10 August 2024

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Dockets Management Branch
Food and Drug Administration,
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CITIZEN PETITION

The undersigned submits this petition under The Biologics Price Competition and Innovation (Subtitle A) of Title VII—Improving Access to Innovate Medical Therapies (H.R. 3590)(1), where Sec. 7002 details "Approval Pathway for Biosimilar Biological Products."

A. Action Requested

The petitioner is requesting the Commissioner to take an administrative action to evoke the orders to stop the US Pharmacopoeia to create modified monographs of biological drugs, allowing removal of side-by-side analytical testing of biosimilars with the reference product. This action does not require any ruling amendment and can be initiated immediately by the FDA.

B. Statement of Ground

a. Status of BPCIA

The BPCIA defines and mandates the information required for licensure of biological products as biosimilar or interchangeable. The most critical data required to qualify a product as a biosimilar is its analytical assessment.

''(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;

The BPCIA further stipulates:

''(ii) DETERMINATION BY SECRETARY. —In the Secretary's discretion, the Secretary may determine that an element described in clause (i)(I) is unnecessary in an application submitted under this subsection.

The following finding by the Petitioner is the basis of the modifications requested in this petition:

While the BPCIA requires that a biosimilar be shown to be similar to its locally licensed originator (that is, a product approved under Sect. 351(a) of the Public Health Service Act of 1942, as amended), it also expressly gives the Agency discretion to vary the information required to establish biosimilarity [See 42 USC 262(k)(2)(A)(ii)].

The BPCIA has been amended as of the end of 2022, removing the term "animal toxicology" and replacing it with "nonclinical testing"(2). Now, the FDA is focusing on further changes to the BPCIA.

The Petitioner is requesting that the FDA consider a major change in its position on the ban it has placed on the US Pharmacopeia from creating monographs for biological products. The petitioner has published a paper detailing the logic of this recommendation and a path that the FDA can adopt to bring biosimilars to a broader market (3).

b. Introduction

While European pharmacopeias continue to create monographs for biological drugs, these are intended for something other than establishing biosimilarity; the US Pharmacopoeia (4) has ended this effort based on the Food and Drug Administration (FDA) instructions. A creative approach to reducing the cost of developing biosimilars without compromising their safety and efficacy is to remove the side-by-side testing for analytical comparison with the reference product; this can be achieved if the USP were to establish release specifications of the finished product based on testing multiple lots of the reference product and provide validated test methods. This paper presents details of how the USP can create a new class of documents labeled as Biological Product Specification (BPS) instead of monographs to make sure the application of BPS is clear. This approach will also allow the harmonization of biosimilars and create universal regulatory approval that will significantly reduce the development cost and encourage the entry of many biosimilars into the market.

The US licensing of a product as a biosimilar or an interchangeable biosimilar (5) is based on the Biologics Price Competition and Innovation Act of 2009 (BPCI Act), which defines and mandates the information required to license biological products as biosimilar or interchangeable. The FDA has been proactive in rationalizing the biosimilar approval guidelines, bringing several changes as scientific rationality has grown with time. However, in the US, legislative actions are necessary for some changes, such as the interchangeable classification, the patent dance, or the selection of reference products.

Initially, the FDA enforced all stipulations of the BPCIA. Still, over time, as the knowledge and understanding about the safety and efficacy of biosimilars enhanced, the FDA took several actions as allowed in the BPCIA:

- FDA withdrew a pivotal guideline for the analytical comparison (6) of biosimilars with their reference products using statistical modeling once it was demonstrated that the modeling was deficient in a citizen petition (7); instead of revising the guideline, the FDA issued a new guideline (8) that notably changed the terminology from “comparison” to “assessment” and removed the challenged tier 1 statistical modeling and made the analytical biosimilarity testing more rational.
- The animal toxicology testing of biosimilars was listed in the BPCIA as one of the requirements; this was removed through a legislative change in the FDA Modernization Act 2.0 (9) that combined a previous US Senate bill (10) based on findings in the paper published in the Science magazine (2).
- The FDA interpreted the clinical efficacy testing requirement of the BPCIA as pharmacodynamic attributes, where available, such as erythropoietin, filgrastim, etc. (11, 12).
- In 2023, the FDA encouraged developers to create testing methods based on generally accepted scientific knowledge (13) and recent change (14) on this basis was made by the FDA, allowing interchangeable status to biosimilars without additional switching and alternating studies that were questioned (15), while a

Senate bill is in place to remove the interchangeable status of biosimilars from the legislation (16).

- In June 2024, the FDA proposed lectin-based assays (17, 18) to compare the glycan profile of biological drugs, a more straightforward solution adaptable for high-throughput analysis. The agency stressed that these comparisons need not be accurate as long as they are comparably resolved (19).

c. Monographs

Pharmacopeia monographs have long served the need to standardize testing methods and product specifications. However, these monographs are unsuitable for establishing a biosimilar product's analytical similarity with its reference product. For example, the European Pharmacopoeia (Ph. Eur.) sets public standards by providing harmonized quality requirements. However, comparison of the biosimilar to a publicly available standard (e.g., a pharmacopeial monograph, is insufficient for comparability). Similarly, the reference standards described in Ph. Eur. monographs are not intended to be used as reference medicinal products (comparators) to demonstrate biosimilarity (20). Table 1 lists the current monographs presented in the European Pharmacopoeia.

Table 1. European Pharmacopoeia Biotherapeutics Monographs (* finished product monographs; § under revision) (https://www.edqm.eu/documents/52006/285146/Biotherapeutics+–+Ph.+Eur.+monograph+portfolio.pdf/b80de0c3-4846-da53-23e4-9decf29c6706?t=1641831765829)

Issued Monographs	New monographs in preparation
Alteplase for injection (1170)* §	Alteplase concentrated solution (3197)
Calcitonin salmon (0471)	Adalimumab (3147)
Erythropoietin concentrated solution (1316) §	Darbepoetin alfa (3009)
Etanercept (2895)	Golimumab concentrated solution (3103)
Filgrastim concentrated solution (2206)	Golimumab injection (3187)*
Filgrastim injection (2848)*	Human coagulation factor VIII (rDNA concentrated solution (3105)
Follitropin (2285)	Human coagulation factor VIII (rDNA) powder for injection (3106)*
Follitropin concentrated solution (2286)	Human coagulation factor VIII (rDNA), B- domain deleted, concentrated solution (3107)
Glucagon, human (1635)	Human coagulation factor VIII (rDNA), B- domain deleted, powder for injection (3108)*
Human coagulation factor IX (rDNA) powder for solution for injection (2994)*	Insulin glargine injection (3129)*
Human coagulation factor IX rDNA concentrated solution (2522)	Pegfilgrastim (2889)
Human coagulation factor VIIa rDNA concentrated solution (2534)	Teriparatide injection (3130)*
Human coagulation factor VIII rDNA (1643)*§	Ustekinumab (3165)
Infliximab concentrated solution (2928)§	Ustekinumab injection (3188)*
Insulin aspart (2084)	
Insulin glargine (2571)	
Insulin lispro (2085)	
Insulin preparations injectable (0854)*	
Insulin, human (0838)	
Interferon alfa-2 concentrated solution (1110)	
Interferon gamma-1b concentrated solution (1440)	
Molgramostim concentrated solution (1641)	

Somatropin concentrated solution (0950) Somatropin (0951) Somatropin for injection (0952)* Somatropin solution for injection (2370)* Teriparatide (2829)	

In addition, the European Pharmacopeia has issued several general chapters, such as Glycan analysis of glycoproteins (2.2.59), Host-cell protein assays (2.6.34), Quantification and characterization of residual host-cell DNA (2.6.35) and Cell-based assays for potency determination of TNF-alpha antagonists (2.7.26) that can be instrumental in creating the Product Monographs. The British Pharmacopoeia (https://www.pharmacopoeia.com) also contains similar monographs for recombinant drugs.

The USP includes several monographs, but it decided to stop this after the FDA wrote to the USP in May 2018 (21), instructing that it should refrain from producing monographs for biological medications. "Because USP's proposed revisions would aggravate existing concerns that a monograph could impede or delay the licensure of biosimilars and other biological products, FDA strongly encourages USP to withdraw its proposal. FDA welcomes future interaction with USP on these issues to ensure that biological product monographs do not create an unnecessary barrier to the availability of biosimilars and other biological products to patients. For example, we see opportunities for optional methodological standards that could encourage innovation and product development."

The FDA was concerned that biologic manufacturers would manipulate the monograph procedure to prevent competition from biosimilars "by incorporating patented characteristics of their product that are not relevant to safety, purity or potency, further impacting competition."

d. Biological Product Specification (BPS)

Next to the clinical efficacy testing, comparative analytical assessment of biosimilars with the reference products is the highest cost and time item. While the FDA has rationalized specific testing requirements (6), there are no recommended protocols for specific biosimilar classes that can be adopted to reduce or remove side-by-side testing of a biosimilar candidate with its reference product. The current testing requires collecting samples of the reference product throughout its expiry to ensure that the variability of the reference product is evaluated. Besides the enormous cost, collecting reference product batches with different expiration dates is challenging, despite the Cures Act (22) and the Red Tape Elimination Act (23) which were supposed to remove this constraint.

One discussion point by the USP was the possibility that the FDA could share the release specification of the reference product, which remains confidential. However, this argument does not hold for multiple reasons. First, the FDA cannot share confidential data, and secondly, the data are always dependent on testing methods; the biosimilar developers will have different testing methods, leading to inevitable side-by-side testing with the reference product.

However, the FDA can take a pivotal action by eliminating side-by-side analytical testing and allowing the USP to establish novel monographs that define release specifications of reference products based on real-time testing of multiple batches of the reference product, just as the developers do. These specifications can also include potency tests that conform to the secondary and tertiary structure without using other biophysical test methodologies. The primary structure is determined by using peptide mapping, a method that can be validated, removing any further need

for side-by-side testing. When these release specifications are provided with validated test methods, the need for side-by-side testing will be removed.

It is noteworthy that analytical assessment is one part of establishing biosimilarity, and other testing, such as clinical pharmacology and clinical efficacy, shall remain dependent on side-by-side testing with the reference product. But these tests are easily managed.

The USP can ensure that the test methods do not infringe on any intellectual property and keep updating the release specifications of the reference product if its formulation or presentation changes.

e. Critical Quality Attributes (CQAs)

The USP testing to establish release specifications and other structural attributes will require prior FDA concurrence that the protocols meet the FDA expectations. Even though the FDA has recently shared (Figure 2) what it considers to be an appropriate protocol for establishing analytical similarity, these protocols are dependent on the type of molecule, not the specific molecule, such as a monoclonal antibody or a cytokine; the FDA and the USP must agree on these generic protocols.

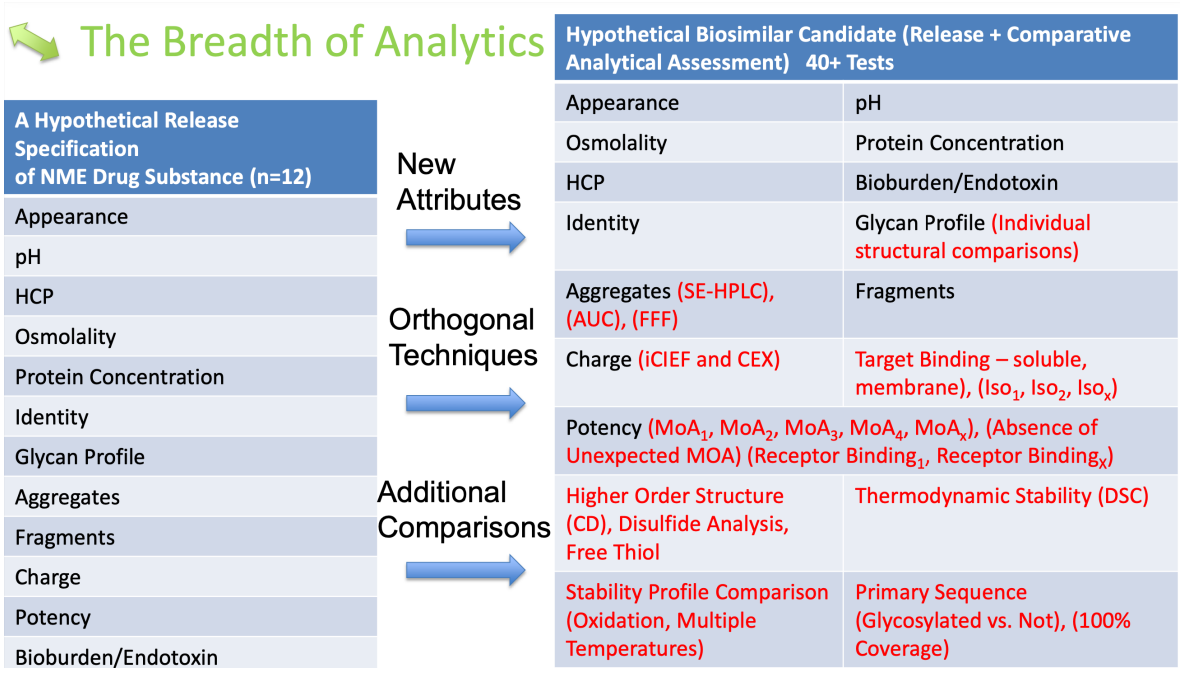


Figure 2. FDA-proposed testing of biosimilars to establish analytical similarity (https://www.fda.gov/drugs/news-events-human-drugs/fda-workshop-increasing-efficiency-biosimilar-development-programs-09192022#event-materials),

This collaboration between the FDA and the USP is critical to making this exercise worthwhile. However, historically, the FDA has established that it is never bound to any pharmacopeial specification for any product, leaving developers doubts about whether this exercise will be fruitful. When these specifications are available, the developers can consult with the FDA in earlier meetings to secure the FDA concurrent that the FDA generally grants. Still, it must be asked so the FDA does not have to present this as global acceptance.

It is worth noting that the release specifications include many more tests used to establish analytical similarity, as shown in Figure 2. (24). Several release attributes are legacy attributes independently tested, such as sterility or endotoxin, for which the USP has already established methods. The USP

can also provide reference standards to validate test methods. In some instances, the release specification can be based on legacy ranges such as having no more than 3% impurity and no single impurity of more than 1% or protein content ±3%; these limits are important to ensure that a biosimilar product is not rejected for irrelevant reasons. The FDA should be open to accepting this suggestion.

f. Advantages

A significant impact of the USP monographs will be to harmonize the testing of biosimilars. Currently, there is a wide range of tests, and the number of tests reported in the filing of biosimilars can be misleading, particularly when the developers mistake extrapolation with repetitive testing, which is a clear step the USP can take. In those cases where validation is not possible, the USP can provide reference standards (not the product) to establish comparability. I do not see any conflict of interest or scientific hurdles in accepting these data.

g. USP Views

Biosimilars licensed based on USP compliance with release specifications can be expected to be more similar to other biosimilars, and thus, eventually, they could be accepted as interchangeable, legally as in the US and otherwise elsewhere. This consideration is vital as newer analytical methods continuously enter the field, yielding results that may not be compared with other methods (25), confounding the differences between biosimilars. This similarity may also lead to the global registration of biosimilars across many regulatory agencies. At the same time, the need for testing against specific reference standards is removed, such as when a biosimilar is approved using essentially the same dossier in different regions (26).

In supporting Professor Niazi's proposition, the SVP of Global Biologicals at the USP, Dr. Fouad Atouf (linkedin.com/in/fouadatouf), said, "It is crucial to remove barriers to testing biosimilars through reference standards, analytical methods, or quality guidelines. USP is prioritizing the development of state-of-the-art analytical tools to accelerate the advancement of biologics and biosimilars. This supports continuous innovation, reduces barriers to market access for quality medicines, and provides solutions available to stakeholders across the global supply chain. Because of our longstanding work with manufacturers and regulators to ensure the quality of medicines, USP is uniquely positioned and eager to partner with government agencies, including the FDA, to remove obstacles and build solutions to bring biosimilars to patients faster."(https://www.usp.org/biologics/biosimilars)

h. Conclusions

Fifteen years since the passage of a bill to introduce biosimilars in the US, biosimilars remain inaccessible as only 21 out of more than 100 molecules eligible as biosimilars await developers due to the high cost of development, despite many concessions given by the regulatory agencies recently such as waiving animal toxicology testing, granting interchangeable status without switching and alternating studies, and in several instances, without efficacy testing in patients. Analytical assessment of biosimilars is the most sensitive test that remains a hurdle not because of the lack of availability of a sufficient number of reference lots despite the Cures Act (22) but due to the difficulties in deciding what constitutes a critical quality attribute to test.

The USP and other pharmacopeias have long been active in resolving quality issues by providing product monographs that include specifications and test methods; however, the FDA has halted this model for biological drugs. The FDA concerns can be removed by creating a novel monograph that

deals with the release specification of a biological product, which will eliminate the need for side-by-side testing of a biosimilar candidate with its reference product.

The FDA has been proactive in creative innovations (1) , calling meetings to discuss biosimilar issues and secure stakeholders' views. Regulatory agencies will go a long way in establishing a credible approach to making biological drugs affordable(27). An excellent example of such collaboration is the FDA-EMA joint advisory program. (28)

However, for this proposition to succeed, the USP will need substantial funding on an ongoing basis; the stakeholders, including the associations supporting biosimilars, should fund these projects; the NIH and the FDA also have significant funding available that can be given to the USP as grants, and finally, the USP may charge a licensing fee for the developers to use its data. Thus, the release specification can be presented as a particular document, Biological Product Specification (BPS), not labeled as a monograph to avoid confusion with other monographs that do not present release specifications.

Regardless, the developers will still need to confirm with their regulatory agencies if the USP specifications are acceptable before commencing the development. When engaging multiple agencies, the developers may plan global registration of their biosimilars. This long-sought plan will significantly reduce patient costs while ensuring harmonization of safety and efficacy.

C. Environmental Impact Statement

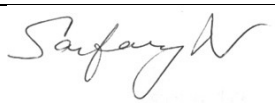
We claim categorical exclusion under 25.30, 25.31, 25.32, 25.33, or 25.34 of this chapter or an environmental assessment under 25.40 of this chapter

D. Economic Impact

Economic impact information will be submitted upon request of the commissioner.

D. Certification

The undersigned certifies that, to the best knowledge and belief of the undersigned, this petition includes all information and views on which the petition relies and that it includes representative data and information known to the Petitioner that are unfavorable to the petition. (21 CFR 10.30).

Signature	
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