December 31, 2011

Submission of comments on

"Concept paper on the revision of the guideline on similar biological medicinal products containing biotechnology-derived proteins as active substance: non-clinical and clinical issues" (EMA/CHMP/BMWP/572828/2011)

Comments from:

Biotechnology Industry Organization

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) for the opportunity to submit comments on “Concept paper on the revision of the guideline on similar biological medicinal products containing biotechnology-derived proteins as active substance: non-clinical and clinical issues.” 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 notes that the concept paper does not address immunogenicity in the context of risk management plans. In some situations, neutralizing antibodies can result in important clinical consequences for patients, and a sponsor may need to provide ongoing antibody evaluation support services to support the risk	

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	management plan; this would also permit a physician to confirm the cause of an unwanted drug reaction (whether immunogenicity or loss of efficacy) and, hence, make a better informed decision on therapy. BIO suggests consideration for more information on extrapolation to sensitive patient populations. It is suggested that the criteria outlined in the World Health Organization (WHO) guideline may be a useful starting place. In particular, it would be helpful to have guidance with an emphasis on studying biosimilarity in these specific patient populations with regards to clinical effect. BIO suggests the criteria for extrapolation should discuss when a similar safety or immunogenicity profile may be inferred from the less sensitive population when these situations might be addressed in a risk management plan, or when comparative studies are required prior to receiving marketing authorization for such indications. Specific, detailed comments 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 2: **Problem Statement**, last sentence		**Comment:** BIO believes there is an overemphasis placed on the 3 R principles (replacement, reduction and refinement) as a driving force for revision of the original non-clinical requirements, which are already greatly reduced compared to ICH S6 or S6R1 requirements for an innovator program. A more balanced framing of the issues is recommended. The following points should be noted in any revision to this general guideline. In vitro assessments alone cannot predict with a high degree of assurance that a biosimilar produced by a new manufacturing process will not have new, unexpected safety issues or unexpected effects on pharmacokinetic (PK) and pharmacodynamic (PD) responses. Major, important safety signals or changes in PK/PD can be screened for in limited in vivo studies in relevant animal models before subjecting clinical subjects to unknown risk. The use of limited numbers of relevant species is consistent with the principles of appropriate use of animals and appropriate numbers of animals used. It should be determined by the Sponsor, on a case-by-case basis, what the scope of testing should be to 'derisk' the molecule adequately and avoid unnecessary testing in human subjects.	

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Section 3: **Discussion**, paragraph 1		**Comment:** BIO believes there is an overemphasis on the importance of the 3 R principles at the expense of assuring the ability to predict human safety from limited non-clinical pharmacokinetic or toxicology studies. Historically, adequate predictions of human safe use conditions have been determined on small group size studies (N = 3 to 5/group) in general toxicology studies conducted in non-rodents. It is not necessary that these studies be powered to allow statistical evaluation and interpretation. Experience with innovator compounds suggests that most clinically important differences can be detected from the limited group size noted above. In the case of a biosimilar, because the study design is controlled to the selected reference compound, the key outcome is the **comparison** of the non-clinical pharmacokinetic and safety profile of the biosimilar to a selected reference compound on the basis of clinical signs, clinical pathology, and anatomic/microscopic changes. In this highly controlled setting, it should be possible to detect important differences. The current language regarding the relevance of such a comparative study is too strong; we suggest stating a more balanced position. **Proposed change:** ~~"According to the principles of 3 R the number of animal experiments should be reduced. The finding of a relevant species is challenging especially when considering the development of monoclonal antibodies and potentially other~~	

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		~~more complex biotechnological medicinal products, as often only non-human primates can be considered to give useful information. The current guideline recommends e.g. to consider at least one repeat does toxicity study. The number of animals that can be used would probably be small, and the relevance of such a comparative study in non-human primates can therefore be questionable."~~ "**Non-clinical pharmacokinetic and toxicology studies conducted to support the safe clinical use of a biosimilar should be designed in consideration of the 3 R principles. The selection of relevant species and the design of studies should be determined on a case-by-case basis based upon product attributes. Non-clinical bioanalytical or in vitro assessments may not be sufficient to predict clinical PK or PK/PD as the new process used to manufacture the biosimilar may produce product characteristics that unexpectedly affect bioactivity, key pharmacokinetic parameters, and/or tissue distribution. The need for and design of such studies should be determined by the Sponsor. These studies may be helpful in assuring the Sponsor that the projected dose of the biosimilar product will be the same as the dose of the reference product. Since bioanalytical or in vitro laboratory studies may not be able to predict unexpected safety issues that are the result of the biosimilar being produced by a new**	

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		manufacturing process, the Sponsor may wish to conduct a limited toxicology study in a relevant species as defined in ICH S6R1. The need for and design of such a study should be determined by the Sponsor. An abbreviated toxicology study design limited to only a single, comparative dose and, single sex, and excluding a recovery evaluation, may be acceptable. In situations where no toxicology study is performed, the initial clinical studies should be conducted at a dose lower than the projected reference dose and a conservative dose escalation design followed."	
Section 3: **Discussion**, Page 3, end of first full paragraph		**Comment:** *"...it would be unlikely that superiority would be found in a phase III study."* By the same logic, it is equally 'unlikely that inferiority' would be found, but it is still important to verify or confirm beyond that of quality, nonclinical and PK/PD assessments. The evaluation for non-inferiority is to confirm (within predetermined margin) that the biosimilar has expected efficacy, and the evaluation of non-superiority is to confirm it does not have more potency or demonstrate a different effect size since that would also indicate a potential for increased untoward effects that are associated with the mechanism of action. **Proposed change:** **"Phase III is a clinical confirmation of equivalent safety**	

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		and efficacy."	
Section 3: **Discussion**, Immunogenicity: paragraph 7, last sentence		**Comment:** The clinical sampling schedule for assessing the potential immunogenicity of a biosimilar should be determined by comparison with the selected reference product. Sampling schedules should be the same in each arm of the clinical study to facilitate comparisons. The role of the bioanalytical assay used in determining the immunogenicity incidence and profile of the biosimilar compared to the reference product should be considered in the evaluation. The duration of the required follow-up period should be justified by the Sponsor and be determined on a case-by-case basis, considering the knowledge of the reference product and frequency of exposure. If the immunogenicity rate of a biosimilar is shown to be less than that of the reference product and this is believed to be the result of an improved manufacturing process, it may be that the new biosimilar product would still be designated as a biosimilar, provided that a highly similar safety, efficacy, non-clinical and CMC profile is demonstrated prior to approval. **Proposed change:** ~~"With regard to the immunogenicity data, one-year follow-up data are requested in the current guideline in case of chronic administration. The guideline does not inform requirements for products not intended for chronic administration. With regard to the measurement of antibodies, an optimal sampling~~	

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		~~schedule should be considered in order to take into account e.g. the onset and duration of the antibody formation as shown by the data of the reference product. Biosimilar products produced with modern technologies may result in a reduced immunogenicity as compared to the reference product, and the BMWP will discuss if these products would still qualify as a biosimilar."~~ "**The clinical sampling schedule for assessing the potential immunogenicity of a biosimilar should be determined by comparison with the selected reference product. Sampling schedules should be the same in each arm of the clinical study to facilitate comparisons. The role of the bioanalytical assay used in determining the immunogenicity incidence and profile of the biosimilar compared to the reference product should be considered in the evaluation. The duration of the required follow-up period should be justified by the Sponsor and determined on a case-by-case basis; follow-up periods of less than one year may be acceptable in certain situations. If the immunogenicity rate of a biosimilar is shown to be less than the reference product and this is believed to be the result of an improved manufacturing process, it may be that the new biosimilar product would still be designated a biosimilar, provided that a highly similar safety, efficacy, non-clinical and CMC profile is demonstrated**	

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		prior to approval."	
Section 3: **Discussion**, Page 3, Last Paragraph of Section		**Comment:** Immunogenicity assays are dependent on concentration, affinity and isotype of the immunogenicity, therefore, it is not valid to compare biosimilar and reference product immunogenicity profiles unless the same assay is used. **Proposed change**: **ADD: "Immunogenicity of a biosimilar must be compared to the reference product using the same assay. The goal should be to establish similarity with sufficient data pre-approval."**	
Section 3: **Discussion**, Page 3, Last Paragraph of Section		**Comment:** If the immunogenicity profile of a biosimilar is different than the reference product, then the negative and beneficial aspects of immunogenicity should be considered before concluding similarity. In some cases, immunogenicity may enhance efficacy through cross-linking or sustaining the circulating levels of the therapeutic. In other cases, higher exposure due to decreased immunogenicity may impact off-target effects. **Proposed change**: If the incidence of immunogenicity of the biosimilar is less than that of the reference product (as demonstrated in head-to-head clinical trials using the same assay), then the impact of immunogenicity on efficacy and	

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		safety should be considered before concluding similarity.	
Section 3: **Discussion**, Page 3, Last Paragraph of Section		**Comment:** Current methodologies may detect a higher incidence of immunogenicity for the reference product than originally reported. The method of communication of this result should be considered. **Proposed change: ADD: "State-of-the-art assay methods for immunogenicity detection should be used in the similarity assessment. Immunogenicity incidence rates should be communicated in relation to the reference product."**	
Section 4: **Recommendation**, page 3, "Non-clinical Issues"		**Comment:** The guidance has little information about potential use of state-of-the-art in vitro and in vivo assays to assess non-clinical safety. Emphasis should be on use of models/assays such as target binding studies, immunological receptor binding studies, evaluation of effector function (for Fc containing molecules), and use of human donor blood assays (e.g., cytokine expression assays). While such tools may not be needed in all cases, it would be helpful for the guidance to indicate when such enhanced tools may be warranted (e.g., differences in relevant quality attributes are detected between the biosimilar and reference product).	

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		Proposed change: BIO proposes that the guideline provide a clearer focus on the circumstances when non-clinical in vivo studies would not be necessary to mitigate risks (in human subjects/patients).	
Section 4: **Recommendation**, Page 3, Beginning of First Paragraph Under "Clinical issues"		**Comment:** *"The guideline should be clearer with regard to the need of pharmacodynamic markers in addition to the PK parameters in phase I studies."* **Proposed change:** BIO suggests changing the word "need" to "use of" so that the sentence reads: "The guideline should be clearer with regard to the use of pharmacodynamic markers in addition to the PK parameters in phase I studies."	
Section 4: **Recommendation**, Page 4, First paragraph of Page		**Comment:** There are situations where PD markers provide a useful, dose-sensitive marker of proximate pharmacological effect without necessarily being accepted as a surrogate for efficacy. Such markers may be valuable for increasing confidence in biosimilarity evaluated in Phase I studies, especially when the accepted clinical endpoints or surrogate endpoints are known to be relatively insensitive to dose. **Proposed change**: It would be useful for the guideline to expand upon the utility of "unvalidated" markers for the overall comparability exercise.	

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Section 4: **Recommendation**, Page 4, Second Paragraph		**Comment:** *"Also the possibility of using a non-inferiority design in the pivotal phase III studies in certain cases will be considered."* Non-superiority should be evaluated in a sequential manner to confirm that the molecule does not have an unanticipated difference in clinical potency or effect that could increase the frequency or severity of untoward effects. **Proposed change**: **ADD: "**If primary study design is non-inferiority, then a pre-specified assessment of non-superiority should be required. In the unlikely circumstance that the biosimilar is superior, then the molecule would not be considered a biosimilar, but can be further developed following regulations for novel biologics."	
Section 4: **Recommendation**		**Comment:** Taking into account the suggested points noted above, BIO supports the recommendation.	

Please add more rows if needed.