JONES DAY

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COMMENTARY

FDA Issues Draft Guidance on Determination of Reference Product Exclusivity for Biologics

On August 4, the U.S. Food & Drug Administration ("FDA") issued a draft guidance titled "Reference Product Exclusivity for Biological Products Filed Under Section 351(a) of the PHS Act." The draft guidance is intended to assist biological product sponsors and applicants in submitting appropriate information to FDA to enable a regulatory determination of the "first licensure" date of a reference biological product under section 351(k)(7)(C) of the Public Health Service Act ("PHS Act"), which was added to the Federal Food, Drug, and Cosmetic Act ("FD&C Act") by the Biologics Price Competition and Innovation Act of 2009.

Background

Under section 351(k) of the PHS Act, an application for a biosimilar or interchangeable biologic may not be submitted to FDA until four years after, or approved until 12 years after, first licensure of the reference biologic, respectively referred to as periods of "data exclusivity" and "market exclusivity." An additional six months of "pediatric exclusivity" may be added to the data and market exclusivities if the biologic meets the requirements for pediatric exclusivity under section 505A of the FD&C Act. In addition, seven years of orphan drug exclusivity may be applied if the biologic is indicated for a rare disease or condition under section 527(a) of the FD&C Act, in which case the biologic may not be licensed for that indication until after the expiration of the seven-year orphan drug exclusivity period or the 12-month market exclusivity period, whichever is later.

Process of Determination of "First Licensure" by FDA

Given the significance of data and market exclusivity, the determination under section 351(k) of the date of first licensure of a reference biological product submitted under section 351(a) effectively decides (i) the product's eligibility for various reference product exclusivities and (ii) the lengths of those periods of exclusivity. However, as noted by FDA in the draft guidance, "[m]aking this determination can present unique challenges given the requirements of section 351(k)(7)," which "are made more acute because of the scientific and technical complexities that may be associated with the larger and typically more complex structures of biological products … as well as the processes by which such biological products are made."

In most cases, the date of first licensure of a reference biological product submitted under section 351(a) will be the initial date the product was licensed by FDA. However, section 351(k)(7)(C) excludes from this determination the date of licensure for the following products:

- A supplement for the biological product that is the reference product; or
- 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
  - a modification to the structure of the biological product that does not result in a change in safety, purity, or potency.

As noted by FDA, "because of these exclusions, for each product licensed under section 351(a) of the PHS Act that may serve as a reference product for a biosimilar application, FDA must make a determination regarding the date of first licensure." In its draft guidance, FDA explains how it intends to make these determinations, and provides concrete examples as illustrations of its intended approach.

Identifying a Licensor, Predecessor in Interest, and "Other Related Entity." FDA explained that it "has experience in construing other provisions that require examination of the relationships between business entities." It has construed "predecessor in interest" to include an entity that has been taken over, merged with, or purchased, or has granted exclusive rights to the application or its data. An entity will be considered related if either entity owns, controls, or has the power to own or control the other entity, or the entities are under common ownership or control. FDA will also find parties related when they are or were engaged in commercial collaborations relating to the product's development.

Whether There Has Been a Structural Modification of the Product. FDA explained that in making this determination, it will consider the products' principal structural molecular features and whether they affect the same molecular target. Also, if a sponsor employs a cell line modified from that used to manufacture the previously licensed product, the sponsor would need to first demonstrate the product has been structurally modified, and then show that the modification resulted in a change in safety, purity, or potency.

If So, Whether There Has Been a Change in Safety, Purity, or Potency. FDA explained that this determination "will be made case-by-case" based on supporting evidence submitted by the sponsor. Such evidence may include preclinical or clinical studies, references to the data and information submitted in the 351(a) application of the previously licensed product, and evidence that the change will result in a meaningful benefit to public health when compared to the previously licensed biological product. Also, FDA generally will presume that a structural modification has resulted in a change to the proposed product's safety, purity, or potency if the sponsor demonstrates the product affects a different molecular target than the original product did.

Suggested Information for Submission by Section 351(a) Applicants

FDA concluded by specifying the information a sponsor should include in its 351(a) application, in correspondence related to the application, or in an amendment, depending on the timing and availability of the information during the application process. Specifically, FDA suggested the following information for submission.

1. A list of all licensed biological products that are structurally related to the biologic being applied for, including those that share some of the principal molecular structural features, target different epitopes of the same target, and share the narrowest target that can be characterized. If a sponsor concludes that no such product has been licensed, it should provide adequate justification for its determination.
2. For those product listed in item 1 above, a list of those for which the sponsor or any of its affiliates is or was a license holder.

3. For those products listed in item 2 above, a description of the structural differences from the proposed product, which for protein products should include 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. For those products listed in item 2 above, evidence of the changes in safety, purity, and/or potency from the proposed product, including how the structural differences relate to these changes.

Comments Should Be Submitted by October 6

To ensure FDA considers comments before issuing the final version of the draft guidance, FDA encourages interested parties to submit comments on the draft guidance by October 6. Comments can be submitted electronically to http://www.regulations.gov [Docket No. FDA-2013-D-1165].

Lawyer Contacts

For further information, please contact your principal Firm representative or one of the lawyers listed below. General email messages may be sent using our "Contact Us" form, which can be found at www.jonesday.com.

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