

October 6, 2014

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

Re: **Draft Guidance for Industry: Reference Product Exclusivity for Biological Products Filed Under Section 351(a) of the PHS Act (Docket No. FDA-2013-D-1165, 79 Fed. Reg. 45448 (August 5, 2014))**

Dear Sir or Madam:

The Biotechnology Industry Organization ("BIO") thanks the Food and Drug Administration ("FDA") for the opportunity to submit comments on the above-referenced Draft Guidance for Industry: Reference Product Exclusivity for Biological Products Filed Under Section 351(a) of the PHS Act (August 2014) ("Exclusivity Draft Guidance" or "Draft Guidance").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, industrial, 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. The implementation of the Biologics Price Competition and Innovation Act of 2009 ("BPCIA") is of significant importance to BIO members, and we commend FDA's efforts in developing the Draft Guidance to provide the agency's current thinking on the exclusivity provisions of the Act. BIO has previously commented on biosimilar and biologics issues and appreciates FDA's consideration of our comments.

We are pleased to provide the following comments on the Exclusivity Draft Guidance:

I. Executive Summary

While BIO commends FDA for issuing guidance on the date of first licensure determination process under section 351(k)(7) of the PHSA, we believe that the proposed process and many of the recommendations set forth in the Draft Guidance are needlessly complicated, unnecessarily burdensome on both sponsors and FDA, and lack sufficient clarity on important issues. As discussed in greater detail below, we also believe that the Agency's proposed approach, in certain respects, appears to go beyond its statutory mandate.

We are particularly focused on the following concerns with respect to the Draft Guidance:

- First, we strongly urge the agency to make clear in any final guidance that it interprets the BPCIA as containing a presumption of reference product exclusivity that operates by statute. Moreover, any 351(a) application that is not a supplement or a "subsequent application" to a previously approved 351(a) application should be granted exclusivity without FDA requiring or recommending that the sponsor provide data regarding the date of first licensure.



- Second, FDA's recommendations regarding the information that 351(a) sponsors should provide to assist the agency in making a determination of date of first licensure are unnecessarily burdensome and appear to go beyond the Agency's statutory mandate. BIO asks that FDA revise its recommendations to request that 351(a) sponsors provide to FDA only information that is not already in the agency's possession, and only information regarding products previously submitted by that applicant or a related party (as so defined).
- Third, we ask that FDA clarify the timeline and process for "first licensure" determinations, including (i) explaining whether FDA will make a "first licensure" determination for all section 351(a) products or if first licensure for any given product will be decided only upon request; (ii) clarifying that not requesting a "first licensure determination" or providing the agency information relating thereto does not result in a waiver of exclusivity or a later determination of first licensure; and (iii) clarifying that, if the date of approval of a supplement or subsequent application is deemed not to be the date of first licensure, the product approved by the supplement or subsequent application nevertheless is protected by any remaining time of the 12-year exclusivity afforded the original licensed product – as occurs under FDA's recently confirmed existing approach.
- Fourth, with regard to FDA's interpretation of "licensor, predecessor-in-interest, or other related entity," we recommend that FDA interpret these terms narrowly to avoid undermining the clear intent of Congress to craft a limited exception to the presumptive 12-year grant of exclusivity. In particular, the term "other related entity" should be interpreted consistent with the intent of the statute to be limited to those situations in which, solely by virtue of a particular type of corporate relationship, a subsequent applicant will be able to shorten its path to approval by relying on data contained in the relevant prior application as essential to approval of the subsequent application. Further, we urge FDA to interpret "other related entities" with a focus on ownership and control, and to not include "commercial collaborations" in its interpretation of "related entities." Such an approach would effectuate the purpose of the exclusivity provision, which is to encourage the massive research and development effort associated with bringing innovative biological products to market, while not rewarding applicants for making changes to their previously approved products that do not also result in a change to the product's safety, purity, or potency.

Finally, we make several recommendations with regard to the process set forth in the Draft Guidance for assessing whether a 351(a) product is a structurally modified version of a previously approved 351(a) product, and whether the modifications result in a change in safety, purity, or potency.

We provide our detailed comments on these and other related issues in the sections that follow.

II. Comments Regarding Exclusivity Presumption and "Subsequent Application"

First and foremost, we strongly urge the FDA to make clear in any final guidance that it interprets the BPCIA as conferring a presumption of reference product exclusivity that operates by statute. BIO believes that the overall approach to reference product exclusivity proposed in the Draft Guidance essentially reverses the actual statutory presumption as to the exclusivity granted to the reference product sponsor. Such an approach disrupts the very balance that the BPCIA intends to strike between continuing to incentivize the research and development of innovative medicines while increasing the availability of therapeutic alternatives by creating an abbreviated approval pathway for biosimilars.



BIO is concerned that the Draft Guidance suggests that a sponsor of a 351(a) biologic must affirmatively seek an exclusivity determination and provide evidence that the sponsor's product qualifies for exclusivity. This is inconsistent with sections 351(k)(7)(A) and (B) of the PHSA, which are drafted so as to confer a presumption of exclusivity for a stand-alone BLA filed under section 351(a) that serves as the reference product for a later biosimilar applicant. Under the PHSA, FDA may not approve a section 351(k) application until 12 years after the date the reference product was first licensed under section 351(a). Section 351(k)(7)(C) explains that such exclusivity shall not apply to a supplement for the reference product, or to certain "subsequent application[s]" filed by the same sponsor or manufacturer (or a licensor, predecessor in interest, or other related entity) *of the reference product*. Specifically, the 12-year exclusivity does not apply to a subsequent application for (i) a change to the biological product that results in a new indication, route of administration, dosing schedule, dosage form, delivery system, delivery device, or strength, or (ii) a modification to the structure of the biological product that does not result in a change in safety, purity, or potency.

In the Draft Guidance, FDA lists various types of information that a sponsor should provide to the agency to assist the agency in determining the date of first licensure of a 351(a) product. As discussed in greater detail in our comments below, BIO believes that the requested information is unnecessary and burdensome. Because section 351(k)(7) provides a presumption of exclusivity for all 351(a) applications that are not supplements or subsequent applications to a previously approved biological reference product, the first step in the process – prior to any request or submission of information to the agency beyond the application itself – should be determining whether the 351(a) application is in fact either a supplement or a subsequent application to a previously approved 351(a) application. If a 351(a) application is neither a supplement or a subsequent application – a determination that generally can be made from the application itself – there should be a default presumption of exclusivity, and the 351(a) product should be granted 12 years of exclusivity beginning on the date of licensure of that 351(a) application in accordance with the clear mandate of the statute.

Further, in the Draft Guidance FDA describes the first licensure determination as "challenging" and fraught with "scientific and technical complexities" and indicates that it views reference product exclusivity as something for which a sponsor must qualify, rather than something that arises by default or presumption. This is inconsistent with the statutory framework, which provides that a statutory exception to this presumptive grant of exclusivity found in Section 351(k)(7)(C) is to be triggered only in certain narrowly prescribed circumstances. The first is in the case of a supplement. Second, a subsequent application does not get exclusivity if it is for a structurally modified product that is no different in safety, purity or potency or if it is for a change *other* than a structural modification that results in a different indication, dosage form, strength, etc. By contrast, FDA's proposed approach in the Exclusivity Draft Guidance appears, in essence, to require applicants to prove in every case that these exceptions do not apply, even if the application is neither a supplement nor a subsequent application.

Accordingly, we recommend that FDA set forth in final guidance how it would interpret "subsequent application," and urge FDA to interpret the term as "a 351(a) application that refers to or relies on, as essential to approval, data from a prior approved 351(a) application, with a right of reference." In other words, if approval of a 351(a) application is based on a full development program, then that 351(a) application is not a "subsequent application" to another or previous 351(a) application. This approach is entirely consistent with the statutory language which describes the subsequent application as being tied to an earlier "reference product."



Adding this predicate step to the first licensure determination process set forth in the Draft Guidance would not only be more consistent with the relevant statutory provisions, but also would greatly reduce the burden on the Agency and sponsors, which, as noted, the Agency describes as challenging and complex. For instance, this approach would simplify the exclusivity determination by significantly decreasing the amount and complexity of supporting materials that the agency would receive from 351(a) sponsors under the Agency's approach in the Draft Guidance. Further, the Agency will be readily aware as to whether it required a full pre-clinical and clinical development program, or instead permitted a sponsor to refer to or rely on a prior approval by the same or related sponsor, and thus whether the presumption is in effect. We emphasize that this approach would merely be a presumption, so as to permit the Agency – whether on its own initiative or in response to a petition from an interested third party – to seek relevant information from a 351(a) sponsor in unclear cases. But this approach would avoid a complicated and uncertain process in the vast majority of cases, minimizing the burden on the Agency's limited resources.

III. Comments Regarding Date of First Licensure and Exclusivity Eligibility Determination Process

We ask that FDA revise the Draft Guidance to address several fundamental questions regarding the first licensure determination process, which we summarize in the sections that follow.

A. Request for Determination

We request that FDA clarify whether it will make a "first licensure" determination for any given innovator product only upon Section 351 (a) sponsor request, or whether the agency intends to make such a determination for all Section 351(a) products, regardless of sponsor request or submission. Although FDA no longer makes explicit reference to a sponsor having to "request" reference product exclusivity in the Exclusivity Draft Guidance, as it did in its "Biosimilars: Question and Answers Regarding the Implementation of the Biologics Price Competition and Innovation Act of 2009" draft guidance, the agency states that sponsors may submit the recommended information, thereby still suggesting that a sponsor affirmatively must seek first licensure determination. In the *Federal Register* notice announcing the availability of the Exclusivity Draft Guidance, FDA estimates that it will receive only 10 "requests for determination of the date of first licensure annually," which further suggests that the agency does not intend to make first licensure determinations unless a sponsor requests that the agency do so.

As described in detail above, any final guidance should make clear that the statute does not require a sponsor to "apply" for the exclusivity period for the biologic product, and accordingly neither the failure to request a designation of first licensure date nor the failure to provide the information recommended by the FDA in this guidance shall result in a waiver of eligibility for the full exclusivity period, with respect both to already approved products but also products yet to be approved.

Rather we suggest that, as described above, in the first instance there should be the presumption that a new biologic product receives the statutory 12-year exclusivity by operation of statute. If FDA is unclear as to whether it is a new product or a modification to a prior product, it may request information from the sponsor along the lines suggested in the guidance. Further, a sponsor may (but is not required to) request a first licensure determination from FDA. In either instance, the guidance should make clear that, should



the FDA determine that more information is required in order to designate a date of first licensure, FDA may request such information from the sponsor, and the sponsor and FDA should engage in a dialogue and sharing of information in order to determine the applicable date of first licensure.

B. Information Submission and Determination Notification Processes

The final guidance should provide clear guidelines regarding the information submission process and the process through which sponsors will be notified of FDA's decision regarding exclusivity and first licensure. FDA's proposed data submission recommendations in the Draft Guidance are directed at both innovators with section 351(a) products in development and those with approved 351(a) applications. For sponsors with a product in development, FDA recommends that the sponsor include the requested information in the 351(a) application. For sponsors of products with previously approved 351(a) applications, FDA recommends that the requested information be submitted "as correspondence to the application," but states as well that the information also can be submitted as an amendment to the 351(a) application. BIO requests that FDA clarify its expectation with regard to the timeline for submission of recommended information by sponsors of 351(a) biologics licensed prior to issuance of the Draft Guidance. Specifically, we ask that FDA clarify that it is at the sponsor's discretion whether to submit a formal amendment or to submit a correspondence to the existing BLA, and that the failure to do either does not constitute a waiver of the product's exclusivity presumption.

While the Exclusivity Draft Guidance goes to great lengths to describe the sponsor's responsibilities in providing FDA with a rationale to justify exclusivity – which as explained above is inconsistent with the statutory presumption – the guidance does not address the timing of the first licensure determination or the process by which FDA will inform sponsors of such determinations. Optimally, the determination would be made at time of the BLA review or shortly thereafter. Previous comments to FDA have flagged the need of section 351(a) application sponsors to know much earlier in the development process whether their products would qualify for reference product exclusivity. Given the significant risk, cost, and time associated with bringing new medicines to the market, it is critical that FDA adopt an approach that mitigates residual uncertainty to the greatest extent feasible. To this end, we urge FDA to provide sponsors with meaningful guidance on eligibility for exclusivity as early as possible during the development process. For example, in those cases where an eligibility determination hinges on an analysis of the relationship between the BLA applicant and another entity, it seems reasonable to expect that a determination could be made well before BLA submission. In those cases where eligibility is dependent upon an analysis of a previously licensed product and the subject of a new submission, we urge that FDA adopt an approach that permits a determination to be made no later than the time of BLA approval and, wherever possible, to provide substantive guidance. While there may be instances where a final determination simply cannot be made at time of BLA approval, we believe that such instances should be considered a narrow exception to the rule. We note that, should the agency adopt our recommended presumptive approach to 351(a) applications that are not supplements or subsequent applications, many such issues and uncertainties can be avoided altogether.

Thus, in the final guidance, FDA should address when, relative to submission of a new 351(a) application or licensure of the product that is the subject of the application, it intends to make a determination regarding the date of first licensure. Likewise, FDA also should address when it intends to make such determinations for biological products with existing BLAs. For both types of products, FDA should detail how it intends to provide



notice regarding its first licensure and exclusivity determinations and to which entities such notice will be provided.

C. Exclusivity Period of Supplement or Subsequent Application Determined Not Eligible for its Own Date of First Licensure

The Exclusivity Draft Guidance fails to address the protection that should be afforded to a 351(a) product licensed through a supplement or subsequent application, the date of licensure of which is deemed not to be a date of first licensure under the statute. BIO requests that the agency make clear that, if a product approved through a supplement or subsequent application is deemed ineligible for its own 12-year exclusivity, the product would nevertheless be protected under any exclusivity remaining on the application for the first licensed product. Failure to implement such a policy would completely deter sponsors from developing modified versions of or new indications for approved products that would not qualify for a new 12-year exclusivity period under the PHSA. Modifying approved biological products and developing new uses for them is a key way that sponsors can provide additional significant benefits to patients. A failure to permit such products to be covered by whatever is remaining of the original product's exclusivity period will disincentivize such innovation and harm public health. Thus, consistent with its approach with regard to the exclusivity of modified drug products,¹ FDA should revise the Exclusivity Draft Guidance to confirm that a reference biological product licensed through a subsequent application filed by the same sponsor of an already-licensed product (or a licensor, predecessor in interest, or other related entity), licensure of which is deemed not to be a date of first licensure under the statute, will be protected by any remaining portion of the 12-year exclusivity period afforded to the first licensure of the prior licensed product.

IV. Comments Regarding FDA's Interpretation of "Licensor, Predecessor in Interest, or Other Related Entity"

Section 351(k)(7)(C) of the PHSA excludes from the date of first licensure the date of approval of certain subsequent applications filed by the same sponsor or a licensor, predecessor in interest, or other related entity. To encourage innovation and new research surrounding biological products, BIO strongly urges FDA to adopt a narrow interpretation of this limitation. In particular, we recommend that FDA's inquiry center on whether, solely by virtue of a particular upstream corporate relationship, a subsequent applicant will be able to shorten its development program by relying on data contained in the relevant prior application. Such an approach would effectuate the purpose of the exclusivity provision, which is to encourage the massive research and development effort associated with bringing innovative biological products to market, while not rewarding applicants for making changes to their previously approved products that do not also result in a change to the product's safety, purity, or potency.

If the agency requires a full pre-clinical and clinical development program, and expressly prohibits a sponsor from referencing or relying to any meaningful extent on a prior approval, then the application should not be considered a "subsequent" application, and

¹ Under FDA's existing drug "umbrella policy," the five-year exclusivity period for a new chemical entity applies not only to the first approved drug product containing no previously approved active moiety, but also applies, with some limited exceptions, to "any other drug product developed that contains the same new chemical active moiety as in the first drug product and that is approved during the 5-year period." FDA, *Draft Guidance for Industry: New Chemical Entity Exclusivity Determinations for Certain Fixed-Combination Drug Products* (February 2014). FDA has explained that such subsequent drug products are protected for the balance of the 5-year period, which runs from the date of approval of the first approved drug product.



therefore an assessment of the corporate ownership or lineage should be unnecessary under the statute. In such circumstances, any licensor, predecessor -in-interest, or other relationship with a prior sponsor is substantively meaningless and should not be the sort of relationship that disqualifies a company from the 12-year reference product exclusivity under PHSA section 351(k)(7)(C).

In the Draft Guidance, FDA states that it intends to interpret the term “predecessor in interest” as it does in the context of 3-year new drug product exclusivity, thus including within the definition any entity that the sponsor has taken over, merged with, or purchased, that has granted the sponsor rights to market the biological product under the 351(a) application, or that had exclusive rights to the data underlying that application. We request that the agency provide guidance on the impact of the timing of merger or other such activities relative to product licensure for purposes of corporate relationship analysis and first licensure determination. In particular, given the purpose of the statutory provision, the guidance should be clarified so that, at the very least, changes to corporate relationships that occur following the submission of a subsequent application do not impact any first licensure determination. This clarification is critical given that FDA has not indicated whether such a determination would in fact be made upon BLA approval or instead might not be made for years after such approval. In addition, and consistent with the recommended focus on whether a corporate relationship has provided the subsequent applicant with the ability to shorten its development program, changes to corporate relationships that occur after a clinical program is complete also should not impact any first licensure determination.

In addition, in lines 168 to 169 of the Draft Guidance, FDA states that, although the BPCIA does not define “other related entity,” FDA “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.” BIO believes it is clear from the statutory scheme that “related” ties back to the previously licensed product in question and would not encompass other types of unrelated “relationships.” Thus, FDA should instead treat the prior applicant as a “related entity” to the subsequent applicant only if one owns or controls the other, or they are under common ownership and control. Such an ownership and control test is reasonable and entirely consistent with the first-licensure provision, and is consistent with commonly understood concepts of related entities. BIO’s recommended interpretation provides for rational decision making, while appropriately avoiding a time-consuming, complex, and protracted analysis of the nature and implications of corporate structures and relationships and the sort of subjective interpretation and outcomes necessitated by any such analysis. We also note that the BPCIA statutory language is very specific in that certain subsequent BLAs may not get their own exclusivity if they were filed by the same sponsor or by entities *upstream* of the sponsor. The BPCIA refers to licensors and , predecessors in interest, not licensees and successors in interest. The FDA should not write these latter terms into the statute by broadly interpreting the term “related entity” when Congress appears to have spoken directly to this issue.

Further, in the Draft Guidance, FDA explains that one of the factors that it intends to consider in analyzing whether the relationship between parties would result in a finding that they were “other related entities” is “the level of collaboration between the entities during the development program.” We believe that FDA’s consideration of the level of collaboration between entities during development in assessing whether entities are related for purposes of reference product exclusivity is beyond the scope of FDA’s BPCIA authority, and is not consistent with the term “related entities” nor indicative of a corporate familial relationship as required by that term. Such an approach could encompass a wide variety of



far-reaching and exceedingly complex commercial relationships, and would require the Agency to make highly subjective and unpredictable determinations of the level of collaboration. Further, as stated at the outset of our comments, the relevant inquiry as to the collaboration between the parties should be whether the application is a “subsequent” application, and whether the application relies on the data from the prior licensed product. Accordingly, we recommend that the phrase “...level of collaboration between entities during development...” in line 177 of the Draft Guidance be deleted in the final guidance, and we urge FDA to interpret “related entities” narrowly, focusing on ownership and control and not including “commercial collaborations” in its interpretation of “related entities.”

In addition, BIO recommends the following revision for clarity:

- Line 168 - 169 of the Draft Guidance, which currently state that FDA “generally will consider an applicant to be a ‘related entity’ in this context if...” should be revised to read “...to be ‘a related entity’ in the context of a specific 351(a) application if ...”

IV. Comments Regarding Modifications to Reference Biological Products

A. Molecular Targets and Mechanisms of Action

In the Draft Guidance, FDA presents a proposed hierarchical approach for a sponsor to determine if a product filed under section 351(a) of the Public Health Service Act (“PHSA”) is a structurally modified version of the same or another section 351(a) product previously licensed to the same sponsor or a licensor, predecessor in interest, or related entity. This hierarchy rests on the presumption that a product may be “structurally modified” as opposed to “an independently developed biologic” simply by virtue of the fact that the subsequent product engages the “same molecular target.”² BIO believes that this broad categorization on the basis of the molecular target goes beyond a plain reading of the statute and risks inappropriately sweeping into its scope products that are not, in any sense of the words, “structurally modified” versions of a prior 351(a) product.

FDA’s proposed approach places an undue burden on the developer of an innovator biological product to conduct a far-reaching exercise to “make its case” for a grant of exclusivity even in the case of a completely unrelated molecular structure with independently developed clinical evidence of safety and efficacy. Moreover, the potential consequences of FDA’s approach raises the possibility that the innovation required to develop that subsequent 351(a) product - with a different molecular structure and independently developed clinical evidence of safety and efficacy - could go unrewarded. Instead, that innovation would be precluded from an exclusivity grant simply by virtue of the fact that its development was supported, in part, by intellectual property relating to a given mechanism of action or molecular structure. This intellectual property need not even be exclusively licensed to the sponsor of the subsequent product, as FDA has defined a “licensor” as “any entity that has granted the sponsor a license to market the biological product, regardless of whether such license is exclusive.”³

² There are multiple examples of products that engage the same molecular target as a previously licensed product, but yet are newly developed products, such as in the case of an antibody-drug conjugate which should be presumed to be a new molecular entity for exclusivity purposes.

³ Nor does the relationship between such licensors and licensees necessarily involve development partnerships or other commercial collaboration. For example, competing manufacturers of independently developed biologic drugs may enter into licensing (or cross-licensing) relationships as a result of patent litigation. Or a developer of an investigational product may obtain a non-exclusive license from a patentee solely to have freedom to operate in

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This construction also changes the burden of proof from a showing that a *derivative* product *is* structurally modified (before further considerations are applied) to a showing for *any* product using the same mechanism of action that there is a clinically meaningful change in safety, purity, or potency. In other words, while Congress intended to exclude common changes to the drug product composition before applying the “purity, potency, safety” criteria to a selected set of structurally modified products, FDA’s interpretation could be read to apply stringent comparative clinical or non-clinical criteria to a much broader set of products.

The burden of proof to meet FDA’s expectations for the clinical criteria is not trivial, and FDA should strive to minimize the impact of this burden on the commercialization of novel biologics. For example, FDA must consider the impact on development of subsequent biologics for new clinical indications that share the same molecular target with a previously licensed biologic used for an unrelated indication. One interpretation of the draft guidance is that a sponsor seeking to develop a subsequent biologic with exclusivity protection might be compelled to demonstrate clinical superiority to the original biologic, but in a clinical setting that is not the intended (or approved) indication for one or the other of the biologics. Such a requirement would be costly, risky, and ethically questionable, and could very well suppress incentives to develop novel and clinically beneficial products.

If Congress had intended to permit exclusivity for only one biologic product derived from intellectual property related to a given *mechanism of action*, this provision would have been included in the statute. Instead, Congress referred to “*structurally modified*” biologics. The definition of “structurally modified” cannot be taken to include the entire possible universe of biologic products that engage the same mechanism of action. There must be some finite bounds on the meaning of “structurally modified” and it should be based on a structure *derived from* the molecular structure of a prior 351(a) product. To implement Congressional intent, FDA should therefore define the boundaries of “modification” without defaulting to the mechanism of action as the common denominator.

Moreover, the Draft Guidance appears to presume that therapeutic molecules operate only on one molecular target, and thus the guidance does not address the first licensure determination process for modifications of biological products that operate on two molecular targets (e.g., antibody-drug conjugates, bispecific antibodies). At a minimum, the covalent attachment of two active moieties should be presumed to be a new molecule for the purposes of data exclusivity, and the final guidance should reflect that determination. To address such molecules, BIO suggests that FDA revise lines 235-239 of the Draft Guidance as follows (new language underlined): “...previously licensed product. Molecules that are bispecific and/or affect multiple molecular targets (e.g., in the case of antibody-drug conjugates) will be presumed to be new molecules for the purposes of data exclusivity unless an existing licensed product already affects those same molecular targets. In the latter case, FDA will consider if the relative effect on each molecular target is altered from the existing licensed product when considering if the new product is eligible for data exclusivity. If a sponsor can provide...”

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the independent development and commercialization of its product. FDA should make clear that such arms-length licensing transactions do not disqualify BLA sponsors from obtaining reference product exclusivity.



B. Evidentiary Standard for Showing that a Modification Results in a Change in Safety, Purity, or Potency

The Draft Guidance places undue burden on the reference drug sponsor to show whether modifications to the structure of a biological product “result in a change in safety, purity, or potency.” In the Draft Guidance, FDA explains that the determination will be made case-by-case based on data submitted by sponsors and recommends that sponsors provide supporting information that includes “measurable effects (typically demonstrated in preclinical or clinical studies...) clearly describing how the modification resulted in a change in safety, purity, or potency compared to the previously licensed product.” FDA further explains that 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. The Draft Guidance also suggests that FDA would factor in evidence of superiority or benefit and require proof that the structural changes are responsible for the increased benefit.

In cases where a modified product affects the same molecular target, the guidance seems to suggest that FDA has set a high evidentiary standard for sponsors to meet in order for licensure of the modified product to be considered the date of first licensure, including possibly requiring clinical efficacy data that conclusively show that the structural changes have caused changes in the safety, purity, or potency of the product. First, there is great uncertainty among BIO members how one would ever be able to demonstrate conclusively differences in safety, purity, or potency in an apples-to-oranges comparison between biological products that are structurally different and that were developed for different indications, have different strengths and dosage forms, or use different delivery systems. Moreover, as FDA is aware, it is generally understood to be difficult, if not impossible, for biological product sponsors to demonstrate conclusively the causal relationship between structural differences and clinical differences. Demonstrating that a product is different in some aspect of safety, purity, or potency is not the same as demonstrating a causal connection between a structural modification and a change in safety, purity, or potency.

Furthermore, BIO believes that requiring such data is not in accordance with the relevant BPCIA provisions. Consequently, we urge FDA to make clear that it does not interpret the BPCIA as requiring sponsors to provide clinical evidence on the effects of the structural change or as requiring direct clinical comparative data between the two products. The final guidance should also make clear that the BPCIA does not require that sponsors provide “substantial evidence” of the change in safety, purity, or potency, nor should the agency require any kind of clinical evidence or head-to-head studies, as such studies could very well be impossible and possibly unethical to conduct. Rather, in this situation, we recommend that FDA adopt a scientifically plausible hypothesis standard, where evidence of product impact from a structural change, supported by published literature or pre-clinical data, would suffice.

Accordingly, BIO recommends that lines 221-224 be revised to state: “Evidence that a structural change to a previously licensed product resulted in change in safety, purity or potency should have a sound scientific basis, for instance as described in the published literature analysis(es) of preclinical data, and may include the sponsor’s explanation of why it believes the change may provide a therapeutic advantage or other benefit. Sponsors are not required to provide data meeting the ‘substantial evidence’ standard in this regard.”



C. Additional Comments

BIO provides the following additional comments regarding FDA's recommendations about product modifications and first licensure determinations:

1. In the Draft Guidance, FDA explains that historically it has interpreted the term "potency" in the context of the PHSA as being synonymous to clinical "effectiveness," and clarifies that evidence of a change in "safety, purity, or potency" may include evidence of a "meaningful benefit to public health such as a therapeutic advantage." It is unclear from this construction how the agency would treat an improvement in dosing schedule. FDA should clarify whether it would consider a significant improvement in dosing schedule related to structural modifications that improve specific potency and/or bioavailability of a biologic, to be a change in "potency." For instance, practitioners and patients may consider it to be a therapeutic advantage to reduce biologic injections from several times a week to once every two weeks, even if there is otherwise no evidence of superior clinical outcomes relative to a frequently injected biologic. Structural modifications supporting such advances in dose efficiency are not trivial "reformulations" of an existing product, must take into consideration the potential impact of the modifications to product safety and immunogenicity, and will require full evidence of safety and efficacy. Innovations that provide such a clear therapeutic advantage for patients and providers should be considered within the scope of a change in "purity, potency, or safety."
2. A more detailed explanation of how the agency interprets the term potency for purposes of the BPCIA provisions also is important in other respects. The Draft Guidance does not provide a formal definition for the term "potency." The term "potency" could be interpreted as referring to measurements in molar (e.g., nM) methods or in mass-based methods. If the latter reading, a change in molecular mass (e.g., amino acid substitutions, additions or deletions, or glycosylation changes) could be considered a change in the potency between a licensed product and a product licensed through a supplement or subsequent application. Thus, FDA should define the term potency or provide additional clarification on how it interprets potency in this context.
3. The BPCIA excludes from the date of first licensure the dates of approval of those modifications to the structure of certain previously licensed reference product that do not "result in a change in safety, purity, or potency." As discussed above, in the Draft Guidance, FDA proposes to make a determination of whether a structural modification results in a change in safety, purity, or potency based on information provided by the sponsor, which FDA states should include "measurable effects" describing how the modification resulted in such a change. FDA states that it will presume this requirement is met "if the sponsor of the proposed product demonstrates that it affects a different molecular target than the original product." We ask that the agency provide greater guidance on the information that a sponsor must provide for FDA to sustain the presumption that the requirement has been met. We also ask that the agency explain how it will determine whether a modification has resulted in a change to safety, purity, or efficacy in cases where the sponsor does not provide information that demonstrates that the product affects a different molecular target than the original.
4. In lines 135-136 of the Draft Guidance, FDA states that "if a sponsor cannot adequately characterize the biological product, FDA recommends that the sponsor



consult FDA for additional guidance.” We recommend that FDA delete this statement altogether or provide clarification in the final guidance on the additional information that could qualify the sponsor for exclusivity in lieu of full characterization.

5. In lines 198-201 of the Draft Guidance, FDA states that “[i]n 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.” Thus, FDA appears to be defining “structural modifications” to exist when there are common “structural features” and the “same molecular target.” FDA’s description fails to capture adequately the scope of “structural features,” given that there exists a spectrum of taxonomic relationships among protein structures, ranging from secondary structures shared by practically all proteins (e.g., alpha helix), common domain motifs shared by many biotherapeutics (e.g., IgG1 Fc domain), and then very specific structural motifs involved with a given mechanism of action. Consequently, FDA should provide further clarification of the definition of “structural features” and should explain that “structural features” are more specific than common protein secondary structural motifs or common domains.

BIO supports FDA’s inclusion of a broad category of potential structural modifications that might qualify for first licensure, provided the other statutory criteria are met. It is important to acknowledge that engineered sequence modifications or post-translational modifications could result in changes to safety or efficacy of a biologic that may merit independent exclusivity. That said, consistent with the plain language of the statute, any change in safety, purity, or potency should qualify the new product for 12 years of exclusivity. The exclusivity grant provides an important incentive for research and development. It achieves the sought-after balance between encouraging innovation while at the same time facilitating competition. Notably, therefore, the BPCIA does not require a demonstration of clinical superiority or benefit, and Congress did qualify the word “change” with any subjective adjective (such as “substantial” or “meaningful”).

V. Comments Regarding FDA’s Recommendations for Information that Section 351(a) Applicants Should Provide to the Agency

In the Exclusivity Draft Guidance, FDA sets forth the type of information that it suggests sponsors provide to the agency in support of a first licensure determination. Consistent with our comments on the Draft Guidance overall, we believe these recommendations place a tremendous and unnecessary burden on sponsors of innovator programs, and in particular the suggestion that the information should (a) be supplied as part of every application, and (b) include information outside of the sponsor’s possession or control. Accordingly, as noted in Section II of our comments above, we believe the sponsor should only be requested to provide such information in instances in which FDA has determined the application is a “subsequent application” and thus necessitates further inquiry.

Assuming that a sponsor’s application has been determined in fact to be a “subsequent application,” we believe that much of the information that FDA recommends sponsors provide to the agency is information that FDA already will have in its possession, or information that is unnecessary to make a determination of exclusivity. In general, we recommend that the agency revise the suggested information list in the Draft Guidance to include only information that is necessary to make a first licensure determination and that would not already be in the possession of the agency.



In addition, as a preliminary matter, given that the four-step assessment set forth in the Draft Guidance is appropriately stepwise, FDA should state explicitly that later items on the list need not be provided if a preceding item demonstrates that the product in question is eligible for its own period of regulatory exclusivity. Accordingly, we suggest that FDA revise the Draft Guidance starting at line 268 to read as follows “...FDA suggests that sponsors provide the following information (the information below can be regarded as logically stepwise, so that a sponsor does not have to provide subsequent information once it has demonstrated eligibility for exclusivity at an earlier step):”

The first item that FDA recommends sponsors provide for a first licensure determination is “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.” The exclusivity limitation at section 351(k)(7)(C)(ii) of the BPCIA provides only that the 12-year exclusivity period will not apply to certain subsequent applications filed by the same sponsor of the biological product that is the reference biological product or by a licensor, predecessor in interest, or other related entity. The provision does not impose limitations on subsequent applications filed by entities that are not related to the sponsor of an already-approved and structurally related product. Accordingly, FDA’s request should be limited in scope to the identification of only those structurally related products for which the sponsor or a related entity holds the BLA. Recommending that sponsors identify all licensed products that are structurally related to the reference product is unnecessarily burdensome, as those products for which the BLA was submitted by an entity other than the sponsor or a related entity have absolutely no bearing on the date of first licensure determination. Since such information is already covered by FDA’s proposed second step in the process, we urge FDA to remove this first step altogether, meaning that the current second step would become the first step. If FDA determines for some reason that such a deletion would compromise the process, we request that the agency both provide its rationale for such a determination given the clear language of the statute to the contrary, and revise this statement to read, at most, that a sponsor should provide a list of structurally related products “of which the sponsor may reasonably be aware.”

FDA also should confirm that, consistent with the statute, if it is determined later that a sponsor inadvertently failed to include one or more structurally related products in the list submitted to FDA, the sponsor has not waived the product’s eligibility for the exclusivity period; rather, the exclusivity period may only be at risk if the information itself would render the product ineligible for the full exclusivity period. In addition, we note that in suggesting sponsors provide a list of all structurally related biological products, FDA suggests that the list may be limited to products that “affect the same molecular target.” FDA cites, in a footnote, the orphan drug regulations definition at 21 C.F.R. 316.3(b)(13) of “same drug” as an example for assistance in defining these products. In light of the recent decision in *Depomed v. U.S. Department of Health and Human Services* and its significant impact on FDA policy in this area, FDA should eliminate the reference to the orphan drug definition of “same drug” in the final guidance.⁴

The second piece of information that FDA recommends sponsors provide to the agency is a list identifying the subset of the structurally related products for which the sponsor or one of its affiliates, including any licensors, predecessors in interest, or related entities, is the

⁴ *Depomed v. U.S. Department of Health and Human Services*, No. 12-CV-1592, 2014 WL 4457225 (D.D.C. September 5, 2014).



current or previous license holder. BIO recommends that the final guidance make clear that if the sponsor concludes that there are no such products, then the sponsor is not required to submit any additional information, and the sponsor's product will receive the 12-year exclusivity unless the agency affirmatively determines otherwise.

We also recommend, as described in detail in Section IV of these comments, that FDA should not require a showing of "substantial evidence" for purposes of demonstrating that there has been a change in safety, purity, or potency between a prior-licensed product and the product that is the subject of a subsequent application by the same sponsor or related entity. We urge the agency to adopt a standard consistent with the statutory framework.

VI. "Purple Book": Lists of Licensed Biological Products with Reference Product Exclusivity and Biosimilarity or Interchangeable Evaluations

On September 9, 2014, FDA announced the release of the "Purple Book," FDA's first published list of licensed biological products, including any biosimilar and interchangeable biological products. BIO notes that the list was published without prior or present opportunity for public comment, and was not in any way mandated or suggested by the statutory language of the BPCIA. Because the subject matter of the Purple Book is largely the same as the Draft Guidance (exclusivity of licensed biological products), BIO here provides initial comments on the format and contents of the Purple Book, while reserving the right for BIO and its members to provide additional feedback to FDA, particularly as BIO members and other interested stakeholders continue to review and contemplate the contents and format.

Specifically, BIO notes that in the Purple Book, biological products are listed by name only, without inclusion of indication(s) or conditions of use. BIO is concerned that, without reference to the approved indication(s) for the licensed biological product, there could be the implication that a listed biosimilar for that product is approved for all of the same conditions of use in the reference product labeling. This may not necessarily be the case, as it may be possible for the biosimilar product to be approved for some but not all of the reference product's indicated uses.

In addition, in the background page on its website, FDA states its intention to update the list periodically, "[a]s resources permit."⁵ BIO appreciates FDA's intention to update the list upon product licensure, or first licensure determinations, and greatly appreciates the resource challenges that the Agency faces generally. BIO is concerned, however, that the utility and reliability of the Purple Book will be greatly undercut if stakeholders and the public cannot rely on the Purple Book's contents to be up to date and reflective of the actual licensure status of biological products. It would be helpful if FDA could explain the resource challenges that could inhibit the Agency from updating the list timely once the product licensure or interchangeability determinations have been completed. In the alternative, FDA should either commit to, or provide an approximation of, a timeline by which stakeholders and the public can expect the list to be updated after a licensure or interchangeability determination.

⁵ "As resources permit, these lists will be updated periodically when FDA licenses a biological product under section 351(a) or section 351(k) of the PHS Act and/or makes a determination regarding date of first licensure for a biological product licensed under section 351(a) of the PHS Act." See <http://www.fda.gov/Drugs/DevelopmentApprovalProcess/HowDrugsareDevelopedandApproved/ApprovalApplications/TherapeuticBiologicApplications/Biosimilars/ucm411424.htm>



Last, as noted above, BIO believes that interested stakeholders should have been (and still should be) provided the opportunity to submit input and feedback to FDA on the content and format of the Purple Book. Stakeholder feedback will be important to enable FDA to create a workable and reliable information repository and notice mechanism for all interested parties. Further, solicitation of such feedback may in fact be required. In particular, the Purple Book may be a guidance document that is subject to the notice and comment requirements set forth in FDA's Good Guidance Practices ("GGPs") regulations.⁶ By publishing final decisions regarding exclusivity, biosimilarity, and interchangeability in the Purple Book without issuing formal guidance on the framework for making those determinations, FDA is essentially using the Purple Book as a guidance document that provides information on FDA's interpretation of the BPCIA and its expectations as to the standards for biosimilarity and interchangeability. Moreover, as the Purple Book is populated with information about 351(k) approvals, state agencies and other entities will view the biosimilarity and/or interchangeability information in the Purple Book as interpretations of FDA's policy, and will likely seek to rely on the Purple Book in issuing regulations and making formulary coverage decisions. Last, BIO notes that section 701(h)(1)(D) of the FDCA requires that FDA ensure public participation when setting forth initial interpretations of a statute or regulation, complex scientific issues, or highly controversial issues.

Thus, because the Purple Book will function to communicate FDA's expectations and interpretation of the BPCIA, we urge FDA to open a formal docket to allow interested stakeholders to submit formal comments regarding the release of the Purple Book. However, as noted, should FDA not open a formal docket, we still urge the Agency to solicit input from, or work with, interested stakeholders on the Purple Book's content and format.

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,

/s/

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⁶ FDA regulations define guidance documents as documents "that describe the agency's interpretation of or policy on a regulatory issue." 21 C.F.R. 10.115(b). As set forth in its GGP regulations, FDA may not use "documents or other means of communication that are excluded from the definition of guidance document to informally communicate new or different regulatory expectations to a broad public audience for the first time," and must follow GGPs whenever regulatory expectations that are not readily apparent from the statute or regulations are first communicated to a broad public audience.