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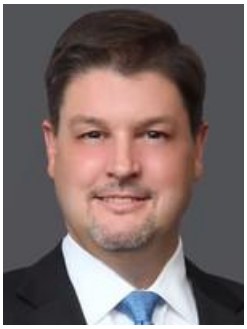
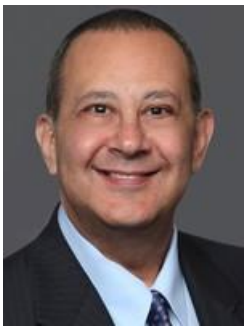
FDA Finally Addresses Interchangeable Biosimilars

Law360, New York (February 28, 2017, 11:54 AM EST) -- The U.S. Food and Drug Administration recently issued long-awaited draft guidance, "Considerations in Demonstrating Interchangeability With a Reference Product" (January 2017), addressing the standards for demonstrating interchangeability of biological products under the Biologics Price Competition and Innovation Act of 2009.



Christopher M. Mikson

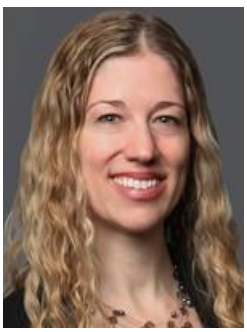
The BPCIA amended the Public Health Service Act to create an abbreviated pathway for FDA licensure of biologics that are biosimilar to, or interchangeable with, a reference product. Under the BPCIA, a product is biosimilar if it is highly similar to the reference product, notwithstanding minor differences in clinically inactive components and if there are no clinically meaningful differences between the two products in terms of safety, purity and potency. Further, a biosimilar is interchangeable if it can be expected to produce the same clinical result as the reference product and if the risk — in terms of safety or diminished efficacy of switching the two products in the same patient — is no greater than when administering the reference product. Such a product may be substituted for the reference product without the intervention of the prescribing health care provider.



Mark Mansour

To date, the FDA has issued a number of guidances addressing the standards for establishing biosimilarity, but this is the first guidance the FDA has issued addressing the higher standard for interchangeability.

General Principles



Emily K. Strunk

In assessing interchangeability, the FDA generally intends to follow the "totality of the evidence" and "residual uncertainty" approaches taken in its earlier series of guidances addressing biosimilarity under the BPCIA, including "Quality Considerations in Demonstrating Biosimilarity of a Therapeutic Protein Product to a Reference Product" (April 2015), "Scientific Considerations in Demonstrating Biosimilarity to a Reference Product" (April 2015), and "Biosimilarity: Additional Questions and Answers Regarding Implementation of the Biologics Price Competition and Innovation Act of 2009" (May 2015).

To that end, the FDA expressly recognizes that the type of data submitted "may vary depending on the nature of the proposed interchangeable product." Such information may include evaluation of quality attributes, analytical differences in the molecules, mechanisms of action, biodistribution in differing patient populations and toxicities. Where there are differences in these parameters, the FDA will require the sponsor to establish a scientific justification for why such differences do not preclude a showing of interchangeability. The FDA tempers that requirement by allowing for the possibility of extrapolation certain data to demonstrate interchangeability. The FDA will also allow a sponsor to seek an interchangeability finding for less than all of the approved uses of the reference product, but recommends that the sponsor seek licensure for all such uses "when possible." The FDA also specifies that it will expect data from switching studies to support an analysis of the risks of switching and that sponsors should account for the effects of any differences in the product's presentation on the appropriate use of the product.

The FDA provides detailed comments on a variety of specific issues related to the data a sponsor may use to support the principal findings required to establish interchangeability. On nearly all points, the FDA emphasizes that a sponsor should proactively discuss their plans with the agency.

Specific Issues Addressed

Product-Dependent Factors

The FDA recommends that sponsors use a stepwise approach to assess interchangeability considerations, beginning during product development. At each step, the sponsor should evaluate whether there may be residual uncertainty on an individual area and identify steps to address that uncertainty. Areas that may need to be addressed include the complexity of the molecule, capabilities of current analytical techniques to characterize the molecule, and product-specific immunogenicity risks. The FDA emphasizes that these factors must be considered together to inform the consideration of residual uncertainty about the data, and provides illustrative examples of how the analysis may vary on a case-by-case basis.

Biosimilar Post-Marketing Data

The FDA believes that current techniques for assessing post-marketing data collected from products first licensed as a biosimilar remain insufficient to support a demonstration of interchangeability, including determination of the pharmacokinetics (PK) and pharmacodynamics (PD) of switching between the proposed interchangeable product and the reference product. However, the FDA notes that in certain circumstances post-marketing data from a licensed biosimilar product may be helpful in considering what data is necessary to support a demonstration of interchangeability. Post-marketing data that may be useful include actual patient experiences in biosimilar switching scenarios, as well as the immunogenicity data obtained from actual use of a licensed biosimilar.

Switching Study Design

The FDA provides detailed observations and recommendations on multiple aspects of switching study design, including endpoints, sample size, sampling of PK/PD, population route of administration, number and duration of studies and integrated study design. Switching studies should evaluate changes in treatment that result in two or more switch intervals and, in the long course of therapy, should take into account dropouts and the scientific bases for addressing the possibility of missing data. The FDA notes that an immune response or adverse event during a switching study could have a carryover effect,

making it difficult to asses which product may have been the cause. The FDA takes a flexible approach to designing switching studies that actual study designs should be assessed in consultation with the FDA on a case-by-case basis.

Extrapolation

If the proposed product meets the statutory requirements for interchangeability in a particular use, the sponsor may seek licensure for additional uses by extrapolation. In that event, the sponsor would need to provide sufficient scientific justification for that approach. The FDA specifies the need to address a variety of areas including mechanism of action, biodistribution, immunogenicity and toxicity. As a practical matter, the FDA suggests sponsors consider condition of use studies that would enable later extrapolation.

Reference Product Used in Switching Studies

In a switching study to establish interchangeability, the reference product should be a U.S. licensed biological product. The FDA distinguishes the use of a non-U.S. product as a comparator in a biosimilarity study. In that case, the comparator serves only as a control, whereas in a switching study the reference product is used in both the active switching arm and the control switching arm. Thus, in a switching study, a subtle difference in immunogenicity might prime the immune system over repeated switching, increasing the immune response. Nevertheless, the FDA allows for the possibility of using a non-U.S. licensed product in a switching study, if the sponsors can provide adequate scientific justification.

Presentation

The FDA notes that administering a biologic generally involves injection or infusion into the body, which may be performed by health care providers, patients, or caregivers. Thus, product administration could potentially vary depending on the design of its presentation, meaning constituent components such as its delivery device and container closure system. Differences in the presentation may be acceptable, so long as there is data demonstrating the changes do not negatively impact the ability of end users to use the products appropriately when one is substituted for another. To that end, the FDA prescribes a series of analyses that should be undertaken to meet these goals, including a threshold analysis of any differences, as well as studies to evaluate their significance, including in vitro or in vivo performance testing in certain circumstances.

Post-Marketing Safety Monitoring

The FDA emphasizes the importance of "robust safety monitoring" for all biological products, including biosimilar and interchangeable products. Such monitoring should consider safety and efficacy respect to the reference product and its class, the proposed interchangeable product in development, the specific conditions of use and features of the target patient population. Adequate pharmacovigilance mechanisms should be in place, and the FDA warns that, as with any biologic, the agency may require a postmarketing study or a clinical trial to evaluate such risks.

Implications

It has been six years since Congress passed the BPCIA as part of the Affordable Care Act. The FDA has issued numerous guidances on the standards for establishing biosimilarity. The BPCIA's patent litigation process –— dubbed the "Patent Dance" years ago because of its complexity as compared to the Hatch-

Waxman litigation process — has been the subject of multiple lawsuits. BPCIA litigation has progressed to the point where a critical step in the "dance" — the provision stating the biosimilar applicant "shall" provide its application to the reference biologics license holder — is now before the U.S. Supreme Court to determine whether it is indeed mandatory. While all of these maneuverings have been under way, the issue of interchangeability has received little more attention than the FDA promising to provide guidance on the standards for establishing interchangeability. The agency has finally taken the first step in fulfilling that promise.

The FDA's draft interchangeability guidance provides a detailed, yet relatively flexible, set of observations and recommendations with respect to the process by which a sponsor can establish a biosimilar as interchangeable. The FDA's general approach to the interchangeability analysis is conceptually similar to that for biosimilarity in that it examines the totality of the circumstances and analyzes residual risks. Not surprisingly, given the complexity and relative novelty of the subject, the FDA repeats throughout the draft guidance that sponsors should consult with the FDA on these issues early and often. As with the guidances on biosimilarity, this guidance will likely be followed by multiple additional guidances that clarify and expand upon interchangeability issues.

The draft is a significant step forward in the FDA's progress toward full implementation of the regulations required by BPCIA. However, the subject remains one of first impression for all stakeholders. To date, only four biosimilars have been approved, and none has been found interchangeable. A biosimilars approval system has been in place in the EU for years and, even there, no product has been found interchangeable. Indeed, many commentators have assessed that finding interchangeability will be difficult to impossible given current technology.

Nevertheless, the possibility of interchangeable biologics has captured the attention of many stakeholders, political leaders and the public. Biosimilars and interchangeable biologics have been touted as an effective means for significantly lowering drug costs. That remains to be seen. Conducting a meaningful assessment is difficult given that only a handful of biosimilars are marketed in the United States at this time. In the EU, biosimilars have demonstrated a relatively modest reduction in prices, at least compared to the price reductions correlated with generic small-molecule drugs. Scores of state legislatures have passed various forms of legislation allowing for the substitution of interchangeable biosimilars under a variety of conditions. The passage of these laws have made headlines, lauded as efforts by political leaders to speed up drug approvals and lower drug costs. But by definition these laws are only applicable to interchangeable products, not biosimilars. Thus, while the eventual licensure of interchangeable biologics implicates many of the same hopes and trepidations as the first generics did in the small molecule industry, it appears that the benefits of such licensing may not be realized until far in the future.

The immediate practical implications of the new interchangeability guidance must be viewed through the prism of the current political, regulatory and legal environment. Recent developments could be dubbed a "perfect storm" for the FDA and FDA-regulated industry. First, the 21st Century Cures Act passed this year, providing additional resources to the FDA and new regulatory processes for streamlining market authorization for therapeutics. Second, just weeks after the Cures Act passed, the Trump administration made a variety of policy pronouncements, simultaneously calling for lowering the costs of therapeutics, speeding up market authorization for therapeutics, rolling back regulations and regulatory practices followed by the FDA, as well as cutting resources to the agency. Third, while the incoming leadership at the U.S. Department of Health and Human Services and (yet-to-be-named) FDA leadership continues to coalesce, the administration has ordered significant regulatory activity to be paused pending the arrival of new agency officials and functionaries. Finally, interchangeability is not

the only aspect of the BPCIA whose development and interpretation is uncertain. As widely reported, the U.S. Supreme Court has granted certiorari in a case that may affect whether and to what extent biologics stakeholders may decide to utilize the BPCIA to gain marketing authorization for their products.

For each of the past six years, practitioners in this area have been advising audiences and clients “we’ll see” how the ultimate scope of the BPCIA is determined. For the moment, we are still waiting to see. But this may well be the year where we see significantly more certainty in the application of the BPCIA, and thus, we will also see whether and to what extent it provides a more efficient and cost-effective pathway to market for biologics .

—By Christopher M. Mikson, Mark Mansour and Emily K. Strunk, Mayer Brown LLP

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