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Healthcare Reform Law: A New Regulatory Pathway for Biosimilar Biological Products

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The Patient Protection and Affordable Care Act of 2010, as amended by the Health Care and Education Reconciliation Act of 2010 (the Healthcare Reform Law), establishes an abbreviated licensure pathway for biosimilar biological products, with provisions covering exclusivity periods, and payment for biosimilars. Implementation of the legislative authorization for the U.S. Food and Drug Administration (FDA, or the Agency) to create a new regulatory pathway for biosimilars will have a broad impact on industry activities for both innovator and follow-on biological products, but uncertainty remains on the specific framework that FDA will implement for biosimilars.

The new approval pathway for biosimilar biological products is created by amending Section 351 of the Public Health Service Act (the PHS Act; 42 U.S.C. Section 262), which provides the statutory framework for Biologics License Applications (BLAs) to allow licensure of biological products as biosimilar or interchangeable. Innovator manufacturers of reference biological products are granted 12 years of exclusive use before biosimilars can be approved for marketing in the United States. These provisions became law upon enactment of the Healthcare Reform Law on March 30, 2010.

I. Biosimilars Provisions

A. Definitions and Regulatory Framework. The Healthcare Reform Law defines the term "biosimilar" or "biosimilarity" to mean products that meet the following criteria:[1]

- The biological product is highly similar to the reference product, notwithstanding minor differences in clinically inactive components.
- There are no clinically meaningful differences between the biological product and the reference product in terms of the safety, purity, and potency of the product.

The term "interchangeable" or "interchangeability" means that the biological product may be substituted for the reference product without the intervention of the healthcare provider that prescribed the reference product. "Reference product" is defined as the single biological product licensed under Section 351, Subsection (a) of the PHS Act against which a biological product is evaluated. The Healthcare Reform Law provides only for one reference product per application.[2]

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1 P.L. 111-148, Title VII, Subtitle A "Biologics Price Competition and Innovation Act of 2009," Section 7002(b).

2 *Id.*, Section 7002(a)(2).

Although there has been extensive discussion on the type of clinical data that could be required by FDA in the marketing application for a biosimilar, the new statutory definitions imply that FDA could reasonably request extensive clinical testing in comparison to the reference biologic to demonstrate non-inferiority for safety and potency. However, the Healthcare Reform Law defines a biosimilar as being approved under an "abbreviated application"[3] and a critical challenge for FDA will be to ensure an adequate demonstration of safety and potency, while maintaining an abbreviated application.

In addition, the specification of no clinically meaningful differences relative to the reference biologic means that FDA will need to develop policies for each product class, because of the differences in potential safety issues for different biologics. The Healthcare Reform Law does not require FDA to issue a guidance document to articulate the policies for each product class, and the nonissuance of guidance does not preclude approval of a biosimilar.[4]

The Healthcare Reform Law gives FDA discretion in deciding whether to approve a product, except for any recombinant protein, through the biosimilar framework if "science and experience" do not allow such approval.[5] Importantly, FDA may indicate in a guidance document that the "science and experience" for a product or product class does not allow approval through the biosimilar framework. However, FDA is not required to approve an application when the science and experience does not allow approval of such an application, even if the guidance document has not been issued. This provides FDA the flexibility to require a full BLA on a case-by-case basis. This is supported by the comments recently made by FDA Commissioner Dr. Margaret Hamburg. Dr. Hamburg said that FDA "must develop a robust biosimilar approval pathway" because "biosimilars raise questions for regulators that are far more complex than those posed by traditional generics."[6] Dr. Hamburg said that "over the coming months," the Agency will address the following questions:

- For particular products, will clinical studies beyond bioequivalence be required?
- Is interchangeability possible for a particular biologic?
- How will the approval process for biosimilars differ from the Biologic License Applications process?

The FDA Commissioner confirmed that "there will not be a one-size-fits-all approach. There will, rather, be a science-driven, case-by-case decision-making process rooted in the regulatory studies." Dr. Hamburg encouraged the generics industry to support these studies, commenting that "FDA can advance some of the science, but we can't do it all."

B. Exclusivity Period for Innovator. The Healthcare Reform Law grants 12 years of exclusive use to innovator manufacturers of reference biological products before biosimilars can be approved for marketing in the United States.[7] An application for a biosimilar product may not be submitted to FDA until the date that is four years after the date on which the BLA for the reference product was first approved. However, the four- and 12-year periods can be extended by an additional six months for pediatric studies requested by FDA. The 12-year exclusivity period is determined from "the date on which the reference product was first licensed" under the PHS Act, and shall *not* apply to either of the

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3 *Id.*, Section 3139(a)(8)(H).
4 *Id.*, Section 7002(a)(2).
5 *Id.*
6 Dr. Margaret Hamburg, Commissioner of Food and Drugs – Remarks at Generic Pharmaceutical Association – 02/18/2010 (available at http://www.fda.gov/NewsEvents/Speeches/ucm201833.htm).
7 P.L. 111-148, Title VII, Subtitle A "Biologics Price Competition and Innovation Act of 2009," Section 7002(a)(2).

following applications:

- An application for the "supplement for the biological product that is the reference product"
- A "subsequent application filed by the same sponsor or manufacturer of the biological product that is the reference product (or a licensor, predecessor in interest, or other related entity) for a change (not including a modification to the structure of the biological product) that results in a new indication, route of administration, dosing schedule, dosage form, delivery system, delivery device, or strength; or for a modification to the structure of the biological product that does not result in a change in safety, purity, or potency."

By excluding from additional exclusivity supplemental BLAs (sBLAs) and other "new" attributes, the legislation limits the development of strategies to extend the 12-year exclusivity period by the sponsor of the reference biologic; for example, by obtaining multiple 12-year exclusivity periods by making sequential changes to a reference product after the initial marketing approval.

C. Approval Requirements. An applicant for a biosimilar product shall submit to FDA information demonstrating that the biological product is biosimilar to a reference product, beyond the bioequivalence required for generic drugs, based upon data derived from the following:[8]

- Analytical studies demonstrating that the biological product is highly similar to the reference product notwithstanding minor differences in clinically inactive components
- Animal studies (including the assessment of toxicity)
- A clinical study or studies (including the assessment of immunogenicity and pharmacokinetics or pharmacodynamics) that are sufficient to demonstrate safety, purity, and potency in one or more appropriate conditions of use for which the reference product is licensed and intended to be used and for which licensure is sought for the biological product

Importantly, the Healthcare Reform Law allows FDA, at its discretion, to waive a requirement for any of the above elements in an application for a biosimilar product. If FDA does not develop guidance specific to a product class, there may be concern about potential inconsistent requirements for similar products, given the Commissioner's comments that there will be a science-driven, case-by-case decision-making process for approval of biosimilars.

In addition, an applicant should submit information demonstrating the following:

- The biological product and reference product utilize the same mechanism or mechanisms of action for the condition or conditions of use prescribed, recommended, or suggested in the proposed labeling, but only to the extent the mechanism or mechanisms of action are known for the reference product
- The condition or conditions of use prescribed, recommended, or suggested in the labeling proposed for the biological product have been previously approved for the reference product
- The route of administration, the dosage form, and the strength of the biological product are the same as those of the reference product
- The facility in which the biological product is manufactured, processed, packed, or held meets standards designed to assure that the biological product continues to be safe, pure, and potent

[8] *Id.*

An applicant shall also include publicly available information regarding FDA's previous determination that the reference product is safe, pure, and potent; and may also include any additional information in support of the application, including publicly available information with respect to the reference product or another biological product. The applicant must also consent to the inspection of the manufacturing facility.

An application for a biosimilar product will be reviewed by the same FDA division that was responsible for review and approval of the application under which the reference product is licensed. This provision will presumably result in consistent approval standards for the biosimilar and reference biologic, because reviewers with similar expertise will be available for evaluating both applications. It is another departure from the generic drug model, where all generic drugs are reviewed by the Office of Generic Drugs, but innovator drugs are reviewed by the Office of New Drugs.

D. Interchangeability. The Healthcare Reform Law provides for information demonstrating that the biological product meets the interchangeability standards to be included in a BLA or sBLA for a biosimilar product.[9] The submitted information should be sufficient to show that the biological product meets the following criteria:

- It is biosimilar to the reference product
- It can be expected to produce the same clinical result as the reference product in any given patient
- For a biological product that is administered more than once to an individual, the risk in terms of safety or diminished efficacy of alternating or switching between use of the biological product and the reference product is not greater than the risk of using the reference product without such alternation or switch.

An interchangeable biosimilar should not be considered to have a new active ingredient under Section 351 of the PHS Act, while a noninterchangeable biosimilar should be considered to have a new active ingredient.[10]

E. Exclusivity Period for First Interchangeable Biological Product. The Healthcare Reform Law provides for exclusivity for the first interchangeable biological product.[11] The second or subsequent biological product cannot be determined to be interchangeable for any condition of use until the earliest of the following occurrences:

- One year after the first commercial marketing of the first interchangeable biosimilar biological product to be approved as interchangeable for that reference product
- Eighteen months after: a final court decision12 on all patents in suit in an action instituted under subsection (l)(6) against the applicant that submitted the application for the first approved interchangeable biosimilar biological product; or the dismissal with or without prejudice of an

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9 *Id.*

10 *Id.*, Section 7002(d).

11 *Id.*, Section 7002(a)(2).

12 For purposes of this paragraph, the term "final court decision" means a final decision of a court from which no appeal (other than a petition to the United States Supreme Court for a writ of certiorari) has been or can be taken.

action instituted under subsection (l)(6) against the applicant that submitted the application for the first approved interchangeable biosimilar biological product

- Forty-two months after approval of the first interchangeable biosimilar biological product if the applicant that submitted such application has been sued under subsection (l)(6) and such litigation is still ongoing within such 42-month period
- Eighteen months after approval of the first interchangeable biosimilar biological product if the applicant that submitted such application has not been sued under subsection (l)(6)

F. Exclusivity Period for Innovator Orphan Biological Product. The Healthcare Reform Law provides for exclusivity for a reference biological product that has been designated for a rare disease or condition (i.e., Orphan product).[13] A biological product seeking approval for such disease or condition as biosimilar to, or interchangeable with, such reference product may be licensed only after the expiration for such reference product of the later of the following:

- Seven years from the date of the approval of the approved application, or the issuance of the license14
- The 12-year period for the innovator biological product as described above[15]

The seven-year period can be extended by an additional six months for pediatric studies requested by FDA.

G. Risk Evaluation and Mitigation Strategies (REMS). The Healthcare Reform Law specifically states that the REMS authority under the Federal Food, Drug, and Cosmetic Act will apply to biosimilar products in the same manner as such authority applies to reference biological products.[16] While this means that FDA can impose specific postmarketing surveillance requirements for the biosimilar, it also provides an opportunity for sponsors to propose a postmarketing study in lieu of extensive preapproval clinical testing to demonstrate safety, or assess immunogenicity arising from switching from the reference product to the biosimilar. It also means that REMS programs for interchangeable biosimilars would not necessarily need to share with or have REMS programs identical to the reference product. Since FDA was granted authority by the Food and Drug Administration Amendments Act (FDAAA) of 2007 to require a REMS, REMS have been approved for 21 BLAs from 2008 to 2010.[17]

H. Biological Products Previously Approved as New Drugs. In general, a marketing application for a biosimilar product must be submitted under Section 351 of the PHS Act.[18] However, the Healthcare Reform Law provides for a biosimilar product in the same product class that has been previously approved as a new drug under Section 505 of the Federal Food, Drug, and Cosmetic Act (21 U.S.C. § 355), such as recombinant human growth hormone, to be also submitted as a new drug, if such application has been submitted to FDA before the date of the Healthcare Reform Law enactment or not

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13 P.L. 111-148, Title VII, Subtitle A "Biologics Price Competition and Innovation Act of 2009," Section 7002(a)(2).
14 The Federal Food, Drug, and Cosmetic Act, Section 527(a) (21 U.S.C. § 360cc(a)).
15 P.L. 111-148, Title VII, Subtitle A "Biologics Price Competition and Innovation Act of 2009," Section 7002(a)(2), amending subsection (k)(7) of Section 351 of the PHS Act.
16 *Id.*
17 Data as of April 6, 2010 (available at http://www.fda.gov/Drugs/DrugSafety/PostmarketDrugSafetyInformationforPatientsandProviders/ucm111350.htm).
18 P.L. 111-148, Title VII, Subtitle A "Biologics Price Competition and Innovation Act of 2009," Section 7002(e).

later than 10 years after the enactment date, and there is no another biological product approved under Section 351(a) of the PHS Act that could be a reference product for such biosimilar application.

I. User Fees for Biosimilar Biological Products. The Healthcare Reform Law provides for developing recommendations to Congress with respect to the goals, and plans for meeting the goals, for the process for the review of biosimilar biological product applications for the first five fiscal years after fiscal year 2012 not later than October 1, 2010.[19] Based on these recommendations, Congress should authorize a user fee program for biosimilars effective October 1, 2012.

J. Reimbursement. The Healthcare Reform Law provides for Medicare Part B reimbursement for a biosimilar biological product using the average sales price (ASP) methodology established for drugs. Reimbursement for a biosimilar is the sum of the ASP for a biosimilar for all National Drug Codes assigned to such product, and 6% of the amount determined for the reference biological product.[20] The Medicare payment provisions for biosimilars in the Healthcare Reform Law will be effective July 1, 2010.[21]

II. Uncertainties in the Implementation by FDA

To implement the newly enacted approval pathway for biosimilars, FDA will have to establish the regulatory framework for approvals and provide guidance to industry on implementation of specific provisions in the Healthcare Reform Law. The FY 2011 FDA Budget proposes for FDA to "update review standards and provide regulatory pathways for biosimilars."[22] FDA is seeking a $2 million budget increase for establishing "regulatory guidance to provide a scientifically sound and safe pathway to characterize and develop biosimilars."[23] The process of developing new regulatory guidance for industry will likely be a lengthy process, as FDA is still issuing draft guidances mandated by FDAAA. However, FDA has already begun issuing new guidance documents relevant to development of biosimilar products, including draft guidance on immunogenicity testing of protein products[24] and a Proposed Rule on exceptions or alternatives to the existing regulation for constituent materials in biological products.[25] Nonetheless, it is widely anticipated that FDA will evaluate any submissions made under the new biosimilars provisions on a case-by-case basis, and that industry will likely submit applications for biosimilars without the benefit of guidance documents being available for public comment.

If you have any questions or would like more information on any of the issues discussed in this LawFlash, please contact the authors of this LawFlash, **Phoebe Mounts** (202.739.5898;

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19 *Id.*, Section 7002(f).

20 P.L. 111-148, Title III, Subtitle B, Part III, Section 3139 "Payment for Biosimilar Biological Products," amending section 1847A of the Social Security Act (42 U.S.C. § 1395w-3a).

21 *Id.* (specifying the effective date as beginning with the first day of the second calendar quarter after enactment of legislation providing for a biosimilar pathway).

22 The President's Fiscal Year 2011 Budget Request for FDA, Margaret A. Hamburg, M.D., before the Senate Subcommittee on Agriculture, Rural Development, Food and Drug Administration, and Related Agencies.

23 FY 2011 FDA Congressional Justification (PDF: 3110KB).

24 "FDA Draft Guidance for Industry: Assay Development for Immunogenicity Testing of Therapeutic Proteins," December 2009 (available at http://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/UCM192750.pdf).

25 FDA Proposed Rule, 21 C.F.R. Part 610, "Revision of the Requirements for Constituent Materials" (75 Fed. Reg. 15,639).

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