November 27, 2013

Submission of comments on 'Guideline on similar biological medicinal products containing biotechnology-derived proteins as active substance: non-clinical and clinical issues' (EMEA/CHMP/BMWP/42832/2005 Rev. 1)

Comments from:

Name of organisation or individual
Biotechnology Industry Organization (BIO) 1201 Maryland Ave SW Suite 900 Washington, DC 20024 USA Contact: Andrew W. Womack, Ph.D., Director, Science and Regulatory Affairs (awomack@bio.org)

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 containing biotechnology-derived proteins as active substance: non-clinical and clinical issues (EMEA/CHMP/BMWP/42832/2005 Rev. 1)." BIO commends EMA on the update of this Draft Guideline, which provides an important international precedent for the development and 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. In general, BIO agrees that a stepwise approach is desirable in biosimilar development, beginning with	

Stakeholder number *(To be completed by the Agency)*	General comment (if any)	Outcome (if applicable) *(To be completed by the Agency)*
	physicochemical similarity before commencing non-clinical and final clinical development. BIO also agrees that '*the nature and complexity of the reference product has an impact on the extent of the (non-) clinical studies to confirm biosimilarity,'* however, we strongly believe that it is ultimately the degree to which the reference product can be elucidated, in terms of both its physiochemical properties at its molecular level and its mechanism of action (MoA), that will have an influence on the amount of work required to confirm biosimilarity. While BIO considers extrapolation between indications an important consideration underlying the biosimilar framework, BIO strongly believes that it is important to ensure that each extrapolated indication is fully justified. BIO believes that it is clear that additional evidence will usually be required, although it may differ depending on clinical experience, available literature data, MoA of the active substance of the reference product in each indication, and the receptors involved. Such additional evidence and justification are necessary to demonstrate separately the safety and efficacy of each of the extrapolated indications. This general principle is set out in the Annex to Directive 2001/83, as amended, and we ask that the competent authorities follow it and carefully	

Stakeholder number *(To be completed by the Agency)*	General comment (if any)	Outcome (if applicable) *(To be completed by the Agency)*
	review the justifications provided by the biosimilar applicants. BIO appreciates this opportunity to comment on the revised "Guideline on similar biological medicinal products containing biotechnology-derived proteins as active substance: non-clinical and clinical issues (EMEA/CHMP/BMWP/42832/ 2005 Rev. 1)." 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 55-56		**Comment:** BIO suggests editing the definition offered for "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 68-69		**Comment:** BIO agrees that the nature and complexity of the reference product will have an impact on the studies required to confirm biosimilarity but believes this will manifest in the ability to characterise the structure and function of the reference product. **Proposed change (if any):** "The extent to which the structure and function of the reference product can be fully characterised ~~nature and complexity of the reference product~~ has an impact on the extent of the (non-) clinical studies to confirm biosimilarity."	
Lines 76-77		**Comment:** BIO believes that the term "suitable biomarkers" should be defined with greater clarity, to include: *i.)* biomarkers used in the development of the reference product, or *ii.)* biomarkers which have a patho-physiological link to the	

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)*
		therapeutic drug effect of the biosimilar. **Proposed change (if any):**	
Lines 77-78		**Comment:** While BIO agrees that the safety profile of the reference product is very important and informative in determining the focus of safety studies, BIO believes that safety studies should also be informed by residual uncertainty remaining from the analytical, early-clinical and clinical biosimilarity assessment. BIO also believes that it is important for immunogenicity studies to be conducted pre- and post-authorisation regardless of the immunogenic profile of the reference product. **Proposed change (if any):** "The safety profile of the reference product will ~~determine~~ inform the focus of the safety studies both pre- and post-marketing. However, immunogenicity studies will always be required."	
Line 116		**Comment:** In line with the step-wise approach recommended by the CHMP for the development of biosimilar products, BIO believes that the guideline should require non-clinical studies to be conducted prior to clinical development. **Proposed change (if any):** "Any ~~N~~non-clinical studies will ~~should~~ be performed before initiating clinical trials."	

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 137-139		**Comment:** BIO suggests providing a recommendation regarding the characteristics of the lots of reference product for *in vitro* biosimilarity testing. **Proposed change (if any):** "They should be performed with an appropriate number of batches of the reference product and of the biosimilar representative of that in clinical use and intended for clinical use, respectively."	
Lines 140-141		**Comment:** BIO appreciates the emphasis on the importance of the *in vitro* non-clinical studies and the fact that these are considered paramount for the non-clinical comparability exercise. BIO believes that these studies should use test systems that are reflective of the underlying disease etiology. Also, BIO recommends specifically mentioning that studies should assess clinically relevant aspects secondary to the primary target. **Proposed change (if any):** "Together these assays should broadly cover the spectrum of pharmacological/toxicological aspects known to be of relevance for the reference product and for the product class, using test systems that are reflective of the underlying disease etiology and current scientific knowledge. Studies should include the assessment of pharmacological/toxicological aspects known to be clinically	

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)*
		important but secondary to the primary target (*e.g.*, multiple clinically active cytokines may be affected indirectly through the activity of a single cytokine agonist or antagonist).”	
Lines 160-162		**Comment:** BIO believes that specific safety or toxicity concerns identified for the reference product should be considered when the need for *in vivo* non-clinical studies is evaluated. An additional factor to be considered in evaluating the necessity and scope of *in vivo* studies is the inability to rule out differences in relevant quality attributes due to the difficulty in characterizing a given product. This difficulty could be due to the inherent complexity or heterogeneity of a product or due to the limited clinical or regulatory experience with a given product or class. BIO suggests that it is especially critical that potential safety issues with such products be evaluated in a step-wise fashion, starting with *in vivo* non-clinical studies. **Proposed change (if any):** “• Relevant differences in formulation, e.g. use of excipients not widely used for biotechnology-derived proteins. • Any specific safety or toxicity concerns that have previously been identified for the reference product. • The inability to rule out relevant quality differences between the reference product and the biosimilar	

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)*
		candidate due to difficulties in characterizing the product, such as for highly complex products, biological substances arising from extraction from biological sources and/or those for which little clinical and regulatory experience has been gained.”	
Lines 179-180		**Comment:** BIO suggests providing a reference to the 3R’s principle to avoid any risk of ambiguity. **Proposed change (if any):** “The principles of the 3Rs (replacement, refinement, reduction) according to Article 4 of Directive 2010/63/EU should be considered when designing any in vivo study.”	
Lines 200-201		**Comment:** Differences with the potential to impact immunogenicity may not be predictive when extrapolating data from animals to humans, and such effects are likely to be very rare and difficult to ascertain. Usually assessment in clinical studies is most relevant and preferred. Since the word “quality” is often used as a general description of excellence of standard or level, this may lead to misunderstandings. BIO, therefore, suggests deleting, since the types of differences referred to in this sentence are already described in the sentence before. **Proposed change (if any):**	

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)*
		"These ~~quality~~ differences may have an effect on immunogenic potential and the potential to cause hypersensitivity."	
Line 209		**Comment:** BIO recommends revising for clarity. **Proposed change (if any):** "...with the intended clinical route of administration, local tolerance..."	
Lines 214-216		**Comment:** BIO recognizes that the scale and site for any given product may not be the same as that used to manufacture the clinical supply, yet it is essential to use the same process that will be employed when the product is approved for commercialization. **Proposed change (if any):** **"**However, it is recommended to generate the clinical data required for the comparability study with the test product derived from the ~~final~~ same manufacturing process and therefore representing the quality profile of the batches to become commercialised."	
Lines 218-221		**Comment:** BIO believes that a stepwise approach is desirable in biosimilar development. **Proposed change (if any):** "The clinical comparability exercise is ~~normally~~ a stepwise procedure that should begin with pharmacokinetic (PK) and~~, if feasible,~~ pharmacodynamic (PD) studies followed by clinical efficacy and safety trial(s)..."	

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 233-236		**Comment:** BIO believes that criteria used in standard bioequivalence studies for chemically-derived products are generally not directly applicable to biological products. BIO also believes that the term "comparability limits" should be defined or referenced to provide greater clarity. **Proposed change (if any):** "While ~~T~~the criteria used in standard clinical bioequivalence studies, initially developed for chemically derived, orally administered products may be acceptable in the absence of specific criteria for biologicals, they are generally not directly applicable. ~~Nevertheless~~ Therefore, the comparability limits for the main PK parameters should be defined and justified prior to conducting the study."	
Lines 237-238		**Comment:** BIO believes the most sensitive test model should be used for demonstration of comparable pharmacokinetics. **Proposed change (if any):** "For the demonstration of comparable pharmacokinetics, ~~it is advisable to select~~ the most sensitive test model should be selected.	
Lines 249-250		**Comment:** BIO believes the anti-drug antibodies discussion would benefit from a discussion of neutralizing versus non-neutralizing antibody formation. **Proposed change (if any):** "Anti-drug antibodies should be	

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)*
		measured in parallel to PK assessment using the most appropriate sampling time points. Studies of anti-drug antibodies should have adequate specificity and sensitivity to discern and quantify the existence of neutralizing vs. non-neutralizing antibodies."	
Lines 256-257		**Comment:** BIO believes secondary parameters should also be measured and quantified. **Proposed change (if any):** "Secondary parameters such as t_{max}, volume of distribution, and half-life, should also be ~~estimated~~ measured and quantified."	
Lines 264-267		**Comment:** BIO's long-standing view, based on the current state of scientific knowledge concerning biotechnology products, is that clinical studies beyond pharmacokinetic/pharmacodynamic (PK/PD) studies are essential for the evaluation of safety and effectiveness for biosimilar products. This is because minor changes made by a manufacturer to starting materials or to manufacturing processes can lead to changes in the product that may not be detectable by any other means **Proposed change (if any):** "Normally, comparative efficacy trials are required for the demonstration of clinical comparability. In certain cases, however, comparative PK/PD studies between the test and the reference medicinal product	

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)*
		may ~~be sufficient to demonstrate~~ inform clinical comparability, provided that all the following conditions are met:"	
Lines 280-282		**Comment:** BIO recommends caution when interpreting that multiple surrogate PD markers/biomarkers would be more valid or sound than a single nonvalidated marker, if none of these multiple markers are themselves validated/accepted. Also BIO believes that examples (as offered in Lines 275-278) of the "sound pharmacological principles" that "may provide sufficient evidence to conclude on clinical comparability" would benefit the utility of the guideline. **Proposed change (if any):** BIO suggests that EMA either omit reference to this concept, or if it remains, provide additional discussion explaining its limitations and providing specific criteria for use of multiple markers where none of them is an accepted surrogate for clinical efficacy.	
Lines 289-291		**Comment:** BIO believes that the study population for efficacy trials should be justified as being the most sensitive for detecting any potential differences between the biosimilar and reference biological products. **Proposed change (if any):** "The study population should be representative of approved therapeutic indication(s) of the reference product and be justified as being the most sensitive for detecting any potential differences between the biosimilar	

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)*
		and the reference in terms of safety, efficacy, and immunogenicity."	
Lines 291-294		**Comment:** BIO believes that the clinical comparability study should be conducted in an approved indication for which the reference product (by default) has been studied, because that informs the design, duration and size of the study. **Proposed change (if any):**	
Lines 295-302		**Comment:** BIO believes the clinical study design section should discuss acceptable margins for determining comparability within equivalence or non-inferiority trials. **Proposed change (if any):** "In general, an equivalence design should be used. The comparability limits for the main outcomes should be defined and justified using scientifically valid, evidence-driven statistical methods prior to conducting the study. The use of a non-inferiority design may be..."	
Lines 328-330		**Comment:** BIO believes that the principle of a step-wise development programme implies that the goal of a pivotal efficacy study is to evaluate and *confirm* biosimilarity in a specific clinical setting rather than to *establish* comparability. **Proposed change (if any):** "Clinical safety is important throughout the clinical development programme and is	

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)*
		captured during initial PK and/or PD evaluations and ~~also~~ as part of the pivotal clinical efficacy study ~~establishing comparability~~.”	
Lines 330-331		**Comment:** BIO believes that the safety profile of the reference product is only one piece of information that informs the need for interrogating safety of a biosimilar candidate; in addition, any signals from already-conducted (non-)clinical studies may be informative to the need and scope of safety studies in the pivotal setting. **Proposed change (if any):** “Comparative safety data should normally be collected pre-authorisation, their amount depending in part on the type and severity of safety issues related to the reference product.”	
Lines 345-346		**Comment:** BIO agrees that the immunogenicity testing of the biosimilar and the reference products should be conducted within the comparability exercise by using the same assay format and sampling schedule, however, it is necessary to be clear that the assays used in all biosimilarity exercises must meet current standards, which may require a new assay to be developed. **Proposed change (if any):** “Immunogenicity testing of the biosimilar and the reference products should be conducted within the comparability exercise by using the same assay	

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)*
		format and sampling schedule, which must meet all current standards."	
Lines 357-359		**Comment:** BIO believes that specific definition of the features of the immunogenicity profile of the reference product (*e.g.*, immunogenicity rate, clinical consequences of immunogenicity, *etc*.) that would justify shorter follow-up data pre-licensing for chronically administered products would benefit the draft guideline. **Proposed change (if any):**	
Lines 361-368		**Comment:** BIO believes that the impact of decreased immunogenicity on safety should also be discussed, in particular the potential risk of over-dosing patients. Also, because lower immunogenicity may act as a sensitive biomarker to signal a potential difference between the biosimilar and the reference product, BIO recommends including a statement that further investigation into the cause of lower immunogenicity is warranted in order to exclude other clinically meaningful differences. **Proposed change (if any):** "A higher immunogenicity as compared to the reference product may become an issue for the benefit/risk analysis and would question biosimilarity. However, a lower immunogenicity for the biosimilar is also possible scenario and for this case the impact on efficacy and	

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)*
		safety should be discussed; depending upon the impact on efficacy and safety, lower immunogenicity~~, which would not~~ may preclude approval as a biosimilar. In case of reduced development of neutralizing and/or clearing antibodies with the biosimilar, the efficacy analysis of the entire study population could erroneously suggest that the biosimilar is more efficacious than the reference product."	
Lines 369-370		**Comment:** Data from the labels of many approved biological products indicate that immunogenicity differs when used and approved in multiple indications. BIO believes, therefore, that it is more appropriate to assume the default that immunogenicity will likely differ among indications. **Proposed change (if any):** "For biologicals with multiple indications, immunogenicity ~~could~~ is likely to differ among indications and absence of immunogenicity assessment in a particular indication for the biosimilar ~~may have~~ will need to be justified."	
Lines 398-400		**Comment:** BIO believes that any specific monitoring imposed on the reference product or product class should be included in the pharmacovigilance plan for the biosimilar product. **Proposed change (if any):** "Within the pharmacovigilance plan, any specific safety monitoring imposed on the reference medicinal product or product class should be ~~taken into~~	

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)*
		~~consideration~~ adequately addressed in the pharmacovigilance plan for the biosimilar product."	
Line 403		**Comment:** BIO recommends that the risk management plan include generation of sufficient safety data for any extrapolated indications. **Proposed change (if any):** "...programme of the biosimilar. If marketing authorization is granted on the basis of indication extrapolation, the risk management plan should include generation of sufficient safety data in the extrapolated populations."	
Lines 404-408		**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):**	

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 409-411		**Comment:** BIO does not consider that the principles of 'switching' and 'interchange/interchanging' fall within the scope of this guidance. **Proposed change (if any):** "~~Depending on the handling of biosimilars and reference medicinal products in clinical practice at national level, 'switching' and 'interchanging' of medicines that contain a given biological might occur. Thus, applicants are recommended to follow further development in the field and consider these aspects as part of the risk management plan. In addition, a~~ Available data on switching should be carefully assessed during the review of adverse reaction reports."	

Please add more rows if needed.