



Your Generics & Biosimilars Industry



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Comments from The Association for Accessible Medicines (AAM) and the Biosimilars Council on behalf of our member companies, regarding Docket # FDA-2018-P-3281 Request that the Food and Drug Administration (FDA) issue guidance to ensure truthful and non-misleading communications by sponsors concerning the safety and effectiveness of biosimilars, including interchangeable biologics, relative to reference product(s).

The Association for Accessible Medicines (“AAM”), and its Biosimilars Council (“Council”) (collectively referred to in these comments as AAM), are pleased to submit comments in support of the Citizen Petition (“CP”) requesting that the FDA issue guidance to ensure truthful and non-misleading communications by reference product sponsors concerning the safety and effectiveness of biosimilars, including interchangeable biologics, relative to reference product(s), as submitted to the Agency by Pfizer on August 22, 2018.

AAM represents the manufacturers and distributors of finished generic pharmaceuticals and biosimilars, manufacturers and distributors of bulk active pharmaceutical chemicals, and suppliers of other goods and services to the generic and biosimilar industry. The Council, a division of AAM, works to ensure a positive regulatory, reimbursement, political and policy environment for biosimilar products, and educate stakeholders and patients about the safety and effectiveness of biosimilars. Member organizations include companies and stakeholder organizations working to develop biosimilar products with the intent to participate in the U.S. market.

AAM appreciates and supports FDA’s continued efforts to foster biosimilar competition in the interest of building a sustainable marketplace for these innovative medicines for America’s patients. A robust biosimilars market is vital to spur future innovation while ensuring that the US health care system benefits from competitive alternatives that provide value and lower costs. Yet, the few launched biosimilar medicines in the United States have been slow to gain market share, to the detriment of patients and the U.S. health system. This is largely due to tactics used by some originator biologic companies that abuse their dominant market position to create barriers to biosimilar approval and uptake. As Pfizer has highlighted in their CP, a prominent anti-competitive tactic employed by some originator manufacturers is to sow seeds of doubt regarding the safety and efficacy of FDA-approved biosimilars through misleading communication to prescribers and patients.

AAM supports Pfizer’s request for additional guidance on manufacturer communications related to biosimilars and interchangeable biologics. We echo FDA Commissioner Scott Gottlieb’s sentiment in a recent interview with the Washington Post, “I am worried that there are either deliberate or unintentional efforts by branded companies to create confusion” about the safety and effectiveness of biosimilars and these campaigns “can potentially undermine consumer confidence in biosimilars in ways that are untrue.”¹

AAM also agrees with some of the other comments submitted to the CP docket² that additional action is needed, beyond guidance, to fully address these misinformation efforts. For example, AAM supports Dr. Gottlieb’s suggested Agency action of issuing warning letters to drug makers engaged in misinformation campaigns.³ Furthermore, we applaud FDA’s commitment to coordinate with the Federal Trade Commission (FTC) as stated in the Biosimilars Action Plan (BAP) to address anticompetitive behavior that interferes with biosimilar development, approval, and overall competition in the marketplace. We believe that such coordination should address misinformation campaigns by originator reference biologic companies.

AAM urges the Agency to act expeditiously to issue the requested guidance on manufacturer communications and to take additional steps to ensure the development of a robust and competitive biosimilars market in the U.S.

Building Stakeholder Confidence is Key to a Robust and Competitive Market and FDA Should Continue to Expand Biosimilar Education Efforts

As FDA has recognized, provider and patient acceptance are key to enabling market adoption. To accomplish this, public education is critical to increasing confidence in biosimilar medicines. A broad range of health care professionals, including doctors, physician assistants, nurses and pharmacists, will be engaged in biosimilar prescribing, dispensing and utilization. Education tailored to each role is important. Similarly, collaboration with patient advocacy groups and disease-specific organizations to improve understanding is essential to the acceptance of biosimilars.

We commend FDA for developing provider educational materials about the FDA approval pathway for biosimilar products, the data and information that FDA reviews to determine biosimilarity, and basic definitions of key terms. FDA has a critical role to play in ensuring that stakeholders—including patients and their health care providers—are well informed about biosimilars. Such efforts must continue in tandem with the emerging marketplace.

As the FDA works to develop additional resources for stakeholders, we urge the agency to expand efforts focused on:

¹ Washington Post. “Marketers are having a field day”. Available online at: <https://wapo.st/2SRsBYK>. Accessed: February 12, 2019.

² For example: <https://www.regulations.gov/document?D=FDA-2018-P-3281-0006>, <https://www.regulations.gov/document?D=FDA-2018-P-3281-0007>, <https://www.regulations.gov/document?D=FDA-2018-P-3281-0008>.

³ Washington Post. “Marketers are having a field day”. Available online at: <https://wapo.st/2SRsBYK>. Accessed: February 12, 2019.

- promoting and instilling confidence in biosimilar safety, efficacy and quality;
- defining and utilizing terminology and key concepts in a manner that is easily comprehended by a variety of stakeholders;
- prioritizing and targeting stakeholder audiences who stand to benefit most from a comprehensive understanding of biosimilar and interchangeable biologic products; and
- tailoring resources for their unique information needs.

Unfortunately, misinformation threatens to slow biosimilar uptake and undermine confidence in FDA-approved biosimilars. Misinformation campaigns by originator reference biologic manufacturers are intended to sow doubt among patients and prescribers regarding biosimilars' safety and efficacy, and construct regulatory, policy and legal roadblocks to competition, as was highlighted in the CP.⁴ This misinformation often takes advantage of the stakeholders' unfamiliarity with biologic medicines, including biosimilars, and the important role these medicines play in addressing serious or life-threatening conditions.

We note that while the CP focuses on misinformation materials from companies, incorrect or misleading information has also been disseminated by other organizations such as physician or patient advocacy groups that are funded by originator reference biologic manufacturers.⁵ This type of misinformation is particularly concerning because it is disseminated by patient advocacy or physician groups that appear to be independent and may be perceived as more credible than the originator pharmaceutical companies themselves.

Furthermore, misinformation threatens the health of the patients who stand to benefit most from these treatments. A recent study found that 1.2 million U.S. patients could gain access to biologics by 2025 as the result of biosimilar availability.⁶ The study also suggests that women, lower income, and elderly individuals would disproportionately benefit from access to biosimilar medicines.⁷ However, lack of patient and provider trust in biosimilars is likely to derail this increase in patient access.

In this regard, we believe FDA should clearly communicate to stakeholders that transitioning patients who are stable on a reference medicine to a biosimilar is safe. In other highly-regulated global geographies with longer experience using biosimilar medicines, such as Europe, physician-led transition from a brand biologic to a biosimilar is a common medical practice, and there is a significant amount of data from the EU showing that the transition from a brand biologic to a biosimilar does not carry increased risk of an adverse event. One review examined 90 biosimilar switching studies conducted on more than 14,000 individuals and involving seven molecular entities used to treat 17 disease indications.⁸ The review concludes, "Overall, the results suggest a low risk of either a safety concern or a loss of efficacy after switching to a biosimilar." One of the study's co-authors, Avalere Senior Vice President Gillian Woollett, M.A., DPhil, stated the

⁴ <https://www.regulations.gov/document?D=FDA-2018-P-3281-0001>

⁵ Washington Post. 'Marketers are having a field day'. Available online at: <https://wapo.st/2SRsBYK>. Accessed: February 12, 2019

⁶ <http://biosimilarscouncil.org/wp-content/uploads/2017/09/Biosimilars-Council-Patient-Access-Study-090917.pdf>

⁷ *Id.*

⁸ Cohen, H.P., Blauvelt, A., Rifkin, R.M. et al. *Drugs* (2018) 78:463.

study is aimed at reassuring all biosimilar stakeholders that, “even though no clinical differences are expected when patients are switched from a reference product to a biosimilar, indeed none are found. Hence, we confirm the expectation already established through the application of sound regulatory science.”⁹

The conclusions of this large systematic review were corroborated by another review that analyzed 53 biosimilar switching studies¹⁰ that included patient switches to biosimilars from originator infliximab, etanercept, adalimumab, and rituximab. These reports are further confirmed by routine post marketing data, which has not identified any difference in the nature, severity or frequency of adverse effects between biosimilars and their reference medicine. In Europe, patients have used biosimilars for more than 10 years, resulting in more than 700 million patient days of safe, effective use.¹¹

Despite this well-documented experience underlying the safe use of biosimilars in treatment-experienced patients, as more biosimilars enter the U.S. market, originator biologic manufacturers are raising the concerns that such use of biosimilars is dangerous. The transition to a biosimilar is often referred to as “non-medical switching”, an ambiguous term that many originator biologics stakeholder organizations use disingenuously to claim that transitioning from an originator to a biosimilar medicine is not safe, a claim that is not scientifically accurate. It also suggests that a decision is being made that is not justified by clinical evidence. FDA should clarify that the term “non-medical switching” in the context of provider-directed transitions to biosimilar medicines is inappropriate.

The use of this term also highlights a gap in stakeholder understanding of the basic science on which biosimilarity is based, and FDA should consider this an education opportunity. FDA should work with stakeholder groups to ensure understanding of important facts about biologic medicines, including biosimilars. For instance, FDA can further clarify that any variation between the originator and biosimilar is within the bounds of variability established by the originator across various lots, and that FDA carefully assesses data regarding the risk of immunogenicity related to both the originator and biosimilar medicine. FDA should also clarify that only those patients who are stable on an originator biologic medicine are candidates for a transition to a corresponding biosimilar, contrary to misleading ‘fail-first’ policies seen in payer formularies that require patients to ‘fail’ on the reference product before they are able to access the biosimilar.¹² In fact, if a patient ‘fails’ on a reference biologic, it would be clinically inappropriate to then have that patient move to the biosimilar, given the “highly similar” nature of the two molecules.¹³

Another opportunity for FDA education is to highlight on the FDA website and in interactions with stakeholders the wealth of data available on patient use of biosimilar medicines, including

⁹ The Center for Biosimilars: “We Do Not Need to Reinvent the Wheel on Biosimilar Safety, Says Avalere’s Gillian Woollett.” Available at: <https://bit.ly/2KrgMDS>.

¹⁰ Moots R, Azevedo V, Coindreau JL, et al. *Curr Rheumatol Rep* (2017) 19:37-53. Available at: <http://dx.doi.org/10.1007/s11926-017-0658-4>.

¹¹ <https://www.medicinesforeurope.com/wp-content/uploads/2016/03/infographic-biosimilars.pdf>

¹² Presentation of Hillel Cohen. AMCP Webinar. Available online at: <https://bit.ly/2tjW4iM>.

¹³ *Id.*

after product transition.¹⁴ To increase confidence in biosimilars, as part of its educational efforts, FDA should publicize such evidence that shows that transitioning from a reference medicine to a biosimilar is common with no clinical differences in safety or efficacy.

In summary, FDA can take immediate action to address biosimilar misinformation by including simple factual statements on its website and in communication to stakeholders outlining:

- Transitioning a stable patient under the guidance of a physician from a reference biologic to a biosimilar does not carry an increased risk of an adverse event;
- Clarifying that the term “non-medical switching” is inappropriate in the context of provider driven transitions;
- Clarify that payer formulary policies that require a patient to ‘fail’ on a reference biologic before being able to access the biosimilar are clinically inappropriate;
- Communicating the wealth of global patient safety data related to use of, and transition to, biosimilars.

FDA Should Clarify the Role of Interchangeability

The U.S. is the only country that differentiates between biosimilar and interchangeable biologic medicines, and originator biologic manufacturers have capitalized on the confusion resulting from this statutory distinction by conflating an interchangeability designation with higher quality, safety and efficacy. FDA has an important role to play in countering this misinformation by clarifying the role of an interchangeability designation as relevant only for automatic retail pharmacy substitution of self-administered biologics, and irrelevant for all physician-administered biologic products. As FDA officials have articulated this point in conference settings, and the FDA press office has confirmed, biosimilars are ‘interchangeable’ for purposes of physician prescribing – meaning that biosimilars may be prescribed for patients already being treated with the reference product as well as for patients newly initiating treatment.¹⁵

As Janssen, Pharmaceutical Companies of Johnson & Johnson, discussed in their response to the CP, “prescriber and patient confidence in biosimilars and interchangeable biosimilars plays an important role in the utilization of these medicines.”¹⁶

The Biologics Price Competition and Innovation Act (BPCIA) specifically states that the “term ‘interchangeable’ or ‘interchangeability’, in reference to a biological product that is shown to meet the standards described in subsection (k)(4), means that the biological product may be substituted for the reference product without the intervention of the health care provider who prescribed the reference product.”¹⁷ Interchangeable biologics are only relevant in the retail pharmacy setting (i.e., self-administered products that a patient will themselves fill at a pharmacy)

¹⁴ Jorgensen KK, Olsen IC, Goll GL, Lorentzen M, Bolstad N, Haavardsholm EA, et al. “NOR-SWITCH” Lancet. 2017;389(10086):2304–16. [https://doi.org/10.1016/S0140-6736\(17\)30068-5](https://doi.org/10.1016/S0140-6736(17)30068-5).

¹⁵ Managed Care Magazine, “FDA’s Gottlieb Aims to End Biosimilars Groundhog Day,” Jan 25 2019, available online at: <https://www.managedcaremag.com/archives/2019/1/fda-s-gottlieb-aims-end-biosimilars-groundhog-day>

¹⁶ <https://www.regulations.gov/document?D=FDA-2018-P-3281-0009>

¹⁷ Section 351(i)(3), 42 U.S.C. 262(i)(3).

as interchangeable biologics can be automatically substituted for the reference product by a pharmacist. Janssen’s infliximab product Remicade, in contrast, is administered via intravenous (IV) infusion in a doctor’s office or in a hospital. Therefore, all biosimilars to Remicade must also be administered in the doctor’s office or in a hospital (i.e., if a reference product’s route of administration (ROA) is IV then the biosimilar must also have the same ROA as defined by the statute¹⁸). For Remicade, as for all physician-administered products, retail pharmacy substitution is not an option.

However, Janssen disingenuously overstates the role the interchangeability designation plays in the biosimilar marketplace as well as what is statutorily outlined for the approval of biosimilar and interchangeable biologic products in the BPCIA. In using the interchangeability designation to cast doubt on the safety and efficacy of biosimilar medicines, Janssen specifically cites that “the fact that a biosimilar product *may work* the same way mechanistically as the reference product (e.g., same [Mode of Action] MOA) does not mean that the FDA has found that the products can be expected to produce the same clinical result” (emphasis added).¹⁹ However, this statement is false and ignores the BPCIA’s requirement that all biosimilars must have “no clinically meaningful differences” from their respective reference product and have the same MOA. As FDA explains, the BPCIA requires that “A manufacturer must also demonstrate that its proposed biosimilar product has no clinically meaningful differences from the reference product in terms of safety, purity, and potency (safety and effectiveness).”²⁰ Put another way, the absence of differences that are meaningful for clinical outcomes between the reference and biosimilar means that the biosimilar is expected to have the same clinical outcome at a population level. All FDA-approved biosimilars will have to have the same safety and efficacy as their reference products. The interchangeability designation simply reflects FDA’s conclusion that the statutory requirements for interchangeability have been met, not that the biosimilar was altered or is of a higher quality.

AAM requests the FDA emphasize, in its educational materials and on its website, that the interchangeability designation is only intended to be pertinent in those situations where there are opportunities for automatic retail pharmacy substitution, and that this is less common for biologics than small molecule drugs, given that the majority of biologics are physician-administered. Further, physicians are free to transition patients from the reference product to the biosimilar and that they do not need to wait for an interchangeability designation. As such, an FDA interchangeability designation is irrelevant to most biologics, and the lack of such a designation should not be considered a reflection on the safety or efficacy of biosimilar medicines. Any misleading statements that conflate an interchangeability designation with higher quality, safety or efficacy must be countered by the FDA.

¹⁸ Section 351(i)(3), 42 U.S.C. 262(i)(3).

¹⁹ <https://www.regulations.gov/document?D=FDA-2018-P-3281-0009>

²⁰ Section 351(i)(2), 42 U.S.C. 262(i)(2);

<https://www.fda.gov/Drugs/DevelopmentApprovalProcess/HowDrugsareDevelopedandApproved/ApprovalApplications/TherapeuticBiologicApplications/Biosimilars/ucm580419.htm#nodiff>

FDA Action on Misinformation

FDA should not only disseminate truthful and non-misleading information regarding biosimilars as broadly and effectively as possible, but also clarify the nature of and consequences for disseminating misleading content related to biosimilars. In this regard, we request FDA bring about corrective actions by organizations who engage in misinformation campaigns about biosimilar products by:

- Establishing with the FTC, under the FTC/FDA Memorandum of Understanding,²¹ a task force to review these campaigns in more detail and take appropriate actions to end them. The FTC/FDA Memorandum of Understanding states that FDA and FTC share the objective of "preventing injury and **deception of the consumer**" (emphasis added). We believe the misinformation and the coordinated nature of the campaigns highlighted by the CP represent deception of the consumer and are adversely affecting healthcare providers and patients. Shared FDA/FTC oversight is necessary to correct previous actions and appropriately deter future campaigns.
- Issuing warning letters, as Dr. Gottlieb has suggested,²² to organizations that conduct biosimilar misinformation campaigns requesting the immediate suspension and withdrawal of campaigns. In warning letters to organizations believed to be engaging in misinformation campaigns, FDA should identify the specific campaign, demand the immediate withdrawal of the materials, warn against any future misinformation campaigns, provide accurate information that counters the misinformation and include information about the FDA's legal and regulatory framework to review and approve biosimilars.
- Establishing a publicly available list on its website that identifies organizations that engage in biosimilar misinformation campaigns. The list should be available on FDA's website, identify the organizations by name, provide a brief summary of the misinformation, and provide corrected or accurate information.

The requested actions will ensure that patients and providers receive factual information to help them make informed medical treatment decisions. Additionally, these actions will help ensure that payers also receive accurate information about biosimilars, to inform their decisions and lead to enhanced patient access to biosimilars by patients.

Conclusion

The BPCIA established a pathway for biosimilar medicines to provide a competitive alternative to costly biologic products. AAM appreciates the FDA's efforts to ensure successful regulatory implementation of the pathway and is encouraged by the increasing number of biosimilar

²¹ M0U225-71-8003, Memorandum of understanding Between the Federal Trade Commission and the Food and Drug Administration (May 14, 1971) accessible at <https://www.fda.gov/AboutFDA/PartnershipsCollaborations/MemorandaofUnderstandingMOUs/DomesticMOUs/ucm115791.htm>

medicine approvals in recent years. However, we believe more must be done by the FDA to clarify policy and educate healthcare stakeholders, especially to combat the rampant misinformation in this space that prevent biosimilar medicines from fully realizing the vision of a competitive marketplace set forth by the BPCIA.

AAM looks forward to continued dialogue with the Agency on these critical topics, and we thank you for your consideration of these comments.

Sincerely,



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Council