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FDA Issues Draft Guidance on Reference Product Exclusivity for Biologics

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On August 4, 2014, the U.S. Food and Drug Administration ("FDA") released a Draft Guidance regarding reference product exclusivity for biologic drug products against filing and approval of applications for biosimilar products under Section 351(k)(7) of the Public Health Service Act ("PHS Act") (codified at 42 U.S.C. § 262(k)(7)), providing draft guidelines for BLA sponsors to establish a reference product's status as a first licensure entitled to exclusivity:

Reference Product Exclusivity for Biological Products Filed Under Section 351(a) of the PHS Act ("Draft Exclusivity Guidance")

The corresponding Federal Register announcement can be found here.

The Biologics Price Competition and Innovation Act of 2009 ("BPCIA") amended the PHS Act to provide an abbreviated pathway for obtaining FDA licensure for "biosimilar" versions of existing biologic products with an approved BLA ("reference product"). *See* 42 U.S.C. § 262(k). Subparagraphs (A) and (B) of Section 351(k)(7) of the PHS Act set forth an exclusivity period for reference products. Specifically, a biosimilar application under Section 351(k) cannot be submitted until 4 years after the date of the reference product's first licensure, and cannot be approved by FDA until 12 years after the date of first licensure. *Id.* at § 262(k)(7)(A)-(B). However, the reference product may not be entitled to such exclusivity if that licensure falls within one of the enumerated excluded categories of Subparagraph (C) of Section 351(k)(7), which reads:

> Subparagraphs (A) and (B) shall not apply to a license for or approval of—
>
> (i) a supplement for the biological product that is the reference product; or
>
> (ii) 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.

Draft Guidance

The FDA's August 4, 2014 Draft Exclusivity Guidance provides clarification on the following three provisions in Section 351(k)(7)(C): (a) "licensor, predecessor in interest, or other related entity," (b) "modification to the structure of the biological product," and (c) "does not result in a change in safety, purity, or potency." *See* Draft Exclusivity Guidance at 4-7. The Draft Exclusivity Guidance further makes recommendations on suggested information that BLA sponsors should provide to FDA in support of a claim to first licensure exclusivity.

A. "Licensor, Predecessor in Interest, or Other Related Entity"

For the terms "licensor, predecessor in interest, or other related entity," the Draft Exclusivity Guidance provides the following interpretations and definitions:

- A "predecessor in interest" will be construed in the same manner as in the 3-year new drug product exclusivity context—*i.e.*, "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 [BLA], or had exclusive rights to the data underlying that application." *Id.* at 5.

- A "licensor" is "any entity that has granted the sponsor a license to market the biological product, regardless of whether such license is exclusive." *Id.*

- An entity is an "other 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," or if "the entities are or were engaged in certain commercial collaborations relating to the development of the biological product(s) at issue." *Id.*

These provisions appear to add further detail to the broad statutory categories of entities whose prior licensures of certain structurally related products could potentially undercut a BLA sponsor's claim to first licensure exclusivity.

B. "Modification to the Structure of the Biological Product"

The Draft Exclusivity Guidance appears to place the burden on the reference drug sponsor to show that the new licensure be a "modification to the structure of the biological product." For example, the Draft Exclusivity Guidance requests that the sponsor "demonstrate that the product has been structurally modified," including "describ[ing] the structural similarities and differences between its proposed product and any previously licensed biological product that was the subject of a [BLA] application filed by the same sponsor or manufacturer (or its licensor, predecessor in interest, or other related entity)." *Id.* at 5-6. For a protein product, this includes setting forth the "differences in amino acid sequence, glycosylation patterns, tertiary structures, post-translational events (including any chemical modifications of the molecular structure such as pegylation), and infidelity of translation or transcription." *Id.*

These provisions appear to provide additional context for the categories of particular structural modifications in a reference product that FDA envisions may potentially be a basis for applying first licensure exclusivity, even where the sponsor or its predecessor-in-interest, licensor or related entity may have previously licensed a related product.

C. "Does Not Result in a Change in Safety, Purity, or Potency"

Likewise, the Draft Exclusivity Guidance also appears to place the burden on the reference product sponsor to show that a modification to the structure of the biological product "result in a change in safety, purity, or potency," before granting exclusivity. The Draft Exclusivity Guidance notes that a showing of such a change in safety, purity or potency "may include evidence that the change will result in a meaningful benefit to public health, such as a therapeutic advantage or other substantial benefit when compared to the previously licensed biological product." *Id.* at 6. The Draft Exclusivity Guidance advises the reference drug sponsor to submit data showing "measurable effects (typically demonstrated in preclinical or clinical studies and shown by relevant methods such as bioassays) clearly describing how the modification resulted in a change in safety, purity, or potency compared to the previously licensed product." *Id.* However, FDA will presume that this requirement is met "if the sponsor of the proposed product demonstrates that it affects a different molecular target than the original product." *Id.*

These provisions appear to provide further guidance as to the types of clinical effects that FDA might consider relevant to showing a "change in safety, purity, or potency," as well as the information that FDA might require to make such a showing.

Suggested Information for BLA Sponsors to Provide in Support of Exclusivity Claim

The Draft Exclusivity Guidance also includes a list of suggested information to be submitted to show that the sponsor meets the requirements described above to qualify for the exclusivity set forth in Section 351(k)(7). *Id.* at 7. This information includes:

- A list of all BLA products that are structurally related to the product that is the subject of the submitted BLA under consideration. *Id.*
- A list identifying which such BLA products are currently or previously held by the sponsor or one of its affiliates, including any licensors, predecessors in interest, or related entities; and further for such products:

  (1) a description of structural differences between those products and the BLA product under consideration, and

  (2) evidence of the change in safety, purity, and/or potency between those products and the BLA product under consideration. *Id.* at 8.

Conclusion

FDA's Draft Exclusivity Guidance provides helpful insight into FDA's view of the provisions of Section 351(k)(7)(C) governing exclusivity of BLA reference products, as well as FDA's initial guidelines on information that BLA sponsors may provide to FDA in making a claim for exclusivity. We note that FDA will be accepting comments on this Draft Exclusivity Guidance through October 6, 2014.

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