wiley

ARTICLE

First Biosimilars Guidances Issued by FDA

February 9, 2012

On February 9, 2012, the Food and Drug Administration (FDA) issued the first three draft Guidances on the development and approval processes for biosimilar products under the Biologics Price Competition and Innovation Act of 2009 (BPCIA). This is an important first step in FDA's implementation of the BPCIA, but as described below, the Guidances are very small baby steps that leave many important questions unanswered. The three Guidances (click through to read) are titled:

- Scientific Considerations in Demonstrating Biosimilarity to a Reference Product,
- Quality Considerations in Demonstrating Biosimilarity to a Reference Protein Product, and
- Biosimilars: Questions and Answers Regarding Implementation of the Biologics Price Competition and Innovation Act of 2009.

In the Scientific Considerations Guidance, FDA describes a "totality of the evidence" approach to the evaluation of data and information submitted in support of the requirement to show that a product is "biosimilar" to the reference biologic product. The Quality Considerations Guidance addresses Chemistry Manufacturing and Controls (CMC) issues as required in a biosimilar application, and provides an overview of the analytical factors it may consider when assessing biosimilarity from a CMC standpoint. This Guidance is, however, specifically targeted to protein biosimilar products. The Q&A Guidance addresses a variety of questions the agency has received from companies interested in developing biosimilar products. These Guidances are described in more detail below.

Practice Areas

Food & Drug

The Scientific Considerations Guidance.

The Scientific Considerations Guidance describes the FDA's totality of the evidence approach in a way that makes clear that different biosimilar products will be evaluated and subject to varying criteria depending upon the nature of, and science related to, that particular product. For example, FDA plans to use a risk-based approach in evaluating available data in connection with a biosimilar product, and advises sponsors to use a step-wise approach in developing the evidence needed to support a demonstration of biosimilarity. With this approach, at each step the sponsor should identify any "residual uncertainty" about biosimilarity as a means to design the next stage of investigation to resolve the uncertainties. This approach will also allow FDA to participate more actively in the development process by providing frequent feedback and recommendations on additional development steps and testing approaches as the product is being developed, as is contemplated by the negotiated terms of the proposed Biosimilar User Fee Act expected to be enacted later this year.

Among the multiple factors FDA will consider in making biosimilarity decisions are such things as the product's complexity, its formulation, stability issues, as well as the usefulness of biochemical and functional characterization. Additional factors to be considered will include the mechanism of action, product structure-function relationships, the clinical experience with the reference product, and the manufacturing processes used.

The Quality Considerations Guidance.

The Quality Considerations Guidance provides an overview of the analytical factors that may be considered by FDA to determine whether a proposed biosimilar protein product and the relevant reference product are "highly similar" as is required for a determination of biosimilarity and ultimate approval. This guidance discusses CMC-related principles including issues of analytical, physical, chemical and biological characterization, the type, nature, and extent of any differences between the proposed biosimilar product and the reference product, and the potential effect of any differences between the products on the safety, purity, and potency of the proposed biosimilar product. This guidance also recognizes that emerging techniques in analytics and manufacturing technology, including quality-by-design approaches may allow for more detailed "fingerprint-like" analyses of such protein biosimilar products and provide bases for designing animal or clinical studies necessary to demonstrate biosimilarity.

The Q&A Guidance.

The Q&A Guidance addresses more than a dozen questions that have been posed to the agency in the time since the BPCIA was enacted. Some of these questions and answers address procedural or technical issues with relatively straightforward answers, but others go to points of contention that have been debated since the first proposed biosimilars laws were floated nearly ten years ago. For example, FDA takes the position that a biosimilar product:

- May have a different formulation than the reference product;

- May have a different delivery device or container closure system than the reference product;
- May be approved for fewer than all of the routes of administration of an injectable reference product
- May be approved for fewer than all presentations (strengths, delivery device, or container closure systems) than the reference product; and
- May be approved for fewer than all of the conditions of use of the reference product.

FDA also advises that a biosimilar product sponsor can use animal or clinical data using a non-U.S. licensed biological product to support biosimilarity of its product to the U.S. approved reference product, that clinical studies to address Qt/Qc cardiac issues is generally *not* required for a biosimilar product, and that a biosimilar product applicant may extrapolate clinical data in one condition of use to support approval of another condition of use.

Interchangeability. One question/answer of particular complexity and interest to industry involves the issue of biosimilar product interchangeability. FDA addresses the question "can an applicant obtain a determination of interchangeability between its proposed product and the reference product in an original 351(k) [abbreviated] application?" FDA's proposed answer is "Yes...FDA can make a determination of interchangeability" in its review of the new original application but, the FDA goes on to state, "[a]t this time, it would be difficult as a scientific matter for a prospective biosimilar applicant to establish interchangeability in an original 351(k) application given the statutory standard for interchangeability and the sequential nature of that assessment. FDA is continuing to consider the type of information sufficient to enable FDA to determine that a biological product is interchangeable with the reference product." The bottom line message from this statement is that *no original 351(k) approvals are likely to include an affirmative interchangeability determination.*

Pediatric Assessments. The interchangeability issue also comes into play with respect to the need for pediatric assessments under the Pediatric Research Equity Act (PREA). FDA states that a biosimilar product that is not deemed to be interchangeable will be considered to have a new active ingredient for purposes of PREA and therefore a pediatric assessment will be required for such biosimilar products, unless FDA grants a waiver or deferral of pediatric studies. Given the expected difficulty of developing biosimilar products generally, the need to additionally develop and study the product for pediatric uses represents a potentially significant additional burden on biosimilar applicants. It will be interesting to observe how FDA responds to waiver and deferral requests in connection with early biosimilar applications.

NDA versus BLA Products. The Q&A Guidance also defines the terms "protein" and "chemically synthesized polypeptide" for purposes of what type of application - a BLA or an NDA - will be required for approval of certain products. These are rather complex issues of science, law, and regulation, with implications for business regulatory strategies. In simplest terms, some amino acid products will be regulated as "drugs" and thus approved under NDAs while others will be biologics subject to BLAs. FDA's Guidance proposes to define a "protein" as "any alpha amino acid polymer with a specific defined sequence that is greater than 40 amino acids in size." Polymers composed of fewer than 40 amino acids will generally be deemed to be "peptides" and not proteins, and therefore subject to NDAs and not BLAs. Moreover, a "chemically synthesized

polypeptide" means any amino acid polymer made entirely by chemical synthesis and which is less than 100 amino acids in size. These molecules too, are not considered biologics, but rather are drugs subject to NDAs instead of BLAs.

Exclusivities. Finally, the Q&A Guidance addresses two questions regarding exclusivity under the BPCIA. One question is, "Can an [innovator] applicant include...a request for reference product exclusivity" in its full 351(a) application? FDA's response is "Yes," but with the caveat that the agency "is continuing to review the reference product exclusivity provisions." Thus FDA recommends that a reference product applicant's request for exclusivity specifically describe how the product meets the statutory requirements for exclusivity and include adequate data and information to support the request. FDA will undoubtedly use such submissions and their supporting explanations and arguments in further developing its regulatory and procedural exclusivity policies. The only other exclusivity related question was how a prospective biosimilar applicant can determine whether there is an unexpired orphan exclusivity for the reference product. The answer, very simply, is to check FDA's website.

Conclusion and Observations.

While the issuance of these Guidances is an important and meaningful first step in FDA's implementation of the law, the Guidances themselves are at a very high level of generality. Moreover, some of the most interesting and challenging legal and procedural issues under of the BPCIA - such as exclusivity standards for reference products, interchangeablility standards for biosimilar products, and issues surrounding the patent litigation procedures established by the BPCIA - remain unaddressed by the agency.

For the most part, the Guidances do not provide any clear road maps for the development and approval of any particular biosimilar product. While this may be disappointing to some, it should not be unexpected for those who have been close to the biologics development process and who followed the crafting of the BPCIA. The law itself, in fact, provides relatively few specifics about the standards necessary for approval of biosimilar products, because Congress recognized that the complexity of biological molecules and their manufacturing processes make it essentially impossible to define in advance the scientific and clinical information that would be necessary for approval of any particular product. Thus the FDA was given wide discretion to define and evaluate the safety and efficacy parameters for biosimilar products, and as many have a long recognized, this process will require a case by case, product-specific evaluation. These Guidances, while helpful in expressing some of the FDA's general approaches, but will be of limited specific value with respect to any particular product.