BIOTECHNOLOGY
INDUSTRY
ORGANIZATION

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30 June 2005

EMEA Biologics Working Party Secretariat
Attention: Linda Olsson
European Medicines Agency
7 Westferry Circus
Canary Wharf
London
E14 4HB
United Kingdom

Re: draft Guideline on Similar Biological Medicinal Products Containing Biotechnology-Derived Proteins as Active Substance: Quality Issues (EMEA/CHMP/BWP/49348/2005)

Dear Ms. Olsson:

The Biotechnology Industry Organization (BIO) submits these comments on the draft *Guideline on Similar Biological Medicinal Products Containing Biotechnology-Derived Proteins as Active Substance: Quality Issues*. BIO members include more than 1,000 biotechnology companies (including major manufacturers and emerging enterprises), academic institutions, and biotechnology centers. Our members invest heavily in the research and development of biotechnology and pharmaceutical products in the European Union (EU) and elsewhere, and employ thousands of highly skilled persons in the EU. We appreciate the opportunity to submit comments on the draft guideline. These comments do not reflect all of BIO's concerns regarding a potential approval process for similar biological medicinal products; rather they focus solely on the specific guideline

referenced above, and supplement our comments on the European Medicines Agency's (EMEA's) draft *Guideline on Similar Biological Medicinal Products* (CHMP/437/04).1

I. General Comments

a. Clinical studies must be an essential component of any development program for similar biological medicinal products

BIO supports certain important assumptions that underlie the framework now being developed in Europe for similar biological medicinal products. For example, BIO agrees with the EU's statement that "generic" marketing authorization applications (MAAs), based on evidence of bioequivalence to reference products, are not appropriate for such products.2 This statement acknowledges the critical fact that the active ingredients of biotechnology-derived products are typically large molecules, with complex three-dimensional structures, patterns of glycosylation, and other characteristics that greatly affect their clinical properties. Using present technology it can be very difficult or impossible to detect critical changes in proteins. More importantly, it is often impossible to determine whether and how changes that are detected will have clinical effects. The physical and chemical tests used to determine essential similarity between a generic and innovator "small molecule" drug are often not scientifically relevant or are not sufficiently predictive for the analysis of protein products.

Due to the complex nature of therapeutic protein products and the importance of protecting patient safety, we urge EMEA not to waiver in its commitment to the scientific principles underlying the review and approval process for pioneer protein products during the development of a process for regulatory review and approval of similar biological medicinal products. We think that in important respects all protein products are unique, that each must be treated as such, and that tests performed by an innovator to demonstrate quality, safety and efficacy of its own product may not be relevant to a biosimilar manufacturer's product. Therefore, BIO does not contend that a biosimilar manufacturer would have to undertake exactly the same development program as that completed by the innovator. BIO does assert that clinical studies must be an essential component of any development program for similar biological medicinal products, in conjunction with appropriate nonclinical studies and a full quality dossier that contains all the details required for an innovator product, including rigorous product characterization and GMP

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1 BIO's comments on EMEA's draft Guideline on Similar Biological Medicinal Products (CHMP/437/04) are available at http://www.bio.org/healthcare/followon/20050228.pdf. BIO uses the term "follow-on protein product" to refer to a product that purports to be similar enough to an innovator product that an application to market the follow-on product can establish safety and effectiveness with less original nonclinical and human clinical data than the innovator had to submit.

2 This is recognized in Part II, Section 4 of Annex I to European Parliament and Council Directive 2001/83/EC, as amended by Commission Directive 2003/63/EC, which creates a special marketing authorization requirement for "similar biological medicinal products." A similar provision is contained in Article 10.4 of the text of Directive 2001/83 as amended by Council Directive 2004/27/EC, which member states must implement by the end of October 2005. Both provisions call for the issuance of detailed guidelines.

controls. In short, any manufacturer – innovator or biosimilar – that seeks to market a medicine in the EU must expect to submit the set of data sufficient to show safety and efficacy, including all of the nonclinical and clinical data needed to support the label being claimed.

To protect patient safety, the quality attributes of an experimental biological medicinal product – innovator or biosimilar – should be very carefully evaluated before any clinical trials begin (including pharmacokinetic and pharmacodynamic studies). Any differences between a claimed-similar and reference product should be identified and evaluated as to whether they may entail safety risks (*e.g.,* differences that increase the risk of immunological reactions or might otherwise affect the safety or efficacy of the product), so that appropriate nonclinical and clinical studies can be designed to take these potential risks in account. It may be useful for EMEA and the Committee for Medicinal Products for Human Use (CHMP) to coordinate the review of clinical trial applications that are submitted to the competent authorities of the member states.

b. Comparability vs. biosimilarity

BIO welcomes EMEA's distinction between comparability exercises for process changes introduced during development, and exercises intended to demonstrate biosimilarity.3 However, the draft Guideline uses the terms "comparability," "similarity," and "biosimilarity" interchangeably. We continue to request that EMEA reconsider its use of the term "comparability" to apply to intermanufacturer situations, as this use is not consistent with other regulatory documents including the International Conference on Harmonization's *Q5E – Comparability of Biotechnological/Biological Products Subject to Changes in Their Manufacturing Process*. It is extremely important that the information contained in such documents concerning manufacturing changes within a company's own process not be adopted as adequate scientific guidance for the development of similar biological medicinal products by a second company. Product comparability testing for intra-manufacturer changes yields meaningful results because the innovator begins from its intimate and exhaustive knowledge of a process that has proven capable of producing a high quality, safe, and effective finished product. Critical manufacturing information and data about the innovator's product, which are needed to provide the proper context in which to assess "comparability," are often protected trade secrets that are not available to another manufacturer. Such information and data may include specific protocols for the manufacturing process, and reference standards or test methods for the reference product. In the absence of such context, the impact of any changes to the product or the process must be assessed differently. To avoid confusion, BIO suggests that the term "comparability" not be used in the discussion of similar biological medicinal products.

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3 Examples include the statement on page 3 (section 1.3) 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 addressed by ICH Q5E" and the statement on page 4 (section 2) that "For the purposes of clarity, any comparability exercise(s) for process changes introduced during development should be clearly identified and addressed separately from the comparability exercise intended to demonstrate biosimilarity to the reference product."

We also note that the term "active substance" is used in the draft Guideline to refer both to the finished bulk drug substance as well as the desired molecular moiety(ies) present in the drug substance. Clarification throughout the document would be helpful.

c. Public Discussion

BIO is participating in the public discussion of the standards that might apply to review of similar biological medicinal products, and we do not believe that these standards should be developed solely in the context of individual MAAs, where scientific advice that is broadly applicable to industry is not open to public consideration and comment until after approval decisions have been made. Therefore we applaud EMEA for establishing several mechanisms whereby the complex and important issues surrounding standards for similar biological medicinal products can be publicly discussed. Such issues include the importance of strong intellectual property protection, which is the key factor for economic growth and advancement in the biotechnology sector, and is essential to the success – and in some instances to the survival – of biotechnology companies. We recognize, for example, that EMEA has allowed for a 5-month comment period on its recently released draft guideline on Nonclinical and Clinical Issues related to biosimilars (EMEA/CHMP/42832/2005), and annexes concerning recombinant human insulin (EMEA/CHMP/32775/2005) and somatropin (EMEA/CHMP/94528/2005). We also understand that EMEA will cosponsor a workshop on similar biological medicinal products in December 2005.

We request that EMEA consider holding open workshops on each product category, to which representatives of the relevant Committee for Medicinal Products for Human Use (CHMP) working parties would be invited along with representatives of all segments of the biotechnology industry, the academic community, and patient organizations. BIO respectfully requests that EMEA refrain from approving applications for similar biological medicinal products until the principal and fundamental scientific and regulatory issues surrounding such products have been aired and addressed in a suitable public participatory process.

II. Specific Comments

1.1 Purpose

We are not sure of the meaning of the second paragraph in this section, "Similar Biological Medicinal Products are manufactured and controlled according to their own development, taking into account relevant and up-to-date information, such as manufacturing processes, product characteristics, stability and comparability data." We suggest that the meaning of the sentence might be clarified by substituting the following: "A Similar Biological Medicinal Product must be manufactured and controlled according to specifications and control limits that have been validated as applicable to the unique

manufacturing process for that product, taking into account relevant and up-to-date information."

We strongly support the statement in the third paragraph in this section, that comparisons of active substance and finished product against "the official data, e.g. pharmacopoeial monographs or … other published scientific data … are not sufficient to establish all aspects pertinent to the evaluation of biosimilarity," and that therefore an extensive comparability exercise will be required to demonstrate that biosimilar and reference products have similar quality, safety and efficacy profiles. Pharmacopeial monographs address minimum standards for parameters such as purity and potency. These minimum quality standards typically provide only a small subset of the information needed for adequate characterization of protein products, and do not provide information relevant to assessing product safety and efficacy. In some cases a single European Pharmacopoeia monograph covers quite distinct products (e.g., two α-interferons) that have different international nonproprietary names, different amino acid sequences, different potencies, and so on. Likewise there are single European Directorate on Quality of Medicines (EDQM) reference standards that are used for two or more distinct products (e.g., erythropoietins) that differ in potency and dosing characteristics, among other things.4 We request that this point be made clear by editing the third sentence in the third paragraph to read "Consequently, an extensive comparability exercise, including clinical and nonclinical studies, will be required . . ."

We are not certain of the meaning of the fourth paragraph in this section: "Based on the comparability approach and when supported by sufficiently sensitive analytical systems, the demonstration of comparability at the quality level may connect the biosimilar product to the nonclinical and clinical data previously generated with the reference product." We request that this sentence be edited to make clear that demonstration of "comparability" at the quality level will not eliminate the requirement for appropriate original safety and efficacy data to support marketing authorization applications for similar biological medicinal products. Also, we are not certain of the meaning of the term "connect" in this sentence; we suggest adding a clarification that the biosimilar manufacturer may not have access to the nonclinical and clinical data generated with the reference product, and may not be authorized to reference that data.

BIO also suggests revising the fifth paragraph in this section by adding the words "and nonclinical" after the phrase "the required clinical" so that the sentence reads "… to generate the required clinical and nonclinical data … ."

3. Comparability exercise for demonstrating biosimilarity

BIO strongly agrees with the first sentence in paragraph 2, which states that "… quality aspects should always be considered with regard to any implications for Safety and Efficacy." We note that minor changes made by a manufacturer to starting materials or

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4 Furthermore we note that resolution AP-CSP (99) 4 of the Council of Europe Public Health Committee, issued on 22 December 1999, states that the certificate of suitability procedure "will not be applicable to direct gene products (proteins) … ."

to manufacturing processes can lead to changes in the product that may not be detectable by current technologies. These include changed impurity profiles and varying carbohydrate composition and glycan structure, which may alter the pharmacokinetic and pharmacodynamic properties of the protein product, and, ultimately, have effects on the product's safety and effectiveness when administered to patients. Therefore we request that the second sentence of the second paragraph in Section 3 be revised to include the phrase "including nonclinical and clinical studies as necessary" so that it reads "A stepwise approach, including nonclinical and clinical studies as necessary, should be undertaken to justify any differences in the quality attributes of the biosimilar versus the reference product . . ."

With respect to paragraph 3 in this section, BIO believes that justification of minor structural differences and impurity profile differences between a reference product and a claimed-similar product could not be accomplished by analytical testing. The nature of biologics is such that not only minor differences but also differences that are undetectable using current analytical technology may have significant clinical effects; therefore the clinical significance of such differences should be properly explored in nonclinical studies and clinical trials. If differences are identified that could significantly affect safety or efficacy, it may be appropriate for the applicant to use the regulatory approval procedure for new active substances rather than the procedure for similar biological medicinal products. We suggest that "will" be substituted for "may" in the last sentence in this section, so that it reads "differences in impurity profiles and significant differences in product related substances will have consequences with regard to the amount of data which will be required … ."

3.1.1. Reference Medicinal Product

BIO supports the requirement that the manufacturer of a similar biological medicinal product choose a specific reference product and use it throughout the development process, and that the same reference medicinal product be used for all three parts of the dossier (*i.e.* Quality, Safety and Efficacy).

We respectfully disagree with EMEA's view that the pharmaceutical form, formulation, strength, etc of the biosimilar product may be different from that of the reference medicinal product. Attributes such as pharmaceutical form, formulation, and strength can significantly affect safety and immunogenicity. Permitting the biosimilar product to differ from the reference protein product with respect to these attributes may introduce an extra and unnecessary degree of risk.

The third sentence in this section states that "In any case, a clear scientific justification of the criteria followed to select the reference medicinal product should be provided, with specific attention to its critical parameters and quality attributes." We note that "critical parameters and quality attributes" of the reference medicinal product will ordinarily be based on nonclinical and clinical studies and other data that are proprietary to the manufacturer of the reference medicinal product, and therefore legally unavailable for use by the biosimilar manufacturer.

3.1.2. Reference Active Substance

It will rarely be possible for the biosimilar manufacturer to demonstrate that its active substance is "representative" of the reference medicinal product's active substance. As EMEA notes in paragraph 1 of this section, the biosimilar manufacturer generally does not have access to the reference product's active substance, and public reference standards (if available at all) may not have known and defined safety and efficacy profiles. In addition, the biosimilar manufacturer may not have access to the assays used by the innovator to evaluate the reference medicinal product's active substance (e.g. analytical, stability, and bioassays; and if the biosimilar manufacturer does have access to such assays, they may not be relevant to the biosimilar active substance.

EMEA suggests that where analytical tools are not capable of directly comparing the biosimilar active substance to the reference product's active substance, "the Applicant should use various approaches to obtain representative reference active substance derived from the reference medicinal product in order to perform the comparative analysis at the active substance level." We recognize that EMEA requires the appropriate validation of the sample preparation process, and request clarification of how such validation should be accomplished.

We also request that EMEA state explicitly some of the ways in which active substance derived from a finished dosage form may differ from the innovator's bulk active substance. For example, the filling and formulation process for the reference product can cause changes such as aggregation, oxidation, and deamidation increase in the active product. Stabilizers (such as human serum albumin or polysorbates, excipients, and manufacturing aids such as silicone oil) will be difficult to remove, and may be another reason why it is difficult to obtain valid results from assays used to compare the biosimilar's active substance and the active substance derived from the innovator's final dosage form.

3.2.1. Analytical considerations

We suggest that the phrase "considered with regard to any implications for Safety and Efficacy" (from the seventh paragraph on page 4 of the draft guideline) be appended to the end of the first paragraph so that it reads "… all aspects pertinent to the evaluation of quality, considered with regard to any implications for Safety and Efficacy."

We suggest that EMEA state that the use of primary standards for the purposes of method qualification and validation (for example standards that may be available from the European Pharmacopoeia and the World Health Organization) may not be sufficient for these purposes, and that the manufacturer is likely to need to generate internal reference standards as well.

3.2.2. Physicochemical properties

Issues related to impurities may be more appropriately addressed in section Section 3.2.4 "Purity and impurities."

4. Specifications

In the first sentence, the word "Products" should be inserted after "Biotechnological/Biological." In the third sentence, "Each acceptance criteria" should be changed to read "Each acceptance criterion."

We suggest that the phrase "based on relevant clinical and nonclinical studies" be appended to the last sentence of the second paragraph, so that it reads "These data should demonstrate, whenever possible, that the limits set for a given test are not wider than the range of variability of the representative reference material, unless justified based on relevant clinical and nonclinical studies."

We thank EMEA for providing stakeholders with the opportunity to provide input on its proposed regulatory framework for similar biological medicinal products. Please do not hesitate to contact us if we can provide more information on any of the topics we address above.

Respectfully submitted,

/s/

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