FDA Issues Draft Guidelines for Biosimilars

Last Thursday, the FDA issued the first set of long-awaited draft guidelines for the regulatory approval of follow-on biologic drug products, or "biosimilars," under the Biologics Price Competition and Innovation Act of 2009 ("BPCIA"). While the pharmaceutical industry has eagerly awaited the FDA's announcement of its views on the regulatory requirements for biosimilar approval, the agency has declined, for now, to provide the type of detailed description many have been seeking. Instead, the draft guidelines set forth general principles to be applied during the approval process and made clear that the regulatory requirements that biosimilar applicants will be required to meet will be highly product dependent. As a result, while these guidelines provide useful insights into the FDA's views on the approval of biosimilar applications, the full scope of the challenges associated with obtaining regulatory approval for biosimilars remains uncertain.

The FDA draft guidelines are composed of three "Guidance for Industry" documents:

- "Quality Consideration in Demonstrating Biosimilarity to a Reference Protein Product" ("Quality Guidelines")
- "Scientific Consideration in Demonstrating Biosimilarity to a Reference Product" ("Scientific Guidelines")
- "Biosimilars: Questions and Answers Regarding Implementation of the Biologics Price Competition and Innovation Act of 2009" ("Biosimilars Q&A").

Although not legally binding, these guidelines provide a description of the FDA's most current thinking about the biosimilar approval process. The Quality Guidelines set forth the analytical requirements for biosimilar approval, while Scientific Guidelines describe the clinical trial requirements for biosimilar approval. The Biosimilars Q&A provides general principles the FDA intends to apply to the approval of biosimilar products. Public comments on the draft guidelines will be accepted for 60 days.

The draft guidelines are directed to the approval of biosimilar therapeutic protein products, although the FDA notes that the scientific principles set out in these guidelines may also be applicable to the approval of other biosimilar products. "Protein" is defined by the draft guidelines to include "any alpha amino acid polymer with a specific defined sequence that is greater than 40 amino acids in size." However, a "chemically synthesized polypeptide" – which is not subject to the biosimilar guidelines – includes "any alpha amino acid polymer that is (a) made entirely by chemical synthesis, and (b) is less than 100 amino acids in size." As a result, whether the draft guidelines will apply to follow-on protein products between 41-99 amino acids will depend entirely upon whether or not they are chemically synthesized.

Similar to the approach adopted in Europe for biosimilar approval, the draft guidelines envision a highly product-specific process in which an applicant's early and frequent consultation with the FDA throughout the approval process will play an integral role in the application's success. At the outset, FDA consultation will determine the appropriate analytical testing to be performed in light of the biologic's physiochemical properties, biological activity, and manufacturing characteristics. In particular, comparative analytical testing between the biosimilar product and the reference product serves, in the view of the FDA, as the "the foundation" of any biosimilar application. In addition to extensive analytical testing, the draft guidelines contemplate reliance on both animal and human clinical studies for approval. The guidelines leave open the possibility that some of the animal and clinical testing requirements may be waived if the biosimilar applicant provides adequate analytical testing and scientific justification to the FDA. While comparative studies with a U.S.-approved biologic are required, comparisons of the biosimilar product with non-U.S. licensed products may also be

relied upon where the relevance of such a comparison, as well as a scientific link between the non-U.S. approved product and the U.S.-licensed reference product, are established.

In considering the testing data provided by the biosimilar applicant, the FDA indicated an intent to adopt a "totality of the evidence" approach to evaluating the evidence of biosimilarity. Further, the FDA envisions a "stepwise" approach to the approval process, in which testing at each stage of the approval process is tailored to the remaining uncertainties surrounding the biosimilarity between the applicant's product and the reference product. The guidelines explicitly contemplate the possibility that extensive and detailed analytical studies may allow a biosimilar applicant to utilize a more targeted approach the animal and clinical studies required for FDA approval.

One of the most significant omissions in these guidelines – which the FDA itself highlights – is any substantive description of the FDA's view on the approval of biosimilars seeking interchangeability status. Under the BPCIA, interchangeable biosimilars, unlike ordinary biosimilars, may be substituted with the reference drug product at the pharmacy level, without need for physician approval. The first approved interchangeable biosimilar for a reference product also receives a period of market exclusivity against other interchangeable biosimilars for that reference product. As a result, the possibility of approval as an interchangeable provides significant financial incentives for a follow-on biologic applicant to seek approval through the biosimilar pathway.

Despite the FDA's disavowal of the relevance of the draft guidelines to the interchangeability approval process, the agency nonetheless expressed its skepticism of a biosimilar protein product's ability to achieve interchangeability status, noting "[a]t this time, it would be difficult as a scientific matter for a prospective biosimilar applicant to establish interchangeability in an original [biosimilar] application given the statutory standard for interchangeability and the sequential nature of that assessment." In addition, the FDA expressed skepticism that the use of clinical comparisons with non-U.S. approval biologics would support an application for interchangeability status.

In sum, the draft guidelines represent an important first step towards a functional biosimilar approval pathway. The open-ended and product-specific nature of the draft guidelines, however, leaves much to the FDA's discretion and does not provide the regulatory certainty that many in the industry had sought. Combined with the lack of standards for approval as an interchangeable biosimilar, the guidelines leave unanswered the question of whether companies interested in follow-on biologics will even utilize the biosimilars approval pathway created by the BPCIA – or instead rely on the traditional biologics licensing pathway. The FDA's handling of the first biosimilar applications will therefore be closely watched by the industry and should provide important insights into the FDA's approval of biosimilar drug products. ◆

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