The Next Frontier for Improved Access to Medicines:

Biosimilars and Interchangeable Biologic Products

The Biosimilars Council
A Division of GPhA

GPhA

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Table *of* Contents

04 Introduction: Putting Medical Breakthroughs Within Reach
07 Innovation and Access: Biosimilars and Interchangeable Biologic Products
10 Who Will Benefit?
14 What is at Stake in the United States?
17 What Does the Law Say?
21 What is FDA's Role?
23 What is a State's Role?
24 How are Biosimilars Developed and Made?
28 Biosimilars in Action: The European Union Experience
32 Safety
34 Glossary

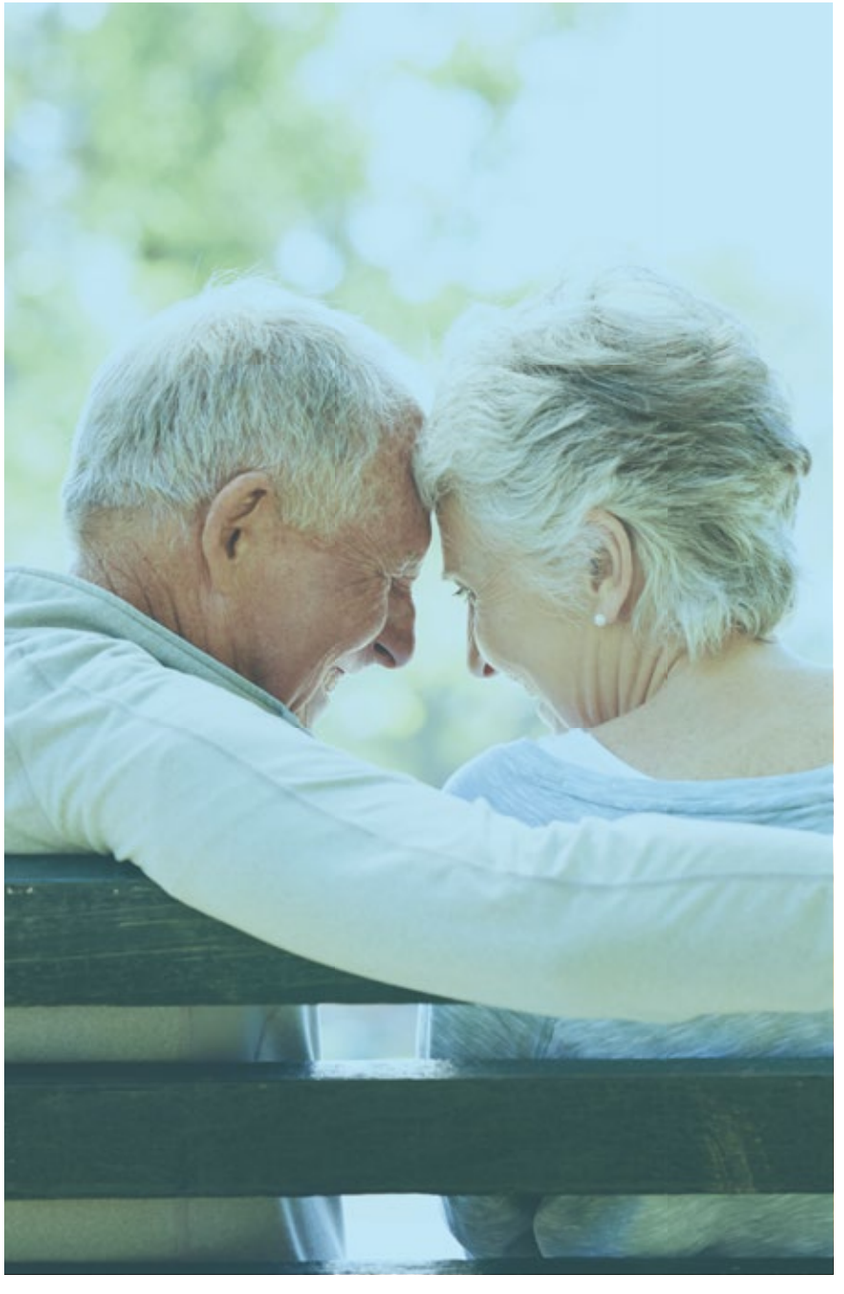
Introduction:
Putting Medical Breakthroughs Within Reach

We live in a time of unprecedented medical breakthroughs for patients. Not only are there therapies available today for conditions that were once life-threatening, there are also more medicines available at a lower cost than ever. Today, we benefit from the impact of generic medicines, which have made millions of doses of costly brand medications available at a lower price.

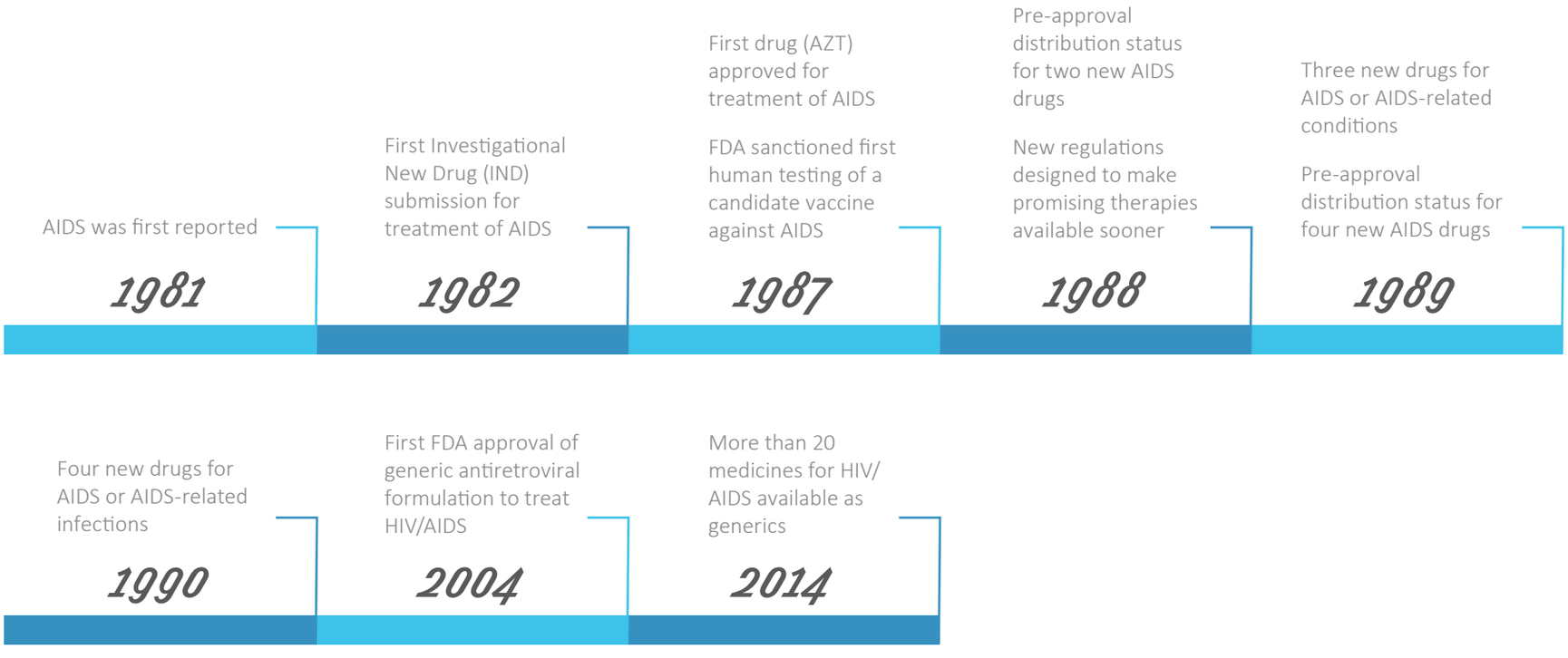
This handbook is designed to be a biosimilars and interchangeable biologics reference tool for experts as well as patients. It is important to define terminology which will be new to some (indicated in bold and listed in the glossary) and clarify some of the underlying science and expertise that goes into making these safe, high-quality medicines.

Soon, FDA-approved biosimilar versions of costly brand biologics will be available for millions of people in the United States with cancer, rheumatoid arthritis or other diseases. Expensive biologic therapies can expect to see the same evolution in competition as traditional drugs have seen with the introduction of generics more than thirty years ago. One example of this evolution is HIV/AIDS.

In the last 35 years, HIV/AIDS has gone from being unknown, to being identifiable without any proven medical interventions, to becoming treatable with expensive therapies. Then, as brand drug patent protections ended, many affordable generic alternatives for HIV/AIDS drugs became available. Today, more than 20 medicines for HIV/AIDS are available as generics.[1]



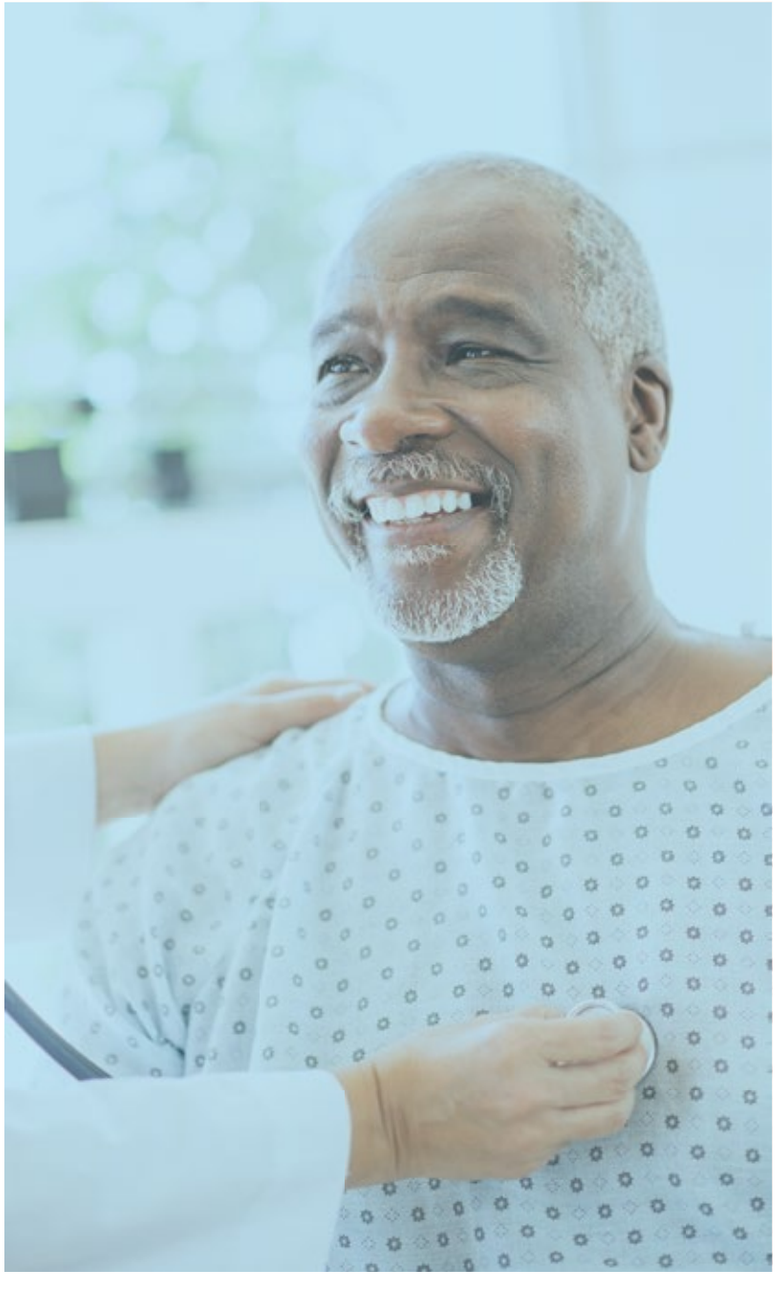
Timeline: HIV/AIDS: 1981-2014



This timeline[2] illustrates the way a traditional chemical medicine progresses from discovery, to availability as a new therapy, to providing greater access in a more affordable generic version. We are now on the cusp of another major expansion in the availability of life-saving medicines. Today's advanced medicines will become available at a lower cost to millions of patients thanks to newer types of **biologic** medicines known as **biosimilars** and **interchangeable biologic products.**

Biosimilars are biologic medicines that are developed to provide safe, effective alternative versions of existing similar biologic medicines (known as **"reference products"**) with scientifically comparable quality, safety and **efficacy**. Interchangeable biologic products are biologic medicines that the **Food and Drug Administration (FDA)** will deem to be highly similar to the original product. They can be treated by healthcare providers as interchangeable as generic drugs are today. Because all biologic medicines, including biosimilars and interchangeable biologic products, are produced from living organisms rather than chemical compounds, they are more complex than most other available medicines and are much larger molecules.

Before they are available for patients, biosimilars and interchangeable biologic products will pass extensive tests to ensure they have high levels of quality, efficacy and safety as the original medicine. The final product is analyzed with some of the most sophisticated and innovative pharmaceutical technology available today and assessed by FDA medical experts. While these therapies are not yet available in the United States, there is great momentum on both the scientific and regulatory fronts: exciting research is underway on new biosimilars and, in July 2014, the FDA accepted the first filing for an approval for a biosimilar medicine, signaling the beginning of a United States biosimilar approval process.



Innovation and Access: Biosimilars and Interchangeable Biologic Products

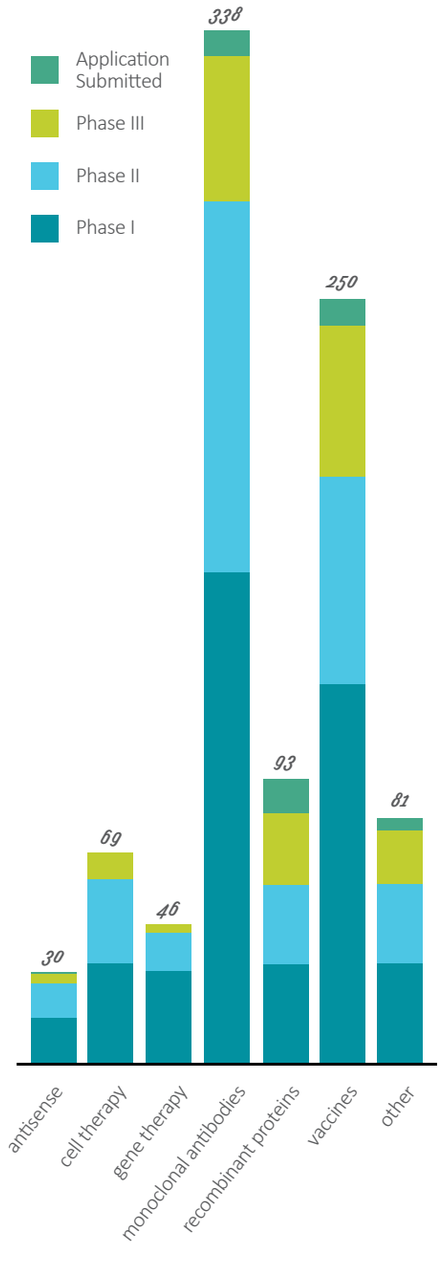
Advancements in the research and development of biologic medicines have pushed the frontiers of science to bring life-saving and life-altering cures to patients suffering with deadly diseases. For example, thanks to biologic research, remarkable progress has been made to combat many types of cancers, and headway is being made in finding new treatments for Alzheimer's disease and other conditions. Biologic therapies have also helped patients make great strides in managing chronic diseases like diabetes, rheumatoid arthritis, and Crohn's disease.

Given the amount of research, it is no surprise that biologic medicines now account for one-third of annual drug approvals in the United States.[4] It is estimated that by 2016 eight of the 10 top-selling medicines will be biologics.[5] This is a sharp increase from just a decade ago when only one biologic was on the top 10 list of drugs prescribed in the United States. Moreover, there are approximately 900 new biologics in development, targeting more than 100 diseases.[6] Notably, the global biologics market is expected to soar to $220 billion by 2019, nearly double the current $120 billion market.[7]

Biologic medicines are costly, and those that do not have a biosimilar version (which includes all biologic therapies in the United States) can cost a patient as much as several hundred thousand dollars per year. Research shows that the average daily cost of a biologic product is approximately 22 times greater than the daily cost for a traditional drug.[8] Data also show that biologic prices keep getting steeper. Between 2011 and 2012, prices for specialty drugs—drugs including biologics—increased by 12.9 percent.[9]

Fortunately, for the many patients who can benefit from biologic treatments and for those providing and paying for healthcare, there is an answer. The approval of biosimilar and interchangeable biologic products will create the competition to significantly lower costs for patients, providers and the whole healthcare system. Just as generic competition has reduced the prices of traditional prescription drugs, biosimilars and interchangeable biologic products will create the market dynamics needed to lower the cost of biologics and provide patients alternatives.

Biologics in Development[3]



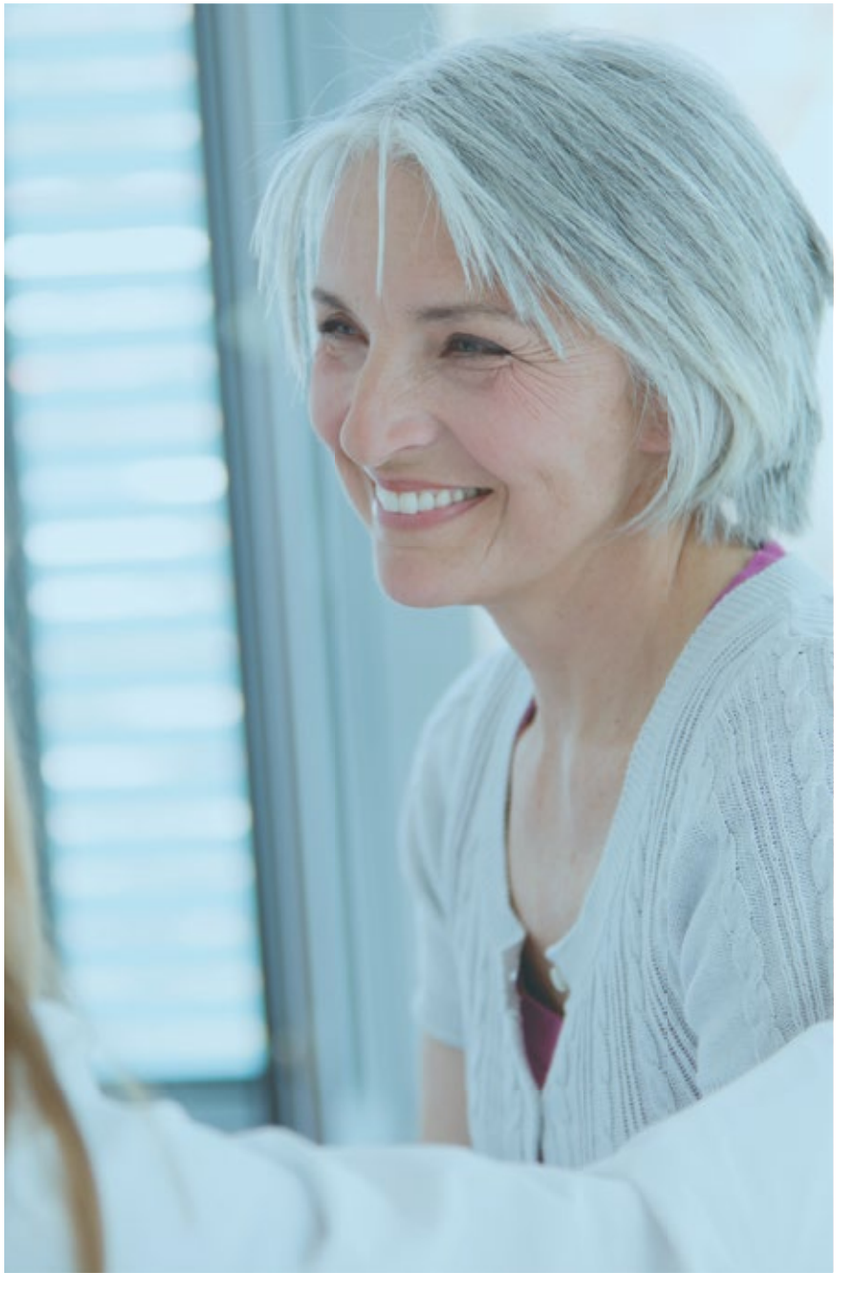
The availability of more affordable biologic medicines (biosimilars) translates into enormous savings for patients, taxpayers, insurers, providers, and state and federal governments.

Who Will Benefit?

Many will benefit from new biosimilars: patients waiting for alternatives to costly biologics; and taxpayers, employers, insurers, state and federal governments and others who help pay for healthcare.

For patients, costly biologic medicines are often the only treatments currently available to those who are suffering with the most severe diseases. Biologics now are being used to combat cancer, heart disease, HIV/AIDS, psoriasis, rheumatoid arthritis, asthma, Crohn's disease, diabetes, multiple sclerosis, and other life-threatening illnesses. While there are not yet cures for many of these diseases, biologic medicines are proving to have better long term outcomes with fewer side effects than many traditional drugs. For patients, this often means quicker recovery times, fewer additional treatments, and improved quality of life. Unfortunately, the high price tags keep biologic treatments out of reach for many. In the coming years, however, many biologic medicines are expected to reach the end of their patents, paving the way for introduction of lower cost alternatives.

The following table provides a list of common diseases and conditions, the biologic medicines that are commonly used to treat them, and the date that the medicine's patent expires, making it eligible for biosimilar competition.



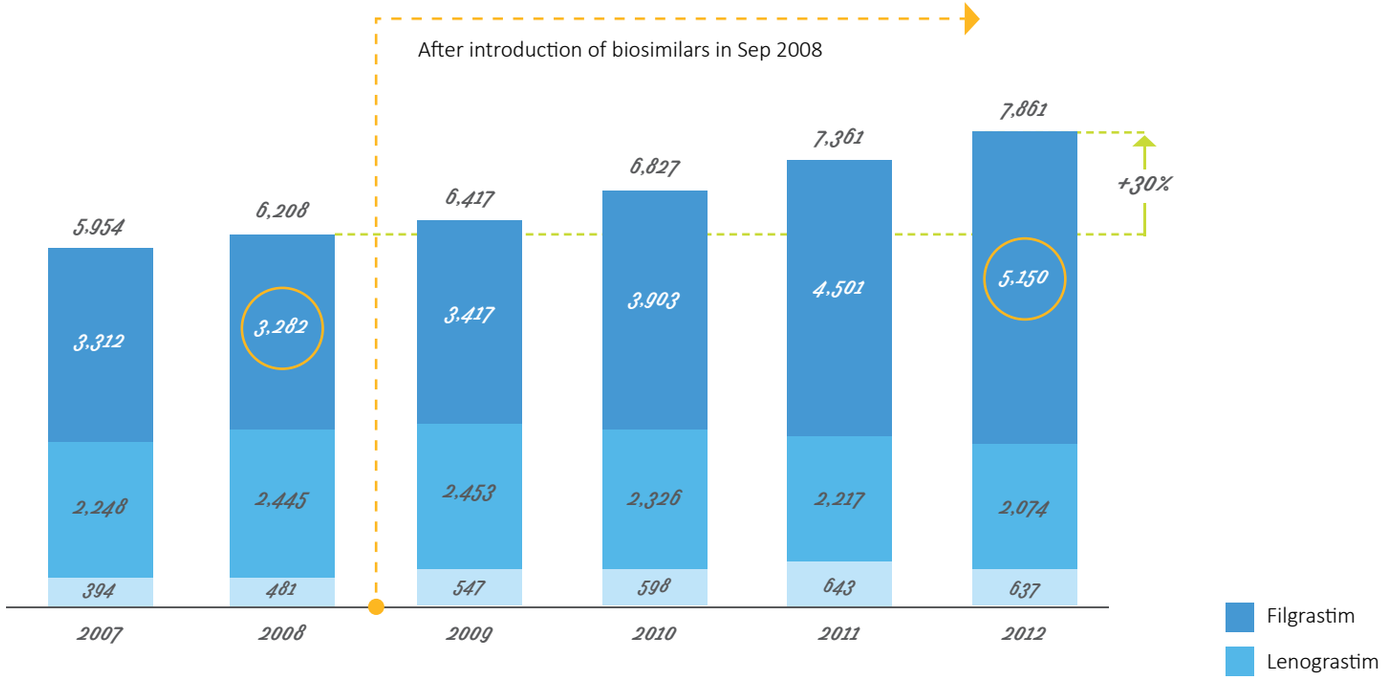
Patients with (Disease/Condition):	Are waiting for (Biologic Product):	U.S. Patent Expiration (Date of eligibility for biosimilar competition)[10]
Rheumatoid Arthritis	Adalimumab (Humira)®	2016
	Etanercept (Enbrel)®	2028
	Rituximab (Rituxan)®	2016
	Infliximab (Remicade)®	2018
Juvenile Idiopathic Arthritis	Adalimumab (Humira)	2016
	Etanercept (Enbrel)	2028
Psoriatic Arthritis	Adalimumab (Humira)	2016
	Etanercept (Enbrel)	2028
	Infliximab (Remicade)	2018
Ankylosing Spondylitis	Adalimumab (Humira)	2016
	Etanercept (Enbrel)	2028
	Infliximab (Remicade)	2018
Crohn's Disease, Ulcerative Colitis	Adalimumab (Humira)	2016
	Infliximab (Remicade)	2018
Plaque Psoriasis	Adalimumab (Humira)	2016
	Etanercept (Enbrel)	2028
	Infliximab (Remicade)	2018
Non-Hodgkin's Lymphoma	Rituximab (Rituxan)	2016
Chronic Lymphocytic Leukemia	Rituximab (Rituxan)	2016
Metastatic Colorectal Cancer	Bevacizumab (Avastin)®	2017
Non-squamous Non-Small Cell Lung Cancer	Bevacizumab (Avastin)	2017
Metastatic Renal Cell Carcinoma	Bevacizumab (Avastin)	2017
Multiple Sclerosis	Interferon Beta-1A (Avonex®, Rebif®)	Expired
HER2 Overexpressing Breast Cancer	Trastuzumab (Herceptin)®	2019
HER2 Overexpressing Metastatic Gastric or Gastroesophageal Junction Adenocarcinoma	Trastuzumab (Herceptin)	2019
Non-Myeloid Malignancies receiving myelosuppressive anti-cancer drugs	Pegfilgrastim (Neulasta)®	2014
Neovascular (wet) Age-Related Macular Degeneration; Macular Edema Following Retinal Vein Occlusion (RVO); Diabetic Macular Edema	Ranibizumab (Lucentis)®	2016

Competition from biosimilars is important because for many patients, the availability of a high-priced brand biologic for their condition does not translate into access to these therapies. For example, many rheumatoid arthritis patients in developed countries like Japan, the United States and the EU do not have access to these medicines. In fact only 50% of severe RA patients receive biologics across the EU, United States and Japan.

Furthermore, in European countries where biosimilars have been introduced, they have increased the number of patients taking the therapy significantly (IMS Health).

Introduction of filgrastim biosimilars in Europe has significantly increased uptake of G-CSF

Total G-CSF market volume in Europe by year
Number of syringes in thousands



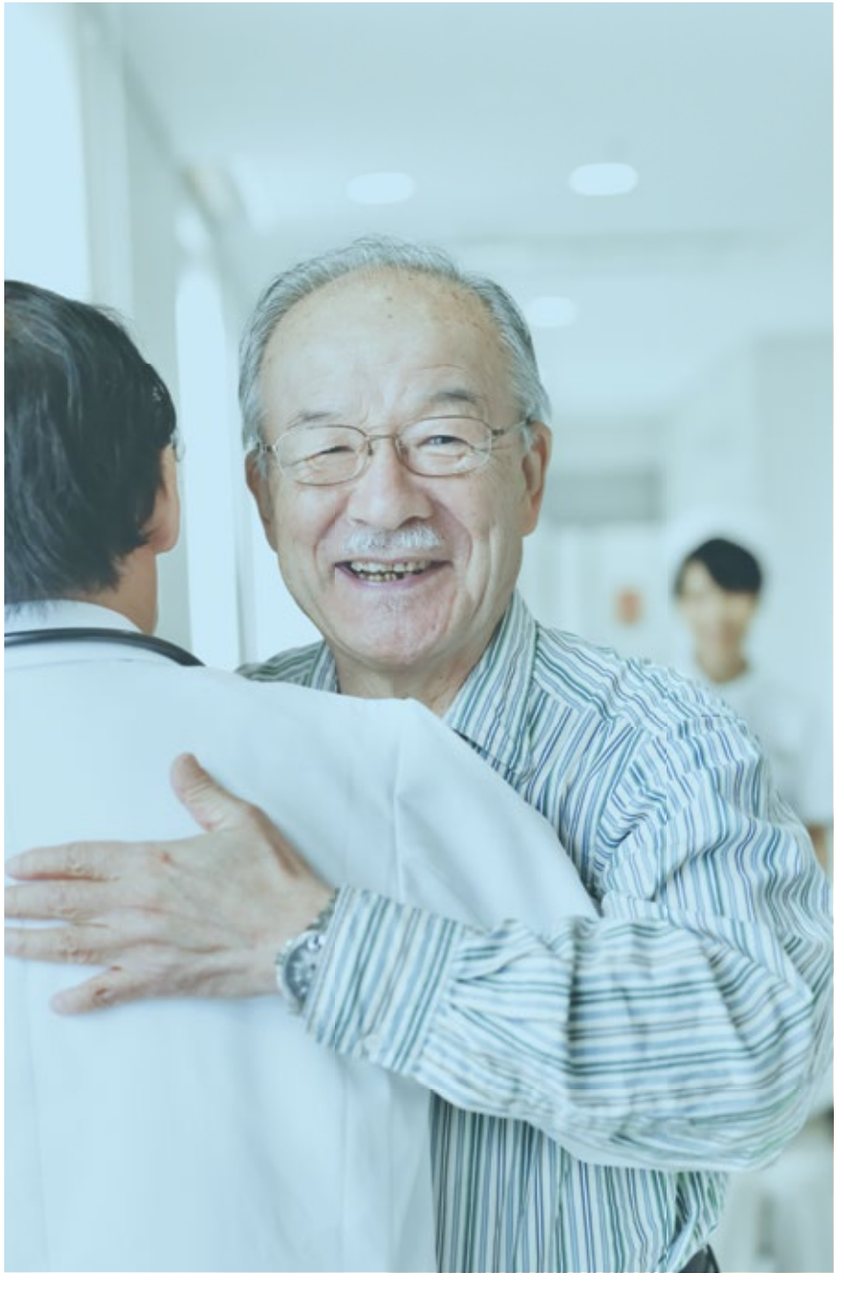
1st cycle treatment + optimal dose & duration = enhanced access for cancer patients

What is at Stake in the United States?

In addition to the opportunity to provide millions of patients with lower-cost alternatives to brand biologic therapies, there are billions of dollars of savings at stake for American taxpayers. The United States Congressional Budget Office has repeatedly warned that the growth of health costs is on a trajectory that makes the nation's deficit unsustainable. Keeping health costs in check is one way to lower that deficit and improve the fiscal soundness of the United States government.

Biologics represent some of the costliest available treatments. Between April 2013 and March 2014, five of the 12 biggest selling drugs in the United States were biologics.[11] Over the next few years, the number of biosimilar medicines available to patients will grow dramatically. In fact, by 2020, brand biologic medicines worth an estimated $81 billion in global annual sales will lose their patents, opening those markets for lower cost biosimilar alternatives.[12]

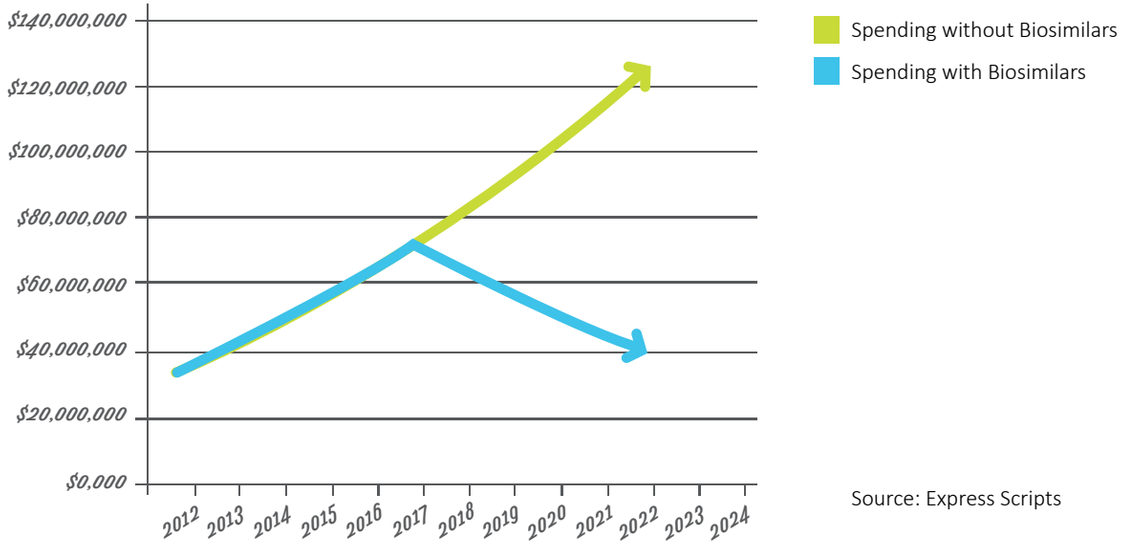
Recent data show that the cost of many biologics is increasing at a faster annual pace than any other component in healthcare. In 2014, United States spending for biologic medicines will reach approximately $115 billion. By 2020, biologic spending is expected to exceed $250 billion (see chart on page 17). This means that nearly $5 out of every $10 the country spends on prescription drugs will be spent on biologics.



With such high spending on biologic medicines, the potential savings from biosimilars is great. Depending on various factors, including the 10-year period examined, estimates from various economic impact studies pin the projected savings from $44 billion on the low end to as high as $250 billion over the first 10 years that biosimilars are available to patients. While statistical assumptions informing each analysis vary, experts agree on the transformative potential and significant savings from biosimilars. The Congressional Budget Office estimated that biosimilars initially will be priced about 25 percent below their brand-name counterparts and, after several years of competition, could be priced as much as 40 percent below the brand (see chart below).

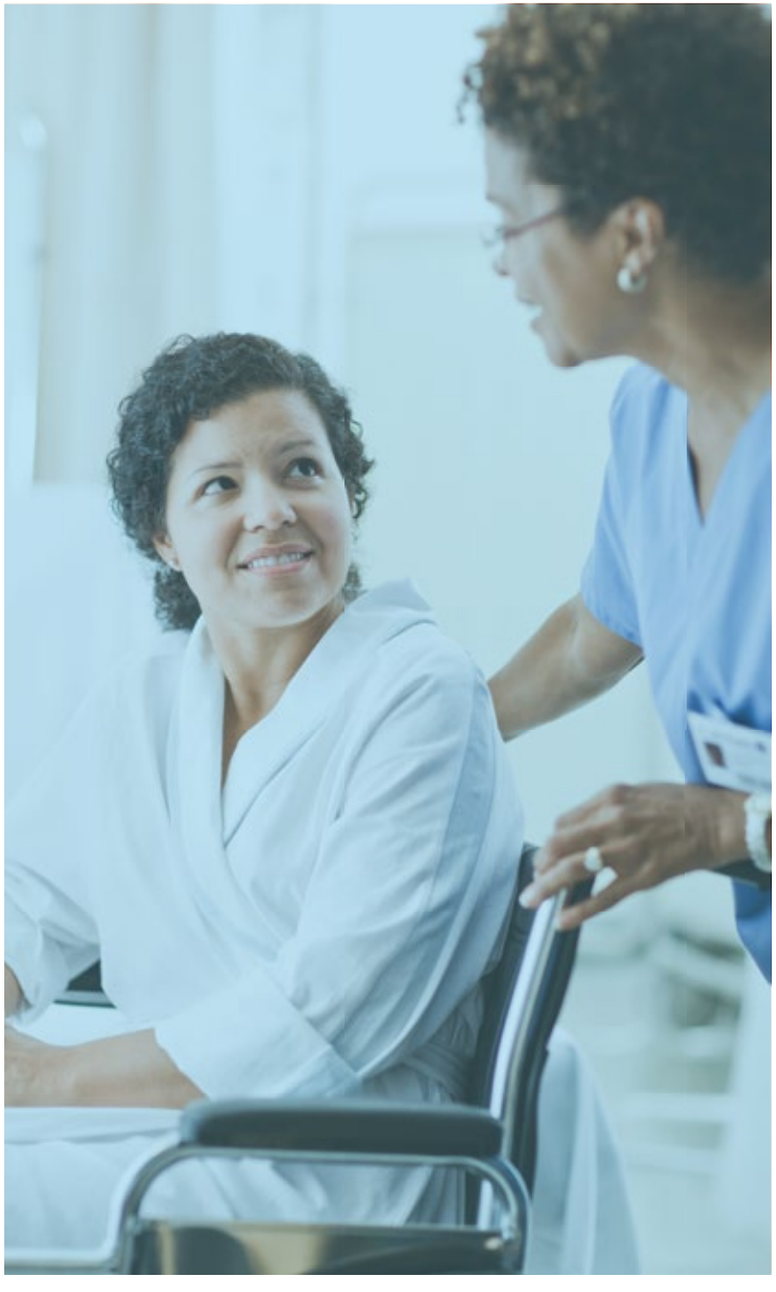
Estimated Savings	Sample	Time Period	
$44 billion	Sales data on 100 biologics	10 years	Mulcahy, Andrew W., Predmore, Zachary, Mattke, Soeren. The Cost Savings Potential of Biosimilar Drugs in the United States. RAND, November 2014. Avaliable at: http://www.rand.org/pubs/perspectives/PE127.html
$67 billion - $108 billion	Top 12 biologic classes	10 years	Shapiro RJ. The Potential American Market for Generic Biological Treatments and the Associated Cost Savings. Sonecon. February 2008. Available at: http://www.sonecon.com/docs/studies/0208_GenericBiologicsStudy.pdf
$250 billion	11 biologics that are most likely candidates for biosimilars	10 years	Express Scripts. Available at: http://lab.express-scripts.com/insights/industry-updates/the-$250-billion-potential-of-biosimilars
$236 billion - $378 billion	Top 12 biologic classes	20 years	Shapiro RJ. The Potential American Market for Generic Biological Treatments and the Associated Cost Savings. Sonecon. February 2008. Available at: http://www.sonecon.com/docs/studies/0208_GenericBiologicsStudy.pdf

Biosimilar Savings: Impact of Biosimilars on Projected Spending for 11 Biologics



Source: Express Scripts

Biosimilars now are available in more than 60 countries around the world.[13] As governments cope with aging populations and an increase in chronic disease, the demand for affordable biologic alternatives will continue to grow. The introduction of FDA-approved safe and effective biosimilar therapies into the markets around the world has been proven to reduce healthcare costs while at the same time delivering lifesaving treatments to patients in need.



What Does the Law Say?

To regulate this emerging field of science, the United States Congress established a new framework for scientists and manufacturers seeking approval to make new biosimilar therapies available to patients. As part of the landmark **Patient Protection and Affordable Care Act (ACA) of 2010**, the **Biologics Price Competition and Innovation Act (BPCIA)** lays out requirements for the approval of biosimilars and interchangeable biologic products and assigns FDA the task of designing the detailed approval pathway for these medicines.

To be approved for use by patients, the BPCIA requires that a biosimilar must demonstrate **no clinically meaningful difference** from its reference biologic in terms of safety and quality metrics like purity and **potency**. This means that the biosimilar will treat the same disease as safely and effectively as the brand product. According to the law, a biosimilar must meet safety, efficacy and quality requirements.

The relevant excerpts from the BPCIA that speak to the safety, efficacy, and quality of biosimilars are below (see appendix for the full text of the law).

Section 351(k)(2)(A)(i) –

1. The biological product is similar to the reference product based upon data derived from:
   (aa) analytical studies
   (bb) animal studies
   (cc) a clinical study or studies (including the assessment of **immunogenicity** and pharmacokinetics or pharmacodynamics);

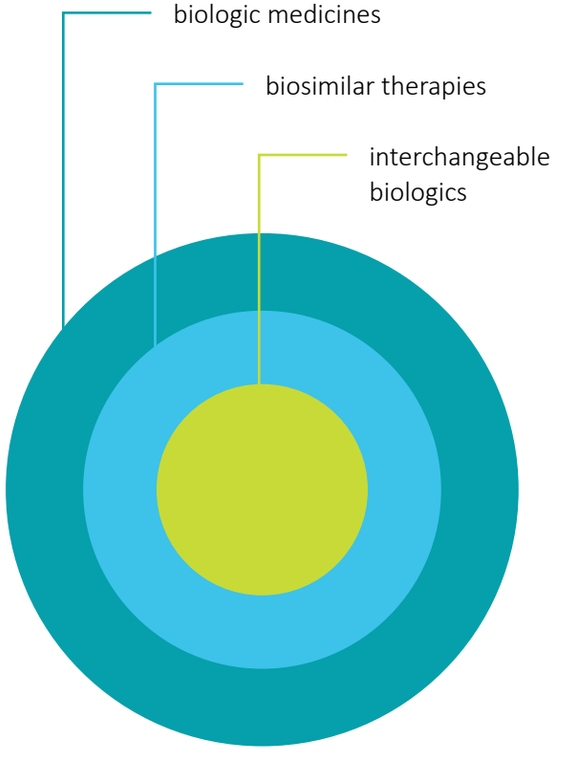
2. The biological product and reference product utilize the same mechanism or mechanisms of action;

3. The condition or conditions of use prescribed, recommended, or suggested in the labeling have been previously approved for the reference product;

4. The route of administration, the **dosage form**, and strength are the same;

5. The facility where the biological product is produced meets standards to ensure that the biosimilar is safe, pure, and potent.

Per section 351(k)(2)(A)(iii), an applicant must also include publicly-available information that the reference product has been proven to be safe, pure, and potent.



The BPCIA further provides that for a medicine to be an interchangeable biologic product, it must be expected to produce the same clinical result in any given patient as the brand biologic. In addition, where a product is administered more than once, it must be shown that alternating between the interchangeable biologic and the original or "reference product" counterpart, just as what is currently done with generics, does not raise concerns. This designation means that an interchangeable biologic product is just that, interchangeable: it may be substituted for an original product without the intervention of the healthcare provider that prescribed the original product.

Section 351(k)(4) of the BPCIA specifies criteria for determining whether a biosimilar is interchangeable with the reference product:

"(4) Safety Standards for Determining Interchangeability. – Upon review of an application submitted under this subsection or any supplement to such application, the Secretary shall determine the biological product to be interchangeable with the reference product if the Secretary determines that the information submitted in the application (or supplement to such application) is sufficient to show that –

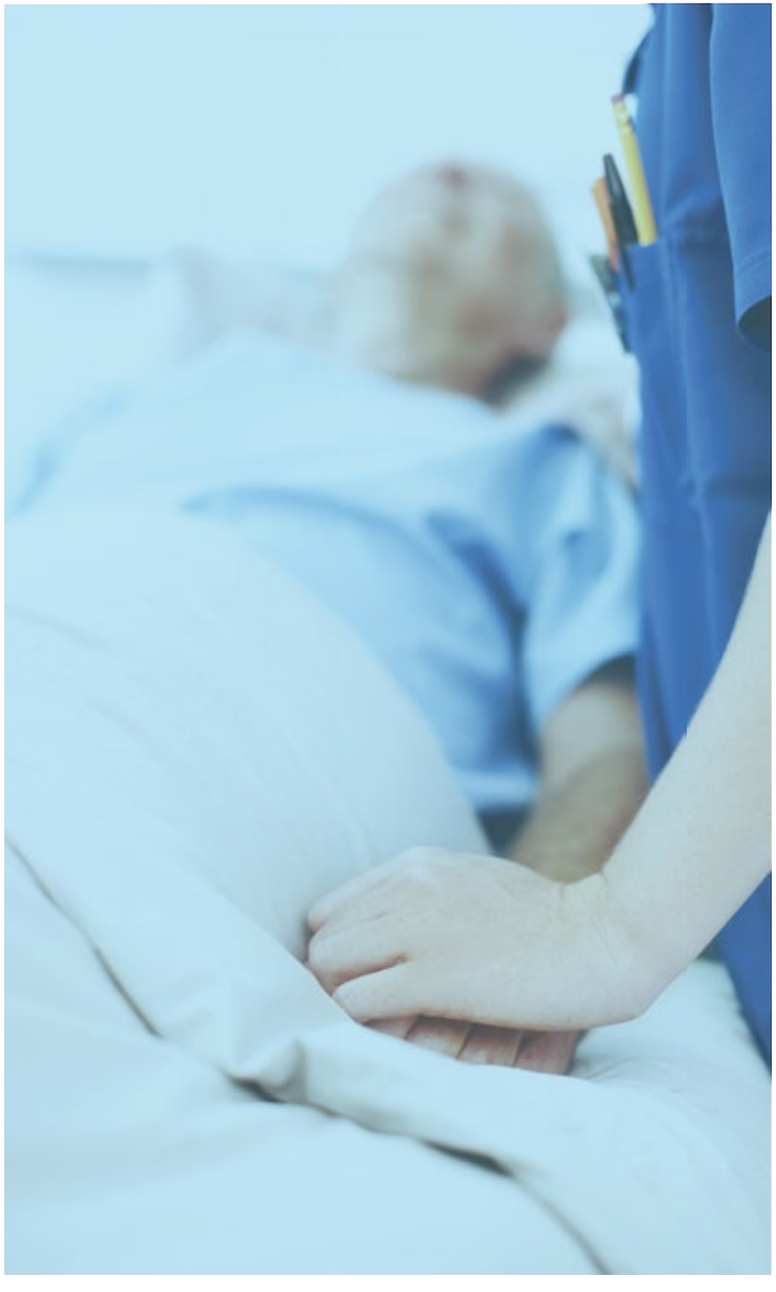
(A) the biological product –

i. is biosimilar to the reference product; and

ii. can be expected to produce the same clinical result as the reference product in any given patient; and

(B) for a biological product that is administered more than once to an individual, the risk in terms of safety or diminished efficacy of alternating or switching between use of the biological product and the reference product is not greater than the risk of using the reference product without such alternation or switch."

The legislation specifies that to meet the standard of "interchangeability," a product can be expected to produce the same clinical result as the reference product in any given patient, and for a biological that is administered more than once, that the risk of alternating or switching between use of the biosimilar product and the reference product is not greater than the risk of maintaining the patient on the reference product.



What is FDA's role?

In the United States, the FDA is the government agency responsible for reviewing and approving new medicines. Because of FDA's experience with advanced medical products and its deep scientific expertise, under the BPCIA, the FDA is responsible for implementing the approval framework and for reviewing and approving applications for interchangeable biological products and biosimilar medicines.

The FDA has already taken several significant steps to develop the biosimilar approval process. The Agency has provided several **guidances** on the steps that manufacturers need to follow when seeking approval for their new medicines, such as securing meetings with the FDA team and demonstrating biosimilarity. As new guidance continues to emerge, the industry and hundreds of thousands of patients eagerly anticipate the day when biosimilars can be made and sold in the United States. In July 2014, the FDA accepted its first filing for an approval of a biosimilar medicine, signaling the beginning of the FDA biosimilar approval process. In January 2015, the FDA Oncologic Drugs Advisory Committee voted unanimously to recommend that the FDA approve filgrastim, a Sandoz biosimilar under agency review, for each of the five indications in the application.

At this time, five guidance documents have been released by FDA:

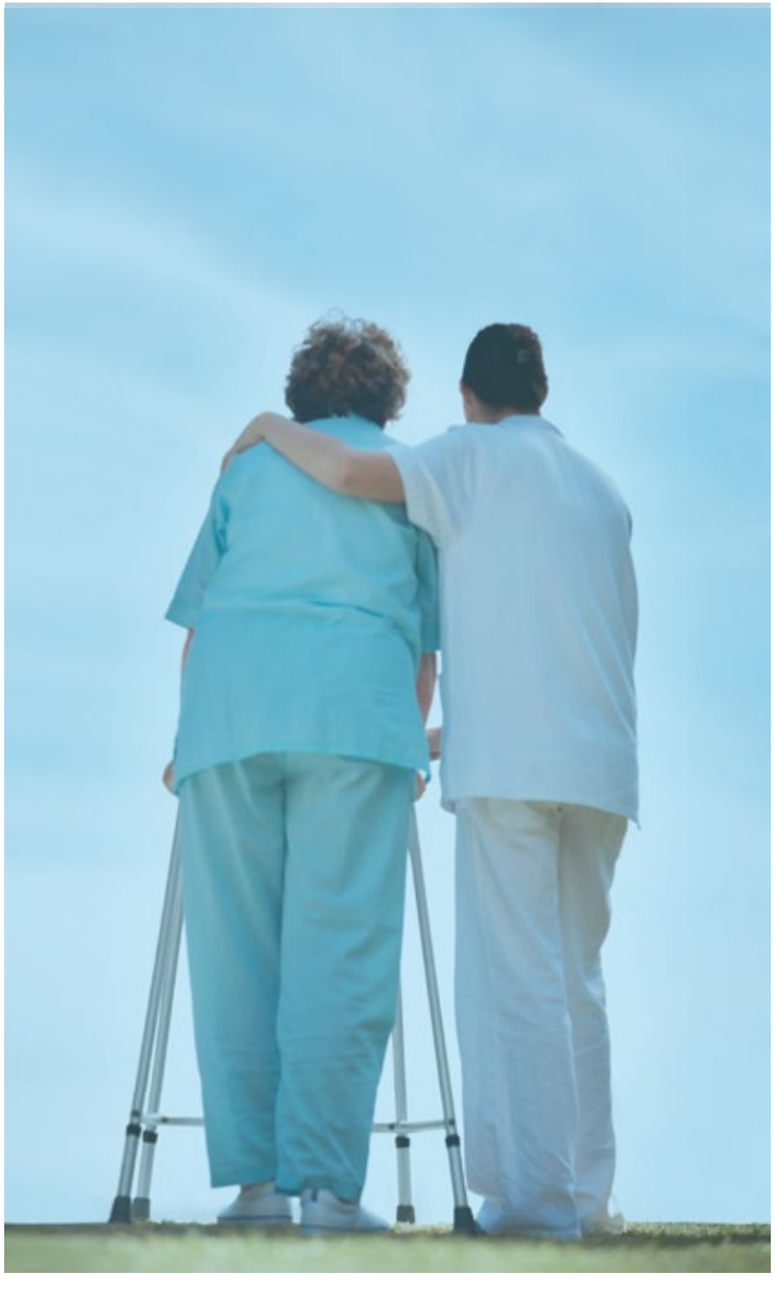
1. Draft Guidance for Industry on Biosimilars: Q&As Regarding Implementation of the BPCI Act of 2009

2. Draft Guidance for Industry on Scientific Considerations in Demonstrating Biosimilarity to a Reference Product

3. Draft Guidance for Industry on Quality Considerations in Demonstrating Biosimilarity to Reference Protein Product

4. Draft Guidance for Industry on Clinical Pharmacology Data to Support a Demonstration of Biosimilarity to a Reference Product

5. Draft Guidance for Industry on Reference Product Exclusivity for Biological Products Filed Under Section 351 (a) of the **Public Health Service Act**



What is a State's Role?

Because biosimilars were not available when generic **substitution** laws were developed, states must update their **pharmacy practice acts** to allow for substitution of interchangeable biologic products. Pharmacy practice acts are the laws, regulations and rules that govern the practice of pharmacy in each state.

States can be assured that once biosimilars become available, the potential savings from these medicines will ease strain on state health budgets and benefit patients, taxpayers and others.

How are Biosimilars Developed and Made?

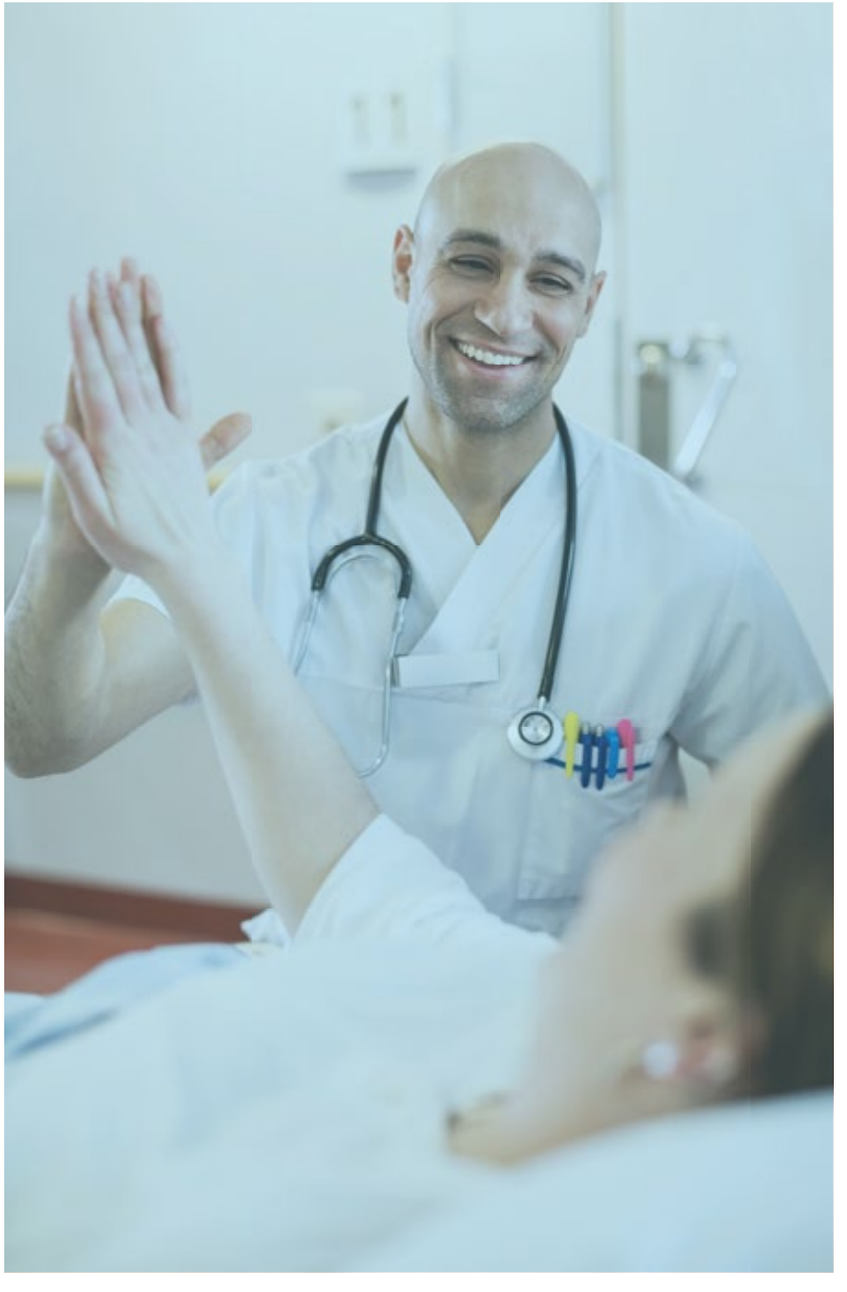
The Goal: "No clinically meaningful difference"

Because they are produced from living organisms, biological products generally have more variability than traditional chemical drugs. In fact, biologic medicines of all kinds have some variability between lots, even when manufactured by a single company. Therefore, the goal in creating a biosimilar is to make a safe therapy that treats a disease the same way as the original biologic medicine.

To achieve this, FDA requires biosimilars demonstrate that they meet a rigorous scientific standard of **similarity** known as highly similar before they are made available to patients. Similarity is achieved and verified through a scientific process that confirms there is no clinically meaningful difference between the biosimilar and the original product. This is the same approach used for changes to brand products.

EMA regulators say clinicians shouldn't be concerned about "Similar, but not identical"

"...the 'similar but not identical' paradigm of biosimilars appears to fuel uncertainties about [biosimilars]. However, this principle is not new to biotechnology; even consecutive batches of originator products are never identical to each other...this is normal and is why adequate controls on batch consistency have to be imposed." [14]



Unlike new medicines, the goal of the scientific testing for a biosimilar therapy is to confirm that the medicine is highly similar to the original, not to re-establish safety and efficacy for the biologic medicine. Those determinations have already been made with the original medicine. Similarity testing occurs multiple times throughout the entire product development process. These tests cover scientific quality and clinical and non-clinical parameters.

The Biosimilar Development Process

Because the development of a biosimilar is based on what is known and proven through **clinical trials** rather than re-proving the same point, the steps for creating a biosimilar focus on supplementing the data from the development of an original medicine to establish the therapy's similarity. Researchers build on what was proven with the original medicine to create alternative approaches that have the same safety and efficacy (see appendix for details).

The biosimilar development process occurs in three major stages: characterization and perfecting the process, confirmation of biosimilarity (and, where sought, interchangeability) and approval.

Step 1: Product Development: Characterization and Perfecting the Process

In development, the first step is a thorough understanding of the reference biologic, accomplished through an examination of structure and function. This is known as characterization**.**

Once this information is obtained, the next phase is the development of the manufacturing process which delivers the highly similar therapy. State-of-the-art biological development technologies and highly-sensitive analytical tools are used to systematically engineer a biosimilar molecule to match the medicine's quality attributes that were identified in the characterization stage. This is an iterative process where each part of the manufacturing procedure is optimized in repeating steps. This continues until the manufacturing process consistently produces a highly similar molecular structure to the original medicine. In many cases, this part of the process – creating a highly similar molecule – takes significantly longer than developing a manufacturing process for a novel biologic. For scientists seeking regulatory designation of their medicine as an interchangeable biologic, additional testing may be performed to demonstrate that a medicine meets the additional standards to earn that classification.

Step 2: Biosimilar Confirmation via Studies and Regulatory Cooperation

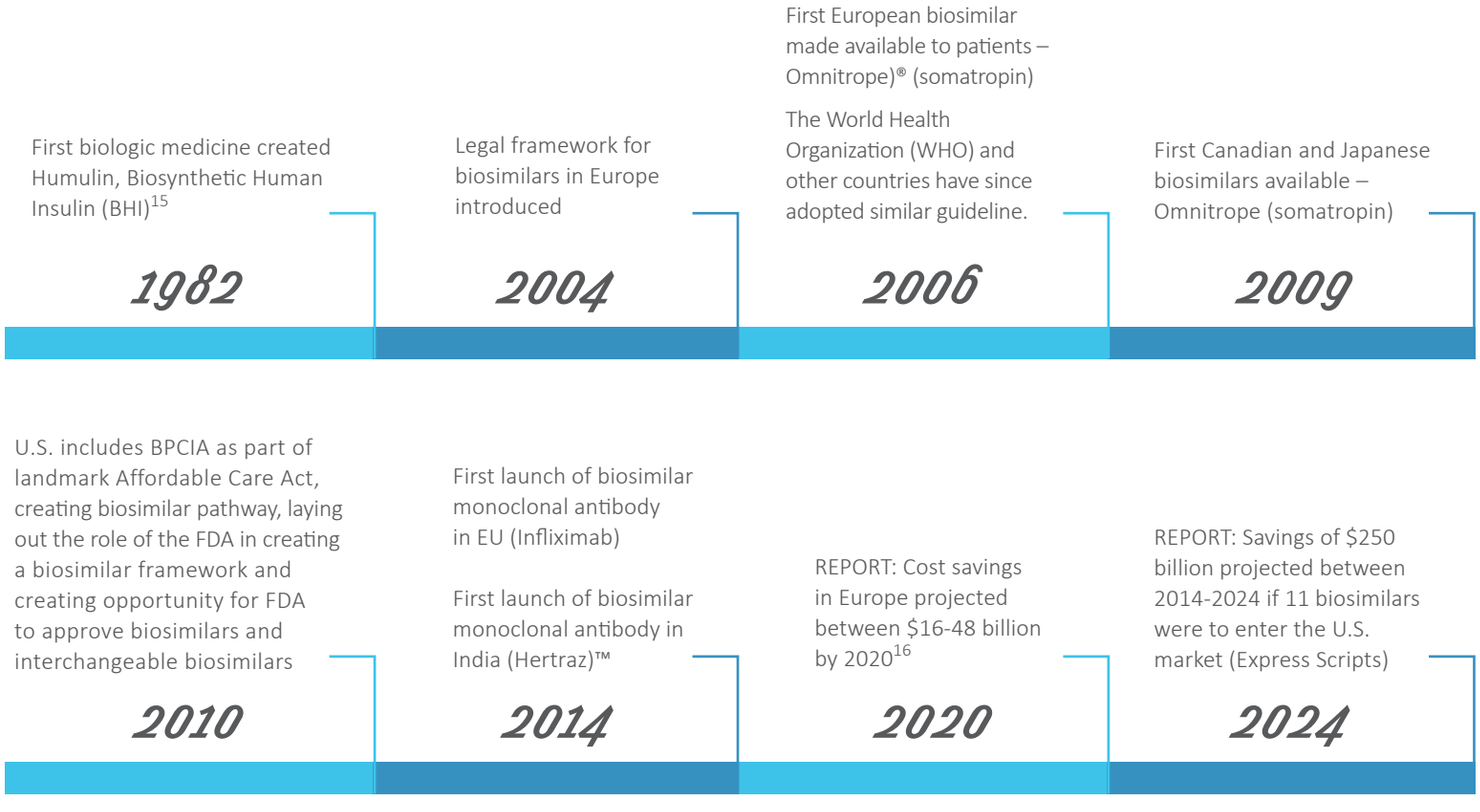
Once high-similarity (for the United States) has been established between the biosimilar and the original biologic medicine through analysis and testing, the next stage begins. FDA reviews all the information and determine the additional non-clinical and clinical studies, if any, that will be required to confirm biosimilarity and interchangeability.

Clinical trials are generally required for biosimilar approval in highly regulated markets, such as the EU, United States, Japan, Canada and Australia. However, the scope and requirements for biosimilar clinical trials will depend on the data submitted. Where there is robust and convincing analytical data, for example, and additional data are required, a more tailored clinical trial program may provide a more effective way to demonstrate biosimilarity and interchangeability.

Step 3: Approval

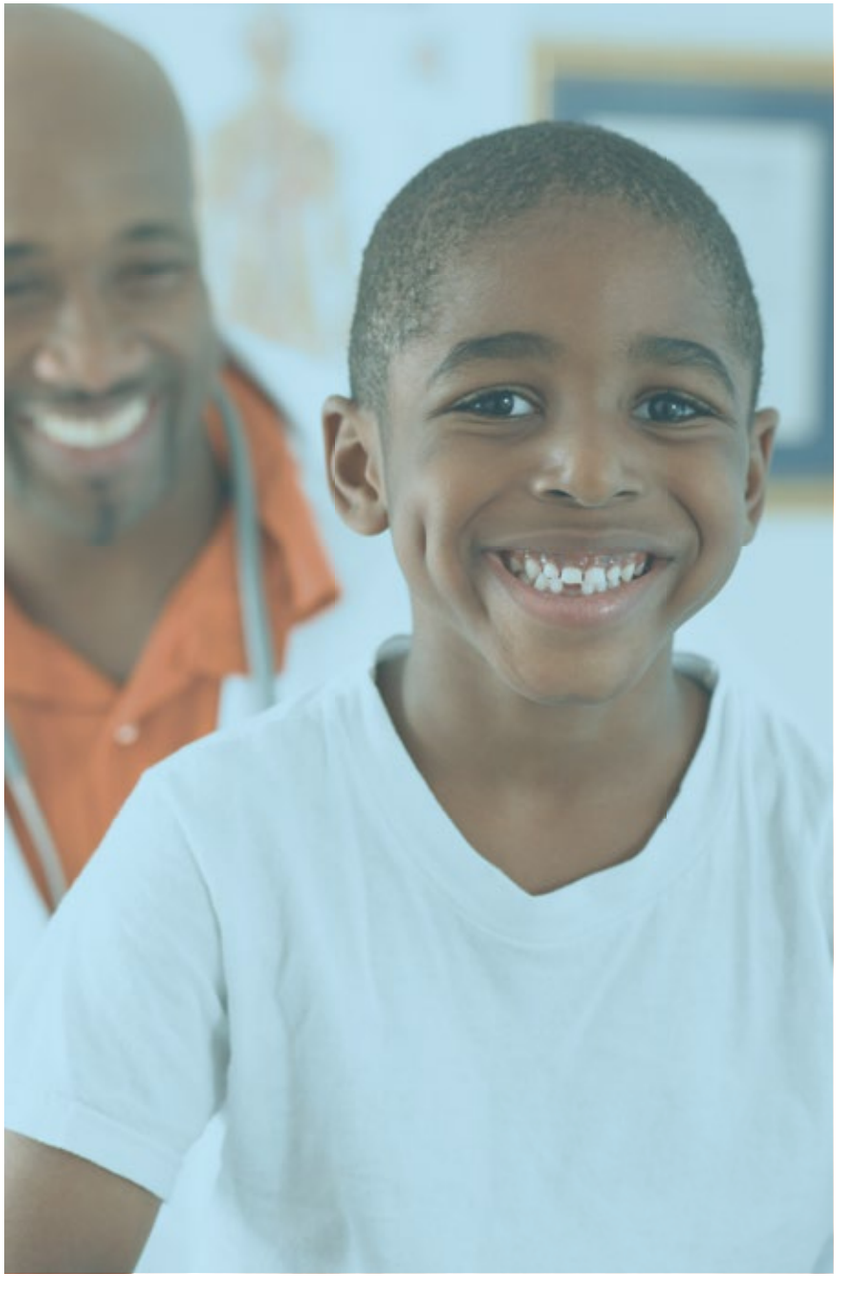
European Medicines Agency (EMA), conducts a rigorous review of all the data to determine whether the applicable scientific standards have been met and decides on whether a biosimilar is approvable for use. Once a biosimilar is approved, it can be produced and distributed legally in the country.

Timeline:



Biosimilars in Action: The European Union Experience

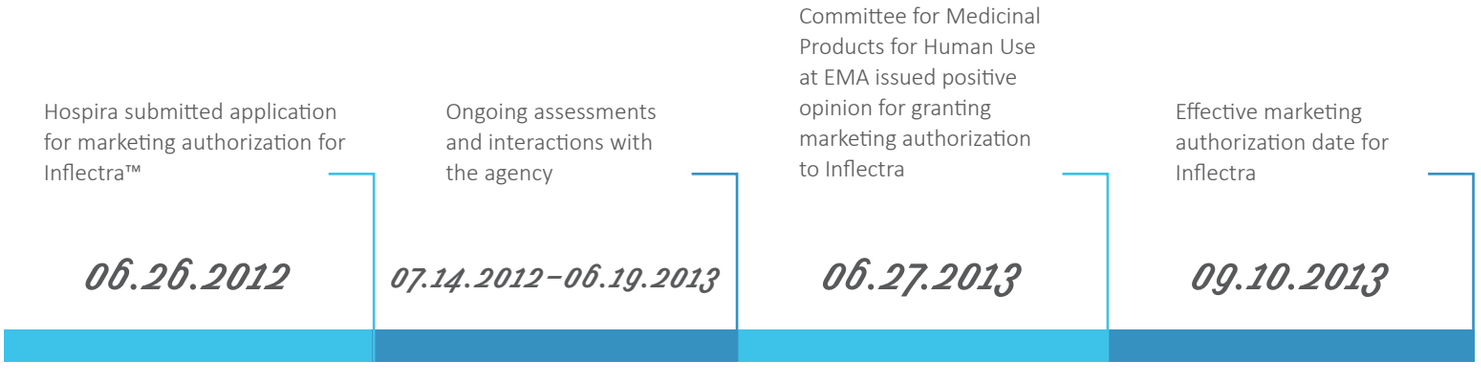
Biosimilar medicines are not yet available in the United States but are being used in Europe and other parts of the world. In the European Union, the EMA laid out a framework for developing and marketing biosimilars in 2004. Since then, 19 biosimilar medicines have been approved and used by patients (see appendix). Total sales of biosimilar medicines in the EU approached an estimated $500 million through 2014. Since they were introduced, biosimilars have been used broadly throughout the European Union to treat patients. In fact, if you count the number of days that patients across the world have taken biosimilar products, it is more than 200 million.[17] Cost savings in Europe from biosimilars is estimated to range from $16 billion to $43 billion by 2020.[18] There are many similarities between the United States and EMA processes, but, unlike the United States regulations, there is no EMA designation for interchangeable biologics (see appendix for full list).



"Our positive experience of biosimilars, since their introduction here in Europe in 2006, now gives our U.S. colleagues reassurance that they too can gain the same benefits of access to better care at better cost."

- Dr. Paul Cornes, Oncologist, UK

Timeline of EU Approval[19]



Above is an example of how these medicines are tested and approved for use in the EU. Source: Hospira

Currently, European companies that want to make and market a biosimilar therapy are required to submit quality data and comparability data. The extent of this scientific process varies by medicine type and each biosimilar is evaluated on a case-by-case basis. Of the 19 biosimilars on the market in the EU, there are multiple therapies that treat many conditions. The first ever biosimilar, Sandoz's Omnitrope® (somatropin), was approved by the EMA in April 2006. Omnitrope is a recombinant human growth hormone indicated in children for treatment of growth failure due to Growth Hormone Deficiency (GHD), Prader-Willi Syndrome, Small for Gestational Age, Turner Syndrome and Idiopathic Short Stature, as well as in adults for treatment of either adult onset or childhood onset GHD. More recently, the EMA approved Hospira's Inflectra™ in September 2013 for the treatment of inflammatory conditions, including rheumatoid arthritis, Crohn's disease, ulcerative colitis and psoriasis. Inflectra is the first biosimilar monoclonal antibody (mAb) therapy approved in Europe and the 14th biosimilar to receive EMA marketing authorization since 2006. The product is a biosimilar for the brand medicine known as Remicade® and gives patients an approved therapeutic alternative to the brand product but at a price that has been reported at as much as 30 percent less than the brand.[20]

"As every rheumatologist knows, the biggest downside about biologics has been their price, and inevitably and appropriately there's been some restrictions almost wherever you practice. And so I guess the excitement about biosimilars, at least in the UK, is that they will be a bit cheaper, and that ought to enable us to treat more patients appropriately."

- Professor John Isaacs, Professor of Clinical Rheumatology at Newcastle University, UK

Safety

In addition to the years of manufacturers' experience with these therapies in Europe, Americans can rely on strict oversight by the FDA to ensure the safety of biosimilars and interchangeable biologics. The FDA has made it clear that approved biosimilars, like all chemical and biologic medicines, must be held to a very high standard and that interchangeable biologics will meet additional requirements in keeping with BPCIA provisions.

FDA currently uses state-of-the-art science to review and approve biologics. FDA's extensive expertise and in-depth understanding of biologic products will be applied to biosimilars and will be evaluated based on the same scientific principles, and the same "highly similar" analytical standards applied to all biologics.

The highly similar regulatory standard is conceptually the same standard currently applied to brand biologics undergoing manufacturing changes—a showing of similarity between batches of active ingredients before and after the change. This enables the FDA to conclude that batches have no clinically meaningful difference, and that they retain the same safety as the product before the change was made. Achieving this distinction will also factor into determining interchangeability.

Once FDA-approved, these medicines will meet scientific and clinical criteria and will have gone through rigorous analysis. Patients, doctors and others can be assured that biosimilars will be safe, effective, high quality alternatives to costly brand biologic drugs.

"The high standards for approval of biosimilar and interchangeable products means that patients and health care professionals can be assured that when those products go to market, they will meet the standards of safety, efficacy and high quality that everyone expects and count on. Efforts to undermine trust in these products are worrisome and represent a disservice to patients who could benefit from these lower-cost treatments."

- FDA Commissioner Margaret Hamburg, MD

Glossary

Affordable Care Act (ACA)
The ACA is a law passed in March of 2010 that laid out many changes to the American healthcare system. Among the many provisions, it includes a measure to pave the way for biosimilar development, licensure and distribution in the United States, and the Biologics Price Competition and Innovation Act (BPCIA).

Biologic
Biological products, or biologics, are medical products made from a variety of natural sources (human, animal or microorganisms) that can be used in the treatment, prevention or diagnosis of diseases and medical conditions.

Biologics can include a wide range of products; vaccines, blood and blood components, allergenics, somatic cells, gene therapy, tissues, and proteins. Examples include growth hormones to treat growth failure, cytokines to treat anemia, monoclonal antibodies to treat cancer. Unlike most traditional, small-molecule prescription drugs that are made through chemical processes, biological products are generally made from human and/or animal materials. Biological products are usually larger and have a more complex structure than most small-molecule prescription drugs.

Biologics Price Competition and Innovation Act (BPCIA)
The BPCIA creates an abbreviated licensure pathway for biological products shown to be biosimilar to, and/or interchangeable with, an FDA-licensed biological reference product. The objectives of the BPCIA are similar to those of the Drug Price Competition and Patent Term Restoration Act of 1984 (Pub. L. 98–417) (commonly referred to as the "Hatch-Waxman Act"), which made safe and affordable generic drugs available to consumers through establishing an abbreviated pathway for their approval under the Federal Food, Drug, and Cosmetic Act (FD&C Act).

Biosimilar
A biosimilar is a biologic medicine that will be approved by stringent regulatory pathways in the EU, Japan, Canada, and Australia showing that the biosimilar is highly similar to a previously-approved brand biologic. Biosimilars are approved for use and made available following the expiration of patents on an original biological product. These products are often available at a lower-cost than expensive brand biologic medicines. The FDA is beginning the process in the United States to review and approve biosimilar therapies based on the pathway laid out in the Biologics Price Competition and Innovation Act (BPCIA,) as part of the Affordable Care Act of 2010.

Center for Biologics Evaluation and Research (CBER)
CBER is the Center within FDA that regulates biological products for human use under applicable federal laws, including the Public Health Service Act and the Federal Food, Drug and Cosmetic Act. CBER protects and advances the public health by ensuring that biological products are safe and effective and available to those who need them. CBER also provides the public with information to promote the safe and appropriate use of biological products.

Center for Drug Evaluation and Research (CDER)
The Center for Drug Evaluation and Research (CDER) within the FDA performs an essential public health task by making sure that safe and effective drugs are available to improve the health of people in the United States. CDER regulates over-the-counter and prescription drugs, including biological therapeutics and generic drugs.

Clinical Trial
An investigation to discover or verify the clinical, pharmacological, and/or other pharmacodynamic effects of a pharmaceutical product to ascertain its safety and/or efficacy. Clinical trials in drug and biologic development are a series of controlled tests following a pre-determined plan or protocol in humans that determines the safety and efficacy of the tested product or treatment. Clinical trials in biosimilar and interchangeable biologic development are controlled tests following a pre-determined plan or protocol in humans that confirm biosimilarity or interchangeability following nonclinical demonstration of biosimilarity and/or interchangeability.

Dosage Form
Pharmaceutical products in the form that they are intended for administration to or by the patient (i.e., injectable, capsule, tablet, liquid).

Efficacy
A measure of the ability of a medicine or treatment to achieve a desired result.

United States Food and Drug Administration (FDA)
The FDA is the federal agency responsible for

protecting the public health by assuring the safety, efficacy and security of human and veterinary drugs, biological products, medical devices, our nation's food supply, cosmetics, and products that emit radiation. The FDA is also responsible for advancing the public health by helping to speed innovations that make medicines more effective, safer, and more affordable and by helping the public get the accurate, science-based information they need to use medicines and foods to maintain and improve their health.

Guidance
Guidance documents represent a regulatory agency's current thinking on a particular subject. According to the FDA, guidance does not "create or confer any rights for or on any person and do not operate to bind FDA or the public. An alternative approach may be used if such approach satisfies the requirements of the applicable statute, regulations, or both."

Immunogenicity
The ability of a substance, such as an antigen, to elicit immune responses in the body. Immunogenic reactions could occur in all therapies that contain antigens, including biologic and biosimilar therapies. Immunogenicity can be triggered intentionally, like a vaccine, where antigens are introduced into the body to produce a specific, desired immune response, such as immunity to pathogens (e.g., smallpox or polio). Unintentional immunogenicity occurs when a person's immune response to an antigen is unforeseen. Some immune systems are sensitive to specific antigens in the environment, leading to allergies and some can mount a response, in some cases with clinical manifestations, to antigens contained in biologic and biosimilar therapies.

Interchangeable Biologic
Interchangeability is the FDA designation made once it has been determined that substituting, or interchanging, a reference product with its equivalent will produce the same clinical result for patients, with no difference in safety or efficacy. Federal law states that interchangeable products can be substituted at a pharmacy without the intervention of a physician.

International Nonproprietary Names (INN)
According to the World Health Organization (WHO), INN is the name given to an active pharmaceutical substance or active pharmaceutical ingredients to facilitate identification. Each INN is a unique name that is globally recognized and is public property. A nonproprietary name is also known as a generic or proper name.

No clinically meaningful difference
No clinically meaningful difference refers to the scientific concept that a biosimilar will treat the same disease with the same safety and efficacy as the brand biologic product. This includes data and statistical analysis showing that the drug is safe, potent and pure.

Pharmacovigilance
The pharmacological science relating to the monitoring, detection, assessment, and prevention of adverse events in humans pursuant to treatment from pharmaceutical products.

Pharmacy Practice Act
Pharmacy practice acts are the laws, regulations and rules that govern the practice of pharmacy in each state.

Potency
A measure of drug activity expressed in terms of the amount required to produce an effect of given intensity.

Public Health Service (PHS) Act
Most, but not all, biologic products are licensed under the PHS Act. Small-molecule prescription drugs are approved under the Federal Food, Drug and Cosmetic Act (the FD&C Act).

Reference (original) Product
Medicine developed and distributed by an original company that has been approved and is being referenced in the creation of a biosimilar therapy.

Similarity
A determination made by the FDA based on a rigorous scientific process that includes testing and analysis to confirm that there is no clinically meaningful difference between a biosimilar or interchangeable biologic and the reference product.

Substitution
The pharmacy practice of dispensing an equivalent and interchangeable medicine to the prescribed medicine without requiring consultation with the prescriber. "Automatic substitution" refers to medicines identified as equivalent and interchangeable that the private or public entity paying for the medication has requested be substituted by the pharmacist.

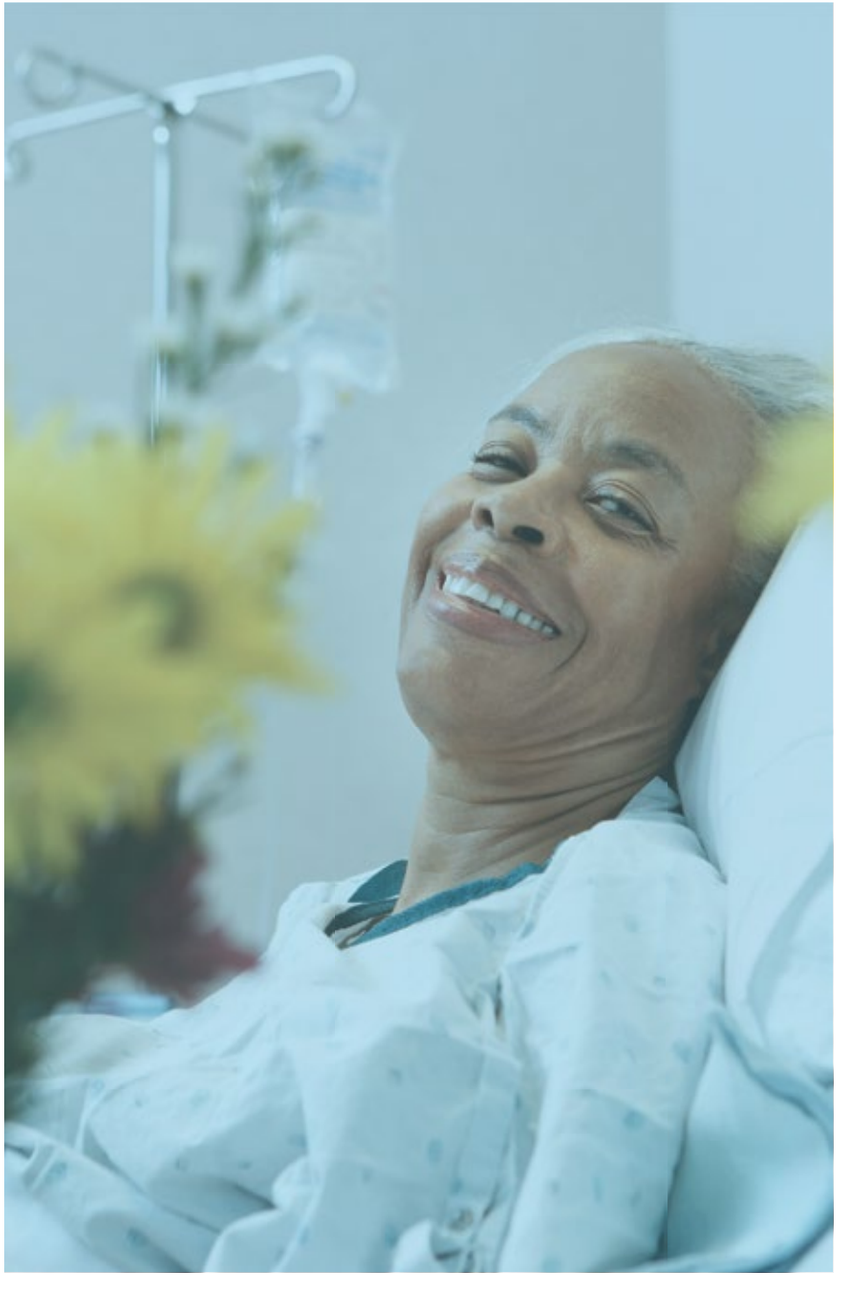
Appendix

Biosimilar Development Process

The approach to biosimilar development is fundamentally different to that of new molecule biologics.

New biologics are approved on the basis of demonstration of a significant clinical benefit. This is done by determining efficacy and safety, either against placebo, or currently available standard of care, and this is done through extensive clinical trials.

Typically, clinical trials are conducted in a series of steps, called phases. Each phase is designed to answer a separate research question (Reference: http://www.nlm.nih.gov/services/ctphases.html). Before a drug is approved, there are generally 3 phases of clinical development:

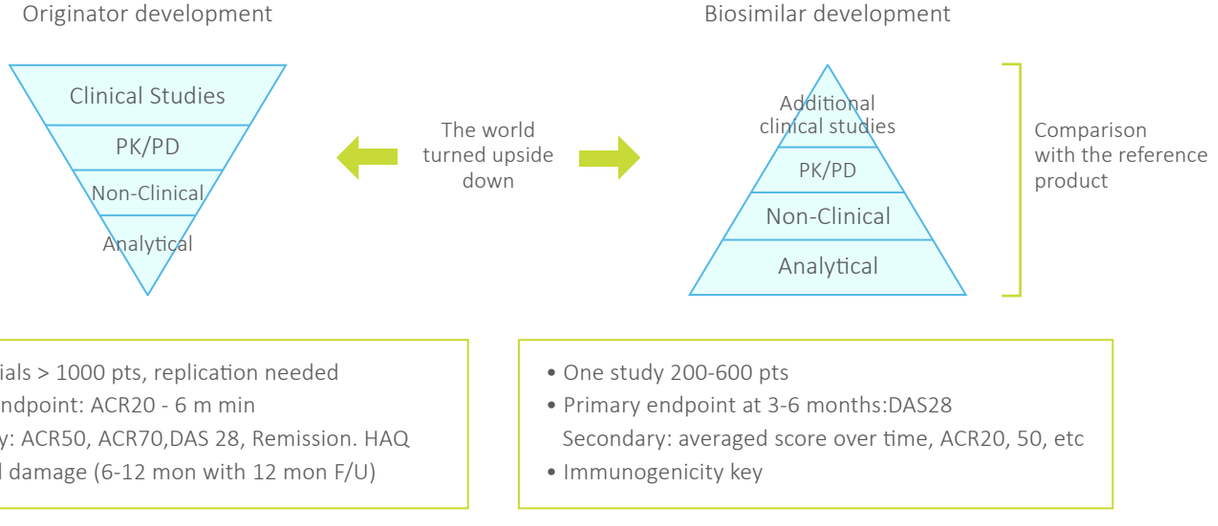


- **Phase I:** A new biologic is evaluated in a small group of patients for the first time, to look at safety, to begin to determine what is the most appropriate dose for use, and to identify side effects. Phase I studies can also include pharmacokinetic (PK) evaluations, designed to determine how the body affects the drug after administration, from absorption to elimination, and pharmacodynamic (PD) evaluations that look at how the drug impacts the body.

- **Phase II:** The biologic is given to a larger group of patients, further evaluating the best dose, determining if it is effective, and to further evaluate its safety.

- **Phase III:** The biologic is given to large groups of patients (hundreds or thousands) to confirm its efficacy and further evaluate its safety. Generally, one phase III study is performed for each sought product indication. As such, the clinical program portion of new biologic development is very extensive, time-consuming and expensive. On the other hand, determination of the new biologic's molecular structure and function, performed through analytical and in vitro evaluation (analytical characterization) is less intense and comprehensive.

Biosimilar Development Turns the World Upside Down



Full Text of BPCIA Law laying out biosimilar pathway-
(Section 351(k) of the Public Health Service Act):

''(k) LICENSURE OF BIOLOGICAL PRODUCTS AS BIOSIMILAR OR INTER-CHANGEABLE.—
(1) IN GENERAL.—Any person may submit an application for licensure of a biological product under this subsection.

(2) CONTENT.—

(A) IN GENERAL.—
(i) REQUIRED INFORMATION.—An application submitted under this subsection shall include information demonstrating that—
(I) the biological product is biosimilar to a reference product based upon data derived from—
(aa) analytical studies that demonstrate that the biological product is highly similar to the reference product notwithstanding minor differences in clinically inactive components;
(bb) animal studies (including the assessment of toxicity); and
(cc) a clinical study or studies (including the assessment of immunogenicity and pharmacokinetics or pharmacodynamics) that are sufficient to demonstrate safety, purity, and potency in 1 or more appropriate conditions of use for which the reference product is licensed and intended to be used and for which licensure is sought for the biological product;
(II) the biological product and reference product utilize the same mechanism or mechanisms of action for the condition or conditions of use prescribed, recommended, or suggested in the proposed labeling, but only to the extent the mechanism or mechanisms of action are known for the reference product;
(III) the condition or conditions of use pre scribed, recommended, or suggested in the labeling proposed for the biological product have been previously approved for the reference product;
(IV) the route of administration, the dosage form, and the strength of the biological product are the same as those of the reference product; and
(V) the facility in which the biological product is manufactured, processed, packed, or held meets standards designed to assure that the biological product continues to be safe, pure, and potent.
(ii) DETERMINATION BY SECRETARY.—The Secretary may determine, in the Secretary's discretion, that an element described in clause (i)(I) is unnecessary in an application submitted under this subsection.
(iii) ADDITIONAL INFORMATION.—An application submitted under this subsection—
(I) shall include publicly-available information regarding the Secretary's previous determination that the reference product is safe, pure, and potent; and
(II) may include any additional information in support of the application, including publicly- available information with respect to the reference product or another biological product.

(B) INTERCHANGEABILITY.—An application (or a supplement to an application) submitted under this sub section may include information demonstrating that the biological product meets the standards described in para graph (4).
(3) EVALUATION BY SECRETARY.—Upon review of an application (or a supplement to an application) submitted under this subsection, the Secretary shall license the biological product under this subsection if—
(A) the Secretary determines that the information sub mitted in the application (or the supplement) is sufficient to show that the biological product—
(i) is biosimilar to the reference product; or
(ii) meets the standards described in paragraph (4), and therefore is interchangeable with the reference product; and
(B) the applicant (or other appropriate person) consents to the inspection of the facility that is the subject of the application, in accordance with subsection (c).

(4) SAFETY STANDARDS FOR DETERMINING INTERCHANGEABILITY.—Upon review of an application submitted under this subsection or any supplement to such application, the Secretary shall determine the biological product to be interchangeable with the reference product if the Secretary determines that the information submitted in the application (or a supplement to such application) is sufficient to show that—
(A) the biological product—
(i) is biosimilar to the reference product; and
(ii) can be expected to produce the same clinical result as the reference product in any given patient; and
(B) for a biological product that is administered more than once to an individual, the risk in terms of safety or diminished efficacy of alternating or switching between use of the biological product and the reference product is not greater than the risk of using the reference product without such alternation or switch.

(5) GENERAL RULES.—
(A) ONE REFERENCE PRODUCT PER APPLICATION.—A biological product, in an application
submitted under this subsection, may not be evaluated against more than 1 reference product.
(B) REVIEW.—An application submitted under this subsection shall be reviewed by the division within the Food and Drug Administration that is responsible for the review and approval of the application under which the reference product is licensed.
(C) RISK EVALUATION AND MITIGATION STRATEGIES.—
The authority of the Secretary with respect to risk evaluation and mitigation strategies under the Federal Food, Drug, and Cosmetic Act shall apply to biological products licensed under this subsection in the same manner as such authority applies to biological products licensed under subsection (a).

(6) EXCLUSIVITY FOR FIRST INTERCHANGEABLE BIOLOGICALPRODUCT.—Upon

review of an application submitted under this subsection relying on the same reference product for which a prior biological product has received a determination of inter changeability for any condition of use, the Secretary shall not make a determination under paragraph (4) that the second or subsequent biological product is interchangeable for any condition of use until the earlier of—
(A) 1 year after the first commercial marketing of the first interchangeable biosimilar biological product to be approved as interchangeable for that reference product;
(B) 18 months after—
(i) a final court decision on all patents in suit in an action instituted under subsection (l)(6) against the applicant that submitted the application for the first approved interchangeable biosimilar biological product; or
(ii) the dismissal with or without prejudice of an action instituted under subsection (l)(6) against the applicant that submitted the application for the first approved interchangeable biosimilar biological product; or
(C)(i) 42 months after approval of the first inter changeable biosimilar biological product if the applicant that submitted such application has been sued under sub section (l)(6) and such litigation is still ongoing within such 42-month period; or
(ii) 18 months after approval of the first interchange able biosimilar biological product if the applicant that sub mitted such application has not been sued under subsection (l)(6). For purposes of this paragraph, the term 'final court decision' means a final decision of a court from which no appeal (other than a petition to the United States Supreme Court for a writ of certiorari) has been or can be taken.

(7) EXCLUSIVITY FOR REFERENCE PRODUCT.—
(A) EFFECTIVE DATE OF BIOSIMILAR APPLICATION APPROVAL.—Approval of an application under this sub section may not be made effective by the Secretary until the date that is 12 years after the date on which the reference product was first licensed under subsection (a).
(B) FILING PERIOD.—An application under this sub section may not be submitted to the Secretary until the date that is 4 years after the date on which the reference product was first licensed under subsection (a).
(C) FIRST LICENSURE.—Subparagraphs (A) and (B) shall not apply to a license for or approval of—
(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.

(8) GUIDANCE DOCUMENTS.—
(A) IN GENERAL.—The Secretary may, after opportunity for public comment, issue guidance in accordance, except as provided in subparagraph (B)(i), with section 701(h) of the Federal Food, Drug, and Cosmetic Act with respect to the licensure of a biological product under this subsection. Any such guidance may be general or specific.
(B) PUBLIC COMMENT.—
(i) IN GENERAL.—The Secretary shall provide the public an opportunity to comment on any proposed guidance issued under subparagraph (A) before issuing final guidance.
(ii) INPUT REGARDING MOST VALUABLE GUIDANCE.—
The Secretary shall establish a process through which the public may provide the Secretary with input regarding priorities for issuing guidance.
(C) NO REQUIREMENT FOR APPLICATION CONSIDERATION.—
The issuance (or non-issuance) of guidance under subparagraph (A) shall not preclude the review of, or action on, an application submitted under this subsection.
(D) REQUIREMENT FOR PRODUCT CLASS-SPECIFIC GUIDANCE.—If the Secretary issues product class-specific guidance under subparagraph (A), such guidance shall include a description of—
(i) the criteria that the Secretary will use to deter mine whether a biological product is highly similar to a reference product in such product class; and
(ii) the criteria, if available, that the Secretary will use to determine whether a biological product meets the standards described in paragraph (4).

(E) CERTAIN PRODUCT CLASSES.—
(i) GUIDANCE.—The Secretary may indicate in a guidance document that the science and experience, as of the date of such guidance, with respect to a product or product class (not including any recombinant protein) does not allow approval of an application for a license as provided under this subsection for such product or product class.
(ii) MODIFICATION OR REVERSAL.—The Secretary may issue a subsequent guidance document under subparagraph (A) to modify or reverse a guidance document under clause (i).
(iii) NO EFFECT ON ABILITY TO DENY LICENSE.—Clause (i) shall not be construed to require the Secretary to approve a product with respect to which the Secretary has not indicated in a guidance document that the science and experience, as described in clause (i), does not allow approval of such an application.

Table: Biosimilars approved in the EU

Resources: FDA.gov

Product name	Active substance	Therapeutic area	Authorization date	Manufacturer/ Company name
Abasria	Insulin glargine	Diabetes	CHMP[21] positive opinion 26 Jun 2014	Eli Lilly/Boehringer Ingelheim
Abseamed	epoetin alfa	Anaemia Cancer Chronic kidney failure	28 Aug 2007	Medice Arzneimittel Pütter
Bemfola	follitropin alfa	Anovulation (IVF)	CHMP positive opinion 23 Jan 2014	Finox Biotech
Binocrit®	epoetin alfa	Anaemia Chronic kidney failure	28 Aug 2007	Sandoz
Biograstim	filgrastim	Cancer Haematopoietic stem cell transplantation Neutropenia	15 Sep 2008	CT Arzneimittel
Epoetin alfa Hexal	epoetin alfa	Anaemia Cancer Chronic kidney failure	28 Aug 2007	Hexal
Filgrastim Hexal	filgrastim	Cancer Haematopoietic stem cell transplantation Neutropenia	6 Feb 2009	Hexal
Grastofil®	filgrastim	Neutropenia	18 Oct 2013	Apotex
Inflectra	infliximab	Ankylosing spondylitis Crohn's disease Psoriatic arthritis Psoriasis Rheumatoid arthritis Ulcerative colitis	10 Sep 2013	Hospira

Product name	Active substance	Therapeutic area	Authorization date	Manufacturer/ Company name
Nivestim	filgrastim	Cancer Haematopoietic stem cell transplantation Neutropenia	8 Jun 2010	Hospira
Omnitrope	somatropin	Pituitary dwarfism Prader-Willi syndrome Turner syndrome	12 Apr 2006	Sandoz
Ovaleap	follitropin alfa	Anovulation (IVF)	27 Sep 2013	Teva Pharma
Ratiograstim	filgrastim	Cancer Haematopoietic stem cell transplantation Neutropenia	15 Sep 2008	Ratiopharm
Remsima	infliximab	Ankylosing spondylitis Crohn's disease Psoriatic arthritis Psoriasis Rheumatoid arthritis Ulcerative colitis	10 Sep 2013	Celltrion
Retacrit	epoetin zeta	Anaemia Autologous blood transfusion Cancer Chronic kidney failure	18 Dec 2007	Hospira
Somatropin Biopartners	somatropin	Growth hormone deficiency	5 Aug 2013	BioPartners
Tevagrastim	filgrastim	Cancer Haematopoietic stem cell transplantation Neutropenia	15 Sep 2008	Teva Generics
Zarzio	filgrastim	Cancer Haematopoietic stem cell transplantation Neutropenia	6 Feb 2009	Sandoz

*Data collected on 12 May 2011, updated on 4 July 2014
IVF: in vitro fertilization.
Source: EMA

Source: http://gabionline.net/Biosimilars/General/Biosimilars-approved-in-Europe

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[15] http://www.fda.gov/AboutFDA/WhatWeDo/History/ProductRegulation/SelectionsFromFDLIUpdateSeriesonFDAHistory/ucm081964.htm

[16] Haustein R, de Millas Christoph et al. “Saving money in the European healthcare system with biosimilars”. Generics and Biosimilars Initiative Journal (GaBI Journal).
2012;1(3-4). 120-6.

[17] Estimates from Sandoz and Hospira

[18] Haustein R, de Millas Christoph et al. “Saving money in the European healthcare system with biosimilars”. Generics and Biosimilars Initiative Journal (GaBI Journal). 2012;1(3-4). 120-6.

[19] For a detailed timeline of the approval process for Inflectra, see:
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