30 November 2012

Submission of comments on 'Guideline on similar biological medicinal products containing biotechnology-derived proteins as active substance: quality issues (revision 1)' (EMA/CHMP/BWP/247713/2012)

Comments from:

Name of organisation or individual
Biotechnology Industry Organization (BIO)

Please note that these comments and the identity of the sender will be published unless a specific justified objection is received.

When completed, this form should be sent to the European Medicines Agency electronically, in Word format (not PDF).

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1. General comments

Stakeholder number *(To be completed by the Agency)*	General comment (if any)	Outcome (if applicable) *(To be completed by the Agency)*
	The Biotechnology Industry Organization (BIO) thanks the European Medicines Agency (EMA or Agency) for the opportunity to submit comments on the "Guideline on similar biological medicinal products containing biotechnology-derived proteins as active substance: quality issues (revision 1)" (the Guideline). BIO represents more than 1,100 biotechnology companies, academic institutions, state biotechnology centers and related organizations across the United States and in more than 30 nations. BIO members are involved in the research and development of innovative healthcare, agricultural, industrial and environmental biotechnology products, thereby expanding the boundaries of science to benefit humanity by providing better healthcare, enhanced agriculture, and a cleaner and safer environment. BIO commends EMA for the issuance of this science-based revision on quality requirements for a biological medicinal product claiming to be similar to one already marketed. The document addresses many relevant issues associated with the topic, and we believe it will assist manufacturers that are developing biosimilar products and help ensure that patients will receive high	

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	quality biosimilar products, especially since the Guideline facilitates a global development approach for biosimilars, including embracing the concept of Quality Target Product Profile (QTPP). BIO welcomes the inclusion of Quality Target Product Profile (QTPP), and we request greater clarity on its intended use. BIO believes that the QTPP has a recognized place in the development of biosimilar products, as it is acknowledged that the first step in developing a biosimilar molecule is to characterise, as fully as possible, the reference product to allow for a meaningful comparability program and process. Accordingly, we agree that the QTPP should be "detailed at an early stage of development" and "form the basis for the development of the biosimilar product and its manufacturing process." BIO continues to welcome EMA's distinction between comparability exercises for process changes introduced during development and exercises intended to demonstrate biosimilarity (see line 77 stating that "This guideline does not address the comparability exercise for changes introduced in the manufacturing process of a given product (*i.e.*, changes during development and post-authorisation), as outlined by ICH Q5E;" and line 123 stating "That for the purpose of clarity, any	

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	comparability exercise(s) for process changes introduced during development should be clearly indentified in the dossier and addressed separately from the comparability exercise versus the reference medicinal product.”). Accordingly, in the past, BIO has requested EMA ensure that it uses the term “comparability” to apply to intramanufacturer situations only, as consistent with other regulatory documents including the International Conference on Harmonization’s (ICH) *Q*5E – *Comparability of Biotechnological/Biological Products Subject to Changes in Their Manufacturing Process*. (See BIO Comments Draft Guideline on Similar Biological Medicinal Products (CHMP/437/04) available at http://www.bio.org/sites/default/files/20050228.pdf; and on *Draft Guideline on Similar Biological Medicinal Products Containing Biotechnology-Derived Proteins as Active Substance: Quality Issues* (EMEA/CHMP/BWP/49348/2005) available at http://www.bio.org/sites/default/files/20050617.pdf) However, because the draft Guideline continues to use the terms “comparability” and “similarity” interchangeably, we urge EMA to formally make a statement explicitly recognizing the difference between conducting a comparability assessment of an innovator product before and after a manufacturing change versus assessments required to establish biosimilarity. This	

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	recognition would serve to clarify the extremely important point that information contained in documents concerning changes within a company's own process are not to be considered and adopted as adequate scientific guidance for the development of similar biological medicinal products by a second company. Specific, detailed comments on the text are included below. We would be pleased to provide further input or clarification of our comments, as needed.	

2. Specific comments on text

Line number(s) of the relevant text *(e.g. Lines 20-23)*	Stakeholder number *(To be completed by the Agency)*	Comment and rationale; proposed changes *(If changes to the wording are suggested, they should be highlighted using 'track changes')*	Outcome *(To be completed by the Agency)*
Section 1. Introduction Lines 55–56 and Section 5.2. Comparability Lines 194-196		Comment: The language disclaiming the use of public standards for assessment of similarity is not strong enough. The term "not sufficient" implies that the evaluation is relevant to the comparability exercise. A public standard is never the basis of comparison with the reference medicinal product, even if the standard may have originally derived from the same Sponsor. Proposed Change: BIO proposes to revise the text as follows: "*Evaluation of a biosimilar with respect to a publically available standard may be relevant to ensure compliance with compendial requirements for identity, quality and potency, but is not otherwise relevant for the purpose of assessing comparability to the reference medicinal product.*"	
Section 1. Introduction Lines 62-65		Comment: The paragraph acknowledges that a biosimilar Sponsor would be unlikely to have complete information regarding a reference product and the process by which it is made to conduct an "exhaustive comparison." However, the Guideline requires the sponsor to provide a level of detail such that "firm conclusions can be made." BIO requests that the Guideline provide greater clarity regarding the levels of detail on what attributes (*e.g.*, comparative assessment of biosimilar candidate versus reference quality and safety attributes) are being asked for, including whether, as suggested by the text,	

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		manufacturing process comparisons are also being requested. BIO recommends that the Guideline assert the need for state of the art comparative characterization complemented by stepwise testing to resolve residual uncertainties. Proposed change (if any):	
Section 4. Manufacturing process of a similar biological medicinal product Lines 127-130		Comment: *"[I]t is advisable to generate the required quality, safety and efficacy data for the biosimilar comparability exercise with product manufactured with the final manufacturing process and therefore representing the quality profile of the batches to be commercialised."* The word "advisable" is used in the context of which material may be used by the biosimilar Sponsor to perform a comparability assessment (*i.e.*, small or pilot scale versus final scale). It appears the intent is to encourage such a Sponsor to use material from an at-scale commercially viable process intended for licensure. BIO believes that any Sponsor should be expected to conduct such definite comparability assessments specifically using materials from their "final manufacturing process," and thus the Guideline language should be strengthened accordingly. Proposed change (if any): BIO proposes the phrase "it is advisable to" be replaced with "Sponsors should be strongly encouraged to" so that the new sentence reads as follows: *"[S]ponsors should be strongly encouraged to generate the*	

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		required quality, safety and efficacy data for the biosimilar comparability exercise with product manufactured with the final manufacturing process and therefore representing the quality profile of the batches to be commercialised."	
Section 5.1. Reference medicinal product Line 134		Comment: The Guideline currently specifies that "several different batches of the reference medicinal product should be used to provide a robust analysis and to generate a representative quality profile." Developing a sufficiently sized reference product specific data set should be a key element of the biosimilar comparative assessment strategy. "Several" could be interpreted to be as few as two. It seems unlikely that a biosimilar Sponsor would be able to develop a reasonable snapshot of reference product variability with such limited data. Proposed change (if any): BIO suggests replacing the word "several" with "multiple" so that the sentence reads: "*Multiple different batches of the reference medicinal product should be used to provide a robust analysis and to generate a representative quality profile.*" Proposed change (if any): BIO proposes adding the following additional language: "*The relative age of the different batches of reference medicinal product should also be considered when establishing the target quality profile. The number of batches of reference product characterised should be sufficient to*	

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		ensure that the extent of variability in the reference product profile is understood throughout its shelf life.”	
Section 5.2. Comparability exercise Line 156		Comment: “The applicant should demonstrate that the desired product and product-related substances present in the finished product of the biosimilar are highly similar to that of the reference medicinal product.” Proposed change (if any): Because, by definition, product includes product-related substances, BIO proposes the phrase “and product-related substances” be removed from the sentence in order to avoid confusion. The edited sentence would read: “*The applicant should demonstrate that the pattern of heterogeneity of the desired product present in the finished product of the biosimilar is highly similar to that of the reference medicinal product.*”	
Section 5.2. Comparability exercise Line 164		Comment: The requirement for “target acceptance criteria” for comparability is not clearly linked to the earlier requirement to develop a Quality Target Product Profile (QTPP). BIO requests clarity as to whether these are the same or different concepts? Proposed change (if any): BIO proposes adding the following additional language: “*These criteria may be derived from the QTPP defined during process development, with refinements as needed based on further characterization of the reference*	

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		medicinal product."	
Section 5.2. Comparability exercise Line 173		Comment: *"[I]t is advisable to generate the required quality, safety and efficacy data for the biosimilar comparability exercise with product manufactured with the final manufacturing process."* The word "advisable" is used in the context of which material may be used by the biosimilar Sponsor to perform a comparability assessment (*i.e.*, small or pilot scale versus final scale). It appears the intent is to encourage such a Sponsor to use material from an at-scale commercially viable process intended for licensure. BIO believes that any Sponsor should be expected to conduct such definite comparability assessments specifically using materials from their "final manufacturing process," and thus the Guideline language should be strengthened accordingly. Proposed change (if any): BIO proposes the phrase "it is advisable to" be replaced with "Sponsors should be strongly encouraged to" so that the new sentence reads as follows: *"[S]ponsors should be strongly encouraged to generate the required quality, safety and efficacy data for the biosimilar comparability exercise with product manufactured with the final manufacturing process."*	
Section 5.3.1. Physicochemical properties		Comment: As drafted, the paragraph appears to focus on structure diversity associated with amino acid sequence and glycosylation related variants only. Proteins are subject to a	

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Lines 216-230		variety of other post-translational modifications (*e.g.* oxidation, deamidation, phosphorylation, etc.) which also contributes to the heterogeneous nature of protein biologics. They are often comprised of diverse populations of related structural variants. For example, fifteen of twenty commonly occurring amino acids are subject to chemical modifications. Proposed change (if any): As such, BIO believes that the Guidance should be broadened to recognize the possibility that multiple post-translational modifications may occur and that comparisons between biosimilar candidates relative to reference products need to take this into account unless suitable justification can be provided.	

Please add more rows if needed.