

Biosimilars Implementation

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Introduction

Mr. Chairman and Members of the Subcommittee, I am Dr. Janet Woodcock, Director of the Center for Drug Evaluation and Research (CDER) at the Food and Drug Administration (FDA or the Agency), which is part of the Department of Health and Human Services (HHS). Thank you for the opportunity to be here today to discuss FDA's implementation of the Biologics Price Competition and Innovation Act of 2009 (BPCI Act). FDA is supportive of and fully engaged with the development and approval of biosimilar and interchangeable biological products. Many of our most important drugs are biological products. Biological products are used to treat patients who have serious and life-threatening medical conditions including rheumatoid arthritis, diabetes, and cancer. It is important for the public health of the U.S. population to have access to safe, effective, and affordable biological products. Biosimilars can provide more treatment options for patients, and possibly lower treatment costs, enabling greater access for more patients.

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To earn and sustain both physicians' and patients' confidence in biosimilar and interchangeable products, FDA must apply a scientifically rigorous review process and approval standard. Healthcare providers have consistently indicated the importance of assurance that biosimilars will have the same clinical performance as the originator, or reference product. FDA is committed to providing this assurance, and recognizes its importance to the uptake and acceptance of these products, and the future success of the biosimilars program.

Biologics Price Competition and Innovation Act (BPCI Act) and Biosimilars User Fee Act (BsUFA): Important Additions to FDA Statutory Authority

As you know, the Affordable Care Act included the BPCI Act, which established a new abbreviated approval pathway for biological products shown to be “biosimilar to” or “interchangeable with” an FDA-licensed biological product. With this new abbreviated approval pathway, a sponsor can get a biosimilar approved by demonstrating, among other things, that it is highly similar to a reference biological product already licensed by FDA. Biological products consist of large, complex molecules that are difficult to define and produce. This is in contrast to “small molecule” drugs that generally are produced through chemical processes, and can be replicated as “generic” drugs that are essentially exact copies. Unlike generic drugs, biosimilars must be highly similar to, not the same as, the reference product to which they are compared. A biosimilar can have certain allowable differences because it is made from living organisms, but it must demonstrate no clinically meaningful differences in terms of safety, purity and potency from its reference product. The complexity of biological products generally makes it more challenging to demonstrate biosimilarity, as compared to demonstrating sameness for a generic drug.

The abbreviated approval pathway permits a biosimilar biological product to rely on certain existing scientific knowledge about the safety and effectiveness of the reference product, saving the sponsor time and resources and thereby encouraging price competition and lower consumer healthcare costs. The ongoing and future impact of this relatively new law cannot be overstated. FDA’s biosimilars program has sparked the development of a new segment of the biotechnology industry in the United States. The development of this new market segment should expand opportunities for technical innovation, job growth, and patient access to treatment.

The BPCI Act directed FDA to develop recommendations for a biosimilars user fee program for fiscal years 2013 through 2017. The first Biosimilar User Fee Act, or BsUFA, was enacted as part of the FDA Safety and Innovation Act (Public Law No. 112-144, enacted on July 9, 2012). BsUFA has allowed FDA to begin development of the infrastructure needed to support this new program. In addition, it has allowed the Agency to work towards devoting additional resources to meeting with companies regarding specific products in the pipeline to help streamline the drug

development process leading to the approval of safe, effective, and possibly less expensive, biosimilar products for patients.

Implementation and Accomplishments

Probably the most exciting accomplishment since the enactment of the BPCI Act is FDA's approval of the first biosimilar in the United States. On March 6, 2015, FDA approved the first biosimilar, Zarxio (filgrastim-sndz), a biosimilar to Neupogen (filgrastim), a reference product licensed by FDA that is used to help stimulate growth of white blood cells in patients with cancer and help them fight infection. On February 9, 2016, FDA's Arthritis Advisory Committee is scheduled to hold a meeting to discuss a proposed biosimilar to Remicade (infliximab), a biological product licensed by FDA to treat conditions such as rheumatoid arthritis, ulcerative colitis and Crohn's disease.

FDA has worked hard to implement this new abbreviated licensure pathway. We established an internal cross-center working group, known as the Biosimilars Implementation Committee, to develop policies and procedures for implementation of the new law in a manner that best serves the public health. We created a multi-disciplinary committee known as the Biosimilars Review Committee, within CDER and the Center for Biologics Evaluation and Research (CBER), to provide central oversight and advice to review staff as they review and consider biosimilar development programs and related issues.

FDA has worked diligently to issue multiple guidances on biosimilars since enactment of the BPCI Act. Scientific guidance is of critical importance to lay the foundation for the development of biosimilar products. Although the BPCI Act does not require FDA to issue guidances before taking an approval action on a biosimilar application, we recognize the importance of guidances in helping to ensure successful implementation of this new pathway. These guidance documents provide transparency to industry, the healthcare community and other stakeholders with regard to FDA's scientific standards and approval criteria.

The necessary first step was to develop guidance regarding implementation of the BPCI Act and demonstrating biosimilarity. FDA published draft guidances and then final guidances on the following topics:

- Scientific Considerations in Demonstrating Biosimilarity to a Reference Product
- Quality Considerations in Demonstrating Biosimilarity of a Therapeutic Protein Product to a Reference Product
- Biosimilars: Questions and Answers Regarding Implementation of the Biologics Price Competition and Innovation Act of 2009
- Formal Meetings Between FDA and Biosimilar Biological Product Sponsors or Applicants

We have also published the following draft guidances since 2012:

- Clinical Pharmacology Data to Support a Demonstration of Biosimilarity to a Reference Product
- Reference Product Exclusivity for Biological Products Filed Under Section 351(a) of the PHS Act
- Biosimilars: Additional Questions and Answers Regarding Implementation of the BPCI Act of 2009
- Nonproprietary Naming of Biological Products

FDA's most recent draft guidance on the Nonproprietary Naming of Biological Products describes FDA's current thinking on the appropriate naming convention to help ensure the safety of patients receiving biological products and maximize the success of biosimilar and interchangeable biological products. FDA believes that both reference products and biosimilars should have nonproprietary names (also called a proper name) that include a core drug substance name and, in order to facilitate safe use and pharmacovigilance, an FDA-designated suffix that is unique for each product.

Consistent with this draft guidance, FDA issued a proposed rule that would designate nonproprietary names that contain a suffix for six previously licensed biological products. These products include four originator biological products that are reference products for an approved or publicly disclosed biosimilar application, a related biological product to one of these reference products, and a biosimilar product.

The Agency is committed to carefully reviewing the comments received as we move forward in finalizing the draft guidances and proposed rule noted above. Upcoming guidances are expected to include:

- Considerations in Demonstrating Interchangeability to a Reference Product
- Statistical Approaches to Evaluation of Analytical Similarity Data to Support a Demonstration of Biosimilarity
- Labeling for Biosimilar Biological Products

Review Program

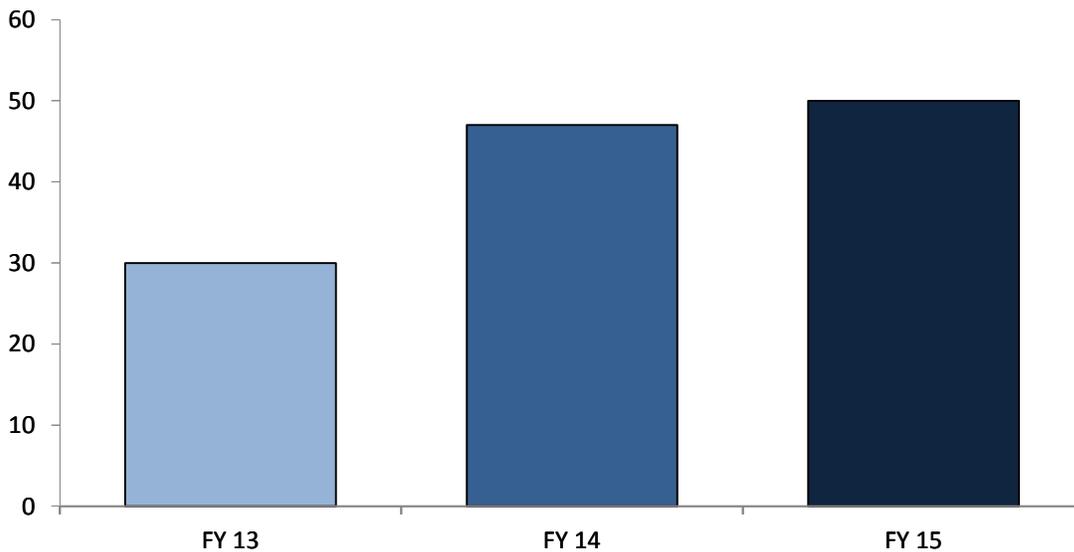
The biosimilar review program has continued to mature over time. As of January 21, 2016, 59 proposed biosimilar products to 18 different reference products were enrolled in the Biosimilar Product Development (BPD) Program. The BPD Program was created as a part of BsUFA to provide a mechanism and structure for the collection of development-phase user fees to support FDA's biosimilar review program activities. When a sponsor joins the BPD Program and pays the associated user fee for a specific product development program, that program is managed by FDA per the BsUFA performance goals and procedures. The number of sponsors in the BPD Program is not absolutely reflective of the overall number of industry programs

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underway, as a sponsor may be in the early stages of interacting with FDA and not yet enrolled in the BPD Program.

In engaging with sponsors regarding biosimilar development, CDER holds development-phase meetings and provides written advice for ongoing development programs. CDER continues to meet with sponsors interested in developing biosimilar products. The number of meeting requests increased 81% from 32 in FY2013 to 58 in FY2015. The number of scheduled meetings also increased 67% from 30 in FY2013 to 50 in FY2015. Additionally, from FY2013 to FY2015, in order to provide ongoing support for biosimilar development programs, FDA provided written advice to sponsors for 16 out of 23 meeting requests that were denied or cancelled due to incomplete or premature requests.

Number of Scheduled Meetings by Fiscal Year



Total number of scheduled meetings continue to grow each Fiscal Year.

As biosimilar development programs mature, the type of interaction with FDA is changing. We have seen a shift in the types of meetings that sponsors request and FDA grants. BsUFA established five meeting types specific to biosimilar development programs. Sponsors can choose the type of meeting or a combination of meetings to match development needs.

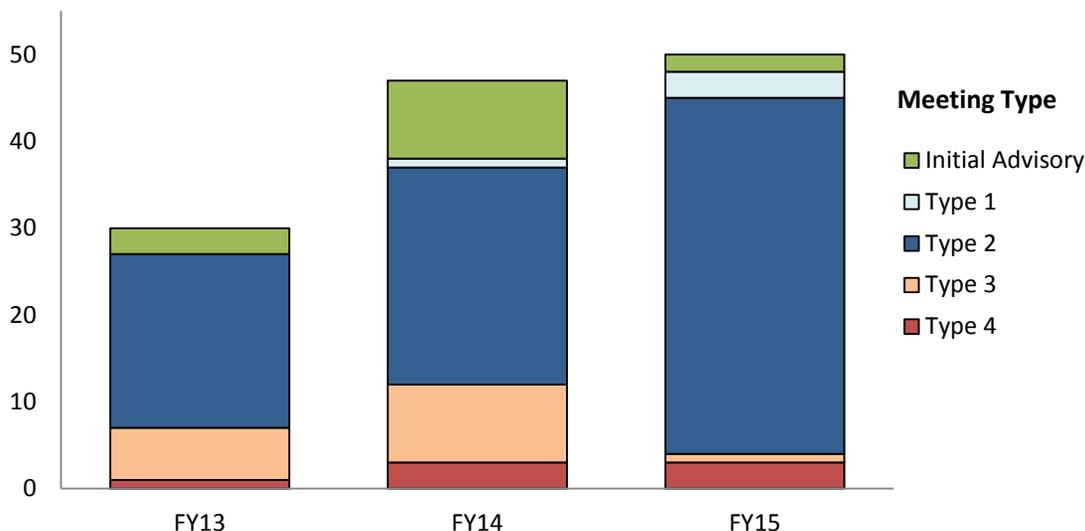
Sponsors are increasingly requesting Biological Product Development (BPD) Type 2 meetings to discuss specific aspects of their development programs. This approach facilitates biosimilar product development by providing a process for iterative advice and clarity throughout the development stage.

The BsUFA program established five meeting types specific to biosimilar development programs:

- A Biosimilar Initial Advisory meeting is an initial assessment limited to a general discussion regarding whether licensure under section 351(k) of the Public Health Service (PHS) Act may be feasible for a particular product.
- A BPD Type 1 meeting is a meeting that is necessary for an otherwise stalled BPD program to proceed. Examples of a BPD Type 1 meeting include discussion of a clinical hold, a special protocol assessment meeting, discussion of an important safety issue, dispute resolution meetings, and discussion of a Complete Response.
- A BPD Type 2 meeting is a meeting to discuss a specific issue (e.g., proposed study design or endpoints) or questions where FDA will provide targeted advice regarding an ongoing BPD program. This meeting type includes substantive review of summary data, but does not include review of full study reports.
- A BPD Type 3 meeting is an in-depth data review and advice meeting regarding an ongoing BPD program. This meeting type includes substantive review of full study reports, FDA advice regarding the similarity between the proposed biosimilar biological product and the reference product, and FDA advice regarding the need for additional studies, including design and analysis. This meeting has no counterpart in the Prescription Drug User Fee Act (PDUFA) program and is unique to BsUFA to support an evaluation of residual uncertainty regarding the demonstration of biosimilarity and to support the concept of stepwise evidence development.

- A BPD Type 4 meeting is a meeting to discuss the format and content of a biosimilar biological product application or supplement to be submitted under section 351(k) of the PHS Act.

Scheduled Meetings by Type and Fiscal Year

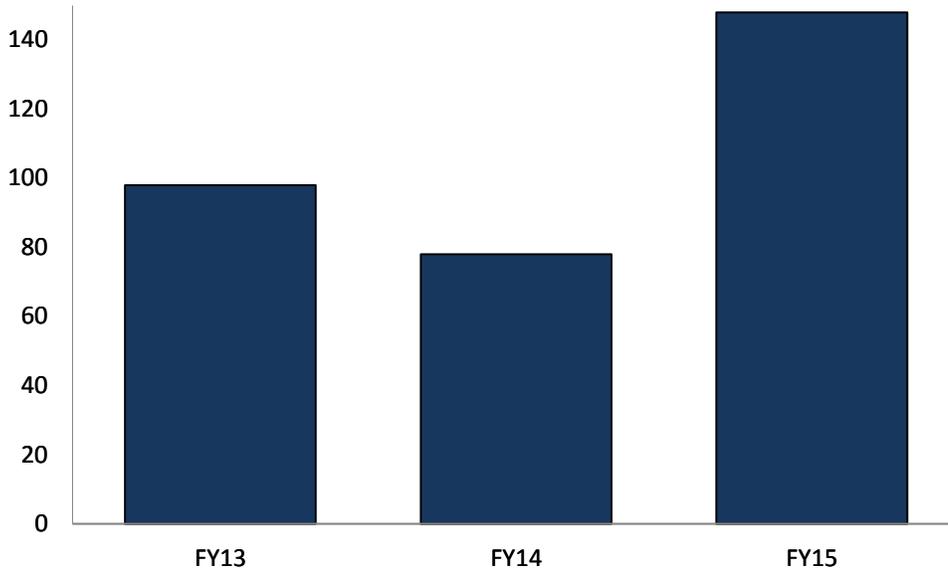


The types of scheduled meetings shift with each fiscal year, with BPD Type 1 and Type 2 meetings becoming a larger portion of scheduled meetings in FY2015

While we have made significant progress in implementing this new program, there is more work to do and, as with any new initiative, there are challenges to address. The biosimilars program was created with passage of the BPCI Act in 2010. In 2013 dedicated funding was made available for this important work through the Biosimilars User Fee Act of 2012. In addition, the BsUFA statutory requirement that FDA spend a certain level of budget authority funding in order to have the authority to spend the user fee funds presents challenges. FDA also is working to recruit additional staff and has continued to allocate increasing resources for this critical regulatory review program. While the FTE expenditure in fiscal years 2013 and 2014 were relatively equal, the FTE expenditure in the first two quarters of FY2015 was equivalent to the

total expenditures in the previous two fiscal years. As projected, FDA expended more FTEs in

FTE Expenditure by Fiscal Year



FTE expenditures from FDA financial reports. The FY 15 numbers is not yet final and will increase slightly.

FY2015 than previous years.

The increase in FTE expenditure is a direct reflection of the change and increase in workload in FY2015. Since program inception and as of December 31, 2015, five companies have publicly announced submission of eight 351(k) BLAs to FDA for proposed products. As mentioned previously, one of these 351(k) BLA for a biosimilar product has been approved, Zarxio (filgrastim-sndz).

FDA will need to hire and train additional staff to support this program. As the BsUFA program matures, FDA expects overall BsUFA performance metrics will improve in coming years.

Global Development

Beyond our borders, we continue to support global development of biologics and biosimilars, and are actively engaged with other national regulatory agencies. We recognize that biosimilar development and regulation are of interest worldwide and FDA can be a leader in this arena. Thus, FDA is an active participant in international regulatory organizations and at international regulatory meetings and scientific conferences.

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FDA has also worked to ease the burden for sponsors of proposed biosimilar products that have previously been approved outside the United States, such as in the European Union, to develop their proposed biosimilar products for the U.S. market. The BPCI Act requires a demonstration of biosimilarity to a U.S.-licensed reference product. This requirement was initially perceived as a barrier to development that necessitated conducting multiple separate studies with a regionally approved comparator product. As a global leader, FDA took steps to address this issue in a scientifically rigorous manner by issuing guidance describing the use of a non-U.S.-licensed comparator in certain studies based on an adequate scientific bridge between the U.S.-licensed reference product and a non-U.S.-licensed comparator product. Following FDA's publication of draft guidance on this topic, the European Medicines Agency adopted the same regulatory approach with the same scientific standards. As noted above, while the BPCI Act requires a demonstration of biosimilarity to a U.S.-licensed reference product and, as a scientific matter, a sponsor will need to directly compare its proposed biosimilar product with the U.S.-licensed reference product in certain studies, the scientific approach outlined above should help prevent unnecessary duplication of other studies.

Education and Outreach

As previously noted, stakeholder confidence is essential to the success of the biosimilar program. FDA has and will continue to actively engage with stakeholders. We have held public and stakeholder meetings. FDA also is undertaking a multi-phase plan for communicating with stakeholders and educating them about biosimilars. The first phase of the communication plan is to lay a solid foundation with understandable definitions and descriptions that health care professionals and consumers can easily understand and adopt. To help guide message development, FDA has a contract to conduct a focus group study and in-depth interviews of prescriber and pharmacist knowledge of biosimilar biological products. FDA also has a contract for Web-based training programs, which includes a biosimilar course to educate health care professionals (physicians, nurses, pharmacists, nurse practitioners and physician assistants) nationwide. Additionally, FDA in FY2016 will conduct education and outreach targeting healthcare professional societies and patient advocacy organizations to increase awareness and understanding of biosimilars. FDA plans to communicate information in various formats to consumers as more biosimilar products are approved and enter the marketplace. We will continue our outreach activities, including interacting with physicians and pharmacists and educating consumers and patients, well into the future.

The Path Forward

Of course, more work needs to be done. FDA will continue to meet with companies to provide advice for individual development programs. Over the past year, we have seen the number of meeting requests and marketing applications grow. We are excited about this growing demand, and we will continue to facilitate development, submission, and timely review of biosimilar product applications.

Even with our challenges, we are optimistic and energized about the future. This new pathway for biosimilar products and interchangeable products has the potential to offer a significant contribution to the public health of many Americans. At FDA, we are working hard to ensure this impact can be realized.