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Commentary

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# Strength and Presentation Differences in Biosimilarity: Controversies in Regulatory Approaches

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The presence of limited information with no detail in biosimilar guidelines of major regulatory agencies, together with findings of clues suggestive of possible controversies between their approaches made the issue of strength one of the most curious areas for the sponsors seeking regulatory authority answers for their questions regarding strength similarity of their proposed biosimilars with the reference products.

One of the main purposes of the Food and Drug Administration's (FDA) Question and Answer (Q&A) guidance documents, which were first published in 2012, is to facilitate biosimilar development programs by answering common questions from biosimilar developers [1,2]. In the Q&A format used in these guidance documents, each Q&A that is in its draft form receives comments from the shareholders and moves to final Q&A guidance after review of suggested comments and incorporation of appropriate changes. The new Q&As are issued by the FDA as Additional Q&A guidance documents and furthermore, if a Q&A in the final guidance requires revision for some aspects, it can be moved from the previous final guidance to the next draft update, or to another FDA guidance [2,3].

Based on the information in the present Q&A guidance documents, under certain circumstances FDA allows sponsors to develop biosimilars with fewer strengths than all licensed strengths of the reference products. Nevertheless, in addition to different strengths, different delivery devices or container closure systems are also considered as different presentations of biological medicinal products, as well [1-4]. Accordingly, the related Q&A I.6 appearing initially in the first Q&A draft guidance dated February 2012 [1] concerned not only the different strengths but also the different delivery devices or container closure systems as different presentations of reference products. The draft answer (A.I.6) simply stated that there is no need for obtaining licensures for all existing presentations of a reference product, but there may be a need for seeking licensure for a specific presentation in case a medical indication necessitates use of that specific presentation of the reference product [1]. It was finalized in 2012 [2] but later updated/retained in Revision 1 [3] and in the newly published (September 2021) Revision 2 of the final Q&A guidance, which is the current version in act [4].

On the other hand, the issue whether a sponsor may develop a biosimilar with a strength different than the licensed strengths of the reference has first come into attention as a new Q&A (I.21) in FDA's New and Revised Draft Q&As on Biosimilar Development and the BPCI Act (Revision 2) draft guidance dated December 2018 [5]. The negative answer referring to the section 351(k) [2] (A) (i)(IV) of the PHS Act and concluding that it is not possible to seek an approval through either a 351(k) or a supplement to an approved 351(k) application, for a strength of a biosimilar different than that of the reference product [5] was retained in the current final Q&A guidance in act [4]. Furthermore, following publication of the new draft guidance of FDA in 2017 for demonstration of interchangeability [6], the Q&A (I.12) related to the demonstration of the sameness of the strength of an injectable biosimilar with its reference in the initial draft [1] and final [2] Q&A guidance documents was revised to include not only the proposed injectable biosimilars but also the proposed injectable interchangeable products. Following withdrawal from the Revision 1 of the final Q&A guidance [3], Q&A (I.12) was first moved to the Revision 2 [5] and then retained in the newly published (September 2021) current version (Revision 3) of the draft new and revised draft Q&As guidance [7], where it was concluded that, in general it is possible to demonstrate the strength sameness of injectable biosimilars or interchangeable products with their references by proving the sameness of the total content (in mass or units of activity) and the concentration (in mass or units of activity per unit volume) of the drug substances through information and data obtained during analytical similarity assessments. Similarly, for biosimilar or interchangeable

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candidates provided as bulk solids such as lyophilized powders for preparation of constituted or reconstituted solutions, demonstration of the same total content of drug substance (in mass or units of activity) of both products provides the basis for the evidence for the strength sameness. Furthermore, the guidance counseled providing information on the concentration of such products when constituted or reconstituted as an injection and that it is the same as for the reference product [7].

Interestingly, in contrast to FDA, both World Health Organization (WHO) and the European Medicines Agency (EMA) express a more flexible approach to the issue of strength: Although there is no recommendation regarding the strength similarity between biosimilar and reference products in its current biosimilar guideline in act [8], WHO addresses the issue in its Q&A document published in 2018 as a complementary to the WHO's biosimilar guideline where it is stated, in answer to QIII-4, that in general, the concentration or the strength of the drug substance of a biosimilar should be same with that of the reference product, but deviations regarding strength may be possible provided that it is justified [9]. Similarly, although EMA requires the confirmation of a comparable strength for the biosimilar and reference product, justifiable deviations from the reference product with respect to strength are possible upon demonstration that any difference does not compromise safety [10,11].

On the other hand, the FDA's strict negative approach regarding the presentation differences derived from the strength does not appear to apply to those derived from the delivery devices or container closure systems since it was clearly answered in response to Q.I.4 in the current final Q&A Guidance that the delivery device or container closure system design differences may be acceptable between biosimilar and reference products provided that the statutory standard for biosimilarity are met together with satisfactory performance data and that these differences do not end up with conditions of use, strengths, dosage forms or administration routes different than the reference product [4]. Similarly, in answer to related question QIII-3, WHO concluded that a proposed biosimilar may have a different delivery device or container closure system than the reference if it can be demonstrated that the container closure system does not affect the stability of the biosimilar during long-term storage and that the delivery device/container closure system has no adverse impact on quality, safety, efficacy, and usability [9]. In accordance, EMA allows differences in container/closure systems upon appropriate justification of potential impact of different presentation on safety and efficacy [10,11]. Thus, for instance, a biosimilar may have a pre-filled syringe or an autoinjector as the delivery device even if the reference has only a vial form provided that the reference and the proposed biosimilar are shown to be comparable [4,9].

As the only regulatory authority with a distinct definition of and a guideline specific for interchangeable biosimilar products [12], container closure system or delivery device differences specific for interchangeable candidates were only brought into attention by FDA among other regulatory agencies. Initially, on the basis of the answer (A.I.4) to the Q.I.4 in the first draft Q&A guidance, it was seen that FDA applied further considerations for interchangeables not only to ensure the absence of significant alterations in critical design attributes, product performance or operating principles, but also to avoid requirements for additional instructions to patients and healthcare providers regarding the safe alternation of switching between interchangeable and reference without the intervention of the prescribing physician [1]. Later, that part of the A.I.4 was retained in following final [2] and draft additional Q&A [13] guidance documents both published in 2015 but withdrawn in the final Q&A guidance dated 2018 [3] with a reference to FDA's new draft guidance specific for interchangeable biosimilars [6]. Although the considerations for developing presentations for interchangeable products were covered quite extensively in section VIII of the draft guidance [6], they are revised very concisely in the current final guidance in act where it is briefly noted that, beyond that for biosimilarity, presentation i.e., container closure system and any delivery device constituent part for the purpose the guidance, may influence the requirements for interchangeability. It has been recommended that sponsors developing a proposed interchangeable product should either generally not seek licensure for a presentation different than the reference product or should discuss the issue of developing such a presentation with FDA to determine, through FDA evaluation, if the presentation for which the licensure is sought could support demonstration of interchangeability [12].

In conclusion, although both EMA and WHO regulations allow deviations in strength of biosimilars from the reference upon justification, FDA shows a strict negative approach requiring the strength sameness of the newly developed injectable biosimilar or interchangeable product with the reference and provides methods for demonstration of the sameness of the strength. Contrastingly, although FDA expresses a much more flexible regulatory approach, just as EMA and WHO, to the other forms of presentation differences between biosimilar and reference products derived from the differences in designs of container closure systems or delivery devices, this flexibility does not involve proposed interchangeable products since FDA recommends sponsors of these agents to develop only the licensed presentations of the reference products. Therefore, sponsors should consider the above-mentioned differences in approaches of different regulatory authorities during development of formulation and presentation of their proposed biosimilars or interchangeables.

## Conflicts of Interests

The authors have no conflicts of interests.

## Author Contributions

Gokce Demiray: Search, writing; Sadi S. OZDEM: Idealization, writing, conceptualization, review of the commentary.

## References

1. U.S. Department of Health and Human Services, Food and Drug

Administration Center for Drug Evaluation and Research (CDER), Center for Biologics Evaluation and Research (CBER) (2012) Guidance for industry. Biosimilars: Questions and answers regarding implementation of the biologics price competition and innovation act of 2009. DRAFT GUIDANCE.

2. U.S. Department of Health and Human Services, Food and Drug Administration Center for Drug Evaluation and Research (CDER), Center for Biologics Evaluation and Research (CBER) (2015) Biosimilars: Questions and answers regarding implementation of the biologics price competition and innovation act of 2009. Guidance for industry.
3. U.S. Department of Health and Human Services, Food and Drug Administration Center for Drug Evaluation and Research (CDER), Center for Biologics Evaluation and Research (CBER) (2018) Questions and answers on biosimilar development and the BPCI Act, guidance for industry. Revision 1.
4. U.S. Department of Health and Human Services, Food and Drug Administration Center for Drug Evaluation and Research (CDER), Center for Biologics Evaluation and Research (CBER) (2021) Questions and answers on biosimilar development and the BPCI act, guidance for industry. Revision 2.
5. Guidance for Industry, DRAFT GUIDANCE. U.S. Department of Health and Human Services, Food and Drug Administration Center for Drug Evaluation and Research (CDER), Center for Biologics Evaluation and Research (CBER) (2018) New and revised draft q&as on biosimilar development and the BPCI act (Revision 2).
6. U.S. Department of Health and Human Services Food and Drug Administration, Center for Drug Evaluation and Research (CDER), Center for Biologics Evaluation and Research (CBER) (2017) Considerations in Demonstrating Interchangeability with a Reference Product Guidance for Industry, DRAFT GUIDANCE.
7. U.S. Department of Health and Human Services, Food and Drug Administration Center for Drug Evaluation and Research (CDER), Center for Biologics Evaluation and Research (CBER) (2021) New and Revised Draft Q&As on Biosimilar Development and the BPCI Act (Revision 3), Guidance for Industry, DRAFT GUIDANCE.
8. (2013) Guidelines on evaluation of similar biotherapeutic products (SBPs). Annex 2, TRS No 977. WHO Expert Committee on Biological Standardization, Sixtieth report. World Health Organization, Geneva.
9. (2018) WHO Questions and Answers: Similar biotherapeutic products. Complementary document to the WHO Guidelines on evaluation of similar biotherapeutic products (SBPs). World Health Organization.
10. (2014) Guideline on similar biological medicinal products. CHMP/437/04 Rev 1 Committee for Medicinal Products for Human Use (CHMP).
11. (2014) Guideline on similar biological medicinal products containing biotechnology-derived proteins as active substance: Quality issues (Revision 1). EMA/CHMP/BWP/247713/2012 Committee for Medicinal Products for Human Use (CHMP).
12. U.S. Department of Health and Human Services, Food and Drug Administration Center for Drug Evaluation and Research (CDER), Center for Biologics Evaluation and Research (CBER) (2019) Considerations in demonstrating interchangeability with a reference product, guidance for industry.
13. U.S. Department of Health and Human Services, Food and Drug Administration Center for Drug Evaluation and Research (CDER), Center for Biologics Evaluation and Research (CBER) (2015) Biosimilars: Additional Questions and Answers Regarding Implementation of the Biologics Price Competition and Innovation Act of 2009, draft guidance for industry; availability.

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