

FDA Finalizes Guidance on Biosimilar Interchangeability, Reiterates Case-by-Case Approach to Data Requirements

Thursday, May 16, 2019

On May 10, 2019, the Food and Drug Administration issued highly anticipated final guidance that gives drug-makers more clarity on how to demonstrate that a proposed biosimilar product meets the statutory interchangeability standard under the Public Health Service Act (PHS Act or the Act). According to the Act, an interchangeable biosimilar may be substituted for the original biological product without the involvement of a prescriber, similar to the way generic drugs are routinely substituted for brand name drugs at the pharmacy level. The [Final Guidance](#), entitled “Considerations in Demonstrating Interchangeability with a Reference Product,” is shorter than the draft version released over two years ago, in response to industry feedback, but generally tracks the original policy positions proposed in the draft, with a few notable exceptions summarized below.

Introduction to Interchangeable Biosimilars

There is no requirement that a new biosimilar product demonstrate itself as “interchangeable” to the reference biological product – that is, the original biological product that the biosimilar sponsor is seeking to rely upon for its own marketing approval. The law contemplates two categories of licensed follow-on biologics, the biosimilar biologic and the interchangeable biosimilar, and this new Final Guidance document does not alter that framework. And although no interchangeable biosimilars have been licensed by FDA since passage of the Biologics Price Competition and Innovation Act (BPCIA), which amended the PHS Act in 2010 to create the legal pathway for biosimilars, at least 45 States have enacted local laws or regulations in order to authorize licensed health care professionals to substitute FDA-approved interchangeable biosimilars if and when they come to market (see our most recent tally of these State laws [here](#)).

So what exactly is an interchangeable biosimilar? In addition to meeting the various criteria for being “biosimilar,” or highly similar, to the reference biologic as FDA has explained that concept in other industry guidance, the PHS Act requires that the product meet the following two criteria before it can be licensed as interchangeable:

1. The biosimilar can be expected to produce the same clinical result as the reference biologic in any given patient; and
2. For a product that will be administered more than once to patients, the “risk in terms of safety or diminished efficacy of alternating or switching between use of the [biosimilar] and the reference product is not greater than the risk of using the reference product without such alternation or switch.”

Biologic drugs remain some of the most expensive products on the market due to the complicated nature of making them from living cells and the fact that such products are used to treat serious chronic conditions, such as cancer, multiple sclerosis, and autoimmune disorders. Congress created these heightened interchangeability



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criteria in an attempt to enhance competition and incentivize the development of cheaper biological product alternatives that would cut costs for patients, governments, and insurance companies in the long run, while at the same time protecting patient safety and ensuring that medical and scientific issues are taken into account during product development and premarket regulatory review. To date, FDA has approved 19 biosimilar products but, as noted previously, none of those have also been approved as interchangeable with the reference biologic. FDA's demanding criteria for this interchangeability designation and the lack of clarity regarding how to achieve or demonstrate that the criteria have been met are cited as contributing factors to the minimal progress in this space over the past several years.

Final Interchangeability Policies Are More Flexible than FDA's First Proposals

The long awaited Final Guidance provides recommendations for the biosimilar industry and introduces more flexibility with respect to the design of the studies required to demonstrate that the interchangeability criteria have been made. In a same-day [statement](#), Acting FDA Commissioner Ned Sharpless summarized the new document this way: "Today's final guidance gives an overview of important scientific considerations in demonstrating interchangeability with a reference product and explains the scientific recommendations for an application or a supplement for a proposed interchangeable product."

More specifically, the final FDA interchangeability guidance goes into the following important scientific topics on which biosimilar sponsors have been seeking greater clarity:

- What data and information are needed to support a demonstration of interchangeability;
- Considerations for the design and analysis of a switching study or studies to support a demonstration of interchangeability;
- Considerations regarding the comparator product in a switching study or studies; and
- Considerations for developing presentations, container closure systems, and delivery device constituent parts for proposed interchangeable products (this last topic is covered in abbreviated form, due to the fact that these will be assessed on a case-by-case basis depending on the product).

In comparison to its proposed policies on interchangeability released in January 2017, FDA has not changed its original recommendation that a biosimilar sponsor submit data and information to show that the proposed interchangeable product "can be expected to produce the same clinical result as the reference biologic" (criterion #1, see above) for all of the reference product's licensed conditions of use. Some commenters on the draft guidance had requested this be revised to take into account the fact the a biosimilar - just as a generic drug - can be approved by FDA for fewer indications that the reference product might be approved for, due to patent or exclusivity protections on a subset of indications.

However, one of the most significant changes in FDA's final recommendations is a welcome one for the still-budding U.S. biosimilar industry. The Agency has moved away from language indicating that only FDA-licensed reference biologics could be used to conduct the "switching studies" that will be necessary in most cases to meet the standard set forth in interchangeability criterion #2 (see above). The switching studies should be done in one or more conditions of use, not necessarily all indications for which the reference product is licensed, and the Agency recommends using a condition "that would be adequately sensitive to assess the risk of alternating or switching" and that would support a scientific justification for extrapolating the data to other conditions of use. Further, the biosimilar sponsor will still need to establish a scientific bridge between a non-U.S.-licensed comparator product and the FDA-licensed version in order to justify to the Agency why the switching study is scientifically appropriate and valid:

If a sponsor seeks to use data derived from a switching study or studies comparing a proposed interchangeable product with a non-U.S.-licensed comparator product as part of the demonstration that the proposed interchangeable product meets the standard described in ... the PHS Act, the sponsor should provide adequate data and information to establish a 'bridge' between the non-U.S. licensed comparator and the U.S.-licensed reference product and thereby justify the relevance of the data obtained using the non-U.S. licensed comparator to an evaluation of whether the requirements of [the Act] have been met.

While the design parameters for these switching studies are flexible and FDA encourages sponsors to consult with its Biosimilars Staff about specific design considerations like primary endpoints and statistical analysis, the Agency is still approaching this interchangeability criterion from the position that switching studies will always be required to make the necessary scientific showing under criterion #2. Therefore, any biosimilar sponsor that does not believe a switching study is needed is likely going to bear a heavy burden of convincing FDA to forego such data when the biosimilar product is intended to be administered to patients more than once. On this point, the

Final Guidance states that: “If a sponsor of a proposed interchangeable product believes that data from a switching study is not necessary, FDA expects the sponsor to provide a justification for not needing such data as a part of the demonstration of interchangeability.” It goes on to note, however, the design of the switching studies can be informed by sponsor’s expectations for how the proposed interchangeable biosimilar may be used in clinical practice.

Finally, Dr. Sharpless indicated in his statement accompanying the final guidance that interchangeability designations aim to increase patient and physician confidence in the safety and effectiveness of biosimilars, which is one goal of the Biosimilars Action Plan released in mid-2018. Similarly, the emergence of interchangeable biosimilars on the U.S. market may help to clarify any confusion or disconnects between the payer and health care provider communities when it comes to the appropriate use and coverage of these products.

Interchangeability in the Statute Doesn’t Include Exceptions - But Will FDA Create One for Insulin Products?

Next up on FDA’s agenda is to focus on the approval of insulin products as biosimilars, following the March 2020 transition of these and certain other drug products from the “drug approval pathway” into the “biologics approval pathway,” as mandated by Congress in the BPCIA. Indeed, whether or not the May 10th release of the Interchangeability Guidance was intentionally timed to coincide with this event, the Agency convened a [public meeting](#) on May 14, 2019 to hear from stakeholders on the development of biosimilar and interchangeable insulin products.

One of the views expressed during the meeting by multiple presenters was that FDA should not require switching studies before approving an insulin as interchangeable under the BPCIA, given the history of clinical experience with these products and the lack of immunogenicity concerns with this small, simple protein product. (As one public presenter put it: “Insulin is not Humira” – a reference to the fact that monoclonal antibody products are much larger and considerably more complex to characterize than these proteins are). Although the insulin market pressures are unique, and a discussion of the complexities triggered by the March 2020 drug-to-biologic transition is beyond the scope of this blog post, we note this confluence of issues because it will be fascinating to see how the Agency responds to these arguments and what policies it announces for insulin products in particular.

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