October 31, 2013

Submission of comments on Guideline on Similar Biological Medicinal Products (CHMP/437/04 Rev1)

Comments from:

Name of organisation or individual
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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).

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) for the opportunity to submit comments on the revised "Guideline on Similar Biological Medicinal Products (CHMP/437/04 Rev1)." BIO commends EMA on the update of this Draft Guideline, which provides an important international precedent for the regulation of biosimilar biological medicinal products. 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 other 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 appreciates this opportunity to comment on the revised "Guideline on Similar Biological Medicinal Products (CHMP/437/04 Rev1)." We would be pleased to provide further input or clarification of our specific, detailed comments, which follow in Section 2, 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)*
Lines 25-29		**Comment:** BIO recommends adding a reference to Article 10.4 of Directive 2001/83/EC, as it is this article that specifically allows for biosimilar products. **Proposed change (if any):** "This Guideline outlines the general principles to be applied for similar biological medicinal products (also known as biosimilars) as referred to in Article 10.4 and Section 4, Part II, Annex I to Directive 2001/83/EC, as amended, where it is stated that '*the general principles to be applied [for similar biological medicinal products] are addressed in a guideline taking into account the characteristics of the concerned biological medicinal product published by the Agency*'."	
Lines 44-47		**Comment:** BIO recommends adding a reference to Article 10.4 of Directive 2001/83/EC, as it is this article that specifically allows for biosimilar products. **Proposed change (if any):** "The Committee for Medicinal Products for Human Use (CHMP) issues specific guidelines concerning the scientific data to be provided to substantiate the claim of similarity (or biosimilarity) used as the basis for a Marketing Authorisation Application (MAA) for any biological medicinal product (as defined by Article 10.4 and in Section	

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		3.2.1.1, Part I, Annex I to Directive 2001/83/EC, as amended)."	
Lines 48-51		**Comment:** BIO recommends providing a reference to article 10.4 of Directive 2001/83/EC, as it states that "The type and quantity of supplementary data to be provided must comply with the relevant criteria stated in Annex 1 and the related detailed guidelines." **Proposed change (if any):** "The scope of the guideline is to fulfil the requirement of Article 10.4 and section 4, Part II, Annex I to Directive 2001/83/EC, as amended, which states that '*the general principles to be applied [for similar biological medicinal products] are addressed in a guideline taking into account the characteristics of the concerned biological medicinal product published by the Agency*'."	
Lines 53-55		**Comment:** BIO recommends adding a reference to ensure compliance with the relevant administrative procedures and policies of the EMA and with the current guideline CHMP/437/04. **Proposed change (if any):** "The CHMP guidelines addressing the planning and conduct of biosimilar comparability studies should always be read in conjunction with relevant scientific guidelines, administrative procedures and legislative provisions in force in the Union."	

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Lines 59-61		**Comment:** BIO suggests further clarification regarding interchangeability. **Proposed change (if any): "**The EMA evaluates biosimilar medicines for authorisation purposes. The Agency's evaluations do not constitute nor include recommendations on whether a biosimilar ~~should~~ can be used interchangeably with its reference product. The decisions on interchangeability and/or substitution rely on national competent authorities/prescribers and are outside the remit of EMA/CHMP. Member States have access to the scientific evaluation performed by the CHMP and all submitted data in order to substantiate their decisions."	
Lines 65-66		**Comment***:* In addition to being the proper legal basis for biosimilar applications, article 10.4 of Directive 2001/83/EC, as amended, also lays down substantive requirements for requiring results of 'appropriate pre-clinical tests or clinical trials,' which should be reflected in this guideline. **Proposed change (if any):** "The data requirements for similar biological medicinal products are found in Article 10.4 and Part II, Section 4 of the Annex of Directive 2001/83/EC, as amended."	
Lines 76-79		**Comment:** BIO suggests editing the definition offered for	

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		"biosimilar" for clarity and consistency. **Proposed change (if any):** "A biosimilar is a biological medicinal product that ~~contains a version of the active substance of~~ is highly similar to an already authorised original biological medicinal product (reference medicinal product)."	
Lines 80-81		**Comment:** BIO believes that deleting the first sentence of the paragraph that begins on Line 80 will better clarify the intended message. **Proposed change (if any):** "~~In principle, the concept of a biosimilar is applicable to any biological medicinal product. However, i~~In practice, the success of developing a biosimilar..."	
Lines 81-82		**Comment:** BIO recommends using consistent nomenclature to describe the nature of biosimilar biological medicinal products. **Proposed change (if any):** "...will depend on the ability to produce a ~~close copy~~ medicinal product that is highly similar to the reference medicinal product..."	

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Lines 86-89		**Comment:** BIO recommends revising the paragraph to better reflect the internationally-aligned scientific opinion on biological/biotechnology-derived products. **Proposed change (if any):** "The standard generic approach (demonstration of bioequivalence with a reference medicinal product by appropriate bioavailability studies) which is applicable to most chemically-derived medicinal products is ~~in principle~~ not appropriate to biological/biotechnology-derived products due to their complexity."	
Lines 91-93		**Comment:** BIO believes that this bullet point conflates the term 'comparability' with 'biosimilarity'. These are distinct exercises. ICH Q5E guidance is appropriate when optimizing an approved process for a product that has undergone significant R&D and a full pre-clinical and clinical regulatory approval process. The assessment of biosimilarity following an attempt to reverse engineer a reference product is necessarily a far more extensive exercise. Comparison of drug substance and drug product at various stages of manufacture is an important part of the comparability exercise. This is not possible as part of a biosimilarity assessment since the manufacturer does not have the extensive manufacturing data and experience of the originator and can only compare their version of the product with the final product of the originator. The biosimilar Sponsor	

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		is therefore required to produce a far more extensive package of analytical, non-clinical and clinical data to support their assertion of biosimilarity than is called for under ICH Q5E. CHMP/437/04 Rev1 should therefore make clear that the two exercises are distinct. BIO suggests making a clear differentiation between a biosimilarity exercise (scope of CHMP/437/04 Rev1) and the process followed after manufacturing changes as described in ICH Q5E. **Proposed change (if any):** "While ~~T~~the scientific principles of such a biosimilar comparability exercise are ~~based on~~ related to those applied for evaluation of the impact of changes in the manufacturing process of a biological medicinal product (as outlined in ICH Q5E), in general, more data and information will be needed to establish biosimilarity."	
Line 104-106		**Comment:** BIO agrees with the premise of this paragraph and believes it would benefit from more specifics on the scope of the "justification or further studies." **Proposed change (if any):** "The posology and route of administration of the biosimilar should be the same as that of the reference medicinal product. Deviations from the reference product as regards formulation or excipients require justification ~~or~~ and further studies to show these deviations do	

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		not have any clinically meaningful impact on safety (including immunogenicity) and/or efficacy."	
Lines 112-113		**Comment:** BIO recommends revising to more accurately reflect the nature and scope of the similarity exercise. **Proposed change (if any):** "Comparative safety and efficacy of biosimilars with their reference products have to be demonstrated in accordance with the data requirements laid down in Directive 2001/83/EC, as amended."	
Lines 117-120		**Comment:** BIO welcomes the Agency's reference to the need for clear product identification to facilitate pharmacovigilance monitoring. However, BIO recognizes that in practice batch numbers of medicinal products are often not recorded, and the recorded name is often the international non-proprietary name (INN), particularly in those countries that are required by law to prescribe by INN or in situations where the name consists of INN plus company name. BIO shares the Agency's concern for proper pharmacovigilance monitoring and believes that assigning unique INNs to all biologics should be a component of any strategy to facilitate robust, reliable pharmacovigilance monitoring. **Proposed change (if any):**	

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Lines 128-134		**Comment:** BIO recommends clarifying that the choice of non-EEA authorised comparator is restricted to ICH countries. **Proposed change (if any):** "However, with the aim of facilitating the global development of biosimilars and to avoid unnecessary repetition of clinical trials, it may be possible for an Applicant to compare the biosimilar in certain clinical studies and in vivo non-clinical studies (where needed) with a non-EEA authorised comparator (i.e. a non-EEA authorised version of the reference medicinal product) which will need to be authorised by a regulatory authority with similar scientific and regulatory standards as EMA (i.e. ICH countries only)."	
Lines 138-143		**Comment:** BIO believes that clinical PK and/or PD bridging studies are necessary additions to three-way, head-to-head comparative analytical exercises between EEA-approved, non-EEA approved reference biologic products and intended biosimilars. **Proposed change (if any):** "As a scientific matter, the type of bridging data needed will typically include data from analytical studies (e.g., structural and functional data) that compare all three products (the proposed biosimilar, the EEA-authorised reference product and the non EEA-authorised comparator), and ~~may~~ will also include clinical PK and/or PD bridging studies data for all three products. All comparisons should meet the target acceptance criteria for analytical and	

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		PK/PD similarity which will be determined on a case-by-case/product-type basis."	
Lines 148-150		**Comment:** BIO recommends revising the sentence to avoid misinterpretation. **Proposed change (if any):** "The guiding principle of a biosimilar development programme is to establish similarity between the biosimilar and the reference product ~~by the best possible means~~, ensuring that the ~~previously proven~~ safety and efficacy proven for ~~of~~ the reference medicinal product also applies to the biosimilar."	
Lines 159-160		**Comment:** BIO believes that the stepwise approach is always recommended throughout the development programme. **Proposed change (if any):** "A stepwise approach is ~~normally~~ recommended throughout the development programme, starting with a comprehensive physicochemical and biological characterisation."	
Lines 164-166		**Comment:** BIO believes that a single study population may not always be adequately sensitive to detect differences between the proposed biosimilar and the reference product; therefore, depending upon the indication sought by the Sponsor, a study in more than one population may be	

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		necessary. **Proposed change (if any):** "The ultimate goal of the comparability exercise is to exclude any relevant differences between the biosimilar and the reference medicinal product. Therefore, studies should be sensitive enough with regard to design, population, endpoints and conduct to detect ~~such~~ any difference~~s~~ that may be relevant to any clinical indication which is sought by the applicant."	
Lines 167-170		**Comment:** BIO is concerned that, depending upon the interpretation of this passage, biosimilars could reach the market that have not been studied sufficiently in humans, meaning safety and efficacy will only be evaluated post-approval. Further, the biosimilar approach already allows for a case-by-case decision to further reduce the data package if warranted by the quality and robustness of the data, which raises the question as to why this specific provision is warranted. **Proposed change (if any):**	
Lines 171-172		**Comment:** The draft guideline indicates that a comprehensive comparative 'PD fingerprint profile' may be sufficient to allow some products to avoid the need for comparative clinical efficacy study. Although it is acknowledged that a fingerprint approach is an extension of the PD concept that is already	

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		discussed in detail in published guidances, this concept is not scientifically appropriate for all classes of biologics and their biosimilars. As such, BIO does not consider that this is a useful or helpful concept for the guideline, as it should only be considered on a case-by-case basis depending upon the number of known PD markers and the complexity of the molecule in question and not as an overarching principle for biosimilarity. **Proposed change (if any):** BIO suggests either omitting the reference to PD fingerprinting from this guideline or adding additional discussion explaining the limitations of this concept and providing specific criteria for use of multiple markers where none of them is an accepted surrogate for clinical efficacy.	