Biosimilars
FORUM

Food and Drug Administration

Center for Drug Evaluation and Research

Office of Therapeutic Biologics and Biosimilars

10903 New Hampshire Ave

Silver Spring, MD 20993

Electronically Submitted to Regulations.gov

RE: FDA-2023-N-0254 BsUFA Research Roadmap

April 5, 2023

To whom it may concern:

A number of immediate and longer-term measures can be adopted to streamline biosimilar development in the US, Europe and elsewhere. The Biosimilars Forum ("Forum") wholly supports such goals and looks forward to sharing our experience and opinions on projects to pursue in order to advance efforts towards streamlined biosimilar development. We appreciate the opportunity to comment on the BsUFA III Regulatory Science Program Roadmap that was published January 26, 2023.

As you are aware, the Biosimilars Forum supported this initiative as part of the BsUFA III negotiations with the FDA and other stakeholders. The Forum strongly believes that improving the efficiency of biosimilar development on a global scale, not just here in the United States, is an urgent issue that will be critical for the long-term sustainability of this industry and our ability to increase access to these therapeutic options for patients. Global science-based regulatory approaches are key to leverage efficiencies within and across markets, thereby enhancing access and affordability to quality, safe and effective biologics, including biosimilars, for all patients.

The members of the Forum represent the companies with the largest portfolio of biosimilars in development today, as well as already on the market in the United States. In addition, our companies contribute to the development and marketing of biosimilars around the world. Collectively, our members represent decades of experience in biologics and biosimilars development, as well as the manufacture of products launched in over 80 countries. It is based on this collective expertise that we submit our comments and recommendations. We are available to contribute further as the Program evolves.

Goals of BsUFA III Regulatory Science Pilot Program:

The BsUFA III regulatory research pilot program has two aims, called demonstration projects:

1. **advancing the development of interchangeable products, and**
2. **improving the efficiency of biosimilar product development.**

The Forum believes that it is possible to streamline aspects of biosimilar development immediately, without waiting until the completion of the ongoing and anticipated BsUFA IIII research projects. Other highly credible and experienced regulatory agencies are already embracing streamlined development by implementing waivers for the confirmatory comparative clinical efficacy studies [often called "Phase III

studies"][1, 2, 3]. It is important to acknowledge these advancements and successful experiences so that developers are not producing data that is no longer scientifically relevant, nor indeed pertinent, to regulatory decision-making. The Forum encourages FDA to join efforts already underway in other highly regulated countries to advance streamlined biosimilar development. The US should not become a bottleneck in global development planning for biosimilars when the FDA has historically led with so much of the established regulatory science for all biologics, including biosimilars[4, 5].

The Forum believes that although improving the efficiency of biosimilar development and advancing the development of interchangeable biosimilars are both identified in the BsUFA III Commitment Letter, higher priority should be given to improving the efficiency of biosimilar development. We believe this is key to the future of biosimilars and our ability to provide access for patients to critical medicines. Notably, none of the efficiencies that the Forum proposes in any manner change the quality, safety or efficacy of the biologics finally approved, whether as biosimilars or as interchangeable biologics.

The Forum encourages FDA to ensure that the research be undertaken in this Program specifically and directly addresses the goals of the BsUFA III Regulatory Research Pilot Program ["Program"], and not include basic research that may only be peripherally related, if at all. For example, a strong suite of chemical and functional assays already exist that can provide the basis for advancing streamlined development. Having undertaken an in-depth analysis of biosimilar monoclonal antibody dossiers, leading European regulators have already published that they believe CMC is predictive for risk-based guideline evolution[6, 7]. Such progress by others can become the basis for a forward-looking Program in the US. In fact, in a comparative assessment, the sensitivity of physico-chemical and functional attributes testing is much higher than that of a clinical study for detecting differences and the potential impact to safety/efficacy.

This approach would provide an accelerated study of empirical evidence and experience gained thus far and be highly valuable to FDA staff as well as to sponsors. Such an effort need not require the disclosure of any sensitive information (often given as a reason that such studies cannot be done) as only the results need to be published.

The Forum appreciates FDA's identification of potential scientific projects to pursue regulatory efficiencies that could help assure timely access of biosimilar competition which, in turn, would help alleviate patient access needs. In addition to this commendable ambition, it is of the outmost importance for health authorities to strive toward global convergence of streamlined development guidance. Thus, the Forum would appreciate further efforts made by FDA, in conjunction with other health authorities, to seek a global biosimilar development pathway to avoid divergence. As an example, FDA currently

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1 https://www.gov.uk/government/publications/guidance-on-the-licensing-of-biosimilar-products/guidance-on-the-licensing-of-biosimilar-products

2 https://www.ema.europa.eu/en/human-regulatory/research-development/scientific-guidelines/multidisciplinary/multidisciplinary-biosimilar

3 https://www.ema.europa.eu/en/human-regulatory/research-development/scientific-guidelines/multidisciplinary/multidisciplinary-biosimilar

4 Demonstration of Comparability of Human Biological Products, Including Therapeutic Biotechnology-derived Products APRIL 1996 Final https://www.fda.gov/regulatory-information/search-fda-guidance-documents/demonstration-comparability-human-biological-products-including-therapeutic-biotechnology-derived

5 COMPARABILITY OF BIOTECHNOLOGICAL/BIOLOGICAL PRODUCTS SUBJECT TO CHANGES IN THEIR MANUFACTURING PROCESS Q5E https://database.ich.org/sites/default/files/Q5E%20Guideline.pdf

6 A Data Driven Approach to Support Tailored Clinical Programs for Biosimilar Monoclonal Antibodies. Guillen et al, 2023, https://ascpt.onlinelibrary.wiley.com/doi/full/10.1002/cpt.2785

7 Regulatory Evaluation of Biosimilars: Refinement of Principles Based on the Scientific Evidence and Clinical Experience Pekka Kurki et al, May 2022, https://link.springer.com/article/10.1007/s40259-022-00533-x

requires a switch component within the clinical efficacy study whereas other stringent regulatory authorities do not. Deleting such an expectation would be the epitome of efficiency. FDA can facilitate such global development, through regulatory reliance, using the Agency's established leadership in the regulatory science for all biologics. The Agency's constructive engagement will be as welcomed now as it was in the past.

SCIENTIFIC AREAS FOR REGULATORY IMPACT

1. **Increasing the accuracy and capability of analytical (structural and functional), and chemistry, manufacturing, and controls (CMC) characterizations (Research Priorities #1a-d)**

The Forum recommends that this should be a priority, albeit only when pertinent to advancing efficiency and streamlining biosimilar development in a regulatorily relevant manner. This research should focus on analytics that are reliable and clinically relevant such that we lessen requirements or eliminate the need for comparative clinical efficacy studies altogether.

As such, analytics must be fit-for-purpose, and focus on encouraging those that are most accurate and relevant for regulatory decision making. We caution that ever better analytics that do not provide immediately acceptable and alternative actionable data are not useful; nor are those that are merely additive to techniques that are already considered adequate today. As such, replacement techniques may have value but only if they are more reliable and accepted as alternatives by regulators, and fit-for-purpose such that they can be broadly applicable.

It is important to state very clearly in any proposal how the proposed research will help increase efficiency of biosimilar development. Indeed, this should be used as a key eligibility criterion when scoring a proposal for funding. When a given project is selected in this area, it is important that the researchers and FDA provide an explanation of how the research will directly enhance biosimilar development efficiency. Proposals funded must have pre-defined sensitivities and specificities that are targeted. If they focus on analytics, it would be useful to provide an explanation of how they compare to current techniques. Open-ended "improvements" without this context will not improve the efficiency of biosimilar development.

a. **Define and standardize approaches for assessing and reporting product quality attributes:**

While the FDA already has guidance to ensure that all CMC analytic methods are standardized and validated[8], the Forum believes that this program can still be helpful for future biosimilars. An FDA summary of currently acceptable critical quality attributes (CQAs) with sensitivities would be valuable and could inform part of future revised FDA guidance, as well as help prioritize further research.

The Forum recommends that the FDA support a retrospective analysis of biosimilar dossiers that FDA has assessed thus far to identify if there are any common differences or concerns across dossiers. It is extremely important that there is an expert evaluation of defining the scope of acceptable 'differences' – considering knowledge gained from the existing risk based biological manufacturing change exercise[9]. FDA's prior experience with such changes is considerable and can contribute meaningfully to prioritization of research now being proposed.

To facilitate this type of study, the Agency could provide access to data from which to do this assessment, and for a paper to be published with the anonymized results. This research would be complimentary to the

[8] https://www.fda.gov/vaccines-blood-biologics/general-biologics-guidances/biosimilars-guidances

[9] Vezer et al (2016) http://dx.doi.org/10.1185/03007995.2016.1145579

recent paper published by the European Medicines Agency[10] and that previously from MHRA[11], and could be foundational to advancing a global regulatory development conversation among regulators.

The Forum believes it would be valuable to have a publicly available resource of commonly used methodologies for the structural and functional characterization of biosimilar candidates, for example, the study recommended above could also be used to create a library of the available and appropriate literature references the agency supports. These would guide biosimilar developers, as well as be a living repository to new research and literature that demonstrate advancements in streamlined development. This resource could be used as an ongoing educational tool for biosimilar developers from the FDA (and indeed within the Agency too as reviewers maintain their skills, as well as train reviewers in the differences between review and approval of an originator biologic and a biosimilar) in the latest thinking and advances in biosimilar development. However, it is also important to be clear that it is not necessary that every possible analytical assay be utilized for every biosimilar, but that an orthogonal set be considered to cover all clinically relevant product quality attributes. While clinically-critical molecular attributes need to be well characterized, there are often multiple suitable methodologies that are available for each attribute.

b. Characterize relationships between product quality attributes and clinical outcomes:

The Forum supports an FDA focus on known relationships between the structure of the molecule and clinical performance (PK, efficacy, safety, immunogenicity) of the reference product for critical quality attributes (CQAs). Previous FDA guidance has been very clear that a link should be made to the mechanism of action (MoA), but only "to the degree to which it is known for the reference product." [12].

Experience to date should be revisited to provide further clarity to biosimilar developers on how to consider MoA, to the extent that it is known for the reference product. This will enable its inclusion in biosimilar development in a timely manner for current and future programs. The FDA may also consider defining reference products CQAs, possibly on a class basis, to offer guidance to sponsors for improved efficiencies.

When developing new CQAs, such as biomarkers, it is important that they not be exploratory under this new program, and that they explicitly add to the efficiency of biosimilar development. The Forum does not support FDA funding open-ended research that does not meet this goal. In particular, the members of the Forum do not support creation and adoption of something wholly new when existing tools provide the necessary data and increased efficiencies are not clearly offered.

A review of publications including those from other regulatory agencies would be beneficial to share as these have established clearly what is indeed known. For example, recently publications by the MHRA[13]

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[10] Elena Guillen, Niklas Ekman, Sean Barry, Martina Weise, Elena Wolff-Holz A Data Driven Approach to Support Tailored Clinical Programs for Biosimilar Monoclonal Antibodies 22 December 2022 https://doi.org/10.1002/cpt.2785)

[11] Marie-Christine Bielsky, Anne Cook, Andrea Wallington, Andrew Exley, Shahin Kauser, Justin L. Hay, Leonard Both, David Brown Streamlined approval of biosimilars: moving on from the confirmatory efficacy trial Drug Discover Today Vol 25, Issue 11, Nov 2020, pages 1910-1918 https://doi.org/10.1016/j.drudis.2020.09.006

[12] https://www.fda.gov/regulatory-information/search-fda-guidance-documents/clinical-pharmacology-data-support-demonstration-biosimilarity-reference-product

[13] Streamlined approval of biosimilars: moving on from the confirmatory efficacy trial, https://pubmed.ncbi.nlm.nih.gov/32916269/

and EMA[14] provide information on the CQAs required in their jurisdictions. Global alignment of development requirements will provide not only the most efficient development approach for a biosimilar but will also provide for global safety standards for these products. The recent changes to the WHO Guidelines[15] can also be considered as a baseline upon which such harmonization is fostered.

c. Improve on and/or develop new analytical technologies:

As discussed earlier, the Forum encourages the FDA to consider what other highly regulated countries require before adopting new analytical technologies. The research of others will develop new methodologies which could be adopted by the FDA. The shared goal between biosimilar developers and regulatory agencies should be to standardize expectations for biosimilars.

If a new method is proposed for further research under this new program, it must be clear whether and how it is an alternative to an existing one; and by funding the proposal FDA must concur that if the study works as proposed, the method is indeed an alternative that will replace current requirements as a regulatory matter. Any new techniques that propose to provide new information need to be relevant to clinical outcomes and offer something that is not available with existing technologies. Otherwise, sponsors face cumulative technology that makes biosimilar development less efficient and product development less feasible[16], not more efficient.

d. Assess the impact of differences of biosimilar or interchangeable, and reference product presentations (e.g., delivery device) and container closure systems on product protection, safety, compatibility, and performance:

The Forum believes that biosimilar manufacturers should be able to innovate in regard to the device as long as it achieves the same clinical outcome. Improvements in the patient's experience, human factors, and patient compliance with their medication are to be encouraged. Given that device/delivery system technology has evolved and improved over the lifetime of the reference product, a biosimilar sponsor should not feel obligated to use a device that is obsolete. Instead, the focus should be on effective and safe drug delivery by intended users and use environment.

Given this, human factor studies for biosimilars are not helpful as results will not be the same as those already conducted for the reference product with a different device. As such, device research for biosimilars is not recommended by the Forum as a priority for more efficient biosimilar development.

However, the Forum requests that FDA publish guidance on interchangeability for products presented in a delivery system to better guide sponsors as they develop product closures and delivery devices for their biosimilars and interchangeable biologics. Such guidance is already specified in the BsUFA III Commitment Letter but is scheduled for completion relatively late, on September 20, 2025. Advancing delivery of this guidance would be practical and more immediately applicable to the development of biosimilars and interchangeable biologics than device research of questionable regulatory relevance. In

[14] A Data Driven Approach to Support Tailored Clinical Programs for Biosimilar Monoclonal Antibodies, https://pubmed.ncbi.nlm.nih.gov/36546547/

[15] The Report of the 75th meeting of the WHO Expert Committee on Biological Standardization (ECBS), held on 4-8 April 2022 is now published in WHO Technical Report Series 1043 (a PDF is available https://apps.who.int/iris/rest/bitstreams/1462954/retrieve - see page 11, section 3.2, September 2022).

[16] Biosimilars in the United States 2023-2027 Competition, Savings and Sustainability, January 31, 2023 https://www.iqvia.com/insights/the-iqvia-institute/reports/biosimilars-in-the-united-states-2023-2027

addition, given that device/delivery system technology evolves and improves, the focus should be on effective and safe drug delivery by intended users and the use environment (human factor data).

2. Developing alternatives to and/or reduce the size of studies involving human subjects (Research Priorities #2e-j)

Every clinical study must have pre-defined value for regulatory decision-making. All clinical studies must be designed to learn something new and thereby be regulatorily actionable. The Forum supports the regulatory science already articulated in ICH Q5E[17] that states comparative clinical studies should be conducted only when there is a specific need. This regulatory experience, already applied to the reference products to which biosimilars are now being made, supports the Agency's focus on the use of analytics versus comparative clinical studies, not least as these are more sensitive to detect any differences that might exist. The expectations for any additional data should be risk-based and carefully considered in anticipation of the results being actionable by regulators. That same thinking should apply across the BsUFA III Regulatory Science Program.

The Forum supports the use of Real-World Evidence (RWE) to support an interchangeability designation where appropriate. This data may have been collected ex-US but its quality and reliability can be comparable to that that would subsequently become available in the US, especially when from ex-US jurisdictions with similar, or sometimes more complete, pharmacovigilance systems.

The Forum is confident that the FDA already has tools to reduce the size of studies involving human subjects. It is key to the long-term sustainability of this industry that FDA work with other regulatory agencies to create a global approach to biosimilar regulations and development by applying these tools in a timely manner. Repetition of country-specific clinical studies are not ethical (for example, ethnic differences, such as dosing, will already have been established for the reference product) and does not provide any additional scientific evidence for approval[18, 19]. Absent such scientific validity there is no ethical validity to the study. That "feel good" studies may have occurred in some instances, or that there are expectations for certain types of clinical confirmatory studies out of habit, does not mean they should be expected in the future, and indeed that is the rationale behind this aspect of the FDA BsUFA III Regulatory Science Research program. There is an expectation that more efficient and streamlined biosimilar development is possible and as such careful reconsideration of any clinical studies and their purpose is fundamental to the success of this research program[20].

The Forum requests that the FDA also consider questions specific to biosimilars for orphan drugs in the pilot program. There are numerous technical, clinical, and regulatory hurdles that need to be overcome before industry can successfully develop biosimilars for these specific populations, and feasibility for any clinical studies is a very significant consideration. As there is lower prevalence of disease with orphan drugs, biosimilar development needs to be tailored to this specific environment. For example, due to a smaller patient population, there have been limited clinical studies with a smaller population of subjects with the reference product which in turn provides smaller amounts of data available for biosimilar

[17] ICH Q5E https://database.ich.org/sites/default/files/Q5E%20Guideline.pdf
[18] An Efficient Development Paradigm for Biosimilars Aug 2019 https://link.springer.com/article/10.1007%2Fs40259-019-00371-4
[19] WMA DECLARATION OF HELSINKI – ETHICAL PRINCIPLES FOR MEDICAL RESEARCH INVOLVING HUMAN SUBJECTS https://www.wma.net/policies-post/wma-declaration-of-helsinki-ethical-principles-for-medical-research-involving-human-subjects/#:~:text=The%20World%20Medical%20Association%20(WMA,identifiable%20human%20material%20and%20data.
[20] Comparability of Biologics: Global Principles, Evidentiary Consistency and Unrealized Reliance. June 2021 https://link.springer.com/article/10.1007/s40259-021-00488-5

development. In addition, due to the smaller number of patients that could be treated, there is limited availability of multiple unique batches of reference products. Biosimilar development of orphan drugs requires a tailored development program given the parameters of orphan drugs overall, but can also already demonstrate the value of analytics.

Looking towards the future, it is important to consider the nature of clinical programs that would be required to establish biosimilarity to antibody-drug conjugates (ADCs). ADCs are important new developments in biological therapy, and while the principles of biosimilarity would be the same, the design of comparative studies could be different.

e. Develop alternatives to the comparative immunogenicity assessment currently conducted as part of the comparative clinical study:

The Forum supports this line of inquiry. However, we also recommend that FDA be open to risk-based streamlined development approaches where immunogenic comparability can be justified from CMC and comparative PK/PD clinical studies.

It is crucial that the FDA consider what is already known about the immunogenicity of reference products when looking at the value of further research on the immunogenicity of biosimilars as there is a considerable amount of relevant data already available.

It is difficult to establish connections from immunoassays to clinical performance, and so we suggest that developing new or optimizing existing immunoassays should be a lower priority objective for the Roadmap. In the context of biosimilar development, we suggest that immunoassays are best considered as tools for risk assessment and mitigation. Comparable CQAs should be utilized as they are scientifically valid in this area too.

The Forum would also like FDA to consider whether there is value in the use of post-approval data as a substitute for comparative immunogenicity studies. This information could come from robust pharmacovigilance approaches that are already in use today.

f. Develop alternatives to the comparative immunogenicity assessment currently conducted as part of the switching study:

The proposed concern about switching back and forth between reference product and biosimilar is based on an argument that has not been sustained in practice. There is no experimental data to support this concern in the 15+ years that biosimilars have been globally available, despite the fact that multiple switching is common in tender-based markets.[21] Real World Evidence (RWE) that has been accrued across multiple jurisdictions demonstrates that there is no increased risk in immunogenicity with use of biosimilars.

With over 12 years of data in the US in the FDA's post-marketing surveillance program and additional years across multiple countries on the safety of biosimilars without any restrictions on switching (as well as no literature anywhere to date that indicates any signal of increased immunogenicity with the switch[22]), the Forum feels strongly that this research proposal should be a lower priority for the program if not eliminated entirely. We suggest that FDA should only require any switching studies on a product-by-

[21] Cohen, H.P., Hachaichi, S., Bodenmueller, W. et al. Switching from One Biosimilar to Another Biosimilar of the Same Reference Biologic: A Systematic Review of Studies. BioDrugs 36, 625–637 (2022). https://link.springer.com/article/10.1007/s40259-022-00546-6

[22] Cohen, H.P., Blauvelt, A., Rifkin, R.M. et al. Switching Reference Medicines to Biosimilars: A Systematic Literature Review of Clinical Outcomes. Drugs 78, 463–478 (2018). https://doi.org/10.1007/s40265-018-0881-y

product basis when there is a specific identified need already known from experience with the reference product. Immunogenicity for biosimilars is always guided by what has been seen with their reference products, and a regulatorily consistent approach is scientifically appropriate here.

The FDA could expand the use of RWE in this area by recognizing and using global RWE. This will build the global foundation for the safety of biosimilars and contribute to the global streamlined development and regulatory harmonization. However, we again offer the caveat that research funded under this program should be specific to biosimilars, and most of the RWE to date on these biologics will be from the reference products. FDA may want to consider facilitating the use of RWE in further developing their guidance on Real-World Evidence (https://www.fda.gov/science-research/science-and-research-special-topics/real-world-evidence) with the addition, as applicable, to biosimilar development especially as biosimilars enable more patients to be treated.

g. Develop alternatives to clinical bridging data for use of a non-U.S.-approved comparator:

The Forum recommends that FDA advance the utilization of a global reference comparator (based on ICHQ5 principles) with no additional clinical bridging requirements between EU-sourced reference product and US reference product being expected. The Agency should allow public information to be used in lieu of a clinical bridge [23] as noted in the FDA and EMA's publicly posted information in guidance. FDA should continue to educate their reviewers on this important guidance and monitor its implementation.

The reality is that the originator reference biologic is often a single product approved worldwide based on the same dossier, clinical trial material, and commercial batches. But since there is not a worldwide alignment of specifications; a biosimilar to that reference biologics currently needs individual dossiers and often faces expectations for repeated clinical studies with locally-sourced reference material. The latter are particularly egregious and not scientifically justified but occur because of the lack of global regulatory harmonization. With each regulatory agency having different requirements, biosimilar sponsors are stymied and must confront multiple individual development programs for each jurisdiction. A global comparator, demonstrable through public and reliable information (for example, the same pivotal clinicals studies cited on the FDA and EMA websites[24]) should support a global biosimilar development program today with no additional data required.

It is also important to put aspersions of supposed "drift" into context. When process or specification changes are proposed by the manufacturer, it is always necessary to demonstrate that the proposed changes do not impact the safety or efficacy of the product that was established with the original clinical data set. Therefore, all process improvements or specification differences that may exist between a US and non-US comparator licensed in a country with a stringent health authority have always been linked back to the original clinical data set and confirmed to the satisfaction of a rigorous health authority. As such regulators are confident that no change in safety or efficacy has occurred. ICH Q5E remains key to any proposals for use of a non-U.S.-approved comparator product, and sources outside ICH-compliant jurisdictions are not proposed by the Forum[25].

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[23] Webster, C.J., Woollett, G.R. A 'Global Reference' Comparator for Biosimilar Development. May 2017, BioDrugs 31, 279–286 (2017). https://doi.org/10.1007/s40259-017-0227-4)

[24] Webster, C.J., Woollett, G.R., A 'Global Reference' Comparator for Biosimilar Development. BioDrugs 31, 279–286 (2017). https://doi.org/10.1007/s40259-017-0227-4

[25] Webster, C.J., George, K.L. & Woollett, G.R. Comparability of Biologics: Global Principles, Evidentiary Consistency and Unrealized Reliance. June 2021 BioDrugs 35, 379–387 (2021). https://doi.org/10.1007/s40259-021-00488-5

The lack of recognition or utilization of a global comparator, even when public and reliable information is available, is not sustainable for biosimilar development over the long term, due to the high cost of reference products and the need to replicate studies for multiple jurisdictions. The FDA can safely and proactively move away from unnecessary clinical 3-way studies by using already available information from those stringent regulatory authorities with whom they already trust and collaborate with. No trade secret or confidential information is needed. Biosimilar reviewers need to better understand the biosimilar development paradigm through further education and specialization in biosimilar development.

Consequently, while this is a particularly important priority for the efficient development of biosimilars, the bridging of US and ex-US sourced reference products is a paper exercise that does not need further research because public information is available. If the pivotal studies upon which the reference comparator product is approved are the same as in the US and the quality assured, FDA can accept its use for biosimilar development. Consequently, FDA should accept reference products sourced from ICH-compliant countries because CMC changes are always bridged to the worldwide clinical studies that supported the initial 351(a) BLA for the reference product. An FDA statement to this effect would be significant and an immediate contribution to making biosimilar development more efficient.

h. Increase use of pharmacodynamic (PD) biomarkers instead of or in conjunction with clinical endpoints:

The Forum believes that where PD biomarkers are available and already acceptable to FDA for regulatory decision making, biosimilar sponsors should be able to use them today. This BsUFA III Program should not attempt to develop any new PD biomarkers that have not already been developed with use of the reference product[26]. Development of PD markers is a lengthy and expensive exercise that often has a low probability of success. Requiring development of PD biomarkers would negatively impact affordability and access. The Forum encourages FDA to instead utilize biological functional assays that are already known to be clinically relevant.[27]

i. Clarify which user interface differences that are likely to affect the safe and effective use of an interchangeable product:

The Forum believes this research should not be a priority for this program as it is of little value and not specific to biosimilars. Just like for any other medicine, the Agency should focus on ensuring that the product license holder provides adequate guidance to both pharmacists and patients on how to use the devices. The Forum believes that thoughtfully designed human factors studies conducted for the biosimilar sufficiently address the issues of safe and effective use of the product. Additional studies should not be required for an interchangeable designation as they are unnecessary and redundant. As with any biologic drug device/presentation, robust pharmacovigilance systems will serve as a resource to identify any issues that may arise from use once the product is marketed.

[26] Gillian R. Woollett, Joseph P. Park, Jihyun Han,Byoungin Jung The Role of PD Biomarkers in Biosimilar Development - To Get the Right Answer One Must First Ask the Right Question CPR 23 September 2022 https://doi.org/10.1002/cpt.2753

[27] Pharmacodynamic Biomarkers for Biosimilar Development and Approval (duke.edu); https://ascpt.onlinelibrary.wiley.com/toc/15326535/2023/113/1

j. Define methodologies to assess differences in user interfaces that may lead to differences in safe and effective use of interchangeable products:

The Forum believes this should not be a priority for this program.

The same methods and analyses that are applied to generic drugs seeking an AB substitution rating should be applied to biosimilars seeking an interchangeability designation. There is nothing unique about user interfaces for interchangeable biosimilars that should require special methodology.

Conclusion:

The funding for the FDA's Regulatory Science Program and associated Roadmap is sourced through BsUFA industry user fees. The Forum recommends that all research support in the Program be prespecified to enhance the efficient development and approval of biosimilars. As such, each proposal considered for funding under the Program needs to have this criterion explicitly applied.

Further, as biosimilars and interchangeable biosimilars must both demonstrate the foundational biosimilarity with no clinical meaningful differences, additional scientific research that is specific only for interchangeable biologics is not recommended. The product quality of a biosimilar and an interchangeable biosimilar are identical and there are no safety concerns between switching between reference products and biosimilars even multiple times. Indeed, real world evidence accrued over the past fifteen years has shown this to be true. As such, it is not an appropriate subject for scientific or clinical research. The Forum supports a focus under this program entirely on improving efficiency of biosimilar development – specifically minimizing or waiving clinical efficacy studies and striving toward a global development plan. This may in turn ultimately also make more interchangeable biologics available as the designation can only be given to biosimilars.

Bridging studies between non-U.S.-approved comparator and US-sourced reference product are unnecessary when reliable public information is available that the pivotal studies are identical[28]. Likewise additional indications for reference cite the same clinical studies across jurisdictions. In ICH compliant countries, the match is maintained (under ICHQ5) along with suitable quality. Recognition of this by the FDA does not require additional research but would substantially impact the efficiency of biosimilar development – the goal of the Program.

Without waiting for further research, FDA can assess all clinical studies through the lens of whether they offer new and regulatorily actionable information. This must be defined before any clinical study is expected and should already be standard practice. FDA can decide whether clinical studies are necessary based on robust CMC and PK comparability data, and entirely waive them when they add no additional regulatorily-relevant information[29]. Similarly, when it comes to MOA, it only needs be known for a biosimilar to the same extent as it is known for the reference product. As such, FDA should not be

[28] Webster, C.J., Woollett, G.R., A 'Global Reference' Comparator for Biosimilar Development. BioDrugs 31, 279–286 (2017). https://doi.org/10.1007/s40259-017-0227-4

[29] Webster, C.J., Wong, A.C. & Woollett, G.R. An Efficient Development Paradigm for Biosimilars. BioDrugs 33, 603–611 (2019). https://doi.org/10.1007/s40259-019-00371-4

developing and validating new PD biomarkers[30]. Research into interchangeability is not useful to biosimilar sponsors, not least as all biosimilars are interchangeable as a scientific and medical matter[31, 32].

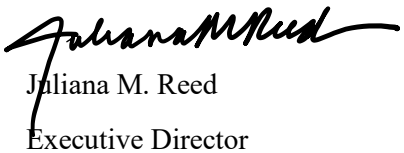
The Forum recommends the development of an industry advisory board for this program to prioritize the Program Review to enable FDA to understand which of the studies that pass scientific review by BsUFA III regulatory science reviewers would likely most impact the efficiency of biosimilar development.

We understand the point of this research Program is to seek ways to improve the efficiency of biosimilar development. To do that the Program itself must be efficient, especially if it is to have an impact within the timelines of BsUFA III. There is an existing, practical concern to patients and their healthcare providers in terms of access and affordability when biosimilar development is delayed. Efficiency will require shared expectations and regulatory approaches by both FDA and industry as well as open-minded collaboration as to what data is necessary while letting go of some of the ways we have achieved it in the past. The Forum is looking for actionable information and a scientific foundation for all regulatory expectations, and regulatory consistency across all biologics. Focusing on this can be an essential research component of the BsUFA III Regulatory Science Roadmap.

The Inflation Reduction Act of 2022 places additional strain on the biosimilar industry that will require a more nimble and faster biosimilar development cycle. Collectively, we need to get this right quickly. FDA, industry, and other health regulatory agencies need to move forward together to accomplish these goals.

Thank you for the opportunity to provide comments on the Biosimilar User Fee (BsUFA) III Regulatory Research Pilot Program: Research Roadmap. The Forum looks forward to continued engagement with FDA on the science that supports the long-term sustainability of biosimilar development.

Respectfully submitted,



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Executive Director

The Biosimilars Forum

[30] Gillian R. Woollett, Joseph P. Park, Jihyun Han, Byoungin Jung The Role of PD Biomarkers in Biosimilar Development - To Get the Right Answer One Must First Ask the Right Question CPT 23 September 2022 https://doi.org/10.1002/cpt.2753

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[32] EMA Q&A on the Statement on the scientific rationale supporting interchangeability of biosimilar medicines in the EU 20Jan23 https://www.ema.europa.eu/en/documents/other/qa-statement-scientific-rationale-supporting-interchangeability-biosimilar-medicines-eu_en.pdf