Guidance for Industry

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

DRAFT GUIDANCE

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U.S. Department of Health and Human Services
Food and Drug Administration
Center for Drug Evaluation and Research (CDER)
Center for Biologics Evaluation and Research (CBER)

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Procedural

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This draft guidance, when finalized, will represent the Food and Drug Administration's (FDA's or the Agency's) current thinking on this topic. It does not create or confer any rights for or on any person and does not operate to bind FDA or the public. You can use an alternative approach if the approach satisfies the requirements of the applicable statutes and regulations. If you want to discuss an alternative approach, contact the FDA staff responsible for implementing this guidance. If you cannot identify the appropriate FDA staff, call the appropriate number listed on the title page of this guidance.

I. INTRODUCTION

This guidance is intended to assist sponsors who are developing biological products, sponsors of biologics license applications (BLAs), and other interested parties in providing information that will help the Agency determine the date of first licensure for a reference product under 351(k)(7)(C) of the Public Health Service Act (PHS Act), as added by the Biologics Price Competition and Innovation Act of 2009 (BPCI Act). Under 351(k)(7), licensure of an application for a biosimilar or interchangeable product under 351(k) of the PHS Act (also known as a 351(k) application) may not be made effective by FDA 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, a 351(k) application may not be submitted to FDA for review until 4 years after the date of first licensure of the reference product. This period of time in which a 351(k) application may not be licensed (or submitted for review) is known as the reference product exclusivity[2] period. Thus, a decision under 351(k)(7)(C) regarding the date of first licensure of a reference product submitted under 351(a) is, in effect, a decision on eligibility for reference product exclusivity and on the date on which such exclusivity begins to run.

Not every licensure of a biological product under 351(a) is considered a "first licensure" that gives rise to its own exclusivity period. Under the terms of 351(k)(7), the dates of licensure of applications for certain changes to previously licensed biological products from the same or certain related sponsors are explicitly not considered the dates of first licensure for purposes of giving rise to a period of reference product exclusivity. As discussed further in this guidance, reference product sponsors generally have superior information about changes to previously

[1] This guidance has been prepared by the Office of Medical Policy in the Center for Drug Evaluation and Research (CDER) in cooperation with the Center for Biologics Evaluation and Research (CBER) at the Food and Drug Administration.

[2] The term *exclusivity* as applied to a particular product generally refers to a statutory limitation on FDA's ability to accept for review or to license or approve certain competing products for a specified period of time. Exclusivity provisions can be found in the Federal Food, Drug, and Cosmetic Act (FD&C Act) at, among others, 505(c)(3)(E), 505(j)(5)(F), 505A(b) and (c), 527(a), and in the PHS Act at 351(k)(7).

licensed products and corporate relationships to other sponsors that are relevant to a determination of the date of first licensure under 351(k)(7)(C). In this guidance, we describe the types of information that reference product sponsors should provide to facilitate FDA's determination of the date of first licensure for their products.

FDA's guidance documents, including this guidance, do not establish legally enforceable responsibilities. Instead, guidances describe the Agency's current thinking on a topic and should be viewed only as recommendations, unless specific regulatory or statutory requirements are cited. The use of the word *should* in Agency guidances means that something is suggested or recommended, but not required.

II. BACKGROUND

The BPCI Act was enacted as part of the Patient Protection and Affordable Care Act (Affordable Care Act) (Public Law 111–148) on March 23, 2010. The BPCI Act amends the PHS Act and other statutes to create an abbreviated licensure pathway for biological products shown to be biosimilar to or interchangeable with an FDA-licensed biological reference product (see sections 7001 through 7003 of the Affordable Care Act). Section 351(k) of the PHS Act (42 U.S.C. 262(k)), added by the BPCI Act, sets forth the requirements for an application for a proposed biosimilar product and an application or a supplement for a proposed interchangeable product.

Section 351(k)(7) of the PHS Act, entitled "Exclusivity for Reference Product," describes reference product exclusivity, the period of time in which a 351(k) sponsor is not permitted to submit and FDA is not permitted to license a 351(k) application that references a reference product, the single biological product licensed under section 351(a) of the PHS Act against which a biological product is evaluated in a 351(k) application.[3] Under this section, exclusivity for the reference product is described in terms of a prohibition on acceptance or approval of an application for a biosimilar or interchangeable product for a period of time starting from the date of first licensure. Specifically, approval of a 351(k) application may not be made effective until 12 years after the date of first licensure of the reference product, which under the statute excludes the date of licensure of supplements and certain other applications.[4] A 351(k) application for a biosimilar or interchangeable biological product cannot be submitted for review until 4 years after the date on which the reference product was first licensed under section 351(a) of the PHS Act.[5] As provided by section 351(m) of the PHS Act, an additional six-month period of exclusivity (in which a biosimilar or interchangeable biological product cannot be licensed or accepted for review) will attach to the 12- and 4-year periods, respectively, if the sponsor conducts pediatric studies that meet the requirements for pediatric exclusivity pursuant to section 505A of the Federal Food, Drug, and Cosmetic Act (FD&C Act).[6] Furthermore, a biological product seeking licensure as biosimilar to or interchangeable with a reference product indicated

[3] Section 7002(b)(3) of the Affordable Care Act, adding section 351(i)(4) of the PHS Act.

[4] Sections 7002(a)(7)(A) and 7002(a)(7)(C) of the Affordable Care Act, adding sections 351(k)(7)(A) and 351(k)(7)(C) of the PHS Act.

[5] Section 7002(a)(7)(B) of the Affordable Care Act, adding section 351(k)(7)(B) of the PHS Act.

[6] Section 7002(g) of the Affordable Care Act, adding section 351(m) of the PHS Act. This period is referred to as the pediatric exclusivity period.

for a rare disease or condition and granted 7 years of "orphan drug exclusivity" under section 527(a) of the FD&C Act, may not be licensed by FDA for the protected orphan indication until after the expiration of the 7-year orphan drug exclusivity period or the 12-year reference product exclusivity period granted under section 351(k)(7) of the PHS Act, whichever is later.[7]

Determining the date of first licensure for a reference product, in turn, determines whether a particular biological product qualifies for a period of exclusivity under 351(k)(7) of the PHS Act and the date on which such exclusivity, if any, will expire. Making this determination can present unique challenges given the requirements of section 351(k)(7) of the PHS Act. These 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 compared with small molecule drugs, as well as the processes by which such biological products are made. Therefore, the 351(a) applicant may provide information to FDA, such as that described in this guidance or other relevant information, to assist FDA with its analysis of the date of first licensure for a biological product under section 351(k)(7) of the PHS Act.[8]

III. DISCUSSION

A biological product submitted for licensure under section 351(a) of the PHS Act (a 351(a) application) 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). In most instances, the date of first licensure will be the initial date the particular product at issue was licensed in the United States.

Under section 351(k)(7)(C) of the PHS Act, however, the date of first licensure does not include the date of licensure of (and a new period of exclusivity shall not be available for) a biological product licensed under section 351(a) of the PHS Act if the licensure is for:

- 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 (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.[9]

[7] Section 7002(h) of the Affordable Care Act.

[8] This guidance 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.

[9] Section 7002(a)(7)(C) of the Affordable Care Act, adding section 351(k)(7)(C) of the PHS Act.

The exclusions noted above indicate that Congress did not intend for every biological product licensed under section 351(a) of the PHS Act to be eligible for a separate period of reference product exclusivity. 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.

Thus, for instance, FDA must determine whether an application is considered 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 such applications, FDA must determine whether a particular application is for a "modification to the structure" of a biological product previously licensed by such an entity. If FDA concludes that a particular application filed by a relevant entity includes a "modification to the structure" of a previously licensed biological product that was the subject of a 351(a) application filed by the same sponsor or manufacturer, or its licensor, predecessor in interest, or other related entity, FDA must also determine whether such a structural modification would result in a "change in safety, purity, or potency."

A sponsor may submit the information described in section IV of 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). If the sponsor cannot adequately characterize the biological product, FDA recommends that the sponsor consult FDA for additional guidance.

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

Section 351(k)(7)(C) of the PHS Act excludes from the date of first licensure the date of approval of supplements and certain subsequent applications filed by the same sponsor or a licensor, predecessor in interest, or other entity that is "related" to the sponsor of a previously licensed biological product. The Agency has experience in construing other provisions that require examination of the relationships between business entities to determine eligibility of a new drug application for exclusivity.[10] For example, in the context of 3-year new drug product exclusivity, the Agency has included studies conducted or funded by the applicant's predecessor in interest in any assessment of eligibility for exclusivity. It has construed the term "predecessor in interest" to mean an entity (e.g., a corporation) that the sponsor has taken over, merged with, or purchased, or from which the sponsor has purchased all rights to the drug [reference product].[11] Also, the Agency has construed a predecessor in interest to include an entity which has granted to the applicant exclusive rights to a new drug application or the data upon which exclusivity is based, which may include licensors, assignors, and joint venture partners, depending on the circumstances of the case.[12]

[10] Sections 505(c)(3)(E)(iii) and 505(j)(5)(F)(iii) of the FD&C Act (requiring that a study be "conducted or sponsored by the applicant" to qualify for 3-year new drug product exclusivity).

[11] 21 CFR 314.108(a); see also 21 CFR 314.50(j)(4)(iii).

[12] See the final rule entitled "Abbreviated New Drug Application Regulations; Patent and Exclusivity Provisions" (patent and exclusivity final rule), published in the Federal Register of October 3, 1994 (59 FR 50338 at 50359 and 50362). Sections 21 CFR 314.108(a) and 314.50(j)(4)(iii) also state that the purchase of nonexclusive rights to a clinical investigation after it is completed is not sufficient to satisfy this definition of predecessor in interest.

With respect to 351(k)(7)(C), the Agency intends to interpret the term "predecessor in interest" as it does in the 3-year new drug product exclusivity context.[13] It will consider 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 to be a predecessor in interest for purposes of the first licensure provisions at section 351(k)(7)(C) of the PHS Act.

The Agency intends to consider a "licensor" under the BPCI Act to be any entity that has granted the sponsor a license to market the biological product, regardless of whether such license is exclusive. This term would include, for instance, 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.

Although the BPCI Act does not define the term "other related entity," the Agency generally will consider an applicant to be a "related entity" in this context 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 for purposes of the BPCI Act if the entities are or were engaged in certain commercial collaborations relating to the development of the biological product(s) at issue.[14] In analyzing whether the relationship between the parties would result in a finding that they were "other related entities," the Agency expects to consider not only ownership and control of the investigational new drug application (IND) and the BLA, but also the level of collaboration between the entities during the development program as a whole.

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

The statute specifies that the date of first licensure excludes (and, therefore, a new period of exclusivity will not run from) the date of approval of an application for a change that results in a new indication, route of administration, dosing schedule, dosage form, delivery system, delivery device, or strength unless that change includes a "modification to the structure of the biological product" and such modification results in a change in safety, purity, or potency. It is thus 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.

Therefore, a sponsor seeking to assist FDA in determining the date of first licensure for a reference product licensed under 351(a), should describe the structural similarities and differences between its proposed product and any previously licensed biological product that was the subject of a 351(a) application filed by the same sponsor or manufacturer (or its licensor, predecessor in interest, or other related entity). For protein products, described structural differences should include, as appropriate, any differences in amino acid sequence, glycosylation patterns, tertiary structures, post-translational events (including any chemical modifications of

[13] Patent and exclusivity final rule (59 FR 50338 at 50362).

[14] This generally would not include service contracts, unless such contracts reflect common ownership or development of the product(s) at issue.

the molecular structure such as pegylation), and infidelity of translation or transcription, among others. In determining whether a biological product includes a modification to the structure of a previously licensed biological product, FDA also will consider the principal structural molecular features of both products and whether the modified product affects the same molecular target as the previously licensed product. If a sponsor employs a cell line modified from that used to manufacture the previously licensed product (for example, one employing a modified gene construct) to manufacture a new product, modification of the structure will not simply be presumed. Instead, a sponsor seeking to demonstrate that this new product is nevertheless eligible for its own period of exclusivity should first demonstrate that the product has been structurally modified. Any demonstration that the structure has been modified should be followed by a demonstration that the change has resulted in a change in safety, purity, or potency, as explained in section III.C below.

C. "Result[s] in Change in Safety, Purity, or Potency"

Section 351(k)(7)(C)(ii)(II) of the PHS Act excludes from the date of first licensure the dates of approval of those modifications to the structure of the previously licensed product that do not "result in a change in safety, purity, or potency."[15] 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. The supporting information provided should include 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. Supporting information can include references to the data and information submitted in the 351(a) application of the previously licensed product. Evidence that a change resulted in 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.

In cases where FDA determines that a proposed biological product includes a modification to the structure of a previously licensed biological product, FDA generally will presume that the modification has resulted in a change to the proposed product's safety, purity, or potency if the sponsor of the proposed product demonstrates that it affects a different molecular target than the original product. A molecular target can be any molecule in the body whose activity is modified by the product, resulting in a desirable therapeutic effect. Such molecular targets can include receptors, enzymes, ion channels, structural or membrane transport proteins, nucleic acids, and pathogens, among others.

[15] The standard for licensure of a biological product as "potent" under section 351(a) of the PHS Act has long been interpreted to include effectiveness (see 21 CFR 600.3(s) and the guidance for industry *Providing Clinical Evidence of Effectiveness for Human Drug and Biological Products*). In that guidance, we use the terms "safety and effectiveness" and "safety, purity, and potency" interchangeably in the discussions pertaining to biosimilar products. We update guidances periodically. To make sure you have the most recent version of a guidance, check the FDA Drugs guidance Web page at http://www.fda.gov/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/default.htm.

If the modified product affects the same molecular target as the previously licensed product, its sponsor should provide data to show that the changes in structure result in a change in safety, purity, or potency of the modified product when compared to the previously licensed product. If a sponsor can provide such data, FDA may determine that the date of licensure of the modified product is the date of first licensure as set forth in section 351(k)(7)(C) of the PHS Act.

If the sponsor does not demonstrate that a modification in the structure results in a change in safety, purity, or potency compared to the previously licensed product, or that the modified product affects a different molecular target than the previously licensed product (resulting in a presumption that there is a change in safety purity or potency), the date of licensure of the modified product generally would not be the date of first licensure, and that product would therefore not be eligible for its own period of exclusivity.

Under 351(k)(7)(C)(ii)(I) of the PHS Act, the date of approval of a change to a previously licensed product from the same sponsor (or a licensor, predecessor in interest, or other related entity) that does not include a modification to the structure of the sponsor's original product but which results in a new indication, route of administration, dosing schedule, dosage form, delivery system, delivery device, or strength is excluded from the date of first licensure; and an application for such a change is not eligible for its own period of exclusivity.

IV. SUGGESTED INFORMATION FOR 351(a) APPLICANTS TO PROVIDE TO FDA

FDA recommends that a sponsor include information such as that described in this guidance at the time the 351(a) application is submitted or, in the case of an already licensed 351(a) application, as correspondence to the application.[16] Alternatively, this information can be submitted as an amendment to the 351(a) application. However, the determination of the date of first licensure and of eligibility for exclusivity may not always be made at the time of licensure, 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 information to make its determination.

To assist FDA in evaluating the date of first licensure as described in section 351(k)(7)(C) of the PHS Act, FDA suggests that sponsors provide the following information:

1. A list of all licensed biological products that are structurally related to the biological product that is the subject of the 351(a) application being considered. This list should include products that share some of the same principal molecular structural features of the product being considered, but generally can be limited to products that affect the

[16] The Agency recommends, however, that any exclusivity request be placed specifically in the electronic common technical document (eCTD) Module 1.3.5.3 (the Exclusivity Claim section of Module 1, Administrative Information) of the application.

same molecular target.[17] Products that target different epitopes of the same molecular target should be included. Where specific molecular targets have not been defined, this list should include products that share the narrowest target that can be characterized. This may be a pathway, cell type, tissue, or organ system. If this assessment results in the conclusion that no product that has the same molecular target or shares some of the same principal molecular structural features has been licensed, a sponsor should provide an adequate justification to support the assertion that there are no previously licensed products that are relevant for purposes of determining the date of first licensure.

2. Of those licensed biological products identified in item 1 above, a list of those for which the sponsor or one of its affiliates, including any licensors, predecessors in interest, or related entities,[18] are the current or previous license holder.

3. Description of the structural differences between the proposed product and any products identified in item 2 above. For protein products, this should include, but is not limited to, 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.[19]

4. Evidence of the change in safety, purity, and/or potency between the proposed product and any products identified in item 2 above. This should include, but is not limited to, a description of how the structural differences identified in item 3 above relate to changes in safety, purity, and/or potency.

Any other information and data that would assist the FDA in making a determination regarding the date of first licensure for a 351(a) application should also be included.

V. PUBLICATION OF DECISION

FDA is reviewing options for making information publicly available regarding reference product exclusivity and dates of first licensure. Once a method is determined, plans to communicate this information will be provided on FDA's Web site.

[17] See, for example, 21 CFR 316.3(b)(13) and its definition of "same drug" as it relates to orphan drug products and the description of structural differences of large molecule drug products.

[18] In compiling this list, "predecessor in interest," "licensor," and "other related entity" should be defined as described in section III.A of this guidance.

[19] Biological activities can be an important measure of structural changes.