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Life sciences companies seeking protection for their biological products gain clarity on the submission procedures and standards of evaluation for reference product exclusivity requests.

Biological Products: New FDA Draft Guidance Sheds Light on Reference Product Exclusivity



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As the Food and Drug Administration (FDA) continues to implement the hotly contested approval pathway for follow-on biologics established by the Biologics Price Competition and Innovation Act (BPCIA) in 2010, the latest milestone came on August 5, 2014, when the Agency announced the availability of a new draft guidance document entitled *Reference Product Exclusivity for Biological Products Filed Under Section 351(a) of the PHS Act*. The draft guidance – which comes less than two weeks after the first public announcement that FDA has accepted a follow-on biologic application for filing¹ – describes the information that sponsors should provide when requesting reference

product exclusivity for biologic products and the principles that FDA will consider when reviewing such requests. This article highlights key points contained in the draft guidance and assesses their potential significance for biologic product manufacturers.

Background: Reference Product Exclusivity Under the BPCIA

The BPCIA amended the Public Health Service Act (PHS Act) by establishing an abbreviated licensure pathway for follow-on biologics under section 351(k).² Section 351(i) of the amended PHS Act defines a reference biological product as “the single biological product licensed under [a biologics license application (BLA)] against which a biological product is evaluated in an application submitted under [section 351(k)].”³ Among other things, section 351(k) provides reference products with limited periods of exclusivity in certain situations. Specifically, section 351(k)(7) provides that the “[a]pproval of an application [for a follow-on biologic] under this subsection may not be made effective by the Secretary until the date that is 12 years after the date on which the reference product was first licensed,”

¹ “Novartis Says Application for Biosimilar Version of Amgen Drug Accepted by FDA,” BNA’s Pharmaceutical Law & Industry Report, July 25, 2014 (12 PLIR 1069, 7/25/14).

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² See 42 U.S.C. § 262(k).

³ *Id.* at § 262(i).

and “[a]n application under this subsection may not be submitted to the Secretary until the date that is 4 years after the date on which the reference product was first licensed.”⁴ This exclusivity is not available for a supplement for the reference product, or for 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 (I) 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 (II) a modification to the structure of the biological product that does not result in a change in safety, purity, or potency.”⁵

In February 2012, FDA issued a draft *Guidance for Industry on Biosimilars: Q & As Regarding Implementation of the BPCI Act of 2009*, which addressed the question “Can an applicant include in its 351(a) BLA submission a request for reference product exclusivity under section 351(k)(7) of the PHS Act?”⁶ In response, FDA answered “Yes. . . . An applicant may include in its BLA submission a request for reference product exclusivity under section 351(k)(7) of the PHS Act, and FDA will consider the applicant’s assertions regarding the eligibility of its proposed product for exclusivity. At this time, FDA suggests that an applicant’s request for reference product exclusivity specifically describe how the proposed product meets the statutory requirements in section 351(k)(7) of the PHS Act, and include adequate data and information to support the request.”⁷

In response to this guidance, FDA received an array of comments from industry groups, manufacturers, government officials and other stakeholders, many of whom argued that sponsors of biologic products should not be required to justify their product’s eligibility for reference product exclusivity. Rather, they argued, exclusivity is presumed under the statute unless one of the “narrow exception[s]” to exclusivity applies.⁸ Other comments offered suggestions regarding the FDA’s interpretation of the phrase “licensor, predecessor in interest, or related entity”; whether or not FDA should assess the significance of structural modifications in determining eligibility for exclusivity; and the need for FDA to address how and when it will respond to requests for exclusivity.⁹ FDA’s new draft guidance addresses many of these issues.

Principles of Eligibility for Reference Product Exclusivity

Although the draft guidance provides detailed suggestions regarding the information to be included in requests for reference product exclusivity, the draft guidance does not explicitly state that such requests must be submitted in order to obtain exclusivity. Rather, the

draft guidance states that “[a] sponsor may submit the information described in . . . this guidance document to assist FDA in determining the date of first licensure for a biological product to determine whether the product is eligible for its own period of exclusivity or is subject to an exclusion described in 351(k)(7)(C)” (emphasis added).¹⁰ However, FDA notes that certain determinations “will generally need to be based on data submitted by the sponsor,”¹¹ and that a decision regarding a product’s eligibility for exclusivity may be delayed if information supporting the decision is submitted late or is incomplete, or if FDA requests additional information.¹² Therefore, perhaps in response to concerns voiced in comments to the Agency, the draft guidance suggests that providing information to justify a product’s eligibility for reference product exclusivity is not strictly necessary; however, FDA recommends providing information in order to facilitate FDA’s determination of eligibility. Failure to provide such information may impact the timing of FDA’s determination.

The new draft guidance also articulates FDA’s proposed interpretation of the phrase “licensor, predecessor in interest, or related entity.” The draft guidance defines a licensor as “any entity that has granted the sponsor a license to market the biological product, regardless of whether such license is exclusive,” including “entities that continue to retain rights to develop, manufacture, or market the biological product, and/or rights to intellectual property that covers the biological product.”¹³ FDA will view “any entity that the sponsor has taken over, merged with, or purchased, or that has granted the sponsor exclusive rights to market the biological product under the 351(a) application, or had exclusive rights to the data underlying that application” as a predecessor in interest, consistent with the Agency’s established interpretation of that term in the context of 3-year new drug product exclusivity.¹⁴ Finally, FDA intends to treat an applicant as a “related entity” if “(1) either entity owns, controls, or has the power to own or control the other entity (either directly or through one or more other entities) or (2) the entities are under common ownership or control. The Agency also may find that two parties are related entities. . . . if the entities are or were engaged in certain commercial collaborations relating to the development of the biological product(s) at issue.”¹⁵ FDA’s assessment of whether an applicant is a related entity will take into account both the ownership and control of the investigational new drug application and the BLA, as well as “the level of collaboration between the entities during the development program as a whole.”¹⁶

¹⁰ FDA, *Guidance for Industry: Reference Product Exclusivity for Biological Products Filed Under Section 351(a) of the PHS Act: Draft Guidance*, at 5 (Aug. 2014), available at <http://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/UCM407844.pdf> [hereinafter “Reference Product Exclusivity Guidance”].

¹¹ *Id.* at 6 (“The determination of whether a structural modification results in a change in safety, purity, or potency will be made case-by-case and will generally need to be based on data submitted by the sponsor”).

¹² *Id.* at 7.

¹³ *Id.* at 5.

¹⁴ *Id.*

¹⁵ *Id.*

¹⁶ *Id.*

⁴ *Id.* at § 262(k)(7).

⁵ *Id.*

⁶ FDA, *Guidance for Industry: Biosimilars: Questions and Answers Regarding Implementation of the Biologics Price Competition and Innovation Act of 2009: Draft Guidance*, at 14 (Feb. 2012), available at <http://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/UCM273001.pdf>.

⁷ *Id.*

⁸ See comments to Docket No. FDA-2011-D-0611.

⁹ *Id.*

With respect to FDA's assessment of structural modifications, the draft guidance states that it is "essential to first determine whether a new product includes a modification to the structure of a previously licensed product to assess whether the licensure of the new product is a first licensure that triggers its own period of exclusivity."¹⁷ The draft guidance therefore recommends that sponsors provide a structural comparison between the proposed product and any biological products previously licensed under a BLA and filed by the same sponsor or manufacturer or its licensor, predecessor in interest, or other related entity.

In particular, for protein products, the sponsor should describe, among other things, any differences regarding:

- Amino acid sequence;
- Glycosylation patterns;
- Tertiary structures;
- Post-translational events (including chemical modifications of the molecular structure); and
- Infidelity of translation or transcription.

The draft guidance adds that "[i]f a sponsor employs a cell line modified from that used to manufacture the previously licensed product. . . to manufacture a new product, modification of the structure will not simply be presumed."¹⁸ In addition, FDA states that it will consider "whether the modified product affects the same molecular target as the previously licensed product."¹⁹ A molecular target may be "any molecule in the body whose activity is modified by the product, resulting in a desirable therapeutic effect," including "receptors, enzymes, ion channels, structural or membrane transport proteins, nucleic acids, and pathogens, among others."²⁰

Information regarding structural modifications should be accompanied by information demonstrating that the modification results in a change to the licensed product's safety, purity, or potency. The draft guidance states that the determination of a change in safety, purity or potency "will be made case-by-case and will generally need to be based on data submitted by the sponsor."²¹ Supporting information should include "measurable effects (typically demonstrated in preclinical or clinical studies and shown by relevant methods such as bioassays)," may include references to the information submitted in the BLA for the previously-licensed product, and may consist of evidence that the structural modification results in a "meaningful benefit to public health, such as a therapeutic advantage or other substantial benefit when compared to the previously licensed biological product."²² FDA "generally will presume" a change in safety, purity or potency where the proposed product includes a structural modification and where the sponsor demonstrates that the modifica-

tion affects a different molecular target than the previously-licensed product.²³

Procedures for Requesting Reference Product Exclusivity

To assist FDA in evaluating the date of a biologic product's first licensure, the draft guidance recommends that sponsors provide the following information to FDA at the time that a BLA is submitted (or as correspondence to the application if the product has already been licensed):

1. *A list of all licensed biological products that are structurally related to the biological product that is the subject of the BLA being considered.* The draft guidance states that this should include products with "some of the same principal molecular structural features of the product being considered," but may generally be limited to products affecting the same molecular target (if the molecular target is not specifically defined, the list "should include products that share the narrowest target that can be characterized," such as a "pathway, cell type, tissue, or organ system").²⁴ If the sponsor concludes that no product has been licensed that has the same molecular target or principal molecular structural features, the sponsor should provide "an adequate justification" to support the position that no previously-licensed products are relevant to determining the date of first licensure.²⁵
2. *If any products are identified in Item 1, a list identifying those products for which the sponsor or its affiliate (including any licensor, predecessor in interest, or related entity) is the current or previous license holder.*
3. *If any products are identified in Item 2, a description of the structural differences between those products and the proposed product.* The draft guidance specifies that, for protein products, this description should include, among other things, changes in amino acid sequence, differences due to post-translational events, infidelity of translation or transcription, differences in glycosylation patterns or tertiary structure, and differences in biological activities.
4. *"Evidence of the change in safety, purity, and/or potency" between any products listed in Item 2 and the proposed biologic product, including a description of the connection between the structural differences described in Item 3 and the change in safety, purity, and/or potency.*

The draft guidance notes that FDA may not have determined a product's eligibility for reference product exclusivity by the time the proposed biologic product is licensed. This may be the case "particularly if the determination presents complicated scientific, legal, or factual issues; if the information to support such a determination is submitted late in the review cycle; if such information is incomplete; or if FDA requests additional

¹⁷ *Id.*

¹⁸ *Id.* at 6.

¹⁹ *Id.*

²⁰ *Id.*

²¹ *Id.*

²² *Id.*

²³ *Id.*

²⁴ *Id.* at 7-8.

²⁵ *Id.* at 9.

information to make its determination.”²⁶ In addition, FDA is currently “reviewing options” to determine the method by which it will publicize its decisions regarding the dates of first licensure and reference product exclusivity for specific products.²⁷ The Agency will make information regarding the method ultimately selected available on the Agency’s website.

Conclusion

In a footnote, the draft guidance states the document “does not include an exhaustive list of information that a sponsor may submit to assist FDA in determining the date of first licensure. FDA recommends that sponsors submit any additional information regarding the date of first licensure that they think supports eligibility for exclusivity and include an explanation of its relevance.”²⁸ Further, “[i]f the sponsor cannot adequately characterize the biological product, FDA recommends that the sponsor consult FDA for additional guidance.”²⁹ As a

²⁶ *Id.* at 7.

²⁷ *Id.* at 8.

²⁸ *Id.* at 3 n.8.

²⁹ *Id.* at 4.

result, while the draft guidance may serve as a useful starting point, submitting the information described therein may mark only the beginning of communication between sponsors and the Agency regarding the availability of reference product exclusivity for specific biologic products. Moreover, various questions regarding reference product exclusivity remain unanswered. These include, for example, questions regarding the anticipated timelines for exclusivity decisions; the public availability of information regarding those decisions; and whether FDA will apply a policy of “umbrella exclusivity” for reference products, whereby supplements and new BLAs for modified products that do not qualify for their own periods of reference product exclusivity may nonetheless be protected by the reference product exclusivity of the original product through the remaining duration of that exclusivity.

Parties interested in submitting comments to FDA on the draft guidance are advised to do so by October 6, 2014, to ensure that FDA considers those comments prior to preparation of the final version of the guidance.