

February 11, 2019

Division of Dockets Management (HFA-305)
Food and Drug Administration
Department of Health and Human Services
5630 Fishers Lane
Room 1061
Rockville, MD 20852

Re: Docket No. FDA-2011-D-0611; AAM Comments on FDA’s Questions and Answers on Biosimilar Development and the BPCI Act (Revision 1) and the New and Revised Draft Q&As on Biosimilar Development and the Biologics Price Competition and Innovation Act (Revision 2)

The Association for Accessible Medicines and the Biosimilars Council (collectively referred to as “AAM”) are pleased to provide comments on the Food and Drug Administration’s (“FDA’s” or the “Agency’s”) Question and Answer guidance documents regarding biosimilar development under the Biologics Price Competition and Innovation Act of 2009 (“BPCIA”).¹ AAM is submitting consolidated comments that address both FDA’s draft guidance entitled *New and Revised Draft Q&As on Biosimilar Development and the BPCI Act* (“Draft Q&A Guidance”) and FDA’s final guidance entitled *Questions and Answers on Biosimilar Development and the BPCI Act* (“Final Q&A Guidance”).

AAM represents the manufacturers and distributors of finished generic pharmaceutical products, manufacturers and distributors of bulk active pharmaceutical chemicals, and suppliers of other goods and services to the generic pharmaceutical industry. Generics represent greater than 90% of all prescriptions dispensed in the U.S. by volume, but only 23% of the cost expended on prescription drugs. AAM is the sole association representing America’s generic pharmaceutical sector in the United States. The Council, a division of AAM, works to ensure a positive regulatory, reimbursement, political and policy environment for biosimilar products, and educates the public and patients about the safety and effectiveness of biosimilars. Areas of biosimilar focus include education, access, the nascent regulatory environment, reimbursement and legal issues. Member organizations include companies and stakeholder organizations working to develop biosimilar products with the intent to participate in the U.S. market.

¹ See 83 Fed. Reg. 63898-902 (Dec. 12, 2018) (Docket No. FDA-2011-D-0611).

AAM appreciates FDA’s effort to bring more clarity and predictability to the development process for biosimilar and interchangeable biological products. To facilitate that goal, AAM’s detailed comments on FDA’s Q&A guidance documents are set forth below.

I. AAM’s Comments

A. Bridging Studies (Q. I.8)²

In the updated Q&A regarding use of a non-U.S.-licensed comparator product in animal or clinical studies to support biosimilarity, FDA recommends that sponsors conduct analytical and clinical bridging studies that directly compare the proposed biosimilar product, the U.S.-licensed reference product, and the non-U.S.-licensed comparator product.³ AAM requests that FDA revise this Q&A to describe the circumstances under which a sponsor could use a non-U.S.-licensed comparator product in animal or clinical studies *without* the need to conduct clinical bridging studies with a U.S.-licensed reference product (“RP”).

Although a 351(k) application ultimately must demonstrate biosimilarity or interchangeability compared to a U.S.-licensed RP, the BPCIA does not mandate how this must be accomplished or require direct comparisons between the proposed biosimilar product and the U.S.-licensed RP. The statute instead grants FDA broad discretion and explicitly states that the Agency may determine, in its discretion, that any specific test is “unnecessary” for purposes of demonstrating biosimilarity.

Recently, FDA has indicated that it is considering allowing 351(k) applicants to use a foreign comparator product in biosimilar development programs without the need to conduct bridging studies. For example, Dr. Gottlieb recently stated that FDA is considering

allowing European products to be used as the reference standard for biosimilar products. So if you’re trying to develop a biosimilar here in the U.S., the question is [whether you] can . . . use the European product rather than the U.S. marketed product as the reference listed product, in cases where we know sometimes that the [U.S. and European] products are manufactured in the same facility, but the knowledge of that might constitute commercial confidential information. So we’re looking at whether or not we can have data sharing agreements in place with our European regulatory authorities and we can use that knowledge to allow biosimilar sponsors to use the European product as the reference listed product.⁴

² FDA’s Questions and Answers on Biosimilar Development and the BPCI Act (Revision 1)

³ Final Q&A Guidance, at 8.

⁴ See, e.g., Remarks from Scott Gottlieb at Politico Pro Summit, at 4:12-5:05 (July 17, 2018), *available at* <https://www.politico.com/video/2018/07/17/170617-fda-full-067139>.

Likewise, in FDA’s July 2018 Biosimilars Action Plan, the Agency stated that it is “exploring the potential for entering into new data sharing agreements with foreign regulators to facilitate the increased use of non-U.S.-licensed comparator products in certain studies to support a biosimilar application.”⁵

While FDA’s thinking about using a global reference comparator is still in its early stages, AAM believes there is merit to this type of proposal because it can be implemented in a manner that (1) is scientifically rigorous; (2) will significantly reduce development costs; and (3) is consistent with the BPCIA. Accordingly, AAM respectfully requests that FDA amend the Q&A to describe when 351(k) applicants can use foreign comparators without the need for clinical bridging studies. Enabling this approach would reduce the development cost for sponsors of biosimilars and interchangeable products, in turn leading to increased patient access to more affordable alternatives to costly reference biologics. AAM’s detailed proposal is set forth below.

As an initial matter, the foreign product must qualify as a “foreign comparator.” To do so, the foreign product must have been authorized by a Stringent Regulatory Authority (“SRA”), *i.e.* by a regulatory authority “in a jurisdiction that has a well-established regulatory framework and principles, as well as considerable experience of evaluation of the biotherapeutic products and post-marketing surveillance activities.”⁶ Accordingly, we propose that the comparator product should be from “a jurisdiction that has formally adopted International Council for Harmonization (ICH) guidelines. This criterion ensures ICH compliant development and manufacturing including that any comparability studies that have been conducted to support manufacturing changes of the reference have been conducted according to an internationally accepted process and standard, and that the reviewing authority is experienced in operating this standard.”⁷

In addition, the comparator product should have been approved according to ICH standards based upon a complete registration dossier. An evaluation report related to the comparator product’s application should ideally be publicly available in the country of origin of the comparator product (*e.g.*, the European Public Assessment Report (“EPAR”) issued by the EMA; the Summary Basis of Approval (“SBA”) issued by the FDA; the Regulatory Summary Decision (“RSD”) issued by Health Canada).

Finally, the comparator product must be fully identifiable by the approved product name, pharmaceutical form and qualitative composition. If the comparator product satisfies these criteria, it can be considered a “foreign comparator” for purposes of biosimilar development.

AAM believes that the bridge between the U.S.-licensed reference product version and the foreign comparator can be established by the applicant in most cases *without* clinical bridging studies if the following criteria are satisfied:

⁵ FDA Biosimilars Action Plan (July 1, 2018), p. 3, *available at* <https://www.fda.gov/downloads/Drugs/DevelopmentApprovalProcess/HowDrugsareDevelopedandApproved/ApprovalApplications/TherapeuticBiologicApplications/Biosimilars/UCM613761.pdf>

⁶ WHO/SBPQ&A/Draft/Dec 2017.

⁷ A “Global Reference” Comparator for biosimilar development – Christopher Webster, Gillian Woollett; BioDrugs- published online: 19 May 2017 <https://bit.ly/2Cn4g3H> (“Webster/Woollett Article”).

- the comparator product must meet the criteria for being a “foreign comparator” described above;
- the foreign comparator must have the same concentration of API as the U.S.-licensed RP;
- the foreign comparator must have the same pharmaceutical form and route of administration as the U.S.-licensed RP;
- the foreign comparator must have the same qualitative composition of excipients as the U.S.-licensed reference product and, if the qualitative compositions of excipients are different, a justification should be provided ensuring that they have been assessed and are not expected to impact clinical efficacy and safety;
- the foreign comparator must have been approved in the foreign jurisdiction based on essentially the same original data package as the U.S.-licensed RP, including clinical safety and effectiveness data (based on data and information in the public domain, such as the EPAR, SBA or RSD); and
- subsequent manufacturing changes for the foreign comparator were regulated according to ICH Q5E principles to ensure that the clinical properties remain unchanged.

AAM believes the above policy regarding clinical bridging studies can be implemented based solely on publicly-available information, such as scientific publications and public clinical trial registries (e.g. ClinicalTrials.gov or the European Clinical Trials Database).

The requirement that the foreign comparator was approved on essentially the same data package is key to addressing the most significant objection – which is that there may be subtle differences between the U.S. and ex-U.S. RP manufacturing that could lead to residual uncertainties of their potential clinical relevance. If essentially the same development data was used to support both approvals (U.S. and ex-U.S.), it is incumbent on the RP sponsor to provide compelling data to support any and all divergence from the material used in the single set of pivotal trials. Effectively, the RP sponsor must provide a bridge to the non-U.S. SRA or FDA from the material used in the pivotal trials to any final approved drug substance or drug product that may diverge in some manner. The data from this bridge establishes that the efficacy and safety of U.S. (and ex-U.S. RP) are unchanged from their common development data and that therefore they are clinically equivalent. This should be adequate to justify use of ex-U.S. RP as a global reference comparator.

The above proposal provides a scientifically rigorous method for providing a bridge between the foreign comparator and the RP without the need for unnecessary and expensive clinical bridging studies. By reducing development costs for 351(k) applicants, the proposal should help spur development of lower-cost, safe and effective biosimilars and interchangeable biological products consistent with the goals of the BPCIA.

Finally, the proposal is consistent with the BPCIA standards for licensure of biosimilars and interchangeable biological products. The statute does not prescribe the specific information required to demonstrate biosimilarity or interchangeability but instead leaves it to FDA’s discretion to determine whether the “information” submitted is “sufficient” on a case-by-case

basis depending upon the specific product in question.⁸ FDA thus has the discretion to determine that information submitted in a 351(k) application is “sufficient” to show biosimilarity or interchangeability even in the absence of clinical bridging studies provided that other data and information provide an appropriate bridge between the foreign comparator and the RP. The foreign comparator would become the “reference standard,” the U.S.-licensed product would remain the formal RP under the statute, and the data and information discussed above (most of which is publicly available) would establish the bridge confirming that the results of testing performed using the foreign comparator are applicable to the RP sourced in the United States.

B. Same Strength for Injectables (Q. I.12)⁹

AAM believes that differences in concentration of drug substance should not, a priori, prevent a proposed injectable biosimilar or interchangeable biological product from being considered to have the same strength as the RP. Foreign versions of the RP often are available in different concentrations than the U.S.-licensed RP for the same indications and conditions of use. The clinical impact of these concentration differences often is negligible, particularly if the biological product is administered via infusion. Moreover, the impact of different concentrations can be assessed in comparative pharmacokinetic studies. AAM thus requests that FDA revise this Q&A to indicate that a proposed biosimilar will be considered to have the same strength as the RP if it has the same total content of drug substance and a concentration which will result in a highly similar pharmacokinetic profile.

C. PREA Requirements for Biosimilars (Q. I.16)¹⁰

AAM supports FDA’s revised position on how a proposed biosimilar applicant can fulfill the requirement for pediatric assessments or investigations under the Pediatric Research Equity Act (“PREA”). Where the RP labeling already contains adequate pediatric information, biosimilar applicants should be allowed to fulfill PREA requirements by extrapolating the pediatric information from the RP labeling based upon a showing of biosimilarity, when scientifically justified. Where the RP labeling does not contain adequate pediatric information because the PREA requirements were waived or did not apply, AAM agrees that a biosimilar applicant should not be subject to PREA at all and thus should not be required to seek a waiver. As FDA rightly explains, the PREA requirement must be interpreted in conjunction with the BPCIA when applying it to biosimilars. Because a 351(k) application cannot be approved for conditions of use for which the RP was not previously approved, including pediatric indications or dosage forms,¹¹ PREA should not be interpreted to require 351(k) applicants to conduct pediatric studies in indications or with dosage forms for which the RP was not previously approved.

⁸ Under the statute, 351(k) applicants are required to provide “information demonstrating that” a proposed biological product is biosimilar to a RP or “information ... sufficient to show” that the biological product is interchangeable with a RP. 42 U.S.C. §§ 262(k)(2)(A)(i), (k)(4).

⁹ New and Revised Draft Q&As on Biosimilar Development and the Biologics Price Competition and Innovation Act (Revision 2)

¹⁰ Ibid

¹¹ 42 U.S.C. § 262(k)(2)(A)(i)(III). AAM does not object to the requirement to obtain a deferral of PREA requirements where the RP has obtained a deferral.

D. Same Conditions of Use (Q. I.22)¹²

AAM agrees that a 351(k) applicant may not seek approval of a condition of use (e.g., indication, dosing regimen) that has not been previously approved for the RP. AAM, however, requests that FDA add information to its proposed answer to Q.I.22 clarifying that a biosimilar applicant does not need to use the exact same labeling language to describe an approved condition of use as the RP labeling. This is necessary because there may be situations where the 351(k) applicant seeks to modify the labeling, commonly to narrow the use in select subpopulations or treatment regimens, to avoid potentially infringing patents covering the RP. In many cases, such revisions can be achieved without resulting in a different condition of use. AAM thus requests FDA to clarify that the requirement that a biosimilar applicant seek approval only of a condition of use previously approved for the RP does not also impose a “same labeling” requirement.

E. REMS Requirements (Q. I.23)¹³

AAM is concerned that originator biologic companies will take advantage of existing regulatory requirements, such as drug safety provisions, to stifle legitimate biosimilar competition in the same way they have done so to thwart legitimate generic competition. One of the most notable anti-competitive tactics used by brand companies in recent years involves abuse of REMS requirements and restricted distribution systems. In particular, brand companies use their REMS or self-imposed restricted access programs to deny generic companies access to the brand company’s RLD samples needed to support ANDAs.

AAM is concerned that the problem of access to samples is likely to be even more acute for biosimilar development as biosimilars are more complex and difficult to develop than traditional generic drugs. Because biosimilars must demonstrate that they are “highly similar” to the brand product, multiple lots of the brand product produced over time and with varying expiry dates will be required. If access to the variability that is inherent in manufacturing of biologics is impeded, the development of the biosimilar will be greatly delayed. Plus, unlike with small molecule generic drugs, the development of biosimilars is more likely to involve clinical trials requiring even more samples of the reference product. Restricted access to samples at any point during the clinical trial could cause a study to fail if patients are forced to drop out of the study due to unavailability of reference product. It is particularly concerning that there already “have been reports” of instances in which the RP holder has refused to sell samples to a biosimilar applicant on the purported grounds that doing so would violate applicable REMS requirements.¹⁴

AAM is pleased that FDA is willing, upon request, to review study protocols and to issue letters to 351(k) applicants and RP sponsors indicating that providing samples to the biosimilar applicant will not violate any REMS provisions to support conduct of biosimilar clinical trials. AAM is also pleased that FDA states explicitly that “[r]equesting such a protocol review or letter is not a legal requirement.” AAM, however, believes there are a number of additional administrative actions FDA could and should take to address this issue holistically. First, FDA

¹² New and Revised Draft Q&As on Biosimilar Development and the Biologics Price Competition and Innovation Act (Revision 2)

¹³ Ibid

¹⁴ Draft Q&A Guidance, at 11.

should affirmatively state that REMS do not apply to studies designed to demonstrate biosimilarity or interchangeability or, more broadly, to any clinical trial conducted pursuant to an IND. Second, FDA should include a REMS violation clause in all approved REMS requiring the timely provision of RP samples to 351(k) applicants. These and other suggestions previously have been described in detail in AAM's previous comments, which are incorporated herein by reference.¹⁵ Finally, although AAM believes FDA can and should do more to exercise its existing authority to counter REMS abuse, AAM also believes that the problem will not be solved without additional legislation. Accordingly, AAM urges FDA to support passage of the CREATES Act to supplement FDA's existing administrative authority.

F. Orphan Indications (Q. I.24)¹⁶

AAM agrees with FDA's new Q&A that a 351(k) applicant can seek approval for one or more indications for which the RP sponsor has unexpired orphan exclusivity. AAM also understands that, until the orphan exclusivity expires, FDA will not be able to approve the proposed biosimilar or interchangeable biological product. AAM requests clarification regarding how FDA will handle such situations. For example, will FDA review the data and information submitted by the 351(k) applicant for the protected indications? And will FDA issue tentative approval letters to 351(k) applicants, as it does for 505(b)(2) applications, if it determines that the 351(k) application meets the scientific and regulatory criteria for approval under the statute but cannot be approved because of orphan exclusivity? How will inclusion and review of the information in the initial application would help facilitate/accelerate the label update once the orphan exclusivity has expired? AAM believes it would be helpful for FDA to clarify these administrative issues.

II. Conclusion

AAM appreciates FDA's consideration of these comments.

Sincerely,



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¹⁵ AAM Comments on Facilitating Competition and Innovation in the Biological Products Marketplace, Docket No. FDA-2018-N-2689 (Sept. 21, 2018).

¹⁶ New and Revised Draft Q&As on Biosimilar Development and the Biologics Price Competition and Innovation Act (Revision 2)

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