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April 16, 2012

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

Re: Docket No. FDA–2011-D-0611: Draft Guidance for Industry on Biosimilars: Questions and Answers Regarding Implementation of the Biologics Price Competition and Innovation Act of 2009

Dear Sir/Madam:

The Biotechnology Industry Organization (BIO) thanks the Food and Drug Administration (FDA) for the opportunity to submit comments on the *Draft Guidance for Industry on Biosimilars: Questions and Answers Regarding Implementation of the Biologics Price Competition and Innovation Act of 2009 (February 2012)* (“Q&A Draft Guidance”).

BIO represents more than 1,100 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Act of 2009 (BPCIA) is of significant importance to BIO members, and we commend FDA’s efforts in developing the Q&A Draft Guidance to illustrate the Agency’s current thinking on certain aspects of the biosimilars approval pathway. BIO has previously commented on biosimilars issues, and appreciates FDA’s consideration of our comments.¹ We are pleased to provide the following comments on the Q&A Draft Guidance and provide recommendations on additional topics for consideration in future guidance.

¹ BIO Comments on the Food and Drug Administration Pathway for Biosimilar and Interchangeable Biological Products, December 23, 2010, <http://www.bio.org/sites/default/files/20101223.pdf>

Q.I.4. Can a proposed biosimilar product have a delivery device or container closure system that is different from its reference product?

Manufacturing and quality aspects are critical components of a biosimilarity assessment that need to be assessed in relation to what knowledge lies in the public domain concerning the reference product, such as the formulation excipients, equipment, the raw materials used in the manufacturing process for the active ingredient, the container closure system and the cold chain distribution system. A difference in any one of these can potentially have a significant impact upon safety or efficacy of the biosimilar product. BIO urges FDA to exercise caution with respect to different delivery devices and closure systems and to require that biosimilar Sponsors affirmatively demonstrate that any design differences do not result in a clinically meaningful difference between the biosimilar and reference product. Further, if a biosimilar is deemed to be interchangeable, it is expected that the product would have an equivalent delivery device and container closure system to those of the reference product to ensure continuity in care and minimize the possibility of medication errors if a patient switches therapies.

Q.I.5. Can an applicant obtain licensure of a proposed biosimilar product for fewer than all routes of administration for which an injectable reference product is licensed?

Q.I.6. Can an applicant obtain licensure of a proposed biosimilar product for fewer than all presentations (e.g., strengths or delivery device or container closure systems) for which a reference product is licensed?

Q.I.7. Can an applicant obtain licensure of a proposed biosimilar product for fewer than all conditions of use for which the reference product is licensed?

Questions I.5, I.6, and I.7 address whether a biosimilar applicant can obtain licensure for a subset of what the reference product is licensed for—in terms of fewer than all routes of administration, fewer than all presentations, and fewer than all conditions of use. FDA’s proposed responses to each of these questions describe the circumstances in which such approvals may be obtained, and describe the types of data that may be necessary to support such approvals.

FDA’s proposed answer to question I.5 states that an applicant may obtain licensure of a biosimilar for fewer than all routes of administration of an injectable reference product, provided that there are no clinical meaningful differences in safety, purity or potency. The Q&A Draft Guidance further states that support for such a determination may include information from studies using a route of administration for which licensure is not requested. FDA’s proposed answer to question I.6 states that a biosimilar applicant may seek approval for fewer presentations than the reference is licensed for, *e.g.*, fewer strengths, delivery device(s), or container closure systems. And FDA’s proposed answer to question I.7 states that a biosimilar applicant generally may obtain licensure for fewer than all conditions of use than the reference biological, provided that the 351(k) application includes information demonstrating that the proposed conditions of use have been previously approved for the reference product.

BIO believes that, in addition to addressing the data and information that might support such applications, it is imperative that FDA address the product labeling implications of having biosimilars on the market with significant differences from the reference product. For example, if FDA were to determine that a biosimilar could be licensed for fewer than all routes of administration than an injectable reference product is licensed for, it would be necessary to clearly and prominently identify such differences in the labeling for the biosimilar product to avoid confusion or misuse of the biosimilar.

As stated in BIO's 2010 Comments to FDA, the labeling for a biosimilar should flow from the fundamental premise that biosimilars are not expected or required to be structurally the same as the reference product.² The biosimilar product labeling must clearly identify the differences from the reference product to avoid being misleading to healthcare providers and patients, and to minimize potential safety risks. Clear, prominent labeling is necessary to inform healthcare providers and users of any important distinctions between the licensed uses or characteristics of the products. Further, while off-label prescribing is a permissible practice of medicine, safety issues could arise if the off-label use has a different immunogenicity profile—one which has not been assessed in the biosimilar.³

Additionally, BIO believes that FDA guidance should address whether a product could be licensed as interchangeable with a reference biologic if the biosimilar is licensed for fewer routes of administration, presentations, or conditions of use than the reference product. We believe an interchangeability determination in that case would present safety risks. Among other concerns, users would likely presume a product to be interchangeable for all routes of administration, presentations, and conditions of use of the reference product. Further, as stated in BIO's 2010 Comments, given the strictness of the legal standard that applies to interchangeability, "the same clinical result...in any given patient," clinical data must be provided for each labeled indication.⁴ Extrapolation of indications may be acceptable for determination of biosimilarity if the mechanism of action is very well understood and is the same for those indications. However, to be deemed an interchangeable biosimilar, the same efficacy and safety should be shown in clinical trials in each of the indications included in the reference product labeling. It may not always be necessary, however, to have a chronic switching study for each indication.

Finally, the Q&A Draft Guidance does not address the circumstance in which a reference biologic Sponsor obtains approval of a new indication after a biosimilar has been approved. BIO requests that FDA guidance address this issue, including what nature and extent of supplements to a 351(k) will be allowed (*i.e.*, post approval indications for which the reference product is licensed) and the contents of a supplement to a 351(k) application seeking approval of the new indication or other modification.

² BIO 2010 Comments at p. 18.

³ See further discussion of labeling in BIO's comments to FDA's "Draft Guidance for Industry on Scientific Considerations in Demonstrating Biosimilarity to a Reference Product" (Draft Scientific Guidance), p. 12, recommending that labeling should be addressed comprehensively in separate guidance.

⁴ See BIO 2010 Comments at p. 15, discussing evaluation of patient outlier results and assessment of post-marketing data from patient registries, pharmacovigilance surveillance, and other sources.

Q.I.8. Can a Sponsor use comparative animal or clinical data with a non-U.S.-licensed product to support a demonstration that the proposed product is biosimilar to the reference product?

FDA's Q&A Draft Guidance sets forth a number of proposed regulatory and scientific factors to be considered in determining when and whether data comparing a prospective biosimilar to a non-U.S.-licensed comparator product may be useful in supporting a 351(k) application. BIO appreciates FDA's recognition of a number of the factors proposed in BIO's 2010 Comments, as they are reflected in the Q&A Draft Guidance. However, the use of foreign comparative data in a biosimilar application raises fundamental concerns from both a legal and scientific perspective.

First, the BPCIA explicitly states that a biosimilar product must be evaluated against only one reference product, and that the reference product must be licensed under section 351(a) of the Public Health Service Act (PHSA).⁵ Thus, there is a statutory constraint against reliance on a foreign reference product for approval of a biosimilar.

From a scientific perspective, a biosimilar applicant faces a high hurdle in seeking to establish the scientific bridge necessary to demonstrate that the data are relevant and supportive. If bridging data demonstrates that the foreign comparator is fully representative of the U.S.-licensed reference, such data may be supportive of biosimilarity.

Factors we believe are critical in considering the use of foreign comparative data are highlighted here and discussed in more detail below:

- The BPCIA mandates that the biosimilar product be evaluated only against one reference product, which itself is licensed under 351(a);⁶
- Data from a foreign comparator product may only be used to support an application when both the foreign and domestic product are released by the same license holder/manufacturer;
- Introducing a second comparator product (in addition to the U.S.-licensed reference product) raises additional scientific questions and necessitates that a highly cautious approach be taken when accepting data from comparative studies using product that may differ from the U.S.-licensed reference product;⁷
- The fundamental support for a biosimilar must include at least one adequate and well-controlled clinical trial comparing the immunogenicity profiles of the proposed biosimilar and the U.S.-licensed reference product;

⁵ The statute states that “[a] biological product, in an application submitted under this subsection, may not be evaluated against more than 1 reference product” and “reference product is defined as “the single biological product licensed under subsection (a) against which a biological product is evaluated in an application submitted under subsection (k).” Sections 351(k)(5)(A) and 351(i)(4) of the PHSA.

⁶See BIO 2010 Comments at p. 19.

⁷See BIO 2010 Comments at p. 19.

- Additional clarity is warranted to describe fully the type of bridging studies (and associated confidence intervals) that could support biosimilar approval, and the scientific bridge should generally include all of the bridging information listed in the Q&A Draft Guidance and the “Draft Guidance for Industry on Quality Considerations in Demonstrating Biosimilarity to a Reference Protein product (“Draft Quality Guidance”);
- FDA should address scenarios where comparator data and bridging studies would not be sufficient to support licensure of a biosimilar, or where additional bridging information would presumptively be required, *e.g.*, where the non-U.S. comparator product has a different strength, dosage form, or route of administration;
- Use of non-U.S. comparator data generally would not be appropriate for particularly complex biological products; and
- The confidential nature of manufacturing facility information must be recognized.

FDA’s Q&A Draft Guidance also should recognize the challenges inherent in use of data comparing a prospective biosimilar to a foreign version of a U.S.-licensed product that is made by a company other than the holder of the U.S.-licensed product, including potential differences in: the structure or purity of the product, manufacturing or raw materials, formulation, filling, packaging, processing or handling, manufacturing and quality control standards, and physical characteristics, such as packaging or presentation – all of which could have clinical implications for patients treated with the product. Comparative trials involving foreign products made by companies that do not also hold the U.S. license should not be accepted by FDA, as it would be very unlikely that such products would be manufactured using the same procedures, materials and quality controls.

In addition, the Q&A Draft Guidance states that if a Sponsor seeks to use animal or clinical data comparing its proposed biosimilar product to a non-U.S.-licensed product, “the sponsor *should* provide adequate data or information to scientifically justify the relevance of these comparative data to an assessment of biosimilarity and to establish an acceptable bridge to the U.S.-licensed reference product.”⁸ BIO believes that the data needed to scientifically justify relevance of comparative data from a non-U.S.-licensed product and to establish an acceptable bridge to the U.S.-licensed reference product is critical to determining whether such data may be used, in part, to support a demonstration of biosimilarity. The Agency’s use of the word “should,” with regard to the need for these data, does not convey how critical these data are. In other parts of the guidances, FDA uses phrases such as “is expected to,” “will need to,” “FDA recommends,” or “are fundamental components” to convey clearer expectations for certain data and information. Accordingly, BIO proposes that the Q&A Draft Guidance state:

⁸Q&A Draft Guidance at p. 7 (*emphasis added*).

“If a sponsor seeks to use data from an animal study or a clinical study comparing its proposed biosimilar product to a non-U.S.-licensed product to address, in part, the requirements under section 351(k)(2)(A) of the PHS Act, the sponsor, as a scientific matter, generally would be expected to provide adequate data or information to scientifically justify the relevance of these comparative data to an assessment of biosimilarity and to establish an acceptable bridge to the U.S.-licensed reference product.”

The Q&A Draft Guidance also states:

“[t]he type of bridging data needed likely would include a clinical PK and/or PD study conducted with the U.S.-licensed reference product.”⁹

Similarly, FDA’s Draft Scientific Guidance states that “under certain circumstances, a Sponsor may seek to use data derived from animal or clinical studies comparing a proposed product with a non-U.S.-licensed product,” and in such cases, a Sponsor “should provide adequate data or information to scientifically justify the relevance of this comparative data to an assessment of biosimilarity and to establish an acceptable bridge to the U.S.-licensed reference product.”¹⁰

With respect to these references in the Q&A Draft Guidance, BIO requests that FDA further discuss in the Guidance(s) what may be acceptable for referencing a non-U.S.-licensed product and the type of bridging studies that might be considered sufficient, including a specific example of what data might be accepted and which circumstances would permit such use.

In discussing use of non-U.S.-licensed comparator product data, FDA’s Q&A Draft Guidance sets forth several issues Sponsors may need to address, including:

“the relationship between the license holder for the non-U.S.-licensed product and BLA holder for the U.S.-licensed reference product, including whether the non-U.S.-licensed product, and/or any components thereof, are manufactured in the same facility(ies) as the U.S.-licensed reference product during the relevant time period,”¹¹

This point indicates that, in assessing biosimilarity, FDA will consider whether a foreign comparator product is manufactured at the same site as a reference product. BIO believes that FDA must also consider the good manufacturing practices (GMP) compliance status of the site. We suggest adding language regarding the status as a registered multi-product biologics facility with a good compliance history, rather than just being manufactured in the same facility. Further, as set forth in BIO’s 2010 comments, even if the same manufacturing facility is used, FDA must consider¹²:

⁹Q&A Draft Guidance at p.7.

¹⁰Draft Scientific Guidance at p. 6, referencing ICH Guidance E5 “Ethnic Factors in the Acceptability of Foreign Clinical Data.”

¹¹Q&A Draft Guidance at p.7.

¹²BIO 2010 Comments at p. 20.

- The foreign comparator product and the FDA-approved reference product were manufactured in facilities licensed and inspected by the ICH regions (U.S., Europe, Australia, Canada, or Japan) in accordance with current GMPs.
- Preferably, the drug substance for reference and comparator products should be manufactured in the same U.S.-registered facilities (as shown by available information).
- Analytical data, and if necessary bioequivalence data, show that the foreign comparator product is fully representative of the U.S. reference product.
- The foreign comparator product has the same formulation as the U.S. reference product.
- The foreign comparator product is approved and has been widely marketed for an appropriate length of time in a region that has a regulatory authority comparable in sophistication and expectations to FDA, as well as a pharmacovigilance system at least as robust as those in the United States.

In addition, FDA's proposed response to I.8 raises significant legal issues regarding the protection of trade secret/confidential commercial information. FDA must recognize that information regarding which products are manufactured at which facilities is confidential commercial information. As discussed in BIO's 2010 comments, the BPCIA directs a biosimilar applicant to include public information related to the reference product in its application, and limits FDA's review to the information presented in the biosimilar application.¹³ In many cases this information will not be publicly available because information regarding where a specific U.S.-licensed biological product (or one of its components) is manufactured may be treated as confidential by the BLA holder and therefore by FDA.¹⁴ Accordingly, to the extent that information regarding where the U.S.-licensed reference product is manufactured is not publicly available, a biosimilar applicant cannot rely on — and FDA cannot use — this information in determining whether it is appropriate to rely on studies involving a foreign comparator product.

Q.I.10. How long should Sponsors retain reserve samples of the biological products used in comparative clinical PK and/or PD studies intended to support a 351(k) application?

The Agency proposes that Sponsors of 351(k) applications retain reserve samples of biologic products used in comparative pharmacokinetics ("PK") or pharmacodynamic ("PD") studies in accordance with regulatory requirements applicable to drug applications

¹³ PHSa § 351(k)(2)(A)(iii) and (k)(3).

¹⁴ 21 C.F.R. § 601.51(f) states that production and distribution data and manufacturing methods or process information for biologics are not available for public disclosure unless the data or information have previously been disclosed to the public, relate to a product ingredient that has been abandoned, or no longer represent trade secret or confidential commercial information.

submitted pursuant to the Federal Food Drug and Cosmetic Act (FFDCA.)¹⁵ While BIO agrees with the importance of reserve sample requirements for PK and PD studies for biosimilars, reliance on the rules for sample retention of bioequivalence studies on drugs approved under Section 505(b)(2) or 505(j) may not be appropriate for all biologic products. For example, in many cases there may be issues with the integrity of biologic products stored for as long as five (5) years. BIO suggests that FDA propose rules that specifically apply to sample retention for 351(k) applications, recognizing the unique characteristics of biologic products, including stability issues. In addition, it may be appropriate to limit the number of reserve samples that are needed to test for identity and quality. Given that there are no compendial requirements for most biologics, and that they may not remain stable, testing for purity may not provide any meaningful data to FDA to ensure the integrity of the PK and PD studies, while imposing potentially burdensome retention programs in terms of both number of samples needed and potentially invalid testing. In the interim, biosimilar applicants should be responsible for obtaining FDA acceptance of sample retention plans for PK and PD studies, and FDA should ensure parity across Sponsors in terms of the requirements imposed.

Q.I.11. Can an applicant extrapolate clinical data intended to support a demonstration of biosimilarity in one condition of use to support licensure of the proposed biosimilar product in one or more additional conditions of use for which the reference product is licensed?

See BIO's comments to the Draft Scientific Guidance, page 8.

Q.I.13. What constitutes "publicly-available information" regarding FDA's previous determination that the reference product is safe, pure, and potent to include in a 351(k) application?

FDA's proposed answer states that "publicly-available information" in this context would generally include the types of information found in the "action package" for a BLA, and that FDA intends to post publicly available information regarding FDA's previous BLA approvals to facilitate biosimilar development programs and submission of 351(k) applications. FDA also notes that the publicly available information posted by FDA in this context does not necessarily include all of the information that would otherwise be disclosable in response to a Freedom of Information Act (FOIA) request.

BIO appreciates that FDA is beginning to address the critical issues related to what information may be public and what should be protected as trade secret/confidential commercial information in the context of the review and approval of BLAs and 351(k) applications. However, what FDA addresses in I.13 is just a small part of the many issues raised in this context. As discussed in BIO's 2010 Comments, FDA must take all appropriate and legally required steps to safeguard the confidentiality of innovator applicants' trade secret and confidential commercial information, and to prohibit

¹⁵ See 21 C.F.R. §§320.28 and 320.63, as applicable to new drug application submissions under section 505 of the FFDCA.

inappropriate reliance on such information in conducting 351(k) application reviews.¹⁶ There are several key points:

- FDA's regulations on disclosure of BLA information must be updated for consistency with the BPCIA.
- Confidential commercial and trade secret information in a BLA must be protected from intentional or inadvertent use or disclosure.
- A 351(k) application must stand on its own, and FDA approval of a 351(k) must be based upon data in the 351(k) and publicly-available information regarding the reference BLA.
- Procedures must be adopted to assure proper review of a 351(k), and avoid potential disclosure or reliance upon the reference BLA.

As an initial matter, we again raise the necessity that FDA's existing regulations on disclosure of data and information contained in a BLA be revised to accurately reflect the existence of a biosimilar pathway. FDA's Part 600 regulations on Biological Products currently state that after a BLA license has been issued, certain data and information in a biologics application are "immediately available for public disclosure unless extraordinary circumstances are shown."¹⁷ As stated in BIO's 2010 Comments, this regulation was consistent with earlier views that such data was not competitively sensitive, but in practice, it is our understanding that FDA does not publicly release this information. As a result of the enactment of the BPCIA, this regulation should be revised to provide – as does the corresponding new drug application (NDA) regulation – that only a "summary" of the safety and efficacy data is releasable when the BLA is approved.¹⁸ This would correctly reflect the evolution in science and the creation of a statutory biosimilars pathway. This technical correction is an important part of ensuring adequate protection of proprietary BLA data and information, especially in light of the Agency's comment regarding FOIA noted above.

Further, we are concerned that FDA's proposed answer could be interpreted to mean that the Agency believes the entire action package or additional information (beyond the action package) might be releasable. While FDA is required to post an "action package for approval" on its website, the FFDCIA clearly states that such documents must be redacted to avoid disclosure of any information considered confidential under FOIA.¹⁹ The action package, as statutorily defined, includes: information generated by FDA related to review of the application, a summary review that documents conclusions from all reviewing disciplines about the product, and the Division Director and Office Director's decision documents – information that is likely to, and often does, contain a BLA Sponsor's trade secret and confidential commercial information.²⁰ Federal law

¹⁶ See BIO 2010 Comments at p. 28-32.

¹⁷ 21 C.F.R. Section 601.51(e).

¹⁸ See 21 CFR 314.430(e).

¹⁹ 21 U.S.C. 355(l)(2)(E), citing 5 U.S.C. section 552(b).

²⁰ 21 U.S.C. 355(l)(2)(C).

requires the Agency to redact trade secrets and confidential commercial information from these documents before placing them on the Agency website.²¹

We also emphasize another critical point from BIO's 2010 Comments: the BPCIA does not authorize or permit reliance on non-public information regarding a reference BLA.²² The statute directs FDA to limit its review to the contents of the biosimilar application and to publicly available information about the reference product. It does not authorize FDA to consider or rely on confidential commercial information or trade secrets in the reference product BLA. Nor does the statute authorize FDA to consider or rely on this information when reviewing an investigational new drug application (IND) filed by a biosimilar Sponsor, or when meeting with that Sponsor to discuss a proposed biosimilar development plan. Any reliance on the information in that BLA for the benefit of the biosimilar applicant, even inadvertent and unintentional, would be contrary to the plain language of the statute.

FDA employees bring both scientific and ethical rigor to their work, and it is highly unlikely that an employee would purposefully access an innovator's trade secrets or confidential information directly when considering a biosimilar application. However, there is the potential that knowledge regarding a reference biologic could be inadvertently disclosed to biosimilar applicants in meetings regarding an investigational new drug application (IND) or biosimilar product development meetings.²³ Accordingly, FDA should adopt systems and procedures to prevent even inadvertent use or disclosure of the reference product Sponsor's trade secrets, including assuring that: the primary reviewer of a reference BLA does not participate in biosimilar product development meetings or review a biosimilar application referencing that BLA; FDA employees who review biosimilar applications should not consult with the individuals who primarily reviewed the innovative application; and electronic safeguards be established to ensure that biosimilar application reviewers are not permitted to access the reference product BLA or other Agency documents related to review of the BLA.

Q.I.14. Can an applicant obtain a determination of interchangeability between its proposed product and the reference product in an original 351(k) application?

As discussed in BIO's 2010 Comments, it is important that a number of factors be taken into account when a designation of interchangeability is to be considered, including: complexity of product structure and formulation; degree of structural similarity between the reference molecule and the biosimilar; the mechanism of action, therapeutic index, and safety and immunogenicity profile of the innovator molecule; post-marketing efficacy and safety data with the biosimilar product; overall risk benefit profile; intended

²¹ 21 U.S.C. 355(l)(2)(E).

²² BIO 2010 Comments at p. 29.

²³ Courts have held that unless individuals exposed to an employer's trade secrets have "an uncanny ability to compartmentalize information," when they go to work for a competitor in a similar field, they will inevitably use the former employer's information for the benefit of the new employer. See, *Pepsico, Inc. v. Redmond*, 54 F.3d 1262, 1269 (7th Cir. 1995). The same concern underlying "inevitable disclosure" – namely, the inability of an individual to ignore facts he or she already knows – would apply to FDA reviewers for a reference product if they were to be involved in the review of a biosimilar for that product.

therapeutic area; route of administration and whether the use would be for acute versus chronic treatment; and patient factors such as age, gender, ethnicity, disease state, comorbidities, and concomitant medications.

BIO appreciates FDA's recognition that the approval criteria for interchangeability are substantively different from those for biosimilarity, and that interchangeability is more difficult to achieve. We look forward to the opportunity to comment on proposed guidance on interchangeability.

Q.I.15. Is a pediatric assessment under the Pediatric Research Equity Act (PREA) required for a proposed biosimilar product?

BIO recognizes the importance of studying new drugs and biologics in pediatric populations – children are not “little adults” and the dosing, safety, and efficacy may differ between adults and pediatric populations. The current pediatric research framework has been remarkably successful in generating appropriate prescribing information for children for innovator products. Because biosimilar products are similar, but not identical, to the reference product and do not contain the same active ingredient, the biosimilar product may impact children differently than the reference product. Additionally, biologic products can produce a highly individualized response in patients associated with, or independent of, protein structural and other product characteristics. Therefore, it is appropriate for a biosimilar Sponsor to study the pediatric indication under PREA.

Part II. PROVISIONS RELATED TO REQUIREMENT TO SUBMIT A BLA FOR A “BIOLOGICAL PRODUCT”

Q.II.1. How does FDA interpret the category of “protein (except any chemically synthesized polypeptide)” in the amended definition of “biological product” in section 351(i)(1) of the PHS Act?

All proteins are polypeptides, but not all polypeptides are proteins. The definition as to when a polypeptide becomes a protein has been somewhat arbitrary over the years. For the purposes of the three guidances, FDA provides a regulatory definition of a “protein” as “any alpha amino acid polymer with a specific defined sequence that is greater than 40 amino acids in size.” In BIO's 2010 Comments to FDA, we suggested that “one commonly accepted distinction as to when a polypeptide should be considered a protein is when a polypeptide has stable higher order structure that is integral to its function. Consequently the scientific and technical factors that FDA should consider relates to the assessment of a stable conformational state with higher order structure which when absent renders the product inactive.” While we continue to believe that higher order structures are an important component defining a protein, we are comfortable with the more administratively straightforward definition put forward by FDA based upon amino acid length. However, we recommend that FDA retain flexibility and discretion to determine on a case-by-case basis whether an amino acid polymer with less than 40

amino acids can be considered a protein, particularly if the polymer exhibits a higher order structure or was produced in a biological system.

Furthermore, FDA defines a “chemically synthesized polypeptide” as “any alpha amino acid polymer that (1) is made entirely by chemical synthesis; and (2) is less than 100 amino acids in size.” BIO had previously suggested that “Utilizing the distinction cited in the previous question, the regulatory definition might focus on chemically synthesized polypeptides that do not have stable higher order structure with stable biologic activity. This would then allow chemically synthesized proteins, which would by definition have stable higher order structure that is required for activity, to be regulated as biologics.” However, we find FDA’s proposed definition to be suitable.

Since these definitions are utilized in all three guidances, but more extensively discussed in the Q&A guidance, we encourage FDA to provide a cross-reference in both the Quality and Scientific guidances to this section of the Q&A guidance to ensure consistent use of the terms.

Part III. EXCLUSIVITY

Q.III.1. Can an applicant include in its 351(a) BLA submission a request for reference product exclusivity under section 351(k)(7) of the PHS Act?

FDA’s proposed answer states that an exclusivity request may be included with a Sponsor’s BLA, and “FDA will consider the applicant’s assertions regarding exclusivity.”²⁴ It further states that the Sponsor should include data and information to support its request and describe how the proposed product meets the statutory requirements for exclusivity. BIO appreciates that FDA is beginning to address the critical issues related to innovator exclusivity. However, with regard to exclusivity for new BLA submissions, the statute clearly provides 12-years of exclusivity, which must be presumed unless any of the exclusion criteria are met. Accordingly, FDA should not place a burden on the Sponsor to supply an exclusivity justification for a product that is being licensed for the first time. The exclusivity provisions of the BPCIA speak to exclusion criteria, not inclusion. In contrast, the data and information the Agency proposes that a BLA Sponsor submit in support of an exclusivity determination would be relevant if an application is for a subsequent application to a previously licensed application. As discussed in BIO’s 2010 Comments, the Agency should address the factors to be considered in determining whether a change or modification in a previously-licensed reference biologic would result in a change in safety, purity, or potency, such that a subsequent BLA would be eligible for 12-year exclusivity of its own.

Where such information would properly be submitted, it is important to consider the role such a determination has in product development, particularly for small, emerging companies that must seek financial support and investment to enable clinical trials to be conducted. Accordingly, BIO requests that FDA provide an opportunity for a product Sponsor to request an initial exclusivity response from FDA at a point that is earlier in

²⁴ Q&A Draft Guidance at p. 15.

development than BLA submission. Further, FDA's Q&A Draft Guidance does not address when FDA would respond to a request for exclusivity, perhaps implying that such determination would be made upon BLA approval. It is critical that this evaluation and response – which could be pivotal in drug development decisions – be available earlier in time and provided to a Sponsor promptly.

In addition to describing in guidance when and how a Sponsor may seek an FDA determination (or preliminary determination) of exclusivity, and the timetable for an Agency response, BIO requests that FDA address whether it intends that such responses would be posted publicly or made publicly available, and if so, in what manner would be confidential or proprietary information related thereto be protected.

BIO requests that FDA address these issues promptly and transparently, including a process for public comment on Agency draft proposals.

Part IV. Other Q&A Issues:

A. Patent Certification:

As discussed in BIO's 2010 Comments, the Agency has an important role in assuring that implementation of the biosimilars pathway is achieved in a manner that maintains the balance of interests established in the BPCIA.²⁵ BIO again encourages FDA to take steps to assure full compliance with the BPCIA to maintain the careful balance of interests established in the statute.

The BPCIA grants a reference product Sponsor the right to two stages of premarket patent litigation with a biosimilar applicant: an immediate stage that begins upon the filing of the biosimilar application, and a later stage that begins shortly before the biosimilar is marketed. The key to the entire BPCIA premarket litigation process is the statutory provision stating that the biosimilar applicant "shall" provide its application and manufacturing process information to the reference product Sponsor "[n]ot later than 20 days after the Secretary notifies the [biosimilar] applicant that the application has been accepted for review."²⁶ Although the statute clearly imposes a mandatory duty on biosimilar applicants to provide this information, it has been suggested by some stakeholders that a biosimilar applicant could choose to withhold such information from the reference product Sponsor. If biosimilar applicants are permitted to ignore the unambiguously mandatory language of the statute, the entire patent information exchange process, which is critical to effective premarket patent litigation, falls apart.

BIO encourages FDA to make clear that the patent resolution and information exchange provisions of the BPCIA are not optional, and that the applicants must fully comply with all statutory provisions. FDA could achieve this simply by requiring 351(k) applicants to submit a statement as part of its application, as follows:

²⁵ BIO 2010 Comments at p. 33.

²⁶Section 351(l)(2) of the PHSA.

Pursuant to 42 USC 262(l)(1)(B) and 262(l)(2), not later than 20 days after receiving notice that this application has been accepted for review, I will provide to the reference product sponsor a copy of this application and information that describes the process or processes used to manufacture the product that is the subject of this application.

FDA should adopt a policy providing that it will refuse-to-file (RTF) a biosimilar application that does not contain a certification that the applicant will comply with section 351(l). This proposed RTF policy would help FDA ensure compliance with the requirements of section 351 and give it a sound basis for referral of violations to the Department of Justice, if warranted.²⁷ This ministerial policy would also benefit FDA in terms of increased efficiency in the Agency's use of resources by avoiding review of applications for a product that subsequent to approval would be involved in patent litigation; minimize confusion among healthcare providers and patients resulting from post-approval patent challenges; and help to facilitate Congressional intent that the patent challenge process run in parallel with the FDA review process.

B. Maintaining the Distinction between the (a) and (k) Pathways:

As discussed in BIO's 2010 Comments, FDA must ensure that BPCIA implementation is consistent with the intent of Congress by maintaining the 351(a) and 351(k) pathways as distinct. This means that FDA should not accept applications under 351(a) that explicitly or implicitly seek to reference an innovator product. Moreover, it should be clear that submission of an abbreviated application that silently invites the Agency to leverage its familiarity with a particular innovative molecule is inconsistent with the statutory framework.

FDA should refuse to file applications under 351(a) that should be filed under 351(k).

C. Other Guidance Provisions:

As discussed in BIO's comments to the Draft Scientific and Quality Guidances, BIO encourages FDA to issue additional guidance on the following topics:

- Interchangeability (Q&A Comments, p.11)
- Non-proprietary naming (Scientific Guidance, p. 11)
- Labeling (Scientific Comments, p. 12)
- Sample retention (Q&A Comments, p. 8)
- Quality attributes that shift over time (Quality Comments, p. 2)
- Product specific guidances (Scientific Comments, p. 2)

²⁷ Note that section 351(f) of the PHSA states that any person who violates any provision of section 351, (including therefore any requirements in section 351(l)), "shall be punished upon conviction by a fine not exceeding \$500 or by imprisonment not exceeding one year, or by both such fine and imprisonment, in the discretion of the court."

Part V. Conclusion:

BIO appreciates this opportunity to comment on FDA's "Draft Guidance for Industry on Biosimilars: Questions and Answers Regarding Implementation of the Biologics Price Competition and Innovation Act of 2009." We would be pleased to provide further input or clarification of these comments, as needed.

Sincerely,

/S/

Sandra J.P. Dennis
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