

## UNRESOLVED POLICY ISSUES IMPACT PATIENT ACCESS TO BIOSIMILARS

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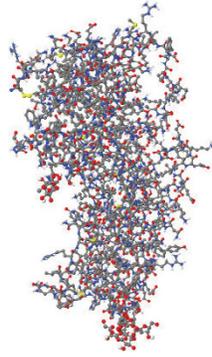
More than five years have passed since Congress approved an abbreviated regulatory pathway for biosimilars under the Biologic Price Competition and Innovation Act as part of the Patient Protection and Affordable Care Act. Biosimilars are biological medications deemed highly similar, but not identical to, those already

licensed by the US Food and Drug Administration (FDA). Congress' vision – patient access to biosimilars – will come to fruition only if physicians have confidence in prescribing these medications. To instill that confidence, regulators must put into place standards that prioritize transparency and safety. Following the first biosimilar approval in March of 2015, healthcare providers, patient advocates, and policymakers should now consider the current status of biosimilars and some of the major issues impacting patient access to these medications: naming, prescribing information, indication extrapolation, and substitution.

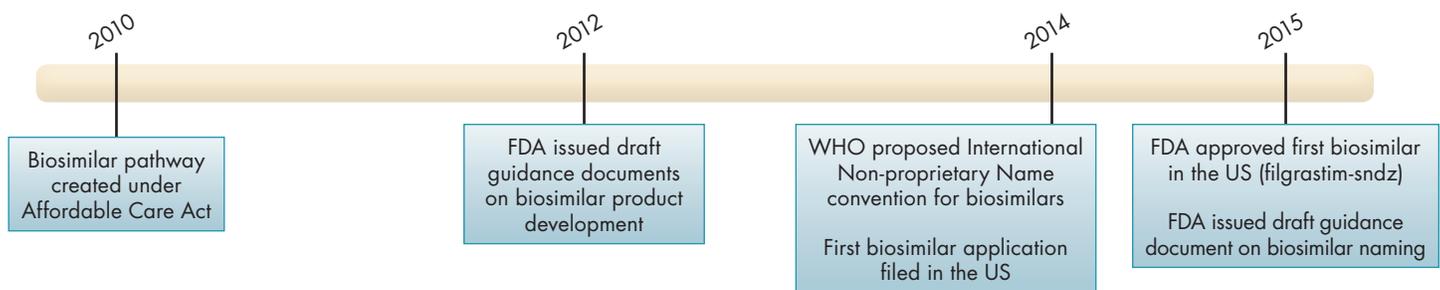
### BACKGROUND ON BIOLOGICS

Biological medications, also known as biologics, are made in living systems or cells. This distinguishes them from conventional drugs like aspirin, which are synthesized using a chemical recipe.

#### Some Differences Between Biological Medications and Conventional Drugs<sup>1</sup>

Characteristic	Biological Medication	Conventional Drug
Source	Made by living cells or organisms	Made in a laboratory using chemical reactions
Size	Large	Small
Structure	Complex	Simple
Example of structure		
Generics possible?	No	Yes

**Figure 1. Timeline of Important Developments Affecting U.S. Biosimilars Since 2010**



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## BIOSIMILAR NAMING

One unresolved question with biosimilars is how to name them and, specifically, the extent to which non-proprietary names (ie, non-brand names) for biosimilars should resemble those of the reference biologic. Some argue that the names should be identical to help prevent physician confusion and reduce the risk of medical errors. Others argue that biosimilar names absolutely must be distinguishable from those of the reference products to permit traceability in case of safety issues, to promote accurate patient records, and to minimize the chance of an unintentional or inappropriate substitution.<sup>2</sup>

Currently, there is no accepted worldwide convention for biosimilar names. Instead, regulatory agencies in different countries have adopted different naming policies. In an attempt to harmonize naming, the World Health Organization (WHO) released draft recommendations for international non-proprietary names in 2014 and may issue final recommendations as early as October 2015. The WHO draft recommendations call for international non-proprietary names to be followed by a so-called “biological qualifier.” The biological qualifier they suggested was a random, 4-consonant code attached to the product’s manufacturing site. However, the random code concept has come under fire for being hard to remember and unconnected to the company responsible for the product’s safety. Moreover, some argue that the method would create confusion for biosimilars manufactured at multiple sites because they would have different qualifiers.<sup>3</sup>

In the US, the only approved biosimilar received a non-proprietary name followed by a 4-letter code signifying the company responsible for marketing the medication. However, in a draft guidance document released in August 2015, the FDA proposed updating this name. The guidance document recommends that biosimilars and reference biologics be given the same non-proprietary names followed by different random, 4-letter codes assigned by the FDA.<sup>4</sup> The FDA states that there is a need to clearly identify biological products for safety purposes. The agency is still considering its position on whether biosimilars deemed “therapeutically interchangeable” should receive the same 4-letter codes as the reference biologics or whether the codes should be different. To date, no therapeutically interchangeable biosimilars have been approved in the US.

**Table 1. Examples of Proposed Naming Conventions For Biological Medications<sup>2</sup>**

ORGANIZATION	PROPOSED BIOLOGICAL MEDICATION NAMING CONVENTION
World Health Organization (WHO)	Non-proprietary name followed by random 4-consonant suffix attached to the product’s manufacturing site
US Food and Drug Administration (FDA)	Non-proprietary name followed by random 4-letter suffix
European Medicines Agency (EMA)	Non-proprietary name followed by company identifier

## PRESCRIBING INFORMATION

All prescription medications approved in the United States are accompanied by printed documents for physicians known as prescribing information. The prescribing information, or PI, gives physicians the details they need to make prescribing decisions for patients. Examples include dosing and administration information, results of clinical studies, safety information, and medical conditions or “indications” for which the medication is approved. Every word in the prescribing information is scrutinized and approved by the FDA.

In the 1980s, the government passed a law allowing generic drugs to use the same prescribing information as the original medications. Given that biosimilars are not generics, it was uncertain how closely the prescribing information of the first biosimilar would match that of the reference biologic. When the first biosimilar was approved in March of 2015, its FDA-approved prescribing information was entirely based on that of the reference biological medication. Although the manufacturer of the first biosimilar conducted studies with its medication in healthy volunteers as well as breast cancer patients,<sup>5,6</sup> the studies are not described or mentioned in the biosimilar’s prescribing information. Instead, the FDA included studies conducted with the reference biological medication. The same was true for the safety information, with adverse events listed for the reference biological medication instead of the biosimilar. Moreover, the biosimilar’s prescribing information does not clearly indicate that the information came from studies conducted with the reference biological medication instead of with the biosimilar.

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The lack of specific information about the first biosimilar in its prescribing information was surprising to many because the FDA required studies examining the medication's pharmacology, safety, and effectiveness in patients. Thus, even though this information was specifically available for the biosimilar, it was not included in the prescribing information. This approach lacks transparency and fails to provide physicians with full information about the biosimilar, even though physicians are responsible for prescribing the biosimilar and treating adverse side effects that may result. It is unclear whether the FDA will continue to use this approach to prescribing information for other biosimilars.

## TESTING, APPROVAL AND INDICATION EXTRAPOLATION

When a medication has successfully completed the studies required by the FDA showing that benefits to patients outweigh the risks, it may receive an “indication,” or an official approval to treat a given medical condition. Indication extrapolation refers to the extent to which biosimilars are granted FDA approvals for indications based on those of the reference biologics. The question is which, if any, indications of the reference biologics should be granted or extrapolated to biosimilars without the biosimilar actually being tested in the specific disease or medical condition.

Historically, the FDA has required each biological medication to be tested for each medical condition in order to receive an official approval and indication for that condition. This practice recognizes that a biologic may not have comparable effects in all patient groups. Thus, if a reference biological medication is approved for five different indications, it has been specifically tested in different patient groups with each of the five different medical conditions.

The first biosimilar approved in the US was granted full indication extrapolation. That is, the biosimilar was granted all indications for which the reference biologic was approved at the time,<sup>7,8</sup> although, as part of the study package submitted to the FDA, the first biosimilar was tested in only one group of patients—those with breast cancer.<sup>6</sup> It is again unclear whether the FDA will use this approach when granting indications for other biosimilars, although the agency has indicated that biosimilars will be evaluated on a case-by-case basis.<sup>9</sup>

## SUBSTITUTION OF THERAPEUTICALLY INTERCHANGEABLE BIOSIMILARS

As more biosimilars enter the market, some companies may

seek a “therapeutically interchangeable” designation from the FDA. In order to receive this designation, a biosimilar would need to undergo additional studies showing that it is similarly safe and effective as the reference biologic at the same doses, based on FDA-defined criteria. Most biosimilars will not be considered therapeutically interchangeable.

Issues related to therapeutically interchangeable biosimilars pertain to the conditions under which pharmacists should be able to substitute them for a reference biologic, and whether prescribing physicians should be notified when a substitution is made. These regulations are determined by states. At least 16 states have enacted legislation or developed rules related to biosimilar substitution, and at least four more states are currently considering such legislation. Most of this legislation specifies whether or not physicians must receive notice of pharmacist substitutions, the circumstances under which substitution is permitted, and the period of time records documenting the substitution must be retained.<sup>11</sup> Of the 16 states that have passed biosimilar substitution legislation, 14 require pharmacies to notify physicians of the substitution, although the notification requirement is provisional in several of these states and set to expire before 2017.<sup>11</sup> Notably, only 10 states require patients to be notified of pharmacist substitution.

Physician notification of pharmacist substitution is critical not only to promote transparency in healthcare, but also for patient safety. If patients experience unexpected side effects, physicians must be able to rapidly identify the product used so that the patient can be switched to a different biologic if needed, and the manufacturer and FDA can be notified.

This is important with biosimilars because, even though some may be deemed therapeutically interchangeable,

***"Physician notification of pharmacist substitution is critical not only to promote transparency in healthcare, but also for patient safety."***

they may possess underlying biochemical or manufacturing differences that could influence how the medications act in individual patients. Consequently, some patients may fare better on one biological medication than another.

## BIOSIMILAR OUTLOOK

Biosimilars are a welcome development in healthcare because they have the potential to improve patient access to biological medications. However, given that only one biosimilar has been approved since passage of the 2010 law, some have suggested

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that the pathway may be bumpier than originally anticipated.<sup>12</sup> For example, the South Korean company Celltrion filed an application for the approval of its biosimilar to the reference biological medication infliximab in August of 2014. However, the FDA postponed the March 17, 2015 meeting of the

arthritis advisory committee due to additional requests related to data analysis.<sup>13</sup> These developments suggest that the complexity of biologics may be making the approval process of biosimilars more difficult than originally anticipated.

## CONCLUSIONS

Following introduction of the first biosimilar in March of 2015, policymakers and regulatory agencies continue to debate important issues surrounding naming, prescribing information, indication extrapolation, and substitution. Resolving these issues has proven challenging due to the biological nature of these products and differences in manufacturing methods. The fundamental policy issues must be addressed, however, to

encourage entry of additional biosimilars into the market and realize the vision of patient access to these medications. The challenges to date suggest that the wisest course in biosimilar policy is to err on the side of transparency and patient safety so that patients and physicians continue to have confidence in biological medications.

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