

FDA's Draft Biosimilars Guidance Documents: Overview and Implications

On February 9, 2012, the US Food and Drug Administration ("FDA" or "the Agency") released for comment its initial draft guidance implementing the Biologics Price Competition and Innovation Act (BPCIA), signed into law as part of the Affordable Care Act, which creates an approval pathway under section 351(k) of the Public Health Service Act (PHS Act) for biological products demonstrated to be "biosimilar" to or "interchangeable" with a licensed "reference" biologic product.¹ In late 2010, FDA held a two-day public meeting² and established a public docket³ to obtain input on implementation of the BPCIA, and stakeholders have been eagerly awaiting the draft guidance documents, which FDA had indicated would be released last year. Comments on the draft guidance documents should be submitted by April 16, 2012 to ensure consideration in the development of the final guidance. In addition, the Agency reportedly plans to convene another public meeting to obtain input on the draft guidance documents prior to the release of final guidance.

The three draft guidances, which together represent FDA's current thinking on the development of biosimilar products, include:

- **Questions and Answers Regarding Implementation of the BPCIA.** This document answers "common questions" and "describes FDA's current interpretation of certain statutory requirements [which] reflect consideration" of comments submitted to the public docket.⁴

¹ The notice on the guidance documents appeared in the *Federal Register* on February 15, 2012. 77 Fed. Reg. 8885.

² More information on the November 2-3, 2011 public meeting, including meeting transcripts and the *Federal Register* notice establishing a public docket, can be accessed at the following FDA website page. FDA, Approval Pathway for Biosimilar and Interchangeable Biological Products Public Meeting, available at <http://www.fda.gov/Drugs/NewsEvents/ucm221688.htm>.

³ 75 Fed. Reg. 69,147 (Oct. 5, 2010).

⁴ FDA, Guidance for Industry: Biosimilars: Questions and Answers Regarding Implementation of the Biologics Price Competition and Innovation Act of 2009 at 1 (Feb. 2012) (hereinafter "Q&A Guidance"), available at <http://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/UCM273001.pdf>.

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Healthcare Reform Chart

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- **Scientific Considerations in Demonstrating Biosimilarity to a Reference Product.** This document explains the types of scientific support necessary to demonstrate that a proposed product is biosimilar to the reference product.⁵
- **Quality Considerations in Demonstrating Biosimilarity to a Reference Protein Product.** This document addresses key considerations for assessing whether a proposed protein product is “highly similar” to the reference product.⁶

Together, the drafts set forth a proposed framework—albeit nonbinding—for the development of proposed biosimilar products that focuses on key scientific and quality considerations necessary to demonstrate the statutory threshold of “biosimilarity” in a 351(k) application, i.e., a biological product that is “highly similar to the reference product ... and there are no clinically meaningful differences between” the products in terms of the safety, purity, and potency).⁷ FDA recommends that sponsors use a “stepwise approach” to demonstrating biosimilarity to a reference product, and the Agency intends to use a “totality-of-the-evidence” approach to review marketing applications.⁸

As expected, FDA did not release product-class specific guidance, which is contemplated but not required under the BPCIA.⁹ In a press conference announcing the draft guidance, Dr. Rachel Sherman, director of the Office of Medical Policy in FDA’s Center for Drug Evaluation and Research, indicated that FDA has not decided whether to issue product-class specific guidance,¹⁰ as the European

Medicines Agency has done for several biological product classes.¹¹ Thus, at least in the near term, sponsors are likely to learn FDA’s views and expectations for particular product classes through agency interactions, and the draft guidance recommends that sponsors meet early with FDA, at which time the sponsor can provide a proposed plan for its development program, “manufacturing process information (including planned methodology and assay validation), and preliminary comparative analytical data with the reference product.”¹² According to Dr. Sherman, FDA has held 21 pre-Investigational New Drug (IND) meetings with sponsors and has received 9 INDs for proposed biosimilar products.

The draft guidance does not address the standards necessary to demonstrate that a biosimilar product is “interchangeable” with a reference product,¹³ but does note that a prospective biosimilar applicant likely could not establish interchangeability in an original 351(k) application.¹⁴ FDA is expected to issue an additional draft guidance document addressing interchangeability, but has not indicated a timeframe for doing so, which suggests that FDA does not anticipate licensing an interchangeable product in the near term. It is also notable that the draft guidance does not interpret with any specificity the BPCIA’s provisions addressing product exclusivity, such as the circumstances under which a biological product that is granted 12 years of market exclusivity may be eligible for another period of exclusivity based on a modification to the licensed product that results in a change in safety, purity or potency,¹⁵ or the

5 FDA, Guidance for Industry: Scientific Considerations in Demonstrating Biosimilarity to a Reference Product (Feb. 2012) (hereinafter “Scientific Guidance”), available at <http://www.fda.gov/>.

6 FDA, Guidance for Industry: Quality Considerations in Demonstrating Biosimilarity to a Reference Protein Product (Feb. 2012) (hereinafter “Quality Guidance”), available at <http://www.fda.gov/>.

7 PHS Act § 351(i)(2), 42 U.S.C. § 262(i)(2).

8 Scientific Guidance at 2.

9 PHS Act § 351(k)(8)(D), 42 U.S.C. § 262(k)(8)(D).

10 See Internal Medicine News, FDA Issues Guidelines on Developing Biosimilar Products (Feb. 9, 2012), available at <http://www.internalmedicine.com/single-view/fda-issues-guidelines-on-developing-biosimilar-products/8ef5b2bf2c.html>.

11 See European Medicines Agency, Multidisciplinary: Biosimilar, available at http://www.ema.europa.eu/ema/index.jsp?curl=pages/regulation/general/general_content_000408.jsp&mid=WC0b01ac058002958c.

12 Q&A Guidance at 4.

13 Under the BPCIA, an “interchangeable” biological product is biosimilar to the reference product and, among other things, “can be expected to produce the same clinical result as the reference product in any given patient” PHS Act § 351(k)(4)(A), 42 U.S.C. § 262(k)(4)(A). An “interchangeable” product “may be substituted for the reference product without the intervention of the health care provider who prescribed the reference product.” PHS Act § 351(i)(3), 42 U.S.C. § 262(i)(3).

14 Q&A Guidance at 11.

15 See PHS Act § 351(k)(7)(C), 42 U.S.C. § 262(k)(7)(C).

BPCIA's patent dispute resolution provisions governing the exchange of data and patent information between a biosimilar applicant and the reference product sponsor.

The remainder of this Advisory reviews key points from the three draft guidance documents.

Questions and Answers Regarding Implementation of the BPCIA

This draft guidance briefly addresses, in a Q&A format, issues including: (1) the various ways in which a proposed biosimilar product may differ from, but still be demonstrated to be highly similar to, the reference product; (2) circumstances under which a sponsor may rely on comparative data with a non-US-licensed product to demonstrate biosimilarity; and (3) the Agency's interpretation of the definition of "biological product" as amended by the BPCIA. FDA intends to update this draft guidance with additional Q&As as appropriate.¹⁶ Important issues addressed in this draft guidance include:

- The draft guidance notes that "some design differences in the delivery device or container closure system" may be acceptable for a proposed biosimilar product (e.g., use of a prefilled syringe even if the reference product is licensed in a vial presentation), where adequate performance data for the different delivery device or container closure system are provided.¹⁷
- The draft guidance states—with limited accompanying discussion—that an applicant may obtain licensure of a proposed biosimilar product: (1) for fewer than all routes of administration for which an injectable reference product is licensed; (2) for fewer than all presentations (e.g., strengths or delivery device or container closure systems) for which a reference product is licensed; and (3) for fewer than all conditions of use for which the reference product is licensed.¹⁸
- A sponsor may use comparative animal or clinical data to a non-US-licensed product to support a demonstration that a proposed product is biosimilar to

the US-licensed reference product. Nevertheless, "as a scientific matter, analytical studies and a least one clinical pharmacokinetic (PK) study, and, if appropriate, at least one pharmacodynamic study, intended to support a demonstration of biosimilarity must include an adequate comparison of the proposed biosimilar product directly with the US-licensed reference product."¹⁹ Issues that may need to be considered when using a non-US-licensed comparator product include the relationship between the license holder for the non-US-licensed product and the license holder for the US-licensed product, and whether the non-US-licensed product was manufactured in a facility subject to similar scientific and regulatory standards as those required by FDA.²⁰

- The draft guidance provides definitions for the terms "protein" and "chemically synthesized polypeptide", which are important because the BPCIA requires that an application for a biological product, amended to include the category of "protein (except any chemically synthesized polypeptide),"²¹ be submitted under section 351 of the PHS Act rather than section 505 of the Federal Food, Drug, and Cosmetic Act (FDC Act). The draft guidance defines "protein" as "any alpha amino acid polymer with a specific defined sequence that is greater than 40 amino acids in size," and "chemically synthesized polypeptide" as "any alpha amino acid polymer that (1) is made entirely by chemical synthesis; and (2) is less than 100 amino acids in size."²² FDA explains that a chemically synthesized polypeptide is not a biological product as defined in section 351, and thus such a product will be regulated as "drug" under section 505 of the FDC Act unless the polypeptide otherwise meets the definition of biological product (e.g., a polypeptide vaccine).²³ The draft guidance also briefly addresses the definition of "product class" for

¹⁶ Q&A Guidance at 2.

¹⁷ *Id.* at 5.

¹⁸ *Id.* at 6-7.

¹⁹ *Id.* at 7.

²⁰ *Id.* at 7-8.

²¹ PHS Act § 351(i)(1), 42 U.S.C. § 262(i)(1).

²² Q&A Guidance at 13.

²³ *Id.* at 13-14.

purposes of the BPCIA's transitional provision,²⁴ under which certain biological products may continue to be submitted under section 505 of the FDC Act until March 23, 2020.

Scientific Considerations in Demonstrating Biosimilarity to a Reference Product

This draft guidance explains that FDA will determine the type and amount of studies necessary to demonstrate biosimilarity on a product-specific basis,²⁵ and due to the various product-specific factors that may influence a biosimilar development program, FDA intends to provide feedback on development of proposed biosimilar products on a case-by-case basis.²⁶

- The Agency intends to utilize a “totality-of-the-evidence” standard in its review of 351(k) marketing applications, which will include an examination of “structural and functional characterization, nonclinical evaluation, human PK and PD data, clinical immunogenicity data, and clinical safety and effectiveness data.”²⁷ As provided under the BPCIA, a proposed biosimilar product with “formulation or minor structural differences” may be able to demonstrate biosimilarity to the reference product if the data supporting the application demonstrate that the differences are not clinically meaningful.
- The draft guidance explains that due to the structural and functional differences between biological products, sponsors will be required to perform analytical, animal, and clinical studies to demonstrate biosimilarity,²⁸ and “comparative safety and effectiveness data will be necessary to support a demonstration of biosimilarity if there are residual uncertainties about the biosimilarity of the two products based on structural and functional characterization, animal testing, human PK and PD data, and clinical immunogenicity assessment.”²⁹

- FDA also states that robust postmarketing safety monitoring will be an important requirement for any biosimilar product, and sponsors should consider, among other things, that post-marketing safety monitoring should have adequate mechanisms to “differentiate between the adverse events associated with the proposed product and those associated with the reference product,” including identification of adverse events not previously associated with the reference product.³⁰

Quality Considerations in Demonstrating Biosimilarity to a Reference Protein Product

This draft guidance addresses factors that a sponsor should consider in assessing whether a proposed biosimilar product is “highly similar” to the reference product. The draft guidance explains that a sponsor’s analytical studies should serve as the foundation for such an assessment, which will also be relevant for preparation of the scientific and technical information contained in the chemistry, manufacturing and controls component of a 351(k) marketing application.³¹

A sponsor should undertake an extensive analytical characterization of a proposed biosimilar product to its reference product, and factors that should be considered include the proposed product’s expression system, manufacturing process, physiochemical properties, functional activities, immunochemical properties, impurities, reference standards, finished product attributes, and stability.³² FDA expects that such factors will be assessed using direct comparative analysis between the proposed product and the reference product, although the Agency acknowledges there may be instances where a sponsor may appropriately rely on animal or clinical data comparing a proposed product with a non-US-licensed product.³³ FDA also explains there may be situations where the proposed product or reference product cannot be adequately characterized, in which case the sponsor should consult

²⁴ See Affordable Care Act § 7002(e).

²⁵ Scientific Guidance at 8.

²⁶ *Id.* at 21.

²⁷ *Id.* at 8.

²⁸ See generally Scientific Guidance at 8-20.

²⁹ *Id.* at 16.

³⁰ *Id.* at 20.

³¹ Quality Guidance at 1, 4.

³² See *id.* at 9-15.

³³ *Id.* at 9.

FDA for guidance on whether submission of 351(k) application is appropriate.³⁴

Key Takeaways from the Draft Guidance Documents

- Biosimilar applicants can expect a more interactive process than the normal biologics pathway—both due to FDA’s step-wise approach and its need to learn from early applications in framing the requirements for biosimilarity and interchangeability.
- FDA’s articulation of the likely data requirements for biosimilars is roughly consistent with the EU approach. The Agency’s step-wise methodology—combined with the concession that comparative animal or clinical data to a non-US-licensed product (with bridging data) can be part of the “totality of the evidence” to support review of biosimilarity to a US-licensed reference product—indicates that FDA is attempting to facilitate a global approach to biosimilar development.
- FDA appears ready to permit slight—but potentially commercially important—differences between biosimilars and reference products, which could facilitate some marketing advantages for certain biosimilar products.
- For the time being, interchangeability will remain a theoretical concept. FDA will see what it learns from early biosimilar reviews, and may issue guidance that could ultimately facilitate an interchangeability finding—but not soon.
- Biosimilar applicants will need to be able to track use of their products post-approval, and should expect very significant post-licensure pharmacovigilance requirements. Although FDA appears comfortable that it can license biosimilars, it wants to be in a position to act quickly should a safety issue arise.

We hope you have found this Advisory useful. Please feel free to contact your Arnold & Porter attorney, or any of the contacts below, if you have further questions:

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³⁴ *Id.* at 8–9.

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