The New Frontier for Improved Access to Medicines:

Biosimilars & Interchangeable Biologic Products







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Bringing Medical Breakthroughs to Patients and their Families

It is an especially exciting time in the advancement of biosimilar technology and treatments. Over the past few years, great progress has been made in the development and approval of biosimilar products in the United States, the European Union (E.U.) and across the globe. Research advances have yielded safe and effective biosimilars that increase the quality and length of patients' lives. Today, there are more than 60 biosimilar products approved worldwide and biosimilar medicines have launched in about 80 countries.

The role of biologic drugs in the health care system is expanding—while only two percent of America's patients use biologics, they account for about 40 percent of prescription drug spending in the U.S. Biosimilars offer the potential for tens of billions of dollars in savings for the American health care system, and improve access for patients. Biosimilar versions of costly brand biologics are now available in the United States for millions of people suffering from cancer, arthritis, Crohn's disease, psoriasis and other diseases. Similar to the advent of generic medications more than 35 years ago, biosimilars have the potential to ensure all patients can benefit from advances in biopharmaceutical research. Continued research is needed to yield new biosimilars and ensure sustained access to these lifesaving medications for patients.

We must never take health care access and savings for granted. The Biosimilars Council looks forward to working with all stakeholders to ensure and expand access to biosimilars—a proven, reliable way to drive down the cost of medicine, which helps patients and benefits our economy and society. This handbook is designed to be a reference tool for health care professionals as well as patients interested in learning more about biosimilars and interchangeable biologics. It is important to define terminology that will be new to some (indicated in bold and listed in the glossary) and clarify the underlying science and expertise that goes into making and approving these safe, high-quality medicines.

We live in an era of unprecedented medical breakthroughs for patients. Not only are there therapies available today to treat conditions once considered life-threatening, the availability of generics means that there are also more medicines available at a lower cost than ever before. Today, patients benefit from the positive impact of generic medicines, which have made millions of doses of costly brand medications available at a lower price.

Biosimilars hold the key to ensuring affordable access to biologic medicines for all consumers. The Biosimilars Council exists to educate, advocate, and promote the development of these products through resources such as this handbook.

Christine Simmon Executive Director, The Biosimilars Council September 2017

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Innovation & Access

Advancements in the research and development of biologic medicines have pushed the frontiers of science to bring lifesaving and life-altering treatments to patients suffering with deadly diseases. For example, thanks to biologic research, remarkable progress has been made in treating many types of cancers. Biologic therapies have also helped patients make great strides in managing chronic diseases like multiple sclerosis, diabetes, rheumatoid arthritis, and Crohn's disease.



The Rising Cost of Biologics

Biosimilar Savings: Impact of Biosimilars on Projected Spending for 11 Biologics \$140 MILLION \$120 MILLION \$110 MILLION \$100 MILLION \$

\$80 MILLION \$60 MILLION \$40 MILLION \$20 MILLION 2012 2013 2014 2015 2016 2017 2108 2019 2020 2021 2022 2023 2024 Source: Express Scripts

> Given the amount of research, it is no surprise that biologic medicines now account for more than a quarter of annual Center for Drug Evaluation and Research (CDER) drug approvals in the United States, compared with only 13 percent from 2004-2008.¹ In 2015, seven of the 10 top-selling medicines were biologics.² 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 907 new biologics in development, targeting more than 100 diseases.³ Notably, the global biologics market totaled \$200 billion in 2013, and is expected to soar to \$387 billion by the end of 2019, at a compound annual growth rate of 10.6 percent.

Biologic medicines are costly. While only 2 percent of the U.S. population uses biological drugs, biologics account for 40 percent of prescription drug spending in the U.S.⁴ Originator brand biologics can cost the health care system as much as several hundred thousand dollars per patient, 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, thus making safe and effective alternatives an imperative for patients. Data also show that biologic prices keep rising. Between 2011 and 2012, prices for specialty drugs—drugs including biologics—increased by 12.9 percent.⁵

Fortunately, more affordable options for many patients who rely on biologic treatments are beginning to enter the market: biosimilars. The approval of biosimilar and interchangeable biologic products will generate competition that lowers costs for patients, providers and the overall health care system. Some estimates suggest that during the first 10 years of biosimilar availability, consumers could save as much as \$250 billion.⁴ Biosimilars and interchangeable biologic products are intended to create the market dynamics needed to lower the cost of biologics and provide patients with much-needed access to lifesaving treatments. Furthermore, biosimilars drive competition to treatment categories where there are few options, if any. This competition stimulates further investment and innovation in health care.

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

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Biosimilars 101

Today's health care arsenal includes **biological** products, or biologics, that are used in the treatment, prevention or diagnosis of diseases and medical conditions. Unlike most traditional small-molecule prescription drugs that are made through chemical processes, biological products are generally made from human and/or animal materials through complex processes. Thanks to newer types of biologic medicine known as **biosimilars** and **interchangeable biologic products**, advanced medicines will become available at a lower cost to millions of patients.

A **biosimilar** is a biologic medicine that is highly similar to a previously approved reference biologic currently on the market. Biosimilars are developed to provide safe, effective alternative versions of existing biologic medicines (known as "**reference products**") with scientifically comparable quality, safety and **efficacy**.

Like a biosimilar, an **interchangeable** biologic product is highly similar to a **Food and Drug Administration (FDA)** approved reference product and meets additional standards for interchangeability. An interchangeable biologic product may be substituted for the reference product by a pharmacist without the intervention of the health care provider who prescribed the reference product, in line with how most patients currently receive generic medicines.

Because all biologic medicines, including biosimilars, are produced from living organisms rather than chemical compounds, they are more complex and have much larger molecules. Due to the nature of a biologic product, the development process for biosimilars is very complex. To this end, biosimilars are subject to the same rigorous FDA standards as their reference products to ensure they have the same safety and efficacy as their biologic counterpart. This is the same process used to assess variations of the reference product over its lifecycle. The final product is analyzed with some of the most sophisticated and innovative pharmaceutical technology available today and assessed by FDA medical, analytical and statistical experts. With the approval of the first biosimilars in the United States and research underway for many more, there is great scientific and regulatory momentum for biosimilars.

Biosimilars: A Safe & Effective Option for Patients

In the U.S., biosimilar usage and approvals are on the rise; access to these safe, effective treatments offers patients improved health outcomes.



What is a Biosimilar?

A biosimilar is a biologic medicine that is highly similar to a brand biologic medicine.

In the U.S., biosimilar usage and approvals are on the rise; access to these safe, effective treatments offer patients improved health outcomes.





In the first 7 years since the passage of the BPCIA, the FDA has approved 7 biosimilars with 60+ more in development^{1,2,3}



In Europe, ~35 biosimilars approved in at least 8 therapeutic classes⁴

Biosimilars are Safe, Effective, More Affordable & Offer Improved Patient Access.



Comparable safety and efficacy as their biologic counterpart



Same

mechanism

of action



Rigorous FDA testing and review; less cost to patients and the health system



Companies that manufacture biosimilars are committed to providing safe, effective products

References

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Biosimilar Approvals in the U.S. and E.U.

Safety & Sameness

Over the last decade, the E.U. monitoring system for safety concerns has not identified any relevant difference in the nature, severity, or frequency of adverse effects with biosimilars and their originator biologic medicines.⁶ In addition to the years of manufacturers' and patients' safe experience with these therapies in Europe, Americans can rely on strict scientific scrutiny by the FDA to ensure the safety of biosimilars. The Patient Protection and Affordable Care Act (Affordable Care Act), signed into law by President Obama on March 23, 2010, created an abbreviated licensure pathway for biological products that are demonstrated to be "biosimilar" to or "interchangeable" with an FDAlicensed biological product. This pathway is provided in the part of the law known as the Biologics Price Competition and Innovation Act (BPCIA). Under the BPCIA, a biological product may be demonstrated to be "biosimilar" if data show that, among other things, the product is "highly similar" to an already-approved biological product. 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.⁷

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



"The high standards for approval of biosimilar and interchangeable products mean 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."

Margaret Hamburg, M.D. Former U.S. FDA Commissioner 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 the new batches have no clinically meaningful difference and they retain the same safety as the product before the change was made. Any FDA-approved biosimilar is within the acceptable range of variability observed between batches of the original reference product.

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



How are Biosimilars Developed and Made?

THE GOAL: "NO CLINICALLY MEANINGFUL DIFFERENCES"

Because biosimilars 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 and effective therapy that treats a disease the same way as the original biologic medicine, while also falling within the same variability limits as batches of the originator biologic medicine. To achieve this, the FDA requires biosimilars to meet a rigorous scientific standard of similarity and be deemed "highly similar" before they are made available to patients. Biosimilar manufacturers use a reverse engineering process to produce a biosimilar; in that, they do not always have access to the original cell line used to produce the originator biologic medicine, but must fall within the originator's batch variability limits for regulatory approval. Biosimilar manufacturers conduct batch analyses of multiple batches of the originator biologic medicine, perform analytical and functional characterizations, and upstream and downstream manufacturing processes developed based on previously defined quality attributes. Similarity is achieved and verified through a scientific process that confirms there is no clinically meaningful difference between the biosimilar and the original product, even if there are slight differences in clinically inactive components. The same approach is used when manufacturing process changes are instituted by the originator biologic company.

According to the FDA, that means patients and health care professionals will be able to rely upon the safety and effectiveness of the biosimilar or interchangeable product, just as they would the reference product.

Unlike with 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 across multiple batches of the originator medicine throughout the product development process. These tests cover scientific quality, nonclinical and clinical parameters. This analysis can also include a wide variety of other techniques beyond costly clinical trials. Newly developed analytical tools allow biosimilar developers to characterize molecules with greater precision than ever before, which will help to expedite these approvals down the road.

THE BIOSIMILAR DEVELOPMENT PROCESS

Because the development of a biosimilar is based on what is known and proven through the originator biologic medicine **clinical trials** with the reference product rather than reproving the same point, the steps for creating a biosimilar focus on establishing that a biosimilar is structurally and functionally highly similar to the reference product. The concept is simple: molecules that have essentially similar structure will generally produce the same reaction in the body.

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

STEP 1: PRODUCT DEVELOPMENT: CHARACTERIZATION AND PERFECTING THE PROCESS

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

Once this information is obtained, the next phase is the development of the manufacturing process, which delivers the highly similar therapy. The fundamental principle for demonstrating biosimilarity is that the biologic active substance a biosimilar contains is established as indistinguishable from that contained within the originator biologic medicine. 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.

There are two regulatory designations in the U.S.: a biosimilar medicine and an interchangeable biologic. For scientists seeking regulatory designation of their medicine as an interchangeable biologic, additional testing must be performed to demonstrate that a medicine meets the supplementary requirements to earn that classification. The FDA requires that a product with a designation as interchangeable can be expected to produce the same clinical result as the originator biologic product in any given patient, and for a biologic that is administered more than once, that the risk of switching is not greater than the risk of maintaining the patient on the originator biologic.



STEP 2: BIOSIMILAR CONFIRMATION VIA STUDIES AND REGULATORY COOPERATION

Once high similarity has been established between the biosimilar and the original biologic medicine through analysis and testing the FDA reviews all the information and determines the additional non-clinical and clinical studies, if any, that will be required to confirm biosimilarity and interchangeability. These analytical and clinical analyses allow FDA to extrapolate multiple indications for the biosimilar without requiring the extensive clinical efficacy trials required for brand biologic approval.

Clinical trials are generally required for biosimilar approval in highly regulated markets, such as the E.U., United States, Japan, Canada and Australia. However, the scope and requirements for biosimilar clinical trials depends on the data submitted. Biosimilar products in the same class may provide clinical trials of different designs and conceivably, clinical trials may not be required at all. Where there is robust and convincing analytical data, for example, and additional data is required, a more tailored clinical trial program may provide a more effective way to demonstrate biosimilarity and interchangeability.

STEP 3: APPROVAL

In the early stages of development, biosimilar manufacturers meet with the FDA to discuss a product development plan and approaches to providing adequate scientific justifications throughout the review process. Before approving any product for patient use, the FDA looks at the totality of evidence and conducts a rigorous review of all the data to determine whether the applicable scientific standards have been successfully met. Once a biosimilar is approved, it can be produced and distributed in the United States.

Patient Access & Savings

Biologic medicines, many of which are specialty medicines, are the most rapidly growing segment of brand-name prescription drug costs in the U.S., with more than \$100 billion in annual spending.⁸ This is creating a disproportionate strain on health spending: while only two percent of America's patients use biologics, they account for about 40 percent of prescription drug spending in the U.S.⁴ As such, the role of biologic drugs in the health care system is expanding. For example, biologic medicines have become the standard of care for many devastating, debilitating and chronic illnesses. While their importance in treating these diseases continues to increase, access to these sometimes lifesaving medicines is denied because health systems simply cannot afford them.

Many stakeholders can benefit from new biosimilars: patients waiting for alternatives to costly biologics; hospitals and care facilities who could reinvest the savings into ongoing in-patient programs, technology, upgraded facilities and additional staff; taxpayers; employers; insurers; state and federal governments; and others who help pay for health care.

For patients, costly biologic medicines are often the only treatments currently available to address many severe diseases. Biologics are used to combat cancer, heart disease, psoriasis, rheumatoid arthritis, asthma, Crohn's disease, diabetes, multiple sclerosis, and other life-threatening illnesses. For patients, biologic medicines often mean quicker recovery times and fewer additional treatments. Unfortunately, the high price tags keep biologic treatments out of reach for many. In coming years, however, many biologic medicines are expected to reach the end of their patents and exclusivity, which will provide an opportunity for a reduction in health care costs and increasing access of lifesaving medicines to patients in need. Access to more affordable biosimilar medicines will improve patients' quality of life and may reduce financial pressures. Increasing access to biosimilars will also help drive down the cost of originator brand biologics, which helps patients and benefits our economy and society.

Competition from biosimilars is important because for many patients, the availability of a high-priced brand biologic for their treatment does not translate into access to these therapies. For example, many rheumatoid arthritis patients in developed countries like Japan, the United States and the E.U. do not have access to these medicines.⁹

Furthermore, in European countries where biosimilars have been introduced, they have increased patient access by as much as 100 percent.¹⁰ The greater use of biosimilars can be attributed to their lower cost, as well as revisions to treatment guidelines that reflect improved cost effectiveness.

The table on page 21 provides a list of patient communities that have a biologic product available but are still waiting for the first or additional biosimilar products to come to market in order to increase access and improve patient outcomes.

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What's at Stake?

Biologics, many of which are specialty medicines, are the most rapidly growing segment of increasing brand-name prescription drug costs in the U.S., with more than \$100 billion in annual spending. Between April 2013 and March 2014, five of the 12 biggest selling drugs in the United States were biologics.¹⁰ 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.¹¹

Recent data show that the cost of many biologics is increasing at a faster annual pace than any other component in health care. It is expected that the biologics market will increase at a rate of more than 20 percent per year, and that by 2025, more than 70 percent of new drug approvals will be biological products.¹² In 2014, United States spending for biologic medicines was approximately \$115 billion, but it is expected to exceed \$250 billion by 2019.⁴ This means that nearly \$5 out of every \$10 the country spends on prescription drugs will be spent on biologics.

In addition to the opportunity to provide millions of patients with lowercost alternatives to brand biologic therapies, there are billions of dollars of savings at stake for America's taxpayers. Estimates from various economic impact studies pin the projected savings from \$44 billion on the low end to as high as \$250 billion over 10 years and \$378 billion over 20 years.¹³ While statistical assumptions for each analysis vary, experts agree on the transformative potential and significant savings from biosimilars. In addition to expanding patient access and reducing health care costs, increasing the affordability of biologic medicines may help to lower the deficit and improve the fiscal soundness of the United States government.

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 safe and effective biosimilar therapies into the markets around the world has been proven to reduce health care costs while at the same time delivering lifesaving treatments to patients in need.

SMART TRADE POLICIES

To achieve the goal of ensuring access to biosimilars throughout the world, it is critical that trade agreements do not erect barriers that would grant lengthy monopoly protections to brand-name biologics manufacturers. U.S. biosimilars companies rely heavily on the ability to market their products abroad. Imposing additional exclusivity in trade agreements would prevent or delay such sales, to the detriment of this growing industry and patient access.

Patients with these conditions:	Are waiting for the first or additional biosimilar products to these biological products in order to increase access:
Rheumatoid Arthritis	Adalimumab (Humira®)
	Etanercept (Enbrel®)
	Rituximab (Rituxan®)
	Infliximab (Remicade®)
Juvenile Idiopathic Arthritis	Adalimumab (Humira®)
	Etanercept (Enbrel®)
Psoriatic Arthritis	Adalimumab (Humira®)
	Etanercept (Enbrel®)
	Infliximab (Remicade®)
Ankylosing Spondylitis	Adalimumab (Humira®)
	Etanercept (Enbrel®)
	Infliximab (Remicade®)
Crohn's Disease, Ulcerative Colitis	Adalimumab (Humira®)
	Infliximab (Remicade®)
Plaque Psoriasis	Adalimumab (Humira®)
	Etanercept (Enbrel®)
	Infliximab (Remicade®)
Non-Hodgkin's Lymphoma	Rituximab (Rituxan®)
Chronic Lymphocytic Leukemia	Rituximab (Rituxan®)
Metastatic Colorectal Cancer	Bevacizumab (Avastin®)
Non-squamous Non-Small Cell Lung Cancer	Bevacizumab (Avastin®)
Metastatic Renal Cell Carcinoma	Bevacizumab (Avastin®)
Multiple Sclerosis	Interferon Beta-1A (Rebif®)
HER2 Overexpressing Breast Cancer	Trastuzumab (Herceptin®)
HER2 Overexpressing Metastatic Gastric or Gastroesophageal Junction Adenocarcinoma	Trastuzumab (Herceptin®)
Non-Myleloid Malignancies receiving myelosuppressive anti-cancer drugs	Pegfilgrastim (Neulasta®)
Neovascular (wet) Age-Related Macular Degeneration; Macular Edema Following Retinal Vein Occlusion (RVO); Diabetic Macular Edema	Ranibizumab (Lucentis®)

Source: Based on publicly available information

State Legislation

When a patient goes to a pharmacy to pick up a prescription, a pharmacist may provide the patient with an equivalent and interchangeable generic medicine without having to consult the prescriber. This practice is called **substitution**. Each state has its own laws or regulation regarding the use of brand-name and generic prescription drugs, such as when a generic medication may be substituted for a brand-name medication. These laws, regulations and rules that govern the practice of pharmacy in each state are called **pharmacy practice acts**.

Because biosimilars were not available when generic substitution laws were developed, states must continue to update their pharmacy practice acts to allow for substitution of interchangeable biologic products.

Policy decisions being made today at the state and federal levels and through regulation about biosimilars must be grounded in science. These policies will create a market dynamic that influences biosimilar development and competition for years to come.

FDA-approved generic prescription drugs have produced more than \$1 trillion in savings to state and federal health care programs over the past decade.¹⁴ As state legislatures look for ways to rein in health care costs, they can be assured that the potential savings from biosimilar medicines will also ease the strain on state health budgets and benefit patients and taxpayers alike.





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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 assigned FDA the task of designing the detailed approval pathway for these medicines.

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 patients and health care professionals can rely upon the fact that a biosimilar medicine or interchangeable biologic will treat the same disease as safely and effectively as the original brand product. It is important to understand that the interchangeability designation does not represent a "higher" standard than for a biosimilar product, but rather adds the requirement for additional scientific data related to multiple switches between products. Per the law, a biosimilar must meet safety, efficacy and quality requirements and can be used for all approved indications of the reference product.

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).

Public Health Service Act-Section 351(k)(2)(A)(i) -

- 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);
- The biological product and reference product utilize the same mechanism or mechanisms of action;
- The condition or conditions of use prescribed, recommended, or suggested in the labeling have been previously approved for the reference product;
- The route of administration, the **dosage form**, and strength are the same;
- The facility where the biological product is produced meets standards to ensure that the biosimilar is 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"

What Does the Law Say?

counterpart 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 health care provider that prescribed the original product.

Section 351(k)(4) of the Public Health Service Act 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—
- the biological product-
 - » is biosimilar to the reference product; and
 - » can be expected to produce the same clinical result as the reference product in any given patient; and
 - » 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."



What is the 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. FDA approval is the gold standard for any medicine sold in the United States.

The FDA has taken significant steps to further develop the biosimilar approval process. The Agency has provided guidance documents on the steps that manufacturers should follow when seeking approval for their new medicines, such as securing meetings with the FDA team and demonstrating biosimilarity, so that biosimilars can be approved and sold in the U.S.

In March of 2015, the FDA approved the first biosimilar medicine, Zarxio® a Sandoz biosimilar for the reference brand Neupogen® approved for each of the five indications sought in its application. Subsequently, five additional biosimilars have been approved in the U.S., and five proposed biosimilars are under FDA review and more than 60 biosimilars are in the pipeline of the FDA's Biosimilar Product Development Program.¹⁵

As of mid-2017, the following guidance documents have been released by FDA:

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

- Guidance for Industry on Scientific Considerations in Demonstrating Biosimilarity to a Reference Product
- Guidance for Industry on Quality Considerations in Demonstrating Biosimilarity to Reference Protein Product
- Guidance for Industry on Clinical Pharmacology Data to Support a Demonstration of Biosimilarity to a Reference Product
- Draft Guidance for Industry on Reference Product Exclusivity for Biological Products Filed Under Section 351 (a) of the Public Health Service Act
- Guidance for Industry on Formal Meetings Between the FDA and Biosimilar Biological Product Sponsors or Applicants
- Draft Guidance for Industry on Labeling for Biosimilar Products
- Draft Guidance for Industry on Considerations in Demonstrating Interchangeability with a Reference Product
- Guidance for Industry on Nonproprietary Naming of Biological
 Products
- Draft Guidance for Industry on Biosimilars: Additional Questions and Answers Regarding Implementation of the Biologics Price Competition and Innovation Act of 2009

Bringing Biosimilars to Patients in the U.S. UNANIMOUS SUPREME EUROPE **BPCIA PASSED INTO FDA APPROVES FIRST** FIRST BIOSIMILAR **COURT DECISION ALLOWS APPROVES** LAW AS PART OF THE BIOSIMILAR **REACHES U.S. BIOSIMILARS MARKETING ITS FIRST** (FILGRASTIM-SNDZ/ MARKET PATIENT PROTECTION **UPON FDA APPROVAL,** BIOSIMILAR AND AFFORDABLE ZARXIO®) **NOT 6 MONTHS AFTER** CARE ACT (ACA) **APPROVAL** 2006 2010 **MARCH 2015 SEPTEMBER 2015 JUNE 2017** Source: Based on publicly available information

THE NEW FRONTIER FOR IMPROVED ACCESS TO MEDICINES: BIOSIMILARS & INTERCHANGEABLE BIOLOGIC PRODU

Barriers to Patient Access: Patent Litigation

The BPCIA created not only an approval pathway for biosimilars, but also a mechanism for resolving patent disputes between brand drug companies and biosimilar manufacturers. This complex, multi-step process is known as the biosimilar "patent dance."

Some brand biologic manufacturers have been using the court system and complex biosimilar patent dance litigation to keep their competitors off the market. These brand manufacturer efforts to create a so-called "litigation backlog" are succeeding—as of October 2017, only seven FDA-approved biosimilars are approved for use in the U.S. and of those, only three are marketed to patients.¹⁶ Despite FDA approval, patent litigation from brand biologic manufacturers is stalling biosimilar entry to the market.

As outlined in the BPCIA, the patent dance begins when the biosimilar applicant shares its biosimilar application with the reference product sponsor. Then, two companies exchange lists of patents that may be

"Biosimilars will provide access to important therapies for patients who need them. Patients and the health care community can be confident that biosimilar products approved by the FDA meet the agency's rigorous safety, efficacy and quality standards."

Margaret Hamburg, M.D. Former U.S. FDA Commissioner infringed by the biosimilar and patents that could be licensed to the biosimilar applicant. The two companies go back and forth for several rounds, negotiating over the validity of the patents and their enforceability, until the final step—when the brand company has a last chance to assert additional patents after the biosimilar applicant has provided 180 days' premarketing notice.

While the BPCIA outlines the patent dance as an avenue to resolve patent disputes, the process is voluntary. In June 2017, the Supreme Court issued a unanimous ruling that under federal law, biosimilar applicants can opt out of the patent dance—they cannot be enjoined to share their respective applications with the reference product sponsor.¹⁷ While reference product sponsors can still litigate possible patent disputes without seeing a product application, the Court's ruling gives biosimilar applicants more control in choosing how and when to resolve patent disputes with a reference product sponsor.

Biosimilars in Action: Why Does **Europe Have Greater Access?**

More than a decade of patient use of biosimilars in the E.U. has shown no difference in health outcomes between patients who use a biosimilar and those who take the originator biologic medicine. The European Medicines Agency (EMA) laid out a framework for developing and marketing biosimilars in 2004 and approved the first biosimilar for use in the E.U. in 2006. Since then, dozens of biosimilar medicines have been approved and used by patients in the E.U.¹⁸ Total sales of biosimilar medicines in the E.U. approached an estimated \$500 million through 2014.

Since they were introduced, biosimilars have been used broadly throughout the E.U. to treat patients. In fact, the biosimilars approved for use in the E.U. have an estimated combined 700 million patient days of clinical experience in markets around the world, confirming their safety, efficacy and quality. Cost savings in Europe from biosimilars is estimated to range from \$16 billion to \$43 billion by 2020.19

"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.

John Isaacs, Professor of Rheumatology Newcastle University, U.K.



Furthermore, the six established therapy areas with biosimilar competition consistently demonstrate reduced average list prices. Overall, this increased competition resulted in greater patient access in the whole European market.²⁰ There are many similarities between the U.S. and EMA processes, but, unlike the U.S. regulations, there is no E.U.-wide legal designation for 'interchangeable' biologic products; EMA approves biosimilar products based on the scientific data, and each Member State determines whether biosimilar and reference biologic products are able to be switched by health care professionals or substituted by pharmacists.

Currently, European companies that want to manufacture and market a biosimilar product are required to submit quality 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 approved biosimilars on the market in the E.U., 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. Since 2006, the EMA has approved biosimilars for the prevention and treatment of various disorders related to blood clots in adults, as well as biosimilars to treat rheumatoid arthritis, anemia, low white blood cell counts, inflammatory bowel disease, skin conditions such as psoriasis and various forms of cancer. These products give patients an approved therapeutic alternative to the brand product, but at an average price of 30 percent less than the brand biologic.²¹

Biosimilar medicines have the same safety and efficacy profiles of biologic medicines (reference products). Thus, manufacturers of biosimilars remain committed to creating safe and effective products that undergo a comprehensive FDA review. Their acceptance and availability will ensure sustained access to a supply of important, lifesaving medications for patients. Biosimilar use in the U.S. can and should increase; manufacturers, government and regulatory groups must work together to create policies where patient access is a top priority.

> "[W]e [FDA] still need to be taking meaningful steps to get more low cost alternatives to the market, to increase competition, and to give consumers more options. This is especially true when it comes to complex drugs and biosimilars."

Scott Gottlieb, M.D. U.S. FDA Commissioner

Glossary

Affordable Care Act (ACA)

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

Biologic

Biological products, or biologics, are medicines 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.²² 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 approved by the FDA as 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 is approved by stringent regulatory pathways in the E.U., 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 or regulatory exclusivity on an original biological product. These products are often available to patients at a lower-cost than expensive brand biologic medicines. FDA is approving 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. 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 FDA that regulates drugs under the Federal Food, Drug and Cosmetic Act. CDER 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 some 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 confirms the high similarity established in analytical tests.

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. Most immunogenic responses are not clinically relevant, but some immunogenic responses can raise very significant and potentially severe safety concerns. It is therefore important to monitor the immunogenicity of all biologics, whether they are originator branded products or biosimilars.

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), the 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 generally 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 originator 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 corresponding 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.²³ Before a drug is approved, there are generally three phases of clinical development:

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. This is called Phase I. 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.

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. This is called Phase 2.

The biologic is given to large groups of patients (hundreds or thousands) to confirm its efficacy and further evaluate its safety in studies that are called Phase III. Generally, one phase III study is performed for each product indication sought. 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

BIOSIMILAR DEVELOPMENT ORIGINATOR DEVELOPMENT Clinical Studies The Additional Comparison **Clinical Studies** PK/PD World with the Turned reference PK/PD Non-Clinical Upside product Non-Clinical Analytical Down Analytical Several trials > 1000 pts, replication • One study 200-600 pts needed Primary endpoint at 3-6 Primary endpoint: ACR20 - 6 m min months:DAS28 Secondary: averaged score over time, ACR20, Secondary: ACR50, ACR70, DAS 28. 50. etc Remission. HAQ Immunogenicity key • Structural damage (6-12 mon with 12 mon F/U)

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 prescribed, recommended, or suggested in the labeling proposed for the biological product have been previously approved for the reference product;

 $\left(\mathsf{IV}\right)$ 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 paragraph (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 submitted 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 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 (I)(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 (I)(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 (I)(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 submitted such application has not been sued under subsection (I)(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

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

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.

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