FDA's Interpretation of the "Deemed to be a License" Provision of the Biologics Price Competition and Innovations Act

A look at how the FDA will administer the transition of NDAs to BLAs

In 2010, Congress passed, and President Obama signed, the Patient Protection and Affordable Care Act,[1] within which is the Biologics Price Competition and Innovations Act (BPCIA)[2] that codified the ability of the Food and Drug Administration (FDA) to review and approve biosimilar medicinal products. To harmonize the regulatory system for biological products in the U.S., the BPCIA included Section 7002(e) which requires that all marketing applications for biological products (as defined in the statute) be submitted as Biologics License Applications (BLA) under the Public Health Services Act (PHSA). Furthermore, Section 7002(e)(4) of the BPCIA requires that any New Drug Applications (NDAs) for biological products that were previously approved under Section 505 of the Federal Food, Drug, and Cosmetic Act (FFDCA) must be "deemed to be a License" for the product under Section 351 of the PHSA. In order to provide time to prepare for this transition from NDA to BLA, the statute set the date for implementation of this requirement to be 10 years after the passage of the BPCIA. As such, the implementation date is March 20, 2020.

In December of last year, the FDA published a final guidance document[3] explaining the FDA's interpretation of the "deemed to be a license" provision and a draft Q&A guidance document[4] providing additional details regarding the implementation of the provision.

This article provides a summary of how the FDA will administer the transition of NDAs to BLAs, as described in these two guidance documents.

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FDA's plans for Implementation of the "deemed to be a license" Section of the BPCIA

As written, Section 7002(e)(4) only applies to approved NDAs and requires their conversion to BLAs on the date that is 10 years after enactment of the BPCIA. The FDA interprets that this date would be the day after March 20, 2020. However, since March 21 is a Saturday (i.e., not a business day), the conversion of the biological product NDAs will occur at 12:00 am on Monday, March 23, 2020. Also, at this date and time, the NDAs for these products will no longer exist in the FDA's data system and the associated products and their applications will commence being regulated under the PHSA as biological products and BLAs, respectively.[5]

There are several potentially important impacts of this change:

- Because these products will no longer have an approved NDA, they will no longer be listed in the Orange Book.
- Because they will no longer be considered "listed drugs," any 3- or 5-year exclusivity will no longer block approval or submission of subsequent BLA applications; exclusivities will be discussed in more detail below.
- Because they will no longer be "listed drugs," they cannot serve as a Reference Listed Drug (RLD) for a 505(b)(2) NDA or ANDA application.

Product	Time to Approval (months)
Aprotinin	---
Beractant	---
Calfactant	35
Choriogonadotropin alfa	10
Chorionic gonadotropin*	---
Chymopapain	---
Desirudin	33
Follitropin alfa	22
Follitropin alfa/beta	50
Follicle stimulating hormone	---
Hyalurionidase	9
Imiglucerase	---
Insulin aspart	21
Insulin degludec	48
Insulin detemir	30
Insulin glargine	12
Insulin glulisine	10
Insulin human	---
Insulin lispro	---
I-125 albumin	---
I-131 albumin	---
Albumin chromated	---
Tc-99m albumin	---
Lepirudin	15
Mecasermin	---
Mecasermin rinfabate	11
Menotropins**	---
Pancrealipase	---
Pegvisomant	28
Poractant alfa	40
Sacrosidase	11
Somatropin	---
Taliglucerase alfa	24
Thyrotropin	---
Urofollitropin	---
Urokinase	---
Velaglucerase alfa	5

Box 1. Biologic Products Currently Regulated under Section 505 of the FFDCA[6]

More on exclusivities

As noted above, any 3-year or 5-year exclusivity applied to an NDA-approved biological product will end at midnight on March 20, 2020, and will not confer to the product when its NDA becomes a BLA at 12 AM on Monday morning March 23, 2020. Likewise, biological product NDAs that are "deemed to be a license" will not

be granted the 12-year and 4-year exclusivity periods provided under 351(k)(7)(A) of the PHSA to BLAs that are first approved under 351(a) of that Act.

The good news is that any orphan drug exclusivity or pediatric exclusivity that an NDA-approved biologic product has will confer to the "deemed to be a license" application.

What about pending or tentatively approved NDAs?

Since the FDA interprets Section 7002(e)(4) of the BPCIA strictly to apply only to approved NDAs, a pending or tentatively approved NDA will not be deemed to be a pending or tentatively approved BLA.

A pending NDA submitted under 505(b)(1) or 505(b)(2) of the FFDCA that doesn't rely on the FDA's finding of safety and efficacy of an RLD will have until midnight on Monday March 23, 2020, to gain approval as an NDA. If it does not achieve approval by this date, FDA will issue a Complete Response (CR) letter to the application.

A 505(b)(2) NDA or ANDA that does not have full approval by midnight on March 20, 2020, will receive a CR Letter. Although, the guidance documents do not provide details on the content of the CR letter, it can be expected that it will include a statement regarding the fact that the RLD, upon which the application depends, is no longer available for reference and that the response to the CR letter will have to be in the form of a new 351(a) or (k) BLA submission.

What happens to NDA supplements that are pending approval when the transition date occurs?

Any pending NDA supplements will be converted to pending BLA supplements at midnight on Monday March 23, 2020. The FDA will keep the same PDUFA goal date for the converted supplement and no additional user fees will be required for clinical supplements.

Strategic Planning for new 505(b)(1) or (b)(2) NDAs and ANDA submissions

If you have been developing your biological product for submission as a standalone NDA (i.e., a 505(b)(1) submission) and are confident that it can be approved before March 20, 2020, then submitting the application as an NDA is a logical strategy. However, it is worth considering that, for 18 NDAs for biological products submitted between 1995 and 2011 (for which public data[6] is available), the average time from submission to approval was 24 months (S.D. = 14 months). See *Box 1* on page 20 for a list of NDA-regulated biological products and their times for approval.

For 505(b)(2) NDAs and ANDAs, if timely approval is not possible because there are patents or exclusivities that would impede final approval until after the March 20, 2020 transition date, then your submission strategy will need to be adjusted. For these types of applications, the critical factor is that, when Monday March 23, 2020 comes, the RLD which your application refers to will no longer be "listed" in the Orange Book. As such, your application will no longer be able to rely on the FDA's finding of safety and efficacy of the previously listed drug.

In such cases when it is unlikely that your NDA will be approved before the applicable transition date, you will probably want to take a different path. If you have the data to support a BLA under 351(a), you can submit such an application at any time. You don't have to wait until after the transition date in March of 2020. Of course, the BLA must meet the existing filing requirements for a 351(a) BLA, including data from clinical safety, efficacy, and immunogenicity studies.

Unfortunately, one cannot submit a 351(k) application for a biosimilar product until an appropriate reference product is approved under 351(a) of the PHSA or an NDA for an appropriate reference product is "deemed to be a license" on March 23, 2020. In addition, it is important to note that many of the differences between the RLD and the proposed product allowable under 505(b)(2) (e.g., change in strength, dosage form, route of delivery, etc.) are not allowed for a biosimilar BLA under 351(k). Specifically, for a 351(k) BLA, the proposed biosimilar product must meet the criteria listed below. Relative to the reference product, the proposed biosimilar product must:

- Be demonstrated to be "highly similar";
- Have the same route of route of administration;
- Be the same dosage form;
- Have the same strength;
- Seek approval for a same condition of use; and
- Efficacy must be based on the same mechanism of action.

What are the regulatory differences for BLAs vs NDAs?

For the most part, the regulatory requirements for NDA products and BLA products are harmonized. However, there are some significant differences that one should be aware of when switching a submission from NDA to BLA:

- Generally, for an NDA, validation of the manufacturing process is completed after approval of the application, whereas for BLAs, approval of the application requires completion of process validation;
- In accordance with 21 CFR 600.13, BLA holders must retain product samples under appropriate storage conditions for at least six months after expiration of the product lot;
- In accordance with 21 CFR 600.14, BLA holders must submit Biologic Product Deviation Reports within 45 calendar days of becoming aware of an event that may affect the safety, purity, or potency of an approved product;
- Every six months, BLA holders must submit Distribution Reports in accordance with 21 CFR 600.81; and
- Labeling for biological products must meet the requirements under 21 CFR 610 Subpart G.

Summary

Facing the future transition of biological products from regulation as new drugs under the FFDCA to regulation as biologics under the PHSA in March of 2020, it is not too early to begin incorporating this transition into your regulatory strategy. Holders of NDAs for biological products and those developing NDAs or ANDAs for biological products should carefully consider the potential impacts on their pre- and post-approval requirements in order to be prepared for the change and minimize any delay of approval of their application. **CP**

For a full list of references please visit the online version of this article at ContractPharma.com.