



# *The State of Biosimilars Policy*

*A White Paper from  
The Biologics Prescribers Collaborative*

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## ***BIOLOGICAL MEDICINES LANDSCAPE***

Biologic medicines first became available 25 years ago and have revolutionized the treatment of some of the most complicated and life-threatening illnesses, including multiple sclerosis, rheumatoid arthritis, and a variety of cancers. These medicines are large molecule drugs made from living cells and are manufactured through highly complex processes. In part, due to the intricate development and manufacturing of these agents, biologics are significantly more expensive than traditional, small molecule medicines.

Spending on prescription medications continues to rise each year in the United States. The increase in drug costs – projected by the Centers for Medicare and Medicaid Services Office of the Actuary to be 12.6 percent in 2014 – has outpaced inflation, which has hovered between zero and two percent over the last three years. According to pharmacy benefits manager Express Scripts, even though only two percent of the population use biologic drugs, biologics account for 40 percent of prescription drug spending in the United States.

Enter the biosimilar, which is what its name implies – a biologic that is “similar” to another biologic drug already on the market. Biosimilars are comprised of complex molecules which cannot be exact copies of the reference biologic. These medicines are an important new category of therapy because they have the potential to increase access to biologic therapies and provide cost savings to patients and the health care system. In the United States alone, the cost savings from using biosimilars in comparison to the original biologic are projected to be between \$40 and \$250 billion over the next 10 years<sup>i</sup>, with the first biosimilar to hit the U.S. market expected to contribute about \$5-7 billion in savings. The CBO anticipates between one and three biosimilar entrants per typical innovator biologic.<sup>ii</sup>

The Biologics Price Competition and Innovation Act (BPCIA) was enacted in 2010 and granted the U.S. Food and Drug Administration (FDA) authority to create an abbreviated approval pathway for biosimilars. While it took nearly five years to get the first biosimilar approval in the U.S., there are now five biosimilar medicine approvals and two biosimilars available in the U.S.

FDA indicated to Congress in a March 2017 hearing on the User Fee Acts that the agency is working on reviewing 64 biosimilar development programs for 23 reference biologics.<sup>iii</sup>

The Biologics Prescribers Collaborative (BPC) believes biosimilars will play an increasingly important role in the U.S., providing patients and physicians with greater access to therapeutic options and cost savings. BPC serves as an educational resource to policy makers as they take actions to encourage the development of these medicines while protecting patient safety and the prescribers’ need for transparent medical data. By educating policymakers, BPC hopes to ensure that policies governing the approval and use of biosimilars are crafted carefully to include the latest science, reflect clinical best practice, and uphold patient safety.

BPC represents physician groups whose members regularly prescribe biologic medicines and therefore has a unique and important perspective about their use.

### **FDA Definitions**

**Biological medicines** include a wide range of products such as vaccines, blood and blood components, allergenics, somatic cells, gene therapy, tissues, and recombinant therapeutic proteins. Biologics can be composed of sugars, proteins, or nucleic acids or complex combinations of these substances, or may be living entities such as cells and tissues. In contrast to most drugs that are chemically synthesized and their structure is known, most biologics are complex mixtures that are not easily identified or characterized.

**Biosimilars** are a type of biological product that are licensed (approved) by FDA because they are highly similar to an already FDA-approved biological product, known as the biological reference product (reference product), and have been shown to have no clinically meaningful differences from the reference product.

**Interchangeable** biosimilars, in addition to meeting the biosimilarity standard, are expected to produce the same clinical result as the reference product in any given patient.

## ***DEVELOPING A REGULATORY FRAMEWORK FOR BIOSIMILARS***

FDA has issued several draft and final guidance documents to address key issues that create the framework for the use and approval of biologic medicines, including naming, interchangeability, indication extrapolation and labeling. These documents serve to assist biosimilar manufacturers in generating the needed data to support their biosimilar applications.

### **NAMING**

Biologic medicines are large, complex molecules that are made from living cells. No two biologic medicines can be identical in the way a generic drug is an exact copy of the original brand name drug. As such, it is important that biosimilars, and all biologics, have distinguishable names, an important way to preserve patient safety. Distinguishable names will aid in keeping patient records accurate and in tracking and tracing these agents via post-marketing surveillance.

#### *FDA supports distinguishable naming*

In January 2017, FDA issued its final naming guidance supporting the need for distinguishable names, calling for all biological products to bear a nonproprietary name that includes a unique four-letter suffix. This reflects FDA's thinking that "there is a need to clearly identify biological products to improve pharmacovigilance, and, for the purposes of safe use, to clearly differentiate among biological products that have not been determined to be interchangeable."<sup>iv</sup> BPC agrees with this reasoning and has always supported distinguishable nonproprietary naming since biosimilars and originator biologics are the products of different cell lines produced by different manufacturers.

For an individual patient, a distinct name facilitates the accuracy of the medical record. For evaluating the effect of the drug among patient populations as a whole, distinguishable names allow data identification to be associated with a given drug name instantaneously.

Furthermore, the extreme complexity and large molecular size of biologic medicines mean that even minor differences between two similar biologics can cause unexpected reactions in patients, including unwanted immune responses. Additionally, biologics are extremely sensitive to any changes in the manufacturing process, which has the potential to change how the medicine behaves in the body. In order to more accurately attribute adverse events in patients to specific medicines, it is important that biologic medicines, including biosimilars and interchangeable biosimilars have distinguishable and easily recognizable non-proprietary names.

#### *BPC supports distinguishable naming, but calls for meaningful suffixes*

BPC is concerned that a suffix consisting of a random set of letters (such as 'dyyb') is not easily recognizable and is devoid of meaning. Given the volume of information prescribers handle every day for patients with complicated medical histories, comorbid conditions, multiple medications and different treatment regimens, we believe the suffix must be memorable, which cannot be accomplished when the suffix is random and meaningless. A randomized four-letter code may complicate the achievement of

FDA's goal to improve pharmacovigilance and prevent inadvertent substitution. On the other hand, a memorable suffix could identify the manufacturer, and be easily memorized by prescribers and users of biologics. A suffix that reflects the license-holding manufacturer equips patients, physicians and pharmacists to accurately recall or ascertain specifics about the biosimilar that may differ from those of the originator product, such as approved indications, administration routes or delivery systems.

As the FDA guidance on *Nonproprietary Naming of Biological Products* reinforces, biological products require robust pharmacovigilance because “[a]lthough safety of biological products is rigorously assessed before approval, safety issues that are specific to a manufacturer may arise after approval with any marketed product.” The agency also notes it must be able to track adverse events to a specific manufacturer. An immediately recognizable suffix reflecting the manufacturer’s name will facilitate prompt, accurate adverse event reporting by patients and physicians to the correct manufacturer.

Physicians overwhelmingly favor a meaningful suffix. In early November, BPC released findings of a SERMO poll representing more than 500 physicians across multiple specialties.\* Eighty percent of physicians preferred a meaningful four-letter suffix that noted the biosimilar manufacturer’s name, versus a random four-letter suffix. Only eight percent of physicians preferred a suffix devoid of meaning while 12 percent had no preference.

### *Interchangeable Biosimilars Should Be Assigned Distinguishable Names*

In the January 2017 final guidance for naming, FDA solicited additional input on the naming convention for interchangeable biosimilars. Recognizing the established naming convention, BPC urges FDA to extend this nomenclature to assign distinguishable names to interchangeable biosimilar products. Distinguishable names for interchangeable biosimilars will ensure that manufacturers can better report any adverse events, complying with the regulatory requirement of appropriate event reporting.

*“Physicians need to interact with FDA so the agency understands our biosimilar concerns”*

*- Dr. Gregory Schimizzi,  
BPC*

The necessity to diligently track-and-trace a medicine is not lessened by the fact that it has been deemed interchangeable. Therefore, interchangeable biosimilar medicines should also be assigned distinguishable names. As such, BPC supports extending distinguishable names to interchangeable biological products. We appreciate FDA’s careful consideration of this important issue and its ruling in favor of distinguishable names. However, as prescribers gain real-world experience using these new medicines, FDA should consider if policies should be amended to achieve greater patient benefit and safety, including potentially evolving to a “meaningful” suffix.

## **INTERCHANGEABILITY**

An *interchangeable* biological product is biosimilar to an FDA-approved reference product that meets additional standards for interchangeability. An interchangeable biological 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 January 2017, the agency published *Considerations in Demonstrating Interchangeability With a Reference Product*, its draft industry guidance regarding the information sufficient to show interchangeability. FDA identifies a proposed interchangeable as a “biosimilar to the reference product” and can be “expected to produce the same clinical result as the reference product in any given patient.” BPC believes that the draft guidance preserves safety and efficacy and promotes uptake of biosimilar products.

### *“Back-and-forth” switching studies needed*

BPC supports FDA’s suggestion, per its recent guidance, that clinical studies should demonstrate multiple switches back and forth between the biologic reference product and the proposed biosimilar, not just one

\*Sermo is the largest global social network exclusively for doctors.

switch from the reference product to the biosimilar. Further, using at least two exposure periods to each drug best simulates a patient's experience with changing formularies.

FDA suggests one or more switching studies in all cases, recommending that patients serve as the subjects and U.S.-sourced reference products serve as comparators. Although non-U.S.-sourced reference products have served as comparators in determining biosimilarity, using them for a switching study would only generate data for an interchangeable pair that could not occur in the U.S. BPC agrees with FDA on this matter.

#### *Rigorous data package must justify interchangeability*

The agency pointed out that the additional data needed to demonstrate interchangeability would vary depending on structural and functional complexity, as well as safety concerns. In some cases, only fingerprint quality analyses may adequately supplement a switching study, while other cases may require the accumulation of real-world evidence of the biosimilar in use before its consideration as interchangeable.

In its guidance, FDA advises selecting a condition of use for analysis, and conducting a switching study that supports extrapolation to other conditions. The study must be "adequately sensitive to assess the risk of alternating" between the reference product and the proposed interchangeable biosimilar. BPC strongly urges FDA to insist on a robust, rigorously developed data package to justify extrapolation scientifically, and to be even more demanding in determining interchangeability. (See Extrapolation)

#### *Manufacturers should seek approval for all indications for an interchangeable biosimilar*

BPCIA does not require applicants to seek approval of a biosimilar as interchangeable for all the reference product's conditions of use. However, the FDA guidance directs applicants to do so. We strongly urge FDA to explicitly resolve this ambiguity in the law via its final guidance on interchangeability in favor of requiring approval for all indications of the reference product. BPC is concerned that an interchangeable biosimilar approved for some reference product conditions of use could be substituted inappropriately for an unapproved condition.

## **INDICATION EXTRAPOLATION**

Indication extrapolation allows for the approval of a biosimilar for diseases or conditions for which it has not been studied based on its similarity to an approved, innovator biological medication.

BPC believes FDA should proceed with thoughtful caution when considering biosimilar application requests for indication extrapolation. Biologic medicines are often used to treat multiple and unrelated disease states and indications. Under the biosimilar approval process, applicants may present data for certain indications but not necessarily for all conditions listed in the application documents. Approval requires only one clinical study to "demonstrate safety, purity, and potency" of the proposed biosimilar; however, applicants may apply for approval for use in all of the innovator's indications.

#### *Extensive analytical and clinical data essential*

BPC does not support *automatic* indication extrapolation of every indication the reference product is licensed to treat. BPC does support extrapolation for additional indications *if* sufficient scientific justification for extrapolating clinical data has been provided. In particular, data should address possible differences in immunogenicity and expected toxicities among sensitive patient populations, as well as the mechanism(s) of action in each condition.



These mechanisms may include:

- the target/receptor(s) for each relevant activity/function of the product;
- the binding, dose/concentration response and pattern of molecular signaling upon engagement of target/receptors;
- the relationships between product structure and target/receptor interactions;
- the location and expression of the target/receptor(s).

When FDA approved filgrastim-sndz\*, the biosimilar for innovator filgrastim, the sponsor was not required to submit clinical study data for every indication. In this case, every indication had the same mechanism of action, which was confirmed as highly similar through analytical studies. FDA relied upon these analytical studies to permit extrapolation of the clinical results – only available for some indications – to all indications sought. Extrapolation of clinical results should only be available for some indications where justified according to pathophysiological mechanisms, but not routinely to all other indications.

However, there are also cases of a biosimilar treating different diseases with distinct mechanisms of action. For instance, the mechanisms of action for the U.S. approved biosimilar, infliximab-dyyb\* differ between inflammatory bowel disease (IBD) and arthritis. Across the globe, regulatory agencies have differed in their approval designations for this medicine.

For example, when presented with analytical data comparing the IBD mechanisms in infliximab and its biosimilar, the Health Products and Food Branch of Health Canadian saw enough variation between these two medicines to exclude IBD from the list of approved indications for the biosimilar. On the other hand, the European Medicines Agency did approve the IBD indication for the biosimilar despite the absence of specific data from clinical trials.

*“The FDA has made great strides in developing guidelines for biosimilars, however, there still remain areas that must be addressed to ensure maximum patient safety and efficacy.”*

*-Dr. Joshua Stalow,  
AfPA & CSRO*

Extrapolation is an essential component of an approval process designed to bring safe and affordable biosimilars to patients. Therefore, FDA must ensure that any extrapolation to additional indications is rigorously conducted, especially where the mechanism of action differs.

Manufacturers should be required to supply extensive analytical characterization data to demonstrate high similarity between a biosimilar and its reference biologic. They must also submit robust clinical and nonclinical data establishing that there are no clinically meaningful differences based on similar pharmacokinetics (PK), efficacy, safety and immunogenicity across various populations.

## LABELING

The label is a critical tool for physicians to make prescribing decisions and manage potential adverse events, and includes side effects and drug-drug interactions. As such, it is of the utmost importance that any drug label be complete and accurate, with a clear statement and clinical proof of biosimilarity.

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\*Per FDA's final naming guidance, approved biosimilar distinguishable names could change should FDA required manufacturers to apply for a distinguishable, random suffix.

A biosimilar label, identical to that of its reference product, omits readily available, product-specific data. It may also imply that a biosimilar is interchangeable with the reference product and approved for all of the same indications when it may not be.

### *Transparency is paramount*

BPC believes the label of a biosimilar product should be transparent and facilitate access to data used in support of the biosimilar application. Doing so will build prescriber confidence in this new class of medicines, which is paramount to successful biosimilars adoption.

To that end, we have asked FDA to modify *Labeling for Biosimilar Products*, its draft labeling guidance which was published last year, by adding provisions in its final labeling guidance that promote transparency and, ultimately, uphold patient safety.

### *Label must include statement on interchangeability*

The label should include a statement on whether the biosimilar is interchangeable with the reference product and/or other biosimilars on the market. This statement will help prevent health care providers from confusing a finding of biosimilarity with a finding of interchangeability. Explicit labeling and transparent communications are needed to ensure the appropriate use of biosimilars in accordance with FDA direction and to discourage commercial insurers, PBMs, specialty pharmacies, and Medicare carriers from adopting and enacting non-medical switching practices as part of formulary designs that substitute a biosimilar for an innovator in patients already on therapy.

### *Label must provide access to full clinical data*

BPC believes that the label should provide a summary of the full clinical data submitted in support of biosimilar approval (or a hyperlink to the FDA's summary basis of approval). The biosimilar label should also include all information on PK and PD differences as well as receptor binding differences and glycosylation differences between the biosimilar and the reference product. BPC members believe that it is not enough to highlight where similarities exist, but also believe it is critical to understand where the biosimilar and reference agent differ. As a collaborative of prescribers, BPC physicians want to analyze the data used to support a biosimilar's approval.

Access to clinical trial data becomes especially important when physicians consider the indications for which the biosimilar is approved as well as immunogenic effects observed. The label should ensure that all mentions of either the reference biologic or the biosimilar include both the proprietary name (if available) and the non-proprietary name. The product label is a critical tool for physicians, especially in the biosimilar space, to make the best prescribing decisions and BPC calls for final guidance that supports fully transparent and clear labels for biosimilars.

## ***OTHER POLICY ISSUES***

### **CMS REIMBURSEMENT**

Beginning with the 2016 Medicare Physician Fee Schedule, Medicare Part B, the Centers for Medicare & Medicaid Services (CMS) has based reimbursement of biosimilars on the weighted average of sales prices under each shared Healthcare Common Procedure Coding System (HCPCS) code. This is because CMS has placed biosimilars of a single reference product into one HCPCS code, known as a J-code.

Yet, the law states the calculation for reimbursing biosimilars shall be made separately, strongly implying that each biosimilar should have its own unique payment calculation and HCPCS code. That is how members of Congress, manufacturers of both originator and biosimilar biologics, and physician groups read the law.

BPC is not convinced that this biosimilar reimbursement policy – grouping in one billing code all biosimilars of a reference biologic and then limiting Medicare Part B reimbursement to the average selling price – supports innovation, access and affordability.

#### *Single J-Codes encourage inappropriate switching and discourage investment*

A single J-Code could lead hospitals and payers to prefer the biosimilar with the lowest cost, rather than the medicine deemed most appropriate by the physician. This perverse cost incentive could encourage inappropriate non-medical switching back and forth between one biological product and another. Inappropriate switching can lead to harmful immunogenic side effects due to the important differences among biological products, compromising patient care and stability.

Biosimilars are likely to be very sensitive to reimbursement levels given the significant investments to bring them to market.

The current CMS J-Code Proposal that provides for one payment level appears to take a generic medicine payment approach to medicines that are not generic by definition. Biologic and biosimilar medicines are not identical to each other nor manufactured using the same processes. It is inappropriate to group their payment in a competition solely based on price.

Payment policies are also known to influence drug availability and can lead to persistent drug shortages, particularly for injectable generics for Medicare patients. A Stanford University study released this year found that declining Medicare reimbursement for these drugs causes shortages by decreasing returns on capacity investments.<sup>v</sup>

The reimbursement policies of CMS should encourage an increase in the number of biosimilars brought to market. Access to a range of biosimilars is important for patients, especially where an individual patient's immune reaction may differ between drugs.

The best way to deliver the promise of biosimilars to patients is a competitive market based on differentiated benefits, including price. For that market to thrive, each biosimilar needs a separate billing code.

### **BUILDING A PATHWAY FOR INNOVATION – THE BIOSIMILAR USER FEE ACT**

Under the BPCIA, the FDA uses a dedicated regulatory pathway for the approval of biosimilars. The creation of this separate pathway encourages innovation and accelerates access to these products.



To provide the additional resources needed to bring biosimilars to market, The Federal Food, Drug, and Cosmetic Act (the FD&C Act), was amended by the Biosimilar User Fee Act of 2012 (BsUFA), to authorize FDA to assess and collect fees from industry from fiscal years 2013-2017 to assist in the review process for biosimilar products. FDA garnered feedback from a variety of stakeholders including physician groups, patients, and regulated industry to inform how BsUFA would be implemented and held a public meeting to review recommendations. The agency is currently undertaking the process to reauthorize BsUFA for fiscal years 2018-2022 and held its first public meeting for this iteration October 2016.

BPC acknowledges that FDA needs additional resources in order to accelerate patient access to safe and effective biosimilars, and to ensure “accuracy, consistency and timeliness” of the guidance. FDA plays an integral role in ensuring public safety for all Americans and BPC supports the agency’s request to increase staff capacity for the review and development of biosimilar-related regulations. Congress should continue to support legislation, such as BsUFA, to provide FDA the resources and authority to continue this important work.

*“In the end, biosimilars give us the opportunity to overcome the trade-off between cost and innovation. We can have the best of both worlds, providing patients with state-of-the-art treatments and manageable prices. It is imperative that our policymakers dedicate more time and resources towards biosimilar policy at the FDA to realize that goal.”*

*-Dr. Angus Worthing,  
ACR*

## CONCLUSION

Biosimilars hold great promise for patients because these new medicines expand choices and lower costs. However, in order to ensure maximum benefit and patient safety, policies that are based on the latest science and clinical best practice are urgently needed. As policies are continuing to evolve, BPC calls for the following:

- **Naming** policies that provide sufficient information to track and trace adverse events.
- **Labeling** that is transparent which would include:
  - a statement of whether the biosimilar is interchangeable with the reference product and/or other biosimilars on the market.
  - either a summary of the full clinical data submitted in support of biosimilar approval or a hyperlink to the FDA’s summary basis of approval, to include where biosimilar properties, structure and function differ from the reference product.
- A requirement for applicants to seek approval of a biosimilar as **interchangeable** for all the reference product’s conditions of use.
- Case by case extrapolation determinations based on extensive analytic and clinical data.
- Unique **J-Codes** that will support innovation and access.
- **BsUFA reauthorization** that provides FDA the resources it needs to support increased staff capacity for the development and review of biosimilar-related regulations.

BPC will continue to provide Congress and the Administration education to create the needed rigorous policy framework that will promote access to and safe use of biosimilars for the millions of patients in America who could benefit from these medicines.

## REFERENCES

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<sup>v</sup> A. Yurukoglu, E. Liebman, D. Ridley, The Role of Government Reimbursement in Drug Shortages, (2012). doi:10.3386/w17987.