August 14, 2014

FDA Releases Guidelines for 12-Year Period of Reference Product Exclusivity for Section 351(a) Biologics

Sterne Kessler Goldstein Fox
ATTORNEYS AT LAW

The U.S. Food and Drug Administration ("FDA") has released its latest "Guidance for Industry" regarding the FDA's interpretation of the Biologics Price Competition and Innovation Act of 2009 ("BPCIA"), which established an abbreviated approval pathway in the U.S. for biosimilar versions of previously approved therapeutic biologics. The proposed guidance, which was released on August 8, 2014, addresses the 12-year period of reference product exclusivity granted under section 351(k)(7) of the Public Health Service Act ("PHS Act"). Under Section 351(k)(7), the FDA may not grant licensure to an application for a biosimilar or interchangeable product under 351(k) of the PHS Act ("a 351(k) application") until the date that is 12 years after the date on which the reference product referred to in the 351(k) application was *first licensed* under section 351(a) of the PHS Act. In addition, the FDA may not accept for review a 351(k) application until 4 years after the date of first licensure of the reference product. The BPCIA provisions make clear that not every licensure of a biologic under 351(a) is considered a "*first licensure*" giving rise to a 12-year period of exclusivity. The proposed guidance is intended to give 351(a) applicants, biosimilar applicants, and other interested parties direction as to what information the FDA will need to make a determination of the date of first licensure for a reference product.

The Guidance specifically recognizes the unique challenges in making such a determination in the context of biologics (as opposed to small molecule drugs). For example, the FDA notes the "scientific and technical complexities that may be associated with the larger and typically more complex structures of biological products as compared with small molecule drugs, as well as the processes by which such biological products are made." (Guidance at 3.)

In general, "a biological product submitted for licensure under 351(a) . . . may be eligible for a period of exclusivity that commences on the date of its licensure unless its date of licensure is not considered a date of first licensure because it falls within an exclusion under 351(k)(7)(C)" of the PHS Act. (Guidance at 3.) "In most instances, the date of first licensure will be the initial date the particular product at issue was licensed in the United States." *Id*. Section 351(k)(7)(C), however, excludes certain 351(a) licensures from eligibility for the 12-year exclusivity. In particular, a 351(a) licensure does not qualify for exclusivity if it is for:

- a supplement for the reference product
- a subsequent application filed by the same sponsor or manufacturer of the biological product (or a licensor, predecessor in interest, or other related entity) for (1) 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 (2) a modification to the structure of the biological product that does not result in a change in safety, purity or potency.

Thus, in determining if a 351(a) licensure is entitled to reference product exclusivity, the FDA must make a number of inquiries: is the licensure for a supplement of the reference product?; is the licensure for a subsequent application by the same sponsor or manufacturer of the reference product (or a licensor, predecessor-in-interest, or other related entity)?; is the application for a modification to the structure of a previously approved biological product?; for a modified structure, has it changed the safety, purity or potency? The Guidance seeks to shed some light on what the FDA will look for in answering these questions.

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

The FDA intends to construe these terms of section 351(k)(7) sin the same manner they are construed in the parallel provisions of the Food, Drug and Cosmetic Act. Thus, *licensor* will be construed to mean any entity that has granted the reference product sponsor a license to market the biological product, regardless of whether such license is exclusive. *Predecessor in Interest* will be any entity that the reference product sponsor has taken over, merged with, or purchased, or that has granted the reference product sponsor exclusive rights to market the reference biological product, or had exclusive rights to the data underlying the application. The FDA will construe the term *other related entity* to mean an entity that either owns, controls, or has the power to own or control the other entity, or entities that are under common ownership or control. The FDA will also look at the relationship between entities in commercial collaborations related to development of the biological product(s) at issue.

"Modification to the Structure of the Biological Product"

In determining whether a 351(a) licensure is for a biological product that includes a modification to the structure of a previously licensed product, the FDA will look to the sponsor to describe the similarities and differences between the new product and any previously licensed 351(a) product. In particular, for protein products the description of differences "should include, as appropriate, any 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, among others." (Guidance at 6.) In addition, the FDA will look at principal structural molecular features of both products, and whether the modified products affects the same molecular target as the previously licensed product.

"Change is Safety, Purity or Potency"

The determination of whether a structural modification results in a change in safety, purity or potency over the previously licensed product will be made on a case-by-case basis. The burden will be on the sponsor to submit data, including measurable effects typically demonstrated in preclinical or clinical studies, clearly demonstrating how the modification produces the change. Importantly, the Guidance states that in cases where the FDA determines a modification of structure exists, the Agency will presume that the modification has resulted in a change in safety, purity or potency if the new product affects a different molecular target than the original product. (Guidance at 6.) In this context, a molecular target can be any molecule in the body whose activity is modified by the product resulting in a desirable therapeutic effect.

Again, the Guidance document is only proposed, and is not intended to create or confer any rights for or on any person and is not intended to bind the FDA. The proposed Guidance is open to comment until October 8, 2014.

For more information, please contact:

Timothy J. Shea, Jr., Director
tshea@skgf.com