disclosure provisions at all—if the applicant does comply with the provisions, then it can refuse to provide notice subject only to the consequences in (*l*)(9)(B). Judge Chen concluded that this "uncomfortable result," in which the provision is interpreted differently based on the (k) applicant's actions, is not supported by the statute as a whole.

As described in further detail below, biosimilar applicants in other pending BPCIA litigation have picked up on this observation by Judge Chen, and have argued that the court's opinion in *Amgen v. Sandoz* holds only that biosimilar applicants who have "completely fail[ed]" to participate in the patent dance are required to provide notice of commercial marketing under (*l*)(8)—and that applicants who engage in at least part of the dance are *not* required to provide notice under the court's interpretation of the statute.

Several questions have arisen regarding the notice of commercial marketing and ensuing second wave of litigation under the BPCIA.

One question, which was litigated and decided in *Amgen v. Sandoz*, concerns the timing of the notice of commercial marketing: *when* may an applicant provide its 180-day notice of commercial marketing to the RPS? In *Amgen v. Sandoz*, the Federal Circuit ruled that Sandoz's purported notice, given shortly after FDA accepted its biosimilar application for review, was legally insufficient under the BPCIA. The Federal Circuit held that notice of commercial marketing under the BPCIA can only be given *after* FDA licensure of the biosimilar product, because only a post-licensure notice would "ensure[] the existence of a fully crystallized controversy regarding the need for injunctive relief." (Op. 17). The Court reasoned that if, per Sandoz's argument, notice of commercial marketing could be given at any time before licensure, then "the RPS would be left to guess the scope of the approved license and when commercial marketing would actually begin." (Op. 17). In other words, the Court reasoned that only after the biosimilar product has been licensed by FDA is there enough certainty of launch and certainty of the product characteristics relevant to patent infringement claims to trigger a motion for preliminary injunction, and since this triggering is the apparent purpose of the notice provision, it therefore makes sense that the notice can only be given once this certainty is reached—i.e. once FDA has approved the biosimilar application and licensed the biosimilar product.

A second question, which is now the focus of ongoing litigation in at least three district court cases discussed below, is whether notice of commercial marketing is always *required* of biosimilar applicants under the BPCIA. The Federal Circuit considered this question in *Amgen v. Sandoz*, but its response left room for further questions and clarifications. The opinion reads: "We … conclude that, ***where, as here, a subsection (k) applicant completely fails*** to provide its aBLA [abbreviated biologics licensing application] and the required manufacturing information to the RPS by the statutory deadline, the requirement of paragraph (*l*)(8)(A) is mandatory." Biosimilar applicants in ongoing BPCIA litigation have picked up on this language to argue that *only* when a biosimilar applicant "completely fails" to engage in the patent dance, as Sandoz did in *Amgen v. Sandoz*, is the notice provision mandatory. Otherwise, some have argued, if an applicant engages in at least part of the dance and provides its biosimilar application and/or manufacturing information to the RPS, the notice provision is just like any other provision of the patent dance: optional, with the consequence of non-compliance being the RPS's ability to bring an immediate suit for patent infringement. One district court has already reached an initial decision on this question in the context

of a motion for preliminary in junction. In *Amgen v. Apotex*, discussed below, the district court for the District of Florida held that Amgen had a substantial likelihood of prevailing on its claim that the BPCIA required *all* biosimilar applicants, including applicants like Apotex that have gone through the patent dance, to provide 180 days' notice prior to commercial marketing and post-FDA approval of the biosimilar application.

Relatedly, some pending cases have raised the question of what constitutes sufficient compliance with the patent dance provisions to render the notice of commercial marketing non-mandatory. If a biosimilar applicant provides only its biosimilar application without any manufacturing information, does this mean it has not "completely failed" to comply with the initial disclosure provision of the patent dance, meaning in turn that the applicant is not required to provide notice of commercial marketing under (*l*)(8)? And, if provision of the biosimilar application without other manufacturing information does not satisfy the initial disclosure provision of the patent dance, but the applicant and RPS proceed through the patent dance steps to arrive at a list of patents for immediate litigation, is the notice of commercial marketing still required? Applicants have argued that if they agree to every patent listed by the RPS for immediate litigation, then there are no patents left to assert in a "second wave" of litigation. Since the notice provision is supposed to trigger this "second wave" of litigation, then, the applicant's reason, the absence of any second wave patents should render the notice provision inapplicable and non-mandatory.

A final, related question that has been raised is: if a biosimilar applicant engages in the patent dance, when may the RPS file for a preliminary injunction, and on what grounds? This question has arisen in two pending BPCIA litigations (*Janssen v. Celltrion* and *Amgen v. Apotex*), where the RPS has sought a preliminary injunction based on the applicant's alleged refusal to comply with the notice provision of (*l*)(8). In these ongoing cases, the applicants have argued that notice of commercial marketing is not required because they have engaged in the patent dance, and therefore do not need to provide notice of commercial marketing under *Amgen v. Sandoz*. In response, the RPSs have sought preliminary injunctions to prevent the applicants from launching their products until 180 days after they provide notice—post FDA-licensure—that they intend to commercially market their approved product. The applicants have challenged the RPS's ability to privately enforce this procedural notice provision of the BPCIA, noting that "[w]hen the BPCIA addresses injunctive relief, it refers to patent-based injunctive relief, not injunctive relief based on the statute." (Apotex opp. to Amgen's Motion for a Preliminary Injunction, at 3). If an RPS wishes to preliminarily enjoin an applicant from launching its biosimilar product, the argument goes, such a motion must be based solely on asserted patent infringement claims, and cannot be grounded in alleged violations of the BPCIA's procedural provisions.

As noted above, these lingering uncertainties about the notice and preliminary injunction provisions of the BPCIA are the subject of ongoing litigation at the district court level. We can expect even further questions about this provision and others to arise as parties dispute the application of *Amgen v. Sandoz* and continue to work out other complexities of the BPCIA. The next section highlights some of the recent legal developments that form the contours of our current understandings and questions concerning the BPCIA.

Janssen v. Celltrion, No. 15-cv-10698 (D. Mass., filed Mar. 6, 2015)

On March 6, 2015, Janssen filed a complaint in the District of Massachusetts, alleging that Celltrion and Hospira had violated the BPCIA by (1) consenting to immediate litigation on all patents listed by Janssen and thereby prematurely cutting off the patent dance, and (2) providing untimely notice of commercial marketing (i.e., before FDA approval of the defendants' proposed biosimilar product referencing Janssen's Remicade® (infliximab)).

Unlike *Amgen v. Sandoz*, Janssen alleged in its complaint that the BPCIA itself creates a private right of action to enforce the provisions of the patent dance, which means that parties can directly enforce the patent dance provisions without resorting to other laws that provide a right to relief connected in some way to a "violation" of the BPCIA (for example, the California unfair competition and conversion state law claims upon which Amgen relied in *Amgen v. Sandoz*).

Both sides moved for partial summary judgment on the question of whether Celltrion's pre-FDA-licensure notice of commercial marketing was legally effective under the BPCIA. After the Federal Circuit issued its decision in *Amgen v. Sandoz*, the parties submitted briefs to supplement their arguments on partial summary judgment. In light of the Federal Circuit's decision, both parties agreed that Celltrion's notice of commercial marketing was not legally sufficient under the BPCIA because it was given before FDA approval; however, Celltrion argued that this did not matter, as it was not required to provide any notice in the first place, since it had timely provided its biosimilar application and manufacturing information in accordance with the patent dance provisions.

Under Celltrion's interpretation, the Federal Circuit in *Amgen* "held that the notice of commercial marketing provision is mandatory *only* where the biosimilar applicant 'completely fails' to participate in the statutory information-exchange process." (6). It is the Court's "completely fails" language that distinguishes Celltrion from Sandoz, according to Celltrion, because unlike Sandoz, Celltrion did timely provide its biosimilar application (including "detailed manufacturing information" satisfying the disclosure requirement for "other information that describes the process or processes used to manufacture" the proposed biosimilar product).

Celltrion has argued that the Federal Circuit "has apparently read the BPCIA to prevent a situation where the applicant does not disclose its application and launches upon FDA approval without any prior notice to the sponsor" (11)—a situation that is preempted if the biosimilar applicant engages in the patent dance and thereby puts the RPS on notice of its biosimilar application and intent to market. Moreover, Celltrion argued, the Federal Circuit made it clear that the notice provision serves "a limited purpose" to "kick-start[] any second litigation phase over patents whose relevance the parties dispute." (17). Since Celltrion accepted Janssen's list of "relevant" patents for immediate litigation, "there are no 'phase-two' patents to litigate," (19) in its case; the 180-day window of (*l*)(8) would therefore not serve its limited purpose, from which it follows that the (*l*)(8) notice provision should not apply.

Janssen has argued in response that the Federal Circuit was clear in its holding that "[p]aragraph (*l*)(8)(A) is a standalone notice provision." Janssen further argued that the notice of commercial marketing must be considered mandatory in order to achieve the "statutory purpose" of "ensuring a 'fully crystallized controversy regarding the need for injunctive relief'" by providing a "pre-launch notice period to allow [the reference product sponsor] to assess the need for and seek such relief." Janssen argued that the declaratory judgment remedy provided for in the statute, which Celltrion has argued is Janssen's sole remedy to redress Celltrion's alleged violation of the notice provision, is not an adequate remedy, because it "does not address the irreparable injury of launch."

Amgen v. Apotex, No. 15-cv-61631-JIC/BSS (S.D. Fla., filed Aug. 6, 2015)

Amgen v. Apotex is the first post-*Amgen v. Sandoz* case to reach a judicial interpretation of the BPCIA's 180-day notice provision. On December 9, 2015, the District Court for the Southern District of Florida granted Amgen a preliminary injunction to prohibit Apotex from launching its proposed biosimilar pegfilgrastim product until at least

180 days after FDA approves the product and Apotex notifies Amgen of its intent to begin commercial marketing of the product. In its order granting the preliminary injunction, the Court held that Amgen had a substantial likelihood of prevailing on the merits of its claim that the BPCIA's 180-day notice of commercial marketing provision is mandatory for all biosimilar applicants, even if, like Apotex, the applicant had engaged in some or all of the patent dance steps.

As background, *Amgen v. Apotex* is the first biosimilar litigation in which the parties have exchanged information in accordance with each step of the patent dance, and are now engaged in the "first wave" of patent litigation under the BPCIA. While the parties agreed on which patents to include in this first wave of litigation, they disagreed about whether Apotex provided Amgen a sufficient notice of commercial marketing under (*l*)(8)(A), and thus disagreed on whether Apotex could launch immediately upon receiving FDA approval of its biosimilar application. Amgen is seeking a declaratory judgment that Apotex's notice is "ineffective," since it was given prior to FDA licensure of its proposed biosimilar product, and also sought a preliminary injunction to prevent Apotex from launching its biosimilar product (referencing Amgen's Neulasta (pegfilgrastim) product) until at least 180 days after the date of FDA licensure and Apotex's subsequent notice of commercial marketing.

In its order granting a preliminary injunction, the district court focused on the word "shall" from the text of the BPCIA notice provision. In sum, the Court wrote, "Amgen argues that 'shall' means shall in all cases, while Apotex argues that 'shall' means shall only in some cases. The Federal Circuit addressed the meaning of 'shall' as used in § 262(*l*)(8)(A) in the *Sandoz* case, 794 F.3d 1347, but left some ambiguity…. [T]he *Sandoz* decision was limited to situations where the subsection (k) applicant 'completely fails to provide its aBLA and the required manufacturing information to the RPS by the statutory deadline ….' Because the situation was not before it, the Court did not address whether the notice provision of § 262(*l*)(8)(A) applies where the applicant, like Apotex, *did* share the information required by § 262(*l*)(2)."

The Court held that 180 days' notice of commercial marketing is mandatory under the BPCIA because "[i]t provides a defined statutory window" between FDA licensure of the biosimilar product, at which point the issues are "fully crystallized," and commercial launch of the biosimilar product. As the Federal Circuit explained in *Amgen v. Sandoz*, this 180-day statutory window exists so that "the court and the parties can fairly assess the parties' rights prior to the launch of the biosimilar product." The *Apotex* court held that this window "exists for *all* biosimilar products that obtain FDA licenses, regardless of whether the subsection (k) applicant complies with § 262(*l*)(2)" (emphasis added). To interpret the provision otherwise, as Apotex proposed, "would result in confusion and uncertainty, as well as inconsistent results, depending on which route a subsection (k) applicant chooses to travel." The Court added that in this case, "depending on when FDA grants Apotex's product a license, one of the patents Amgen has filed suit on in this Court may well expire before the 180-day period ends; under Apotex's construction of § 262(*l*)(8)(A), the Court would be forced to rule on the validity of that patent now, even though that patent claim may be moot by the end of the 180-day period. This fact helps illustrate the value and the purpose of applying the 180-day notice provision to all biosimilar applicants."

The Court's grant of a preliminary injunction means that Apotex cannot launch its biosimilar pegfilgrastim product until Apotex gives Amgen notice after FDA licensure and the 180-day notice period has expired.

Amgen v. Hospira, No. 15-cv-839-RGA (D. Del., filed Sept. 18, 2015)

On September 18, 2015, while its petition for rehearing *en banc* in *Amgen v. Sandoz* was pending before the Federal Circuit, Amgen initiated a new suit alleging familiar claims about the interpretation of the BPCIA and its patent information exchange provisions. In its complaint, Amgen requested a "declaration of its rights under the [BPCIA]" and injunctive relief enforcing Amgen's interpretation of the patent dance provisions, and also asserted two patents against Hospira.

The background of the case is similar to that of the other litigation in which Hospira is a party, *Janssen v. Celltrion*: on February 23, 2015, Hospira notified Amgen that its 262(k) application for a biosimilar version of Amgen's Epogen® (epoetin alfa) product had recently been accepted for filing by FDA. On March 3, 2015, Hospira provided Amgen a copy of its biosimilar application, which Hospira contends includes ample information regarding the manufacture of its biosimilar product. Amgen disagrees, and alleges that Hospira failed to provide manufacturing information meeting the requirements of § 262(*l*)(2)(A). The parties thereafter exchanged lists and detailed statements regarding patents that could reasonably be asserted against Hospira for its biosimilar epoetin product. Instead of negotiating with Amgen to narrow the list of patents to be litigated, however, Hospira agreed that every patent Amgen listed could be asserted in a first wave of patent litigation.

On April 8, 2015, Hospira provided Amgen with a notice of commercial marketing purportedly in accordance with § 262(*l*)(8). After the Federal Circuit issued its decision in *Amgen v. Sandoz*, Hospira notified Amgen that it would actually not provide any notice of commercial marketing under § 262(*l*)(8), as such notice was not required given Hospira's engagement in the patent dance information disclosure steps.

Following the Federal Circuit's decision in *Amgen v. Sandoz*, Hospira also moved to dismiss Amgen's BPCIA-based allegations, arguing that Amgen was improperly seeking "to privately enforce statutory provisions despite the fact that Congress did not create a structure for private enforcement of paragraph (2)(A) or paragraph (8)(A)."

In its motion to dismiss the BPCIA claims, Hospira denied that it failed to comply with the disclosure provisions of (*l*)(2)(A), as it timely provided its biosimilar application, which "contained hundreds of thousands of pages providing comprehensive and detailed information concerning Hospira's product and the processes employed to make Epoetin Hospira" within the 20-day BPCIA timeframe. And even if Amgen could demonstrate that Hospira had failed to comply with the (2)(A) disclosure provision, Hospira argues, the Federal Circuit in *Amgen v. Sandoz* made it clear that "the alleged violation would be precisely an act of infringement under Section 271(e)(2)(C)(ii), for which Section 271(e)(4) provides the only remedies. As such, Amgen's only remedy is to sue for patent infringement under Section 271, something it has already done in the Complaint." (internal quotation marks and citations omitted).

On the notice issue, Hospira has argued that *Amgen v. Sandoz* "established that a notice of commercial marketing pursuant to paragraph (8)(A) is not mandatory unless the applicant 'completely fails' to participate in the BPCIA patent exchange process," and "even assuming that a notice of commercial marketing is mandatory, there is no

evidence of congressional intent that would allow a private enforcement of paragraph (8)(A) to stand." Hospira has asserted that it did not "completely fail" to participate in the BPCIA patent exchange process, as it timely provided its biosimilar application to Amgen, provided a "detailed factual and legal basis" for its opinion that the three patents identified by Amgen as patents for which a claim of infringement could reasonably be asserted pursuant to (*l*)(3)(B) were invalid and/or would not be infringed, and agreed to proceed to trial on the three listed patents, thereby "end[ing] the negotiations contemplated under paragraph (4)(A)." Therefore, Hospira has argued, the (8)(A) notice provision is not mandatory.

According to Hospira, the "fatal flaw" in both of Amgen's BPCIA claims is that "[t]here is no evidence that Congress intended to create a private right of action to enforce paragraph (2)(A) or paragraph (8)(A). "Indeed," Hospira notes, "the BPCIA sets forth the explicit consequences for failing to abide by these provisions. *See* 35 U.S.C. § 271(e)(4); 42 U.S.C § 262(*l*)(9)(B)-(C). Congress could have created a private right of action if that is what it intended. Congress did not do so, even though it did expressly provide a remedy for statutory violations elsewhere in the BPCIA." Hospira takes the Federal Circuit's observation that "the BPCIA contains 'certain similarities in its goals...., and procedures' to 1984's Hatch-Waxman Act" as a jumping-off point to support its claims regarding the lack of a private right of action, noting: "In the Hatch-Waxman context, the Federal Circuit declined to create a private right of action where the statute did not explicitly provide one. Similarly, there is no evidence here that Congress intended to create a private right of action to enforce compliance with paragraph (2)(A) or paragraph (8)(A)."

BIOSIMILARS AT FDA

Biosimilar Application Activity at FDA

On March 6, 2015, FDA approved the first biosimilar application submitted under the 262(k) pathway for Sandoz's Zarxio®. Zarxio® is based on the reference product Neupogen® (filgrastim), and is a growth factor used to prevent infections in cancer patients receiving certain treatments that result in a decrease in infection-fighting white blood cells. FDA approved Zarxio® for all of the same indications for use as those approved for Neupogen®.[27]

Six other biosimilar applications are pending review before FDA:

- On August 8, 2014, Celltrion announced that FDA had accepted its application for a biosimilar version of infliximab that is based on the reference product Remicade®, a monoclonal antibody ("mAb") used to treat autoimmune disorders such as rheumatoid arthritis. In February 2015, FDA announced that it was postponing an advisory committee meeting for Celltrion's biosimilar version of infliximab because of pending information requests to the company. A future date has yet to be announced.

- Currently, there are two biosimilar applications pending before FDA relating to pegfilgrastim, the generic name for Amgen's blockbuster Neulasta®. Apotex announced the filing of its biosimilar application in December 2014, while Sandoz's application was accepted in November 2015.

- On February 13, 2015, Apotex announced the filing of its second biosimilar application that like Sandoz's biosimilar product is also based on Amgen's Neupogen®.

- In October 2015, FDA accepted Sandoz's 262(k) application for a biosimilar version of etanercept, which is based on Amgen's Enbrel® and is used to treat a range of autoimmune diseases including rheumatoid arthritis and psoriasis.

- Finally, Amgen submitted a biosimilar application based on the reference product Humira® (adalimumab) in November 2015. At the time of submission, Amgen believed this to be the first 262(k) application that had relied on Humira®, an anti-TNF-α mAb that is used for the treatment of various inflammatory diseases.

On October 16, 2015, FDA issued a complete response letter to Hospira for epoetin alfa, informing the company that its application could not be approved in its present form. Epotein alfa is based on Amgen's Epogen®, a protein-based therapeutic with glycosylation used to increase the production of red blood cells. According to Pfizer, the new parent company of Hospira, it intends to resubmit the biosimilar application during the first half of 2016.

Although the submission of biosimilar applications remains low, FDA has seen a modest uptick in interest in biosimilar product development through a variety of activities.[28] As a result, the agency continues to allocate increasing resources to its biosimilar review program.

As of July 31, 2015, sponsors of 57 proposed biosimilar products for 16 different reference products enrolled in FDA's Biosimilar Product Development (BPD) Program. The BPD Program was created as part of the Biosimilar User Fee Act of 2012 (BsUFA), and is intended to facilitate the collection of development user fees that, in turn, will support FDA's biosimilar review program. By joining the program and paying associated fees, FDA is subject to pre-specified performance goals and procedures for various review activities and interactions during development of the proposed biosimilar. Sponsors of an additional 27 proposed biosimilar products have had a Biosimilar Initial Advisory (BIA) Meeting with FDA, but have not yet joined the BPD Program.

Likewise, the number of development-phase meetings for proposed biosimilar products has increased since 2013. From fiscal year 2013 to 2014, the number of meeting requests increased 69% and the number of meetings actually scheduled increased 57%. According to the agency, "[b]ased on the current and projected workload analysis, FDA expects continued modest growth in the number of meetings requested and scheduled through Fiscal Year 2015." FDA also has seen a change in the type of meetings with the agency, with an increase in the number of interactions for specific issues relating to ongoing clinical development of proposed biosimilar products (e.g., discussions about study designs and endpoints). This development suggests that more and more companies undertaking clinical development of their respective proposed biosimilar products.

While staffing for the review of biosimilar applications remained unchanged at the end of 2014, the agency claims that it is "working to recruit additional staff and continues to allocate increasing resources for this critical regulatory review program."[29] So far, the full-time employee ("FTE") expenditure for the first two quarters of fiscal year 2015 was equivalent to the total expenditures for 2013 and 2014, respectively, which was about 70 FTEs per year.

As the BsUFA program matures and FDA gains greater experience with biosimilar applications filed under the 262(k) pathway, improved interactions with the agency and, thus deliverables, should follow.

FDA Guidances for Biosimilar Applications

As part of its ongoing implementation of the BPCIA in 2015, FDA finalized four guidance documents relating to biosimilar product development. Substantively, each of the final guidance documents is similar to its predecessor draft, with minimal changes. The more significant changes are discussed below. The agency also issued an additional "Q&A" draft guidance to provide greater clarity for sponsors interested in developing proposed biosimilars. To date, FDA has released a total of seven guidance documents in final or draft form, each of which is included in Appendix 1:

Final Guidance	Date Issued
Biosimilars: Questions and Answers Regarding Implementation of the Biologics Price Competition and Innovation Act of 2009	04/28/2015
Scientific Considerations in Demonstrating Biosimilarity to a Reference Product	04/28/2015
Quality Considerations in Demonstrating Biosimilarity to a Reference Protein Product	04/28/2015
Formal Meetings Between FDA and Biosimilar Biological Product Sponsors or Applicants	11/17/2015

Draft Guidance	Date Issued
Clinical Pharmacology Data to Support a Demonstration of Biosimilarity to a Reference Product	05/13/2014
Reference Product Exclusivity for Biological Products Filed Under Section 351(a) of the PHS Act	08/04/2014
Biosimilars: Additional Questions and Answers Regarding Implementation of the Biologics Price Competition and Innovation Act of 2009	05/12/2015

FDA also identified three additional guidance documents that it plans to publish in the future:

- Considerations in Demonstrating Interchangeability to a Reference Product
- Labeling for Biosimilar Biological Products
- Statistical Approaches to Evaluation of Analytical Similarity Data to Support a Demonstration of Biosimilarity

The following are summaries of the seven guidance documents published thus far:

1. **Biosimilars: Questions and Answers Regarding Implementation of the Biologics Price Competition and Innovation Act of 2009**

The final guidance continues to group questions and answers into three categories: (i) biosimilarity or interchangeability; (ii) provisions relating to the definition of a "biological product"; and (iii) exclusivity. Like the draft, the bulk of the final guidance focuses on demonstrating biosimilarity and whether certain differences preclude that outcome. For example, FDA maintains its positions that a proposed biosimilar can have a different formulation than the reference product; a proposed biosimilar can utilize a different delivery device than the reference product; and a proposed biosimilar can have fewer routes of administration, presentations (e.g., strengths), and conditions of use than the reference product.

The final guidance also discusses in detail the use of bridging studies for applicants who intend to rely on data for a non-U.S.-licensed product. In such instances, "the type of bridging data needed will always include data from analytical studies . . . that directly compare all three products (i.e., the proposed biosimilar product, the U.S.-licensed reference product, and the non-U.S.-licensed comparator product), and is likely to also include bridging clinical PK and/or PD study data for all three products." The final guidance also reaffirms FDA's general requirement for analytical studies and at least one clinical PK and (if needed) PD study between the proposed biosimilar and U.S.-licensed reference product. This guidance, however, offers an exception to that rule: "unless it can be scientifically justified that such a study is not needed." The agency concludes its discussion on bridging data with a number of issues that may impact the amount of data needed to permit reliance on bridging studies, such as the complexity of the products at issue and differences in formulation, dosage form, and strength between the U.S. and non-U.S.-licensed products.

FDA also expands its discussion on indication extrapolation, specifically noting that — for any differences found between conditions of use for the proposed biosimilar and reference products — "[a] scientific justification should address these differences in the context of the totality of evidence supporting a demonstration of biosimilarity." But in departing from the draft guidance, which was silent on the issue, FDA warns sponsors against seeking extrapolation for indications approved under FDA's accelerated-approval pathway when such condition has not been verified in post-marketing trials yet.

Finally, the final guidance omits five questions and answers that appeared in the prior draft document. These questions and answers were included in either revised or original form in the draft guidance discussed below, "Biosimilars: Additional Questions and Answers Regarding Implementation of the Biologics Price Competition and Innovation Act of 2009." This final guidance is available in Appendix 1.

2. Scientific Considerations in Demonstrating Biosimilarity to a Reference Product

In the final guidance, FDA reiterates its preference for a stepwise approach to develop the necessary data and information to demonstrate biosimilarity. Thus, where residual uncertainty exists about biosimilarity at a certain step, the sponsor should evaluate and "identify next steps to try to address that uncertainty." Notably, however, the agency opens the door to investigations conducted "in parallel," but continues to maintain that sponsors should incorporate FDA's advice after its review of data and information at various milestones.

When relying on data for non-U.S.-licensed products, FDA relaxes the general requirement for analytical studies and at least one clinical PK and (if needed) PD study with the U.S.-licensed reference product where "scientifically justified that such a study is not needed." Also, like the final Q&A guidance discussed above, the sponsor still should "provide adequate data or information to scientifically justify the relevance of this comparative data [i.e., between the proposed biosimilar and non-U.S.-licensed comparator product] to an assessment of biosimilarity and to establish an acceptable bridge to the U.S.-licensed reference product."

The final guidance also provides for extrapolation across indications so long as the sponsor provides "sufficient scientific justification for extrapolating clinical data to support a determination of biosimilarity for each condition of use" sought. In doing so, FDA recommends that the sponsor "consider choosing a condition of use that would be adequately sensitive to detect clinically meaningful differences between the two products."

FDA states that it will continue to assess the totality of the evidence provided by the sponsor when evaluating whether biosimilarity exists between the proposed biosimilar and reference products. This final guidance is available in Appendix 1.

3. Quality Considerations in Demonstrating Biosimilarity of a Therapeutic Protein Product to a Reference Product

This final guidance provides specific recommendations to sponsors about the scientific and technical information for inclusion in the chemistry, manufacturing, and controls (CMC) section of a 262(k) application. FDA reaffirms

its position that sponsors use "state-of-the-art technology" with "adequate sensitivity and specificity to detect and characterize differences between the proposed product and the reference product." Moreover, the agency encourages sponsors to submit comprehensive analytical similarity data early in the development process — e.g., the pre-IND stage and with the original IND submission — and at various subsequent milestones during development. Any observed structural and functional differences between the two products should be assessed and supported during investigations to the extent necessary. This final guidance is available in Appendix 1.

4. Formal Meetings Between FDA and Biosimilar Biological Product Sponsors or Applicants

This final guidance provides recommendations on formal meetings between FDA and biosimilar sponsors or applicants, and is intended to assist sponsors or applicants in generating and submitting a meeting request and subsequent meeting package to the agency. Five types of meetings can occur between the sponsor or applicant and FDA, each of which is briefly discussed below. Sponsors or applicants need not request meetings in sequential order, and the meeting type requested depends on the stage of the development program or advice being sought.

- Biosimilar Initial Advisory meeting: This meeting is an initial assessment limited to a general discussion about the feasibility of pursuing product approval under the 262(k) pathway and, if so, FDA's expectations for the development program.
- Type 1: This is a meeting to address an otherwise stalled development program — e.g., to discuss clinical holds.
- Type 2: This is a meeting to discuss either a specific issue (e.g., proposed study design or endpoints) or questions where FDA will provide targeted advice for an ongoing development program.
- Type 3: This meeting provides in-depth data review and advice regarding the ongoing development program. It may include a substantive review of full study reports or FDA advice on the similarity between the proposed biosimilar and the reference product based on a comprehensive data package.
- Type 4: This is a meeting to discuss the format and content of a 262(k) application or supplement.

Outside of the Biosimilar Initial Advisory meeting, the sponsor or applicant must be a participant in, and thus pay for access to, the Biological Product Development (BPD) Program. There are three types of fees for this program: an initial fee, an annual fee, and a reactivation fee. The initial fee is due at the earlier of the submission of an IND application for a proposed biosimilar product or within five days after FDA grants the sponsor's or applicant's request for a Type 1, 2, 3, or 4 meeting. This final guidance is available in Appendix 1.

5. Clinical Pharmacology Data to Support a Demonstration of Biosimilarity to a Reference Product (Draft)

This draft guidance builds on the 2012 guidance titled "Scientific Considerations in Demonstrating Biosimilarity to a Reference Product" to further describe the step-by-step process for showing that a proposed biosimilar is "highly similar" to a reference product. In particular, this guidance describes the role of clinical pharmacology data in a showing of biosimilarity. FDA states that in a stepwise assessment of biosimilarity, comparative structural and

functional studies should be performed to evaluate whether the proposed biosimilar product and the reference product are "highly similar." The analytical characterization "may reveal differences between the proposed biosimilar product and the reference product" and "lead to one of four assessments within a development-phase continuum":

- Not similar: Further development through the abbreviated biosimilar pathway is "not recommended."
- Similar: Additional analytical data or other studies are necessary. "Comparative PK and PD studies of the proposed biosimilar product and the reference product," for example, may "help resolve that some differences … would be within an acceptable range [so as] to consider the proposed biosimilar product to be highly similar to the reference product."
- Highly similar: "The results of the comparative analytical characterization permit high confidence in the analytical similarity of the proposed biosimilar and the reference product," and the sponsor may "conduct targeted and selective animal and/or clinical studies to resolve residual uncertainty and support a demonstration of biosimilarity."
- Highly similar with fingerprint-like similarity: "The results of these fingerprint-like analyses permit a very high level of confidence," and a sponsor may "use a more targeted and selective approach to conducting animal and/or clinical studies to resolve residual uncertainty and support a demonstration of biosimilarity."

The guidance also states that clinical pharmacology studies are "normally a critical part of demonstrating biosimilarity," and explains what type of pharmacokinetic and pharmacodynamic data should be collected. This draft guidance is available in Appendix 1.

6. Reference Product Exclusivity for Biological Products Field under Section 351(a) of the PHS Act (Draft)

Section 262(k)(7), entitled "Exclusivity for Reference Product," describes the reference product exclusivity period, which is the period of time in which a 262(k) sponsor is not permitted to submit, and FDA is not permitted to approve, a 262(k) application that references a reference product. Approval of an application for a biosimilar under 262(k) may not be made effective until the date that is 12 years after the date on which the reference product referred to in the 262(k) application was first approved under section 262(a). A 262(k) application may not be submitted to FDA for review until 4 years after the date of first approval of the reference product.

The BPCIA includes certain limits on 12-year exclusivity. In particular, the 12-year exclusivity period does not apply if the approval is for:

(i) a supplement for the biological product that is the reference product; or

(ii) a subsequent application filed by the same sponsor or manufacturer of the biological product that is the reference product (or a licensor, predecessor in interest, or other related entity) for –

(I) a change (not including a modification to the structure of the biological product) that results in a new indication, route of administration, dosing schedule, dosage form, delivery system, delivery device, or strength; or

(II) a modification to the structure of the biological product that does not result in a change in safety, purity, or potency.

This draft guidance is intended to help sponsors developing biological products, sponsors holding biologics license applications, and other interested parties in providing information and data that will help FDA determine the date of first licensure of a reference product under 262(k)(7). This draft guidance is available in Appendix 1.

7. Biosimilars: Additional Questions and Answers Regarding Implementation of the Biologics Price Competition and Innovation Act of 2009 (Draft)

In May 2015, FDA issued a new draft guidance that provides additional questions and answers to help clarify the agency's interpretation of the BPCIA. Although FDA styles the draft guidance as a "revision" of the original 2012 draft guidance, it includes a collection of new, old and revised questions and answers.

The draft guidance provides new information on how sponsors can comply with the requirements of the Pediatric Research Equity Act (PREA)[30] through the extrapolation of data, whether a separate IND is needed for the importation and use of a non-U.S.-licensed product in clinical trials in the U.S. (no), and the type of application needed for an antibody-drug conjugate (BLA). FDA also offers an interpretation of "dosage form" for injectable products that sponsors must demonstrate is the same as the reference product under the BPCIA. The agency considers the "dosage form" to be "the physical manifestation containing the active and inactive ingredients that delivers a dose of the drug product." Accordingly, based on the draft guidance, an "injection" (e.g., a solution) is a different dosage form than "for injection" (e.g., a lyophilized powder). FDA also regards emulsions and suspensions of products intended for injection as distinct dosage forms.

In an attempt to revive past yet unresolved issues, FDA restates prior questions and answers from the 2012 draft guidance — one of which touches on interchangeability. Like the prior version, FDA acknowledges that it can make a determination of interchangeability in the initial 262(k) application or any supplement thereto; but, in absence of further guidance from the agency, "it would be difficult as a scientific matter for a prospective biosimilar applicant to establish interchangeability" in an original application. FDA has stated that guidance on demonstrating interchangeability to a reference product is forthcoming.[31] The House Appropriations Committee has directed the agency to issue such guidance by November 30, 2015.[32]

And finally, the agency revises earlier questions and answers, clarifying its position on the retention of samples used in clinical investigations and the general lack of need for biosimilar applicants to conduct cardiac repolarization (QT/QTc) and drug-drug interaction studies. This draft guidance is available in Appendix 1.

Naming

The naming convention for biosimilars and the manner in which biosimilar names compare to reference product names are important issues with far-reaching implications. Generic small molecule products are automatically assigned the same nonproprietary name as the innovator product. Biosimilars have no clinically meaningful differences from the reference product in terms of safety, potency and purity. Approved biosimilars also have the same mechanism of action, route of administration, dosage form and strength as the reference product. But, due to the complex way in which biological products are manufactured, allowable differences exist between the biosimilar and the reference product. Since biosimilars are "highly similar," and not identical, to an FDA-approved biological reference product, a question exists as to whether a biosimilar and its reference product should have the same name, and, if not, how different the names should be. Significant policy arguments are offered on both sides of this issue.

FDA has weighed in on this issue, releasing a draft "Nonproprietary Naming of Biological Products" Guidance for Industry (Appendix 1). In its Guidance, FDA proposed naming reference products and biosimilars with:

- a nonproprietary name (proper name) that reflects certain scientific characteristics of the product, such as chemical structure and pharmacological properties;
- and a unique, hyphenated FDA-designated suffix.

The suffix would be composed of four lowercase letters that are devoid of meaning. For example, a biologic product would be named replicamab-cznm, while its biosimilar would be named replicamab-hixf. FDA Guidance at 8.

In its Guidance, FDA states that the proposed naming scheme seeks to: (1) help prevent inadvertent substitution of biological products that are not determined to be interchangeable by FDA, and (2) support safety monitoring of all biological products on the market, by making it easier to accurately track usage of biological products in all settings of care, such as outpatient, hospital and pharmacy settings.

Some members of the biosimilar community and government entities have objected to FDA's proposal on the grounds that it undermines competition from biosimilars. For example, the Federal Trade Commission (FTC) has argued that the proposed naming convention may confuse doctors and prevent the prescription of biosimilars. The FTC rejected FDA's proposed naming convention stating that: the naming proposal may increase product differentiation because "physicians may mistakenly believe that different suffixes indicate clinically meaningful differences between a biologic and its biosimilar," and that the perceived product differentiation will dampen price competition. The FTC points to the European example of Hospira's Retacrit epoetin zeta biosimilar for the proposition that biosimilars with distinct nonproprietary names are less commercially successful than those with the same nonproprietary names, and the FTC argues that FDA's proposal will create for pharmacists unnecessary coding and system inefficiencies and costs. To minimize these effects, the FTC suggested that "FDA consider pursuing physician education programs and testing how prescribers will react to its proposed nomenclature changes before implementing them." The FTC even recommended that FDA explore alternative methods, *i.e.*, the use of trade names, or FDA's Purple Book, for information about biologic products.

This issue has yet to be resolved, but because of its importance we expect significant activity and debate with respect to naming in the future.

Labeling

In the world of small molecule generic drugs approved under the Hatch-Waxman Act, FDA requires the filer of an Abbreviated New Drug Application to copy, essentially verbatim, the labeling of the reference listed drug.[33] While FDA has not yet issued any formal guidelines regarding biosimilar product labeling, its actions so far suggest that it will use a similar "same labeling" approach for biosimilars. For example, in a November 19, 2013 meeting with FDA, Sandoz asked to use "essentially the same" product labeling for its Zarxio® biosimilar as that used with Amgen's Neupogen® (filgrastim) product. FDA responded that the Neupogen® labeling was "a reasonable starting point" for Sandoz's submission. In February 2015, FDA provided the Neupogen® label to Sandoz for use "as a template" in developing its label, instructing Sandoz to track the changes made to the Neupogen® label. The next month, FDA approved Zarxio®, the first licensed biosimilar under the BPCIA, with a label that is nearly identical to that of the reference Neupogen® product.

Several innovators of biologic products have criticized the Hatch Waxman-like approach to labeling that FDA has taken with Zarxio®. These companies have challenged FDA for, among other things, not requiring biosimilar product labeling to state that the product is a biosimilar of, or interchangeable with, the reference product.

On June 2, 2015, AbbVie submitted a Citizen Petition requesting that FDA require that labeling for licensed biosimilar products contain:

(a) a clear statement that the product is a biosimilar, that the biosimilar is licensed for fewer than all the reference product's conditions of use (if applicable), and that the biosimilar's licensed conditions of use were based on extrapolation (if applicable);

(b) a clear statement that FDA has not determined that the biosimilar product is interchangeable with the reference product (if applicable); and

(c) a concise description of the pertinent data developed to support licensure of the biosimilar, along with information adequate to enable prescribers to distinguish data derived from studies of the biosimilar from data derived from studies of the reference product.[34]

AbbVie argues that the additional labeling requirements will provide more information for prescribers and "avoid potentially unsafe substitution of biosimilars and reference products."[35] According to AbbVie, without such information in the label, "biosimilar labeling will not reflect the unique licensure provisions established by the BPCIA and will be materially misleading in violation of the FDCA and FDA regulations."[36] AbbVie further argues that it would be "legally unsound" for FDA to adopt the "same labeling" approach that its uses in the context of generic drugs under the Hatch-Waxman Act because the BPCIA does not contain a corresponding "same labeling" provision and permitting biosimilars to be labeled as if they are "bioequivalent" would compromise public health and safety due to, for example, biosimilars having different immunogenicity profiles than their reference products.[37]

Amgen submitted a comment in support of AbbVie's Citizen Petition, "urg[ing] FDA to promulgate a labeling policy that begins with transparency, supports consumer confidence, and facilitates appropriate use."[38] Amgen's comment emphasized the importance of distinguishing between the concepts of "biosimilar" and "interchangeable" because "[w]hile both biosimilar and interchangeable products will be safe and effective options for patients, only interchangeable products will have been evaluated and deemed by FDA to be safe and effective for a patient to experience multiple switches."[39] According to Amgen, the biosimilarity or interchangeability status of a product needs to be specifically identified in the product labeling, as opposed to only in the Purple Book, because, unlike a pharmacist, prescribing physicians do not use the Orange Book and similarly will not use the Purple Book.[40] Amgen's comment also asks FDA to require information in the biosimilar label to aid physicians in understanding the similarities and differences between the biosimilar and reference products, including (a) an identification of the source of clinical data, and (b) clinical studies regarding the safety implications of transitioning patients from the reference product to the biosimilar when they are currently responding to the reference product.[41]

Genentech also submitted a comment to FDA in support of AbbVie.[42] In addition to the issues raised in AbbVie's petition, Genentech's comment asks FDA to require biosimilar product labeling to "describe the design of the key studies on which the biosimilarity determination was based and transparently identify the studied drug when describing clinical studies of the reference product sponsor."[43] Genentech further requests that "biosimilar and reference product labeling be updated independently over the products' life cycles, to reflect product-specific postmarket pharmacovigilance data as well as differences due to manufacturing changes."[44]

In opposition to AbbVie's petition, Sandoz submitted a comment to FDA arguing that, based on its extensive experience and discussions with FDA on the pertinent issues throughout the development of Zarxio®, the label format that FDA applied to Zarxio® "is appropriate and accurate for advising health care providers on how to use this product[,] [a]nd … should be the basis for U.S. labels for future biosimilars."[45] According to Sandoz, "[a]ll biologics, including biosimilars, approved by FDA are safe, pure and potent for their conditions of use and must be so labelled, and consequently the label for Zarxio® must match that of its reference product Neupogen®."[46]

Momenta, another developer of biosimilar products, also submitted comments opposing AbbVie's petition.[47] According to Momenta, AbbVie's insistence that biosimilar products be labeled differently than their reference products is designed to "create barriers to the development and commercialization of biosimilars and interchangeable biologics," and "turns the BPCIA on its head" because "[t]here is nothing in the BPCIA that supports the message that biosimilars are clinically different from the reference biologic."[48] Instead, Momenta asks FDA to adopt a case-by-case approach to product labeling: "The rational approach, we believe, is for FDA to do what Congress intended – review the science in each application, ask the applicant to propose labeling based on the science in its application, and depending on the application and the product in question, consider whether the product should or should not have the same labeling as the reference product."[49]

As of the publication date of this guide, FDA has yet to respond substantively to AbbVie's Citizen Petition. On September 17, 2015, Janet Woodcock, M.D., the director of FDA's Center for Drug Evaluation and Research, testified to a congressional hearing that FDA is actively working on establishing labeling guidelines, but could not commit to a date by which FDA would publish them. On December 1, 2015, FDA issued a one-page letter to AbbVie, stating that the "FDA has been unable to reach a decision on your petition because it raises complex issues requiring extensive review and analysis by Agency officials."

Citizen Petition Activity

The advent of biosimilars has spurred members of the biological industry to submit citizen petitions on issues raised by the biosimilar applications and related statutes and regulations.

FDA released its "Citizen Petitions and Petitions for Stay of Action Subject to Section 505(q) of the Federal Food, Drug, and Cosmetic Act [FD&C Act]" Guidance for Industry in November 2014 (Appendix 1). The guidance seeks to address FDA's approach to determining (1) if the provisions of section 505(q) apply to a certain citizen petitions, and (2) if a petition would delay approval of a pending abbreviated new drug application (ANDA), 505(b)(2) application, or biosimilar application.

In its guidance, FDA confirmed that the scope of citizen petition activity related to biosimilars was governed by Section 505(q) of the Federal Food, Drug, and Cosmetic Act. The general scope of section 505(q) can be summarized by reference to section 505(q)(1)(A), which provides:

> The Secretary shall not delay approval of a pending application submitted under subsection (b)(2) or (j) of this section or section 351(k) of the Public Health Service Act because of any request to take any form of action relating to the application, either before or during consideration of the request, unless–
>
> > (i) the request is in writing and is a petition submitted to the Secretary pursuant to section 10.30 or 10.35 of title 21, Code of Federal Regulations (or any successor regulations); and
> >
> > (ii) the Secretary determines, upon reviewing the petition, that a delay is necessary to protect the public health.

Here, we outline the citizen petitions that have been filed to date on biosimilar issues, and the way that FDA has addressed them.

Prior to the guidance being released, several citizen petitions regarding the legality and practicality of a biosimilars pathway were filed. For example, Genentech, relying on the idea that the manufacture of biological products is intertwined with confidential or trade secret processes, requested that FDA refrain from (1) publishing a draft guidance document setting forth standards for so-called follow-on or generic biotechnology-derived products, and (2) approving an application filed under section 505(b)(2) of the FD&C with respect to a biotechnology product that relies on trade secret and confidential commercial data and information of an innovator. FDA denied Genentech's request, stating that issuing a guidance on the standards of similarity would be within its authority and mandate to protect the public health.

In the event that FDA decided to issue a guidance on standards of similarity for biological products, Genentech also requested that FDA provide advance notice and a pre-deprivation hearing, arguing that the issuance of such a guidance would deprive Genentech of its property (i.e., trade secret or confidential information) relating to biological

products (in other words, a takings). FDA also denied this request stating, "FDA's Biosimilars Guidances do not implicate, disclose, or rely upon Genentech's (or any other company's) confidential commercial or trade secret information."

Biotechnology Industry Organization (BIO) submitted a related but narrower request – that FDA refrain from preparing, publishing, circulating or issuing any new guidance for industry, whether in draft or final form, concerning follow-on applications for therapeutic proteins, particularly human growth hormone or insulin, under a section 505(b)(2) of the FD&C Act. FDA denied BIO's requests for related reasons.

Several citizens' petitions centered on naming biosimilars have also been denied. This issue is still subject to ongoing debate, as discussed in the naming section above.

More recently, Amgen filed a citizen petition requesting that FDA accept applications under the abbreviated pathway only if the applicants first certify that they will comply with the patent dance provisions. Specifically, Amgen requested FDA to require biosimilar applicants – before their applications are accepted for review by FDA – to certify to FDA that they will comply with PHS Act § 351(l)(2)(A) by providing the reference product sponsor with a copy of the 351(k) application "and such other information that describes the process or processes used to manufacture the biological product that is the subject of such application" within 20 days after FDA informs the biosimilar applicant that its 351(k) application has been accepted for review. FDA declined to require the certification requested by Amgen, reasoning that unlike with the Hatch-Waxman Act Section 505(b), "[n]either section 351(k) nor section 351(1) requires FDA to impose a certification requirement as part of the biosimilar review process." FDA characterized the patent dance procedures as "parallel to, but separate from, FDA review process," noting that the BPCIA "generally does not describe any FDA involvement in monitoring or enforcing the information exchange by creating a certification process or otherwise."

AbbVie also filed a citizen petition on the issue of similarity of biosimilars labeling. As of the date of this publication, FDA has only responded with a one-page letter explaining that FDA has not yet been able to reach a decision on the petition because it raises "complex issues requiring extensive review." For further information, see the labeling section above.

FDA Is Easing Burden for Sponsors with Biosimilar Approvals from the EMA

FDA's guidance documents leave some unanswered questions about how applicants may establish biosimilarity. FDA has indicated that it is looking at the approach taken by the European Medicines Agency (EMA), which has approved 22 biosimilar products to date, and has released several product-specific guidance documents. These documents include guidances on similar biological medicinal products, on similar biological medicinal products containing biotechnology-derived proteins as active substances, on similar biological medicinal products containing monoclonal antibodies, and on non-clinical and clinical development of similar biological medicinal products containing low-molecular-weight heparins. FDA stated that it has "worked to ease the burden for sponsors of proposed biosimilar products that have previously been approved outside the United States, such as in the

European Union, to develop their proposed biosimilar products for the U.S. market."[50] Specifically, FDA sought to address the potential barrier to development that results from the BCPIA's requirement to demonstrate biosimilarity to a U.S.-licensed reference product.[51] To address this issue in a "scientifically rigorous manner", FDA issued "guidance describing the use of a non-U.S.-licensed comparator in certain studies based on an adequate scientific bridge between the U.S.-licensed reference product and a non-U.S.-licensed comparator product."[52]

As discussed in more detail above, under FDA's guidance, "a sponsor may use a non-U.S.-licensed comparator product in certain studies to support a demonstration that the proposed biological product is biosimilar to the U.S.-licensed reference product."[53] However, FDA states that "as a scientific matter, analytical studies and at least one clinical pharmacokinetic (PK) study and, if appropriate, at least one pharmacodynamic (PD) study, intended to support a demonstration of biosimilarity must include an adequate comparison of the proposed biosimilar product directly with the U.S.-licensed reference product unless it can be scientifically justified that such a study is not needed."[54] Moreover, FDA states, "the type of bridging data needed will always include data from analytical studies (e.g., structural and functional data) that directly compare all three products (i.e., the proposed biosimilar product, the U.S.-licensed reference product, and the non-U.S.-licensed comparator product), and is likely to also include bridging clinical PK and/or PD study data for all three products."[55] FDA intends to evaluate the acceptability of a "non-U.S.-licensed comparator product "on a case-by-case basis", and will make a "final determination about the adequacy of the scientific justification and bridge . . . during the review of the application."[55]

FDA Likely to Require Substantial Clinical Data for "Interchangeable" Biosimilars

A "biosimilar" product has no clinically meaningful difference from "the safety, purity and potency" of its reference product, and "[i]s highly similar [thereto] notwithstanding minor differences in clinically inactive components."[57] An "interchangeable" biosimilar product, on the other hand, is one that "can be expected to produce the same clinical result as the reference product in any given patient[.]"[58] If a biologic is intended to be administered more than once to a patient, interchangeability requires that switching between the reference product and the biosimilar presents no greater risk in terms of safety or diminished efficacy than continued use of the reference product.[59]

One important distinction between these two classes of biosimilars is that FDA will almost certainly require clinical data in order to demonstrate interchangeability. Although no such requirement appears in the statute— the Patient Protection and Affordable Care Act passed in 2010 does not mention clinical studies—comments made by FDA have indicated that this is a very real possibility.

Indeed, how to demonstrate interchangeability remains very much unclear. In draft guidance issued in May 2015, FDA stated that "[a]t this time, it would be difficult as a scientific matter for a prospective biosimilar applicant to establish interchangeability in an original 351(k) application given the statutory standard for interchangeability and the sequential nature of that assessment. FDA is continuing to consider the type of information sufficient to enable FDA to determine that a biological product is interchangeable with the reference product."[60] The agency indicates that guidance on interchangeability is currently under development, with one Congressional committee directing the agency to issue such guidance by November 30, 2015.[61]

Because clinical testing is both time-consuming and expensive, any such requirement may tend to erode the incentives for pursuing a biosimilar pathway in the first place. Indeed, as U.S.-based Hospira has observed, expensive clinical trials may mean a "far smaller" interchangeability pipeline: "It's going to cost us anywhere from $70 to $250 million per drug to do it."[62]

Nonetheless, requiring clinical data could offer some potential upsides to manufacturers of interchangeables. For instance, clinical data may help convince prescribing physicians and patients to accept biosimilars. Interchangeability may also lead to automatic substitution at the pharmacy level, which has the potential to drive market uptake in a manner similar to small molecule generic drug products.

REGULATION OF BIOSIMILARS OUTSIDE OF THE U.S.

The regulation of biosimilars outside the United States continues to evolve, as jurisdictions which have approval pathways evaluate current guidances and determine whether changes need to be made to improve access to biosimilars, while other jurisdictions are adopting new regulations to permit such approval pathways.

Exclusivity Under the Trans-Pacific Partnership Agreement (TPP)

One of the most significant developments in the past six months is the completion of the negotiation of the Trans-Pacific Partnership Agreement (TPP), a free trade agreement between several pacific countries concerning a variety of matters, including intellectual property and pharmaceutical products. On June 23, 2015, the U.S. Senate authorized President Obama to negotiate the TPP on a "fast-track" basis. Negotiations over TPP had been taking place since 2008, and escalated in the past year. In addition to the United States, Brunei, Chile, Singapore, New Zealand, Australia, Canada, Japan, Malaysia, Mexico, Peru, and Vietnam participated in the TPP negotiations, and other countries, such as Taiwan, Korea, Columbia, and the Philippines, have expressed an interest in joining the negotiations and the trade agreement. The TPP will become the largest free trade zone, linking 40% of the world's economy.

One of the most controversial aspects of the trade negotiations had been the exclusivity period for biologics. The United States has a 12-year exclusivity for new biologics, which resulted following much debate and negotiations between different constituents in Congress regarding the duration of exclusivity for these molecules. Many other countries in the TPP, however, provide five years of data protection for new biologics, which is the same amount of time provided in those countries for new pharmaceutical products containing small molecules.

Agreement on the TPP was reached on October 5, 2015, and on November 5, 2015, President Barack Obama notified Congress of his intention to sign the TPP, as required under the bill authorizing fast-track negotiation. The text of TPP has also now become available (https://ustr.gov/trade-agreements/free-trade-agreements/trans-pacific-partnership/tpp-full-text).

According to "**Article 18.52: Biologics**" of the TPP, the party-signatories are required to enact measures providing for exclusivity over biological products for at least eight years unless a party-signatory enacts "other measures", in view of its recognition of market considerations providing for protection, but maintains at least five years of exclusivity. This section of the article states in part:

> (a) with respect to the first marketing approval in a Party of a new pharmaceutical product that is or contains a biologic, 60, 61 provide effective market protection through the implementation of Article 18.50.1 (Protection of Undisclosed Test or Other Data) and Article 18.50.3, mutatis mutandis, for a period of at least eight years from the date of first marketing approval of that product in that Party; or, alternatively,
>
> (b) with respect to the first marketing approval in a Party of a new pharmaceutical product that is or contains a biologic, provide effective market protection:

(i) through the implementation of Article 18.50.1 (Protection of Undisclosed Test or Other Data) and Article 18.50.3, mutatis mutandis, for a period of at least five years from the date of first marketing approval of that product in that Party,

(ii) through other measures, and

(iii) recognising that market circumstances also contribute to effective market protection

This language, likely the result of a compromise among the negotiating parties, permits countries to enact laws providing for less biologics exclusivity than in the U.S. market, which has 12 years of exclusivity for biologics. Each party-signatory has one of two options: (1) enact measures that provide for a period of at least eight years from the date of first marketing approval, or (2) enact measures providing for a period of at least five years from the date of first marketing approval as well as providing protection through "other measures" and "recognizing that market circumstances also contribute to effective market protection." In the U.S., therefore, the 12-year exclusivity period satisfies TPP's requirements. It remains to be seen how the other party-signatories implement these options, particularly those countries that currently have less than an eight-year exclusivity period for biologics such as Australia, New Zealand and Mexico. This provision of TPP may also be a focus of debate in Congress during the ratification procedure, which is believed to take place in 2016. Article 18 of TPP, which governs Intellectual Property issues, can be found in Appendix 1.

Europe

Since as early as January 2001, the European Union has focused on the development of a less expensive, abbreviated pathway for the regulatory approval of comparable protein-like drugs. At that time, a working group discussed the comparability of such biological products. In 2003, the European Commission amended the provisions of EU legislation setting forth requirements for marketing authorization of applications for medicinal products and created a category of applications for "similar" biological medicinal products. Finally, in 2005, the European Medicines Agency (EMA) issued a general guideline on similar biological products that set forth guidelines for the introduction of similar biological medicinal products and detailed the basic principles to be applied for approval. The EMA approved its first biosimilar in 2006 and, to date, has approved 20 biological products using this abbreviated biosimilar pathway, and refused marketing authorization for at least one product (Alpheon), which showed unacceptable differences from the reference medicinal product in impurity, side effects, and stability properties.

In 2014, the EMA adopted its revised "Guideline on similar biological medicinal products containing biotechnology-derived proteins as active substance: quality issues (revision 1)" and "Guideline on similar biological medicinal products." As outlined in the Guidelines, a company may develop a new biological medicinal product claimed to be similar (similar biological medicinal product) in terms of quality, safety, efficacy and biological activity to a reference medicinal product that has been granted a marketing authorization on the basis of a complete dossier in the European Union. "The development of a similar biological medicinal product (biosimilar) relies in part on

the scientific knowledge gained from the reference medicinal product, provided that the active substance of the biosimilar has been demonstrated to be similar, in physicochemical and biological terms, to the active substance of the reference medicinal product."

The EMA Guidelines make clear that a comparison of the biosimilar to a publicly available standard, such as a pharmacopoeial monograph, is insufficient for the purpose of demonstrating comparability and a complete characterization must be performed on the basis of a reference medicinal product that has been approved in the European Community. "Consequently, an extensive comparability exercise with the chosen reference medicinal product will be required to demonstrate that the biosimilar product has a similar profile in terms of quality, safety and efficacy to the reference medicinal product." The applicant must submit sufficient data such that "firm conclusions" on the physicochemical and biological similarity can be made.

Documentation for biosimilar products should capture two distinct aspects of the medicinal product. First, the molecular characteristics and quality attributes (QA) of the target product profile should be comparable to the reference medicinal product. Second, the documentation must demonstrate the performance and consistency of the manufacturing process of the biosimilar on its own.

The quality target product profile (QTPP) of a biosimilar should be based on obtained information about the chosen reference medicinal product, including publicly available information and data obtained from extensive characterization of the reference medicinal product. The QTPP should form the basis for the development of the biosimilar product and its manufacturing process. The manufacturing process must be carefully developed to achieve the QTTP.

The formulation of the biosimilar should be selected taking into account state-of-the-art technology and need not be identical to that of the reference medicinal product. The suitability of the proposed formulation should be demonstrated with regard to:

- stability;
- compatibility (i.e. interaction with excipients, diluents and packaging materials);
- integrity, activity and strength of the active substance.

The Guidelines advise that the quality level of the reference medicinal product must be clearly identified (e.g. brand name, pharmaceutical form, formulation, strength, origin of the reference medicinal product, number of batches, lot number, age of batches, use), and that multiple batches of the reference medicinal product should be used for characterization.

The applicant must demonstrate that the biosimilar product and the reference medicinal product are similar at the level of the finished medicinal product.

> It is not expected that all quality attributes of the biosimilar product will be identical to the reference medicinal product. However, where qualitative and/or quantitative differences are detected, such differences should be justified and, where relevant, demonstrated to have no impact on the clinical performance of the product. This may include additional non-clinical and/or clinical data, as outlined in the Guideline on similar biological medicinal products, as well as in the Guideline on similar biological medicinal products containing biotechnology-derived proteins as active substance: non-clinical and clinical issues. Particular attention should be given to quality attributes that might have an impact on immunogenicity or potency, or that have not been identified in the reference medicinal product. (EMA/CHMP/BWP/247713/2012)

Quantitative ranges must be established, and those ranges should not be wider than the range of variability of the representative reference medicinal product batches, unless otherwise justified.

Analytical characterizations studies must be selected to demonstrate that the biosimilar is comparable to the reference medicinal product, and that the selected methods would be capable of detecting slight differences in quality between the products, should they exist.

Other characteristics that must be established include:

- A **physicochemical characterization** that includes a determination of the composition, physical properties, primary and higher order structures of the biosimilar, and the presence and extent of post-translational modifications (e.g. glycosylation, oxidation, deamidation, truncation) should be appropriately characterized.
- **Biological activity**, i.e., the specific ability or capacity of the product to achieve a defined biological effect, must be carefully studied and completely characterized.
- The **immunochemical properties**, including the immunological functions of monoclonal antibodies and related substances (e.g. fusion proteins based on IgG Fc), should be fully compared.
- The **purity** and **impurity profiles** of the biosimilar and the reference medicinal product should be compared both qualitatively and quantitatively by a combination of analytical procedures.

In January 2015, EMA published a final version of its "Guideline on similar biological medicinal products containing biotechnology-derived proteins as active substance: non-clinical and clinical issues." This Guideline became effective in July 2015.

As the title suggests, the Guideline outlines non-clinical and clinical requirements for, among other things, the design of non-clinical studies, the use of pharmacodynamics markers, clinical-trial design and the potential use for surrogate and clinical endpoints in efficacy trials, the design of immunogenicity studies, and data extrapolation. The complexity of the reference product will dictate the scope and rigor of the non-clinical and clinical studies needed to support biosimilarity. And, as with guidance from the U.S., EMA recommends a stepwise approach to assess similarities and differences between the two products throughout development.

Extrapolation is available if the sponsor has demonstrated biosimilarity in at least one therapeutic indication, but it will need to be scientifically justified and will be considered in light of the totality of data (i.e., quality, non-clinical, and clinical). If the data demonstrate that safety and efficacy in one indication may not be relevant for another, the sponsor will need to provide additional data. Moreover, the Guideline suggests additional data will be required in other situations, such as:

- The active substance of the reference product interacts with several receptors that may have a different impact in the tested and non-tested therapeutic indications.
- The active substance itself has more than one active site and the sites may have a different impact in different therapeutic indications.

The sponsor also will need to scientifically justify extrapolation of immunogenicity from the studied indication to other uses of the reference product given the interplay between immunogenicity and multiple factors, including patient- and disease-related issues.

India

In 2012, the Central Drugs Standard Control Organization's Department of Biotechnology published its "Guidelines on Similar Biologics: Regulatory Requirements for Marketing Authorizations in India." [Appendix 3]. This document "lays down the regulatory pathway for a similar biologic claiming to be similar to an already authorized reference biologic."

Prior to the publication of the Guideline, the CDSCO, working with the Review Committee on Genetic Manipulation (RCGM), had approved "similar biologics" under an *ad hoc*, case-by-case approach that sought to address the nation's acute need for access to cost-effective biologics in a scientifically rigorous but relatively speedy manner.

The Guideline sets forth a framework in which the applicant must demonstrate similarity to an already approved innovator reference product via a comparative assessment of safety, efficacy and quality. Similar biologics that demonstrate sufficient comparability may qualify for reduced pre-clinical and/or clinical data packages. Interestingly, the reference product need not be marketed in India. If it has not been marketed in India, the innovator product must have been licensed and "widely marketed" for at least four years in a country with a "well established regulatory framework." The dosage form, strength and route of administration should be the same.

The analytical methods used to determine comparability must do so with respect to "critical quality attributes" of the product, and it is "customary to use multiple, orthogonal methods." "Extensive state of the art analytical methods should be applied to detect even "slight differences" in all relevant quality attributes", and be performed in accord with ICH guidelines and Indian Pharmacopoeia Monographs, as applicable. Such studies should address physicochemical properties, biological activity, immunological properties, functional assays, purity, contamination, strength and content.

Clinical trials should be sufficient to establish comparability to the reference biologic when manufactured at the clinical scale. Comparative, parallel-arm or crossover pharmacokinetic and pharmacodynamic studies should be conducted to establish the relative pharmacokinetics, safety and efficacy between the similar and reference biologics. Extrapolation of efficacy and safety data to other indications approved for the reference product is permitted.

Japan

In 2009, the Japanese Pharmaceuticals and Medical Devices Agency (PMDA) issued its "Guidelines For the Quality, Safety and Efficacy of Follow-On Biological Medicinal Products." [See Appendix 3 for English translation]. In it, the PMDA set forth guidelines that should be considered in developing "follow-on biological medicinal products" (FOBMPs). The PMDA may approve FOBMPs only after (1) all patent protection for the reference biologic product (RBP) has expired, and (2) the re-examination period for the RBP has elapsed, and thus the marketing and clinical experiences for the RBP have been established for a sufficient period of time.

A FOBMP is a product with quality attributes that may not be completely the same as the RBP, but nevertheless are highly similar to those of the RBP. Any differences have been "scientifically considered" to have no adverse impact on the safety or efficacy of the final product.

The RBP must be a product approved in Japan. Comparability should be established using clinical and non-clinical data, and should be conducted in accord with the ICH Q5E guideline "Comparability of Biotechnological/Biological Products Subject to Changes In Their Manufacturing Process." These include physicochemical studies, bioactivity assays, and non-clinical/clinical data. Comparability studies should be conducted with both the FOBMP and the RBP if possible, but may be conducted with the RBP alone if the FOBMP is not available. Literature information and other published data about the RBP may be used where available.

Characterization of the FOBMP should analyze structure/composition, physicochemical properties, biological activities, immunochemical properties, and impurities using up-to-date techniques. Product- and process-related impurities should be assessed.

Safety in humans should be confirmed before clinical trials are commenced, including toxicity studies. Clinical studies to establish the pharmacokinetics (PK) and pharmacodynamics (PD) should be conducted, as well as PK/PD analyses conducted. Where PD markers reflecting the clinical efficacy of the product have been identified, the comparison of PD markers may be useful. Where comparable clinical efficacy cannot be confirmed based on PK, PD and PK/PD studies, clinical studies should be performed to confirm comparable clinical efficacy for the intended indication. Extrapolation to other indications approved for the RBP is permitted when the pharmacological action for other indications is expected to be similar. Clinical studies establishing safety, including immunogenicity, will usually be needed.

Korea

In 2009, the Korean Food and Drug Administration issued the "Guidelines On the Evaluation of Biosimilar Products," which was developed in consultation with the WHO [Appendix 3].

No regulation in Korea prevents an application for a biosimilar from being filed or approved at any time after an innovator's product has been approved, but the six-year "re-examination" period that is usual in Korea, in which post-approval data are developed to assess the safety and efficacy of the innovator product, may as a practical matter ensure market exclusivity for at least six years.

The definition of a biosimilar in Korea is a biologic that has been proven to be "comparable" to an already approved reference product via quality, non-clinical and clinical studies. The reference product must be one that has already been approved in Korea based on a full regulatory dossier. The dosage form, strength and route of administration should be the same as the reference product.

A reduction in the non-clinical and clinical data needed for approval of a biologic may only be had after a comprehensive characterization and comparison at the quality level provides a basis for such a reduction. That characterization should include extensive side-by-side characterization of physicochemical properties (including immunochemical properties), biological activity, impurities and stability, and should be established using state-of-the-art analytical techniques capable of detecting slight differences in quality attributes.

Minor structural differences and differences in impurities may be acceptable but must be justified.

Comparative clinical trials to establish clinical efficacy, safety and pharmacokinetics are required. Trials to establish clinical equivalence are preferred.

A final determination of "comparability" will be based on a combination of quality, clinical and non-clinical evaluations. The dossier for a biosimilar must contain the full measure of quality data required for a biologic, plus comparability data. The non-clinical and clinical data may be reduced if comparability data justify a reduction.

Extrapolation to other indications approved for the reference drug may be permitted if scientifically justified.

China

In February 2015, the China Food and Drug Administration (CFDA) issued "Technical Guideline for Development and Evaluation of Biosimilars (Interim)," the country's first final guidance on the development of biosimilars. Effective immediately, the final guideline according to CFDA seeks to "guide and standardize the development and evaluation of biosimilars and promote the sound development of biomedicine industry."[63]

The guideline offers broad principles relating to, among other issues, the approval pathway for biosimilars, criteria for establishing biosimilarity, and considerations for sampling and comparative research. Generally, the guideline follows positions previously established by the agency's U.S. and European counterparts, such as proposing a stepwise approach for development and requiring a structural and functional analysis along with nonclinical and clinical data to support biosimilarity. The amount of data needed to demonstrate biosimilarity will depend on the differences, and extent of differences, between the proposed and reference products. Significantly, the sponsor of a proposed biosimilar cannot rely on a reference product, unless that product is approved in China at the time clinical trials are initiated.

OTHER RECENT LEGAL DEVELOPMENTS THAT MAY IMPACT BIOSIMILARS

As previously discussed, the legal and regulatory frameworks specific to biosimilars continue to evolve. The courts also have handed down a few general decisions on induced infringement and the statutory safe harbor of 35 U.S.C. § 271(e)(1) that will prove to be important in biosimilars litigation. Each of these legal developments is discussed below.

Recent Case Law on Induced Infringement and Pharmaceutical Patents

One area that has been the focus of decisional law is inducement of infringement for pharmaceutical patents claiming methods of use or treatment. In *Takeda Pharmaceuticals U.S.A., Inc. v. West-Ward Pharmaceutical Corp.*, 785 F.3d 625 (Fed. Cir. 2015), the Federal Circuit held that off-label uses of a drug cannot be the predicate for induced infringement absent some active encouragement by the seller to use the drug in the off-label, patented, manner. In *Takeda*, the Federal Circuit affirmed the district court's denial of a motion for preliminary injunction that Takeda had sought to prevent West-Ward from the launch and sale of a colchicine product to treat gout. Colchicine is a drug that has been used for centuries to treat gout. Takeda owns patents on specific methods of the use of colchicine to treat acute gout flares, and had approval from FDA to sell its colchicine product, Colcrys, for the treatment and prophylaxis of gout flares. West-Ward later received approval from FDA to sell its colchicine product, Mitigare, for the prophylaxis of gout flares. West-Ward did not file a paragraph IV certification regarding Takeda's patents because its label did not include the indication for the treatment of acute gout flares, and therefore, according to West-Ward, Mitigare did not infringe Takeda's patents. Takeda, however, moved the district court for a preliminary injunction, asserting that doctors would prescribe Mitigare not only for the prophylaxis of gout flares, the only indication included in its label, but also for the treatment of gout flares, and, therefore, West-Ward would be liable for induced infringement. The district court denied the motion because it found that Takeda had not met its burden of establishing a likelihood of induced infringement.

The Court of Appeals for the Federal Circuit affirmed the district court decision, explaining that inducement can only be found where there is "evidence of active steps taken to encourage direct infringement which can in turn be found in advertising an infringing use or instructing how to engage in an infringing use." Furthermore, the Court of Appeals held that West-Ward's knowledge of "possible infringement by others does not amount to inducement; specific intent and action to induce infringement must be proven." Because Mitigare's label did not include an indication for the treatment of gout flares, the Court of Appeals held that Takeda had not met its burden to establish a probability of success on the issue of infringement.

Another development in the law of induced infringement came from the U.S. Supreme Court's decision in *Limelight Networks, Inc. v. Akamai Techs.*, Inc., 134 S. Ct. 2111 (2014). In its decision, the Supreme Court reversed an *en banc* decision of the Federal Circuit and held that for direct infringement to occur and act as the basis for a finding of induced infringement, "performance of all of the claimed steps [must] be attributed to a single person." The Federal Circuit, further addressing the issue on remand, explained that a court should hold a single entity responsible for others' performance of method steps such that the complete performance of the method constitutes direct infringement under two circumstances: (1) where that entity directs or control others' performance, including when an alleged infringer conditions participation in an activity or receipt of a benefit upon performance of a step or steps of a patented method and establishes the manner or timing of that performance; and (2) where the actors form a joint enterprise.

The impact of that decision on the induced infringement of pharmaceutical method use or treatment patents is currently being litigated in the district courts. In *Eli Lilly and Co. v. Teva Parenteral Medicine, Inc.*,[64] the District Court for the Southern District of Indiana, applying the *en banc* decision in *Akamai*, held that a patent to a method of use of a drug that included a patient's self-administration of folic acid followed by a doctor's administration of premexetred, a chemotherapeutic agent, to that patient is directly infringed when a patient performs the first step (self-administration of folic acid) and a doctor performs the second step (administration of premexetred to the patient). This case is on appeal and the decision in this case could have an impact on biosimilars.

As biologic drugs become more prevalent, and new uses for existing drugs are discovered, patents covering their use for new methods of treatment will likely play an important role in protecting these drugs. The law of induced infringement described above is therefore important to keep in mind while drafting patents for methods of use of biologics. First, as the Federal Circuit held in *Takeda*, a potential infringer may escape liability simply by including only non-patented uses on its label, even if the drug is commonly used for other, patented uses. This may limit the value of method of use patents for drug that are used for more than one indication.

Recent Case Law Affecting the Statutory Safe Harbor

The patent laws provide a safe harbor that exempts certain activities from constituting infringement: "[i]t shall not be an act of infringement to make, use, offer to sell, or sell within the United States…a patented invention…solely for uses reasonably related to the development and submission of information under a Federal law which regulates the manufacture, use or sale of drugs...." 35 U.S.C. § 271(e)(1). This safe harbor is often invoked by generic manufacturers to defend against claims of patent infringement attributable to activities related to filing an ANDA. The courts have recently given further definition to the types and timing of activities that are within this safe harbor.

In *Momenta Pharmaceuticals, Inc. v. Teva Pharmaceuticals USA, Inc.*, 2015 WL 6875186 (Fed. Cir. Nov. 10, 2015). Momenta accused two generic companies, Teva and Amphastar, of infringing its patents that claimed methods for analyzing a product by filing ANDAs with FDA. Teva's proposed generic product was both tested and manufactured by a third party outside of the United States. Momenta sued Teva under 35 U.S.C. § 271(g) for selling a drug in the United States that Momenta alleged was "made by" a patented process outside of the United States. The Court held that Teva did not infringe because the patent only claimed "analyzing" the product. Because "analyzing" is not "making," Teva's testing of the product, even if within the scope of the patent, is not infringement under section 271(g), the only statutory section that applies to activity outside the United States. Unlike Teva's proposed product, Amphastar's proposed generic product was manufactured and tested within the United States. Amphastar attempted to rely on the 35 U.S.C. § 271(e)(1) safe harbor to shield it from infringement. The Court held that the testing patented by Momenta and done by Amphastar was required by FDA as a routine, quality control step of the bulk manufacture of the product, and is therefore not covered by the safe harbor of section 271(e)(1).

In another case, *Shire LLC v. Amneal Pharmaceuticals, LLC*, 802 F.3d 1301 (Fed. Cir. Sept. 24, 2015), the Federal Circuit considered both induced infringement and the statutory safe harbor. In *Shire*, a third party, Johnson Matthey Pharmaceuticals, provided the active pharmaceutical ingredient (API) to the ANDA-filer for batches of its product that were tested to comply with FDA testing requirements for an ANDA. Johnson Matthey was also listed in the ANDA as the supplier of the API for commercial batches of the proposed ANDA product. Shire sued Johnson Matthey for induced infringement both for providing the API for the test batches and for the future provision of API for the commercial batches. The Court held that (1) the statutory safe harbor applied to Johnson Matthey's contribution to the test batches, and (2) Johnson Matthey could not be sued for future activities as it was not the ANDA holder.

ENDNOTES

1. Source: Global Biosimilars Market 2015-2025 from Roots Analysis

2. The Biologics Price Competition and Innovation Act ("BPCIA") amended § 351 of the Public Health Services Act to create the § 351(k) biosimilar approval pathway. That provision is codified at 42 U.S.C. § 262(k). Although this guide refers to the biosimilar application as a 262(k) application, and the applicant as a 262(k) applicant, they are sometimes referred to another materials as a 351(k) application and a 351(k) applicant, respectively.

3. http://www.fda.gov/NewsEvents/Newsroom/PressAnnouncements/ucm436648.htm

4. http://www.fda.gov/NewsEvents/Newsroom/PressAnnouncements/ucm436648.htm

5. *Id.*

6. http://www.apotex.com/global/about/press/20150217-2.asp

7. http://www.law360.com/articles/610321/hospira-joins-biosimilars-race-with-fda-application

8. https://www.novartis.com/news/media-releases/fda-accepts-sandoz-regulatory-submission-proposed-biosimilar-etanercept

9. https://www.novartis.com/news/media-releases/regulatory-submission-sandoz-proposed-biosimilar-pegfilgrastim-accepted-fda

10. http://www.hhs.gov/asl/testify/2015/09/t20150917a.html

11. *Id.*

12. Source: Global Biosimilars Market 2015-2025 from Roots Analysis

13. Source: Global Biosimilars Market 2015-2025 from Roots Analysis

14. http://www.prnewswire.com/news-releases/boehringer-ingelheims-biosimilar-candidate-demonstrated-pharmacokinetic-bioequivalence-to-adalimumab-300167521.html

15. http://www.prnewswire.com/news-releases/amgen-presents-detailed-results-from-phase-3-study-demonstrating-clinical-equivalence-of-biosimilar-candidate-abp-501-with-adalimumab-300175207.html

16. https://www.novartis.com/news/media-releases/sandoz-begins-phase-iii-clinical-trial-biosimilar-adalimumab

17. Sources: http://www.fda.gov/downloads/Drugs/DevelopmentApprovalProcess/HowDrugsareDevelopedandApproved/ApprovalApplications/TherapeuticBiologicApplications/Biosimilars/UCM439049.pdf, http://www.fda.gov/Drugs/DevelopmentApprovalProcess/HowDrugsareDevelopedandApproved/DrugandBiologicApprovalReports/ucm081677.htm, http://www.fda.gov/Drugs/DevelopmentApprovalProcess/HowDrugsareDevelopedandApproved/DrugandBiologicApprovalReports/ucm081676.htm, http://www.fda.gov/Drugs/DevelopmentApprovalProcess/HowDrugsareDevelopedandApproved/DrugandBiologicApprovalReports/ucm081673.htm, http://www.fda.gov/Drugs/DevelopmentApprovalProcess/HowDrugsareDevelopedandApproved/DrugandBiologicApprovalReports/ucm081690.htm, http://www.fda.gov/downloads/Drugs/DevelopmentApprovalProcess/HowDrugsareDevelopedandApproved/DrugandBiologicApprovalReports/UCM200924.pdf

18. Source: European Medicines Agency

19. Source: Regulatory Framework for Biotherapeutic Products including Similar Biotherapeutic Products [PDMA Presentation 2015]

20. Source: http://www.gabionline.net/Biosimilars/General/Biosimilars-approved-in-South-Korea

21. Source: http://www.gabionline.net/Biosimilars/General/Similar-biologics-approved-and-marketed-in-India

22. Source: IMS Institute for Healthcare Informatics, "Assessing biosimilar uptake and competition in European markets" (October 2014)

23. Source: EU Consensus Information Paper 2013, "What you need to know about Biosimilar Medicinal Products" (Via Biosimilars: A Global Perspective of a New Market – Opportunities, Threats and Critical Strategies 2014 from Thompson Reuters Bioworld)

24. Source: EU Consensus Information Paper 2013, "What you need to know about Biosimilar Medicinal Products" (Via Biosimilars: A Global Perspective of a New Market – Opportunities, Threats and Critical Strategies 2014 from Thompson Reuters Bioworld)

25. http://www.fda.gov/downloads/Drugs/DevelopmentApprovalProcess/HowDrugsareDevelopedandApproved/ApprovalApplications/TherapeuticBiologicApplications/Biosimilars/UCM281991.pdf).

ENDNOTES

26. The Hatch-Waxman Act requires FDA to publish the "Orange Book," i.e., Approved Drug Products with Therapeutic Equivalence Evaluations, which contains a list of approved drug products and their applicable patent and non-patent exclusivities. The BPCIA does not require FDA to publish a similar list for biologic products. Nevertheless, FDA has elected to publish the "Purple Book," i.e., Lists of Licensed Biological Products with Reference Product Exclusivity and Biosimilarity or Interchangeability Evaluations, which lists all approved biological products, including any biosimilar and interchangeable biosimilar products, and any applicable exclusivities. The Purple Book does not include a list of applicable patents.

27. Since Zarxio®'s approval, however, Amgen received approval of another indication for Neupogen®: increase survival in patients acutely exposed to myelosuppressive doses of radiation (Hematopoietic Syndrome of Acute Radiation Syndrome). As of December 21, 2015, Sandoz has yet to receive approval for such indication for Zarxio®.

28. Source: Biosimilars Implementation Before the S. Comm. on Health, Education, Labor, and Pensions, 114th Cong. (2015) (statement of Janet Woodcock, M.D., Director, Center for Drug Evaluation and Research, U.S. Food and Drug Administration).

29. *Id.*

30. PREA generally requires investigations in pediatric populations for new drugs or biologics.

31. Source: FDA Acting Commissioner Stephen M. Ostroff, M.D., Speech to the Missouri Biotechnology Association, Oct. 1, 2015, available at http://www.fda.gov/aboutfda/commissionerspage/ucm466279.htm (last accessed on Nov. 10, 2015); Biosimilars Implementation Before the S. Comm. on Health, Education, Labor, and Pensions, 114th Cong. (2015) (statement of Janet Woodcock, M.D., Director, Center for Drug Evaluation and Research, U.S. Food and Drug Administration).

32. H.R. Rept. No. 114-205, at 65 (2015).

33. *See* 21 C.F.R. § 314.94(a)(8)(iv).

34. *See* Regulations.gov, Docket ID FDA-2015-P-2000-0005, at 1

35. *Id.*

36. *I d.*

37. *Id.* at 3.

38. *See* Regulations.gov, Docket ID FDA-2015-P-2000-0005, at 1

39. *Id.* at 2.

40. *Id.*

41. *Id.* at 3-4.

42. *See* Regulations.gov, Docket ID FDA-2015-P-2000-0009.

43. *Id.* at 1, 5-6.

44. *Id.* at 1, 6.

45. *See* Regulations.gov, Docket ID FDA-2015-P-2000-0008, at 1-2, 11.

46. *Id.* at 11.

47. *See* Regulations.gov, Docket ID FDA-2015-P-2000-0006

48. *Id.* at 1.

49. *Id.* at 5.

50. Biosimilars Implementation Before the S. Comm. on Health, Education, Labor, and Pensions, 114th Cong. (2015) (statement of Janet Woodcock, M.D., Director, Center for Drug Evaluation and Research, U.S. Food and Drug Administration), at 10

51. *See Id.*

52. *Id.*

53. FDA Guidance for Industry, Biosimilars: Questions and Answers Regarding Implementation of the Biologics Price Competition and Innovation Act of 2009 (April 2015), at 8.

54. *Id.*

55. *Id.*

56. *Id.*

57. 42 U.S.C. §262(i)(2)(A)-(B).

58. 42 U.S.C. §262(k)(4)(A)(ii).

59. 42 U.S.C. §262(k)(4)(B).

ENDNOTES

60. Biosimilars: Additional Questions and Answers Regarding Implementation of the Biologics Price Competition and Innovation Act of 2009, Draft Guidance for Industry, at 7 (May 2015).

61. FDA Acting Commissioner Stephen M. Ostroff, M.D., Speech to the Missouri Biotechnology Association, Oct. 1, 2015, available at http://www.fda.gov/aboutfda/commissionerspage/ucm466279.htm (last accessed on Nov. 10, 2015); Biosimilars Implementation Before the S. Comm. on Health, Education, Labor, and Pensions, 114th Cong. (2015) (statement of Janet Woodcock, M.D., Director, Center for Drug Evaluation and Research, U.S. Food and Drug Administration); H.R. Rept. No. 114-205, at 65 (2015).

62. FDA News, Sept. 26, 2012, Vol. 29 no. 19.

63. Source: CFDA.gov.cn, available at http://eng.cfda.gov.cn/WS03/CL0757/115203.html (last accessed on Nov. 6, 2015).

64. 2015 WL 5032324 (S.D. In. Aug. 25, 2015)

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Big Molecule Watch Blog
A firm blog that represents a first-of-its-kind resource for the biosimilars industry.
www.bigmoleculewatch.com

Pharmaceuticals at the Patent Trial & Appeal Board
http://www.goodwinprocter.com/PTAB_Guidebook

PTAB Post Grant Proceedings: A Tactical Guide for Practitioners
www.goodwinprocter.com/ptab_guide

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