May 13, 2016

Division of Dockets Management (HFA-305)
Food and Drug Administration
5630 Fishers Lane, Rm. 1061
Rockville, MD 20852

Re: Draft Guidance for Industry: Implementation of the "Deemed To Be a License" Provision of the Biologics Price Competition and Innovation Act of 2009 (Docket No. FDA-2015-D-4750 (March 14, 2016))

The Biotechnology Innovation Organization ("BIO") welcomes the opportunity to submit comments on the Food and Drug Administration's ("FDA's") draft guidance entitled "Implementation of the 'Deemed to be a License' Provision of the Biologics Price Competition and Innovation Act of 2009" issued on March 14, 2016 ("Draft Guidance").

BIO represents more than 1,000 biotechnology companies, academic institutions, state biotechnology centers, and related organizations across the United States and in more than 30 other nations. BIO members are involved in the research and development of innovative healthcare, agricultural, and environmental biotechnology products, thereby expanding the boundaries of science to benefit humanity by providing better healthcare, enhanced agriculture, and a cleaner and safer environment.

Implementation of the Biologics Price Competition and Innovation Act ("BPCIA") is of significant importance to BIO members, and we greatly appreciate FDA's efforts to provide clarity on the agency's current thinking on the transition provisions. As detailed below, we do have concerns about the agency's proposed interpretations of the provisions as outlined in this Draft Guidance. In finalizing the Draft Guidance, we strongly urge the agency to consider our comments and requested changes.

I. FDA's Proposed Revocation of Unexpired Regulatory Exclusivity Cannot Stand

A. FDA's Proposed Interpretation to Revoke Unexpired Exclusivity Periods Is Contrary to the Terms of the BPCIA

As proposed by FDA in the Draft Guidance, biological products approved under the Food, Drug, and Cosmetic Act ("FDCA") that have any periods of unexpired exclusivity, other than orphan drug exclusivity, when they transition to, and are deemed licensed under, the Public Health Service Act ("PHSA") on March 23, 2020 will lose any such remaining period of that exclusivity upon transition. By this dictate, in other words, the new drug application ("NDA") sponsor would lose any and all remaining period of data exclusivity, including 5-year new chemical entity ("NCE"), 3-year new clinical investigations ("NCI"), and the 6-month pediatric exclusivity period attached to any such period of data exclusivity. In addition to forfeiting that exclusivity entirely, as proposed by FDA, neither will those products that transition to the PHSA

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be considered to have been "first licensed" under section 351(a) of the PHSA, and thus will not receive a period of reference product exclusivity under section 351(k)(7) of the PHSA. To the contrary, FDA takes the position that "[n]othing in the BPCI Act suggests that Congress intended to grant biological products approved under section 505 of the FD&C Act -- some of which were approved decades ago -- a period of exclusivity upon being deemed to have a license under the PHS Act that would impede biosimilar or interchangeable product competition in several product classes until the year 2032."

As explained in greater detail below, BIO disagrees with FDA's interpretation of the transition and exclusivity provisions of the BPCIA. First, we do not believe that it was Congress' intent for FDA to render null and void pre-existing, unexpired data exclusivity for those products that transition to biologic status on March 23, 2020, nor are we aware of anything in the BPCIA that supports such an interpretation. The language of the BPCIA discusses where an applicant files its transition product. It nowhere states or even suggests that rights granted as an approved product under the statute filed are revoked or otherwise cease to exist upon transition.

Neither does the legislative history of the BPCIA suggest that Congress intended that sponsors of transition products be stripped of any and all data exclusivity as of the transition date. Notably, FDA looks to the legislative intent in support of its position that transition products are not eligible for a grant of the 12-year data exclusivity period provided to biological products under the BPCIA. Yet, FDA appears to choose to disregard entirely legislative intent when contrary to its proposal to revoke data exclusivity lawfully granted to biological products under the FDCA prior to transition. This is not only conflicting reasoning, but problematic from a legal perspective as discussed below.

Although section 7002(e) of the BPCIA requires applications for biological products to be submitted under section 351 of the PHSA, it provides an explicit exception from this requirement for any biological product in a product class for which a biological product in such class was the subject of an approved application under section 505 of the FDCA as of the date of enactment of the BPCIA. For such products, section 7002(e)(2) of the BPCIA provides that an application for the product *may* be submitted under section 505 of the FDCA if it is submitted no later than March 23, 2020. FDA's interpretation in the draft guidance as it relates to the FDCA exclusivity of such transition products is wholly inconsistent with a sponsor's legal authority to submit an NDA under the FDCA up until March 23, 2020, as the legal right to the exclusivity periods granted under the FDCA to those products is summarily quashed by FDA after that point in time. In other words, FDA's interpretation removes from the sponsor the meaningful choice provided under the BPCIA for submission of NDAs for such products. This is completely contrary to the BPCIA's explicit grant to sponsors of the option to submit an NDA up until March 23, 2020. There is nothing to suggest that the statutorily granted NDA "option" is devoid of certain legal rights associated with it, including exclusivity for eligible products.

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B. FDA's Proposed Interpretation to Revoke Unexpired Exclusivity Raises Constitutional Concerns

FDA's proposed interpretation of the BPCIA that results in revocation of unexpired exclusivity raises Constitutional concerns arising under the Fifth Amendment's prohibition on the government's taking of private property without just compensation.

The Takings Clause of the Fifth Amendment prohibits the government from taking private property "for public use, without just compensation."[1] When determining whether a regulatory taking has occurred, courts assess the factors delineated in *Penn Central Transportation Co. v. City of New York*: (1) the character of the government action; (2) the economic impact of the regulation on the property owner; and (3) the regulations' interference with the property owner's reasonable investment-backed expectations.[2] Under this test, revoking unexpired exclusivity is a regulatory taking for which the government must pay just compensation. First, the character of the government action is a taking: FDA's proposal extinguishes the regulatory exclusivity that the sponsor lawfully earned and that the FDA lawfully granted to the sponsor. Second, sponsors of transitioned products whose exclusivity is revoked could suffer significant economic loss as a result of such revocation due to competitors' reliance for approval on such product as the Reference Product. Third, FDA's proposed unconstitutional revocation would interfere with the sponsors' reasonable investment-backed expectations. Since FDA's interpretation of the BPCIA constitutes a regulatory taking for transition products, then it follows that the interpretation is flawed, as FDA should not be interpreting the BPCIA in conflict with the Constitution.

FDA's proposed interpretation to revoke unexpired exclusivity for transitioned products risks a regulatory taking for all transition products that will have unexpired exclusivity as of the transition date. This includes sponsors who designed registration programs based on the explicit statutory authority that NDAs could be submitted up until the 2020 transition date.

These sponsors could not have anticipated that FDA would revoke their regulatory exclusivity upon transition given that the BPCIA provided a choice of pathways by which they could file and receive approval. Such sponsors had no notice or indication that the agency intended to revoke the remaining periods of exclusivity and FDA's guidance provides no indication of how the government will provide just compensation for such property loss.

Sponsors of such products invested significant resources in developing their products and obtaining approval through the NDA pathway in accordance with the statutory language of the BPCIA, the plain text of which, for certain classes of products, allows submission of NDAs under section 505 of the FDCA up until March 23, 2020. In seeking or obtaining approval

[1] U.S. Const. amend. V, cl. 4.

[2] 438 U.S. 104, 124-25 (1978).

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through section 505 of the FDCA, sponsors of such products had a reasonable expectation that the exclusivity rights associated with approvals through the section 505 pathway (i.e., 5-year NCE, 3-year NCI, and pediatric exclusivity) would apply until expiry of their applicable terms.

There is nothing in the BPCIA to suggest that if a sponsor elected to submit an NDA rather than a BLA during the transition period, the sponsor would forfeit remaining data exclusivity as of the transition date. Given the considerable investment made by sponsors of such products, the plain language of the BPCIA, and FDA granting those sponsors the applicable regulatory exclusivity, the sponsors of FDCA- currently filed and approved or subsequently approved biological products have a reasonable investment-backed expectation that its full statutorily provided exclusivity period would be protected. Approving an application for a biosimilar product that references a transition product prior to the full term of exclusivity appears to violate the Fifth Amendment's prohibition on the taking of private property without just compensation.

Finally, even assuming *arguendo* that FDA has the statutory authority to revoke previously granted data exclusivity – and BIO submits that it does not -- FDA's proposal would effectively amend prior regulations at 21 C.F.R. 314.108(b), which provide for 5- and 3-year periods of data exclusivity for certain applications for NDA-approved products, by essentially retrospectively changing the duration of such data exclusivity, including any associated pediatric exclusivity as it relates specifically to protein products approved through NDAs. Relying on guidance to effectively amend a prior legislative rule is in violation of the Administrative Procedure Act. Consequently, FDA should not, through guidance, interpret the BPCIA's transition provision in a manner that would purport to retrospectively amend existing regulations.

C. FDA Should Recognize All Residual Regulatory Exclusivity Rights For Protein Products Deemed Licensed Under the PHSA Effective March 23, 2020

As an alternative to FDA's revocation proposal – a proposal that we believe is contrary to the statute – BIO asks that, consistent with the BPCIA, FDA recognize any period of residual regulatory exclusivity rights for protein products deemed licensed under the PHSA effective March 23, 2020. Under this approach, FDA would continue to recognize that exclusivity until the initially granted terms have expired. Quite simply, for any protein product approved under the FDCA that is deemed licensed under the PHSA effective March 23, 2020 but that has been granted exclusivity or an expected right of exclusivity under the FDCA, FDA should not approve an application for a biosimilar or interchangeable product referencing that protein product until expiry of the remaining period of such exclusivity. This approach is entirely consistent with the plain language of the BPCIA, and the explicit grant of authority to sponsors of transition products to file under the NDA pathway up until the transition date.

II. FDA Should Keep Transition Products Listed in the Orange Book Until the Expiry of All Relevant Exclusivities, and Transition Products Should Retain All Patent Rights and Any Related Stay Periods

BIO also asks that FDA address the effect of transition on NDA-approved products that are the subject of ongoing patent infringement disputes pursuant to the processes set forth in the FDCA. Because the BPCIA lacks a provision analogous to the 30-month stay provision of the Drug Price Competition and Patent Term Restoration Act ("Hatch-Waxman"), transitioned products with ongoing stay periods are at risk of losing any remaining time on the stay periods at the time of transition on March 23, 2020. BIO believes that FDA should consider an approach that FDA continues to recognize the exclusivity and patent-challenge rights granted as part of the NDA pathway for those transition products that were approved as an NDA.

In the Draft Guidance, FDA states that upon transition, "any patents listed in the Orange Book would no longer be relevant for purposes of determining the timing of approval of a 505(b)(2) application (or ANDA)." We ask that the agency clarify whether for transitioned products, patents listed in the Orange Book will have any relevance with respect to the patent notification provisions of the BPCIA. This has significant implications for the rights of applicants, as FDA's current interpretation would appear to negate the expectations of patent holders as to the applicability of the 30-month stay, and, to date, the patent notification provisions of the BPCIA have been held to be voluntary.

FDA cannot and should not ignore potential ongoing litigation happening at around the time of the transition period, and, we are not aware of anything that suggests Congress intended for the BPCIA to be interpreted in such a manner as for transition products to lose granted exclusivity rights or to negatively impact ongoing litigation related to data or patent exclusivity awarded to NDA-approved products. Thus, we ask not only that FDA reconsider its proposal to void the regulatory effect of listed patents for transition products, but also to reconsider its proposal to remove approved products from the Orange Book effective March 23, 2020. To this end, we ask that transition products and their data and patent exclusivity information remain in the Orange Book, at least until the expiration of any such remaining exclusivity. At a minimum, FDA should permit the public an additional period of comment to address its position on these patent issues.

III. FDA's Proposal to Require NDAs and Supplements Pending Before FDA as of March 23, 2020 to Refile Under the BLA Pathway Is Unduly Burdensome and Poses Potential for Negative Public Health Consequences

In addition to voiding any residual exclusivity that remains for an FDCA-approved transition product as of March 23, 2020, FDA has proposed to require any "application for a protein product that has been submitted under section 505 of the [FDCA] and is pending on March 23, 2020" be withdrawn and submitted under section 351(a) or 351(k) of the PHSA. This interpretation has the potential to affect at least two types of submissions: NDAs for new drugs, and supplements to NDAs ("sNDAs") for changes to an approved drug. FDA's proposal is

highly problematic as it relates to both types of applications. For NDAs for new drugs, as discussed in greater detail above, the BPCIA allows submission of NDAs for certain product classes up until March 23, 2020, which clearly reflects that Congress intended for any NDAs pending at the time of transition to be allowed to be approved as NDAs under the FDCA, irrespective of how long the review process takes. If the product has been filed as an NDA, the choice of pathway was made by the sponsor and the application should be continued to be reviewed and approved as an NDA.

Although in the Draft Guidance FDA does not specifically address the treatment of pending sNDAs, the agency statement that applications for transitioned products that are pending under section 505 of the FDCA as of the transition date be resubmitted under the PHSA would appear to also apply to sNDAs. Indeed, pursuant to 21 C.F.R. 314.3, "application" is defined to include not only the application itself, but also supplements and amendments to that application.

We caution that FDA's proposal as it relates to sNDA submissions would slow down the approval of changes that may offer significant benefit to the public health (e.g., new indication, dosage form, or other change that enhances patient compliance or safety). While manufacturers that are considering an NDA for a new product may have more flexibility to choose a BLA over an NDA from the start, a manufacturer pursuing a supplement is forced to work with the regulatory status of the currently approved product and thus would have to choose, essentially, between waiting until March 23, 2020 to submit its supplement or otherwise go ahead and submit as an SNDA only to then have to resubmit as an sBLA after March 23, 2020. In this way, FDA's proposal creates the very real potential of a regulatory dead-zone, to the detriment of not only the company sponsor but also to the patients in need of that medicine.

Furthermore, in addition to prior approval supplements, FDA's proposal would also affect "Changes Being Effected in 30 Days" ("CBE-30") supplements, as well as CBE supplements under 21 C.F.R. § 314.70(c)(6) for changes for which distribution can occur when FDA receives the supplement. For CBE-30 supplements that are pending as of the transition date, FDA's proposal to have sponsors resubmit the submission would appear to re-start the 30 day period, and for CBE supplements under (§ 314.70(c)(6)) that are implemented at the time of submission, FDA's proposal would result in sponsors resubmitting a supplement for a change that has already been implemented.

BIO believes the most efficient and equitable approach with respect to both NDAs and sNDAs for transition products would be to permit any pending NDAs and supplements to be licensed as BLAs and sBLAs without requiring refiling – treating those sponsors with an application still pending as of the transition date the same as those sponsors who may have fortuitously obtained NDA or sNDA approval just a day prior to the transition date.

Should, however, FDA proceed with its proposal to require refiling, BIO asks that FDA make abundantly clear that upon refiling as a BLA, there would be no additional user fee and that the clock running on PDUFA timelines/goals in effect as of March 23, 2020 not be restarted upon resubmission as a BLA. To facilitate as seamless of a transition as possible, it is critical that the

substantive requirements of the NDA or sNDA not be adversely affected in the midst of the review process. This consistency across the review of transition products will help to ensure the timely and efficient review and approval of those affected submissions.

We also ask that FDA provide guidance on how post-approval commitments and requirements (PMRs/PMCs) should be handled if they occur on, or in close proximity to, March 23, 2020, and to clarify whether the agency's proposal to require refiling of pending applications would extend to submissions made to an NDA file to submit results of a required post-approval study or other commitment. If FDA's refiling proposal would require refiling of submissions relating to post-approval requirements or commitments, the agency should make clear that for purposes of assessing whether a sponsor has met a post-approval commitment deadline, the agency will consider the date the sponsor first submitted the commitment as the submission date, not the date of refiling necessitated due to the agency's interpretation of the BPCIA's transition provisions.

V. Transition Products Approved Under Section 505(b)(2) of FDCA

A. FDA Should Address Whether Transitioned A-Rated Products, if Any, Will Be Considered Biosimilar to or Interchangeable with Their Reference Products

FDA should address whether an NDA-approved transition product with an "A" equivalence rating under the FDCA, if any are approved prior to transition date, is to be deemed biosimilar to its respective reference product, or whether it would be deemed interchangeable to its reference product. Given the two distinct statutory standards – one for therapeutic equivalence under the FDCA and the other interchangeability under the PHSA – we urge that FDA consider a previously A-rated protein product that transitions to the PHSA as biosimilar but not interchangeable absent the sponsor providing supplemental data to demonstrate that the transitioned product satisfies the BPCIA standards for interchangeability relative to its transitioned reference product. In any case, clarity to stakeholders on this issue is needed.

B. FDA Needs to Address Whether or Not Transition Products First Approved Under Section 505(b)(2) of the FDCA Should Be Deemed Licensed Under Section 351(a) of the PHSA

BIO understands that FDA intends to address the transition of 505(b)(2) products issue in a separate guidance. BIO agrees that due to the unique aspects of the FDCA 505(b)(2) approval pathway, and the differences between it and both the PHSA 351(a) and 351(k) pathways, clarification on this issue is needed. For example, 505(b)(2) approval relies upon comparative data with a reference product versus a full dossier as is the case with licensure under the PHSA 351(a) pathway. In addition, there are also notable differences between the 505(b)(2) pathway and that of 351(k). Specifically, products approved under section 505(b)(2) of the FDCA can differ from their "reference product" in ways that are not permissible for a biosimilar, including,

for example, indication, dosage form, strength, or route of administration. Therefore, in the separate guidance that FDA suggests is forthcoming, BIO encourages FDA to address how a determination will be made as to whether such product will be "deemed" as licensed under section 351(a) or 351(k) of the PHSA, including what additional requirements may need to be satisfied in either case.

BIO also asks FDA to also clarify that the 505(b)(2) approval pathway remains viable for those protein products that do not meet the definition of "protein" and thus do not transition to the PHSA.

C. FDA Should Publish a Full List of NDA-Approved Products that Will Be Deemed Licensed Under the PHSA Effective March 23, 2020

BIO asks that FDA publish a full list of FDCA-approved products subject to the BPCIA transition provisions. As discussed previously, FDA should leave transitioned products listed in the Orange Book until expiry of any applicable exclusivity and listed patents, after expiration of which a transitioned product would be moved to the Purple Book.

D. Miscellaneous Regulatory Questions Left Unanswered

There are many regulatory questions left unanswered by the Draft Guidance, and it is unclear how and when a sponsor will receive input to these practical and important implementation questions. We raise certain of those issues below, and, we also ask that in finalizing the Draft Guidance, FDA address how sponsors affected by the transition provisions can receive answers to specific questions relating to transition that are not addressed in the Draft Guidance.

- **Effect of NDA v. BLA Data Differences for "Deemed" Licensed Transition Products**

BIO applauds FDA for confirming in the Draft Guidance that the NDAs for existing approved transition products will be replaced by "Approved" BLAs, with the Draft Guidance stating that "FDA interprets [section 7002(e)(4)] to mean that on March 23, 2020, applications for biological products that have been approved under section 505 of the FD&C Act will no longer exist as New Drug Applications (NDAs) (or, as applicable, Abbreviated New Drug Applications (ANDAs)) and will be replaced by approved Biologics License Applications (BLAs) under section 351(a) or 351(k) of the PHS Act, as appropriate." In other words, FDA will not require additional data to be submitted and a substantive finding made before "re-approving" the transition products under the FDCA. The same seamless transition process should be made available to all transition products for which an NDA has either been approved or is pending prior to the transition date.

- To this end, FDA should provide guidance, and ample opportunity for stakeholder feedback, on the process for resolution of issues that may arise for "deemed" licensed products due to data and other differences between approval through the NDA pathway and licensure through the BLA pathway. It is critical to understand how FDA will handle

post-marketing supplements that are submitted after the transition date for a deemed licensed product.

For example, although the transition product is automatically an approved BLA product on the transition date, it may not, in certain respects, have the label or data on file that would typically be associated with a BLA product. Thus, to the extent that there are data, format, or other differences between an NDA and BLA that could have bearing on submission of a BLA supplement to a product that was originally approved though an NDA, FDA should provide guidance on how sponsors should deal with such differences when submitting a BLA supplement for an originally NDA-approved product. It is not clear that FDA would require sponsors of transition products to update their previously approved NDAs upon subsequently filing a sBLA post-transition. In any case, we urge the Agency to refrain from doing so. Such a requirement would create unnecessary administrative burden not only on the sponsor but also on Agency resources. As such products have already been approved as safe and effective, there is no urgency created merely by the fact that the product is now "deemed" to be licensed under the PHSA.

- **Review and Inspection Oversight Over Transitioned Products**

BIO asks that FDA make clear that NDA-approved protein products that are "deemed licensed" under the PHSA effective March 23, 2020 will remain within the same review office in the same CDER review division as the currently approved NDA product. In addition, we ask that FDA make clear that transitioned products will remain within the same inspection program as prior to transition.

- **Transition of Fixed-Dose Combination Products**

FDA should clarify the handling of the transition of combination products, where prior to enactment of the BPCIA both components were considered drug components and thus were reviewed and approved under the NDA pathway, but, where post-BPCIA one of the two components is considered a "protein" that is regulated as a biologic under the PHSA. While FDA should address this issue as it relates to all such combination products, we especially ask that the agency provide guidance with respect to fixed-dose combination products where the combination product is made up of polypeptide sequences where one component of the combination product remains in the FDCA pathway and the other component transitions. In finalizing the Draft Guidance, FDA should address how it will determine which component accounts for the "primary mode of action" for assessing whether such a product will transition to biologic status and be deemed licensed under the PHSA.

- **Drug Master Files**

In footnote 12 of the Draft Guidance, FDA states that it has taken measures to minimize differences in the review and approval of products required to have approved BLAs under section 351 of the PHSA and products required to have approved NDAs under section

505(b)(1) of the FDCA. FDA notes, though, that for sponsors of proposed protein products who intend to submit a BLA, a Type II Drug Master File ("DMF") for a drug substance, drug substance intermediate, or drug product would not be acceptable for a BLA because a license holder is expected to have knowledge of and control over the manufacturing process for the biological product for which it has a license. FDA acknowledges that it is considering a mechanism that, in limited circumstances, would allow holders of approved NDAs that reference a Type II DMF to continue to do so post-transition. Notably, however, FDA does not address use of other types of DMFs. In finalizing the Draft Guidance, FDA should confirm that there are no such considerations with respect to other types of DMFs, and make clear that if an NDA application has been referencing the other DMF types (III, IV or V) prior to transitioning, the application should be able to continue referencing the DMF.

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BIO appreciates the opportunity to submit these comments, and we would be happy to provide further input or clarification of these comments, as needed.

Respectfully submitted,

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