BIOTECHNOLOGY
INDUSTRY
ORGANIZATION

1225 Eye Street NW, Ste. 400
Washington, DC 20005

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EMEA Biologics Working Party Secretariat
Attention: Denisa De Chiara
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: Non-Clinical and Clinical Issues (EMEA/CHMP/42832/2005)

[via E-Mail to Denisa.dechiara@emea.eu.int]

Dear Ms. De Chiara:

The Biotechnology Industry Organization (BIO) submits these comments on the European Medicines Agency's (EMEA's) draft *Guideline on Similar Biological Medicinal Products Containing Biotechnology-Derived Proteins as Active Substance: Non-Clinical and Clinical 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 (SBMPs); rather they focus on the specific guideline referenced above, and supplement our comments on EMEA's draft *Guideline on Similar Biological*

Medicinal Products (CHMP/437/04) and draft *Guideline on Similar Biological Medicinal Products Containing Biotechnology-Derived Proteins as Active Substance: Quality Issues* (EMEA/CHMP/BWP/49348/2005).1

I. General Comments

In our earlier written submissions to EMEA regarding SBMPs, we have explored the three general comments below in greater depth. We are reiterating these comments briefly here as they are also relevant to the present draft guideline.

a. Clinical studies must be an essential component of any development program for SBMPs

BIO supports certain important assumptions that underlie the framework now being developed in Europe for SBMPs. 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 current technology it can be very difficult or impossible to detect critical changes in proteins, and more importantly it is often impossible to determine whether and how changes that are detected will be clinically relevant.

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 claimed-similar product. Therefore, BIO does not contend that an SBMP 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 SBMPs, in conjunction with appropriate non-clinical studies and a full quality dossier that contains all the details required for an innovator product, including rigorous product characterization and GMP controls. In short, any manufacturer – innovator or SBMP – that seeks to market a medicine in the EU must expect to submit the set of data sufficient

1 BIO's comments on EMEA's draft guidelines on SBMPs are available at http://www.bio.org/healthcare/followon/. 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 non-clinical 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.

to show safety and efficacy, including all of the non-clinical and clinical data needed to support the label being claimed.

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. similarity

BIO welcomes EMEA's distinction between comparability exercises for process changes introduced during development, and exercises intended to demonstrate similarity between an SBMP and an original/reference product.3 However, the draft guideline uses the terms "comparability" and "similarity" 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 (ICH) Guideline *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 and manufacture of an SBMP using a different process created by a different company. Please refer to our more detailed explanations of the difference between intramanufacturer and intermanufacturer manufacturing process changes in our previous written submissions to EMEA.

c. Public Discussion

BIO applauds EMEA for establishing several mechanisms whereby the complex and important issues surrounding standards for SBMPs 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 will cosponsor a workshop on SBMPs December 8-9, 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 SBMPs until the principal and fundamental scientific and regulatory issues surrounding such products have been aired and addressed in a suitable public participatory process.

3 Examples include the statement on page 3 (Section 2) 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."

II. Specific Comments

Section 1. Introduction; Subsection 1.1. Purpose

Paragraph 3

We ask EMEA to clarify that the reference product must be authorized according to the EU laws, regulations, and guidance by which EMEA operates; it cannot be a product authorized only outside the European Union (EU), or authorized within the EU but not according to EU law.

However as noted in our earlier comments to EMEA on SBMPs (and elsewhere in these comments), even when the reference product is authorized according to EU law, regulations, and guidance, substantial and critical portions of the data contained in the MAA for an innovator product are likely to be inapplicable and/or unavailable to the MAA for a claimed-similar product, for important scientific and legal reasons.

Paragraph 5

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

As we have noted in our previous comments to EMEA, attributes such as pharmaceutical form, formulation, and strength can significantly affect safety and immunogenicity. Permitting the SBMP to differ from the reference product with respect to these attributes may introduce an extra and unnecessary degree of risk.

Paragraph 6

The draft guideline asserts that when a reference product has more than one indication, "it may be possible to extrapolate therapeutic equivalence shown in one induction [sic] to other indications of the reference product." BIO believes that data supporting the approval of one indication for a claimed-similar product should not be automatically extended to support approval of other indications for that product. We request that this issue be addressed in greater detail in the guideline to emphasize, and explain why, extrapolations from one indication to another may be of concern.4

We note for example that if a protein is indicated for two different patient populations, the protein may induce different immunogenic responses in the two populations or the immunogenic response in one population may be significantly enhanced. These differences would likely not be detected without clinical studies designed to detect them

4 The EU's 2003 Directive also specifies that for each claimed indication of a biosimilar product, the safety and effectiveness must be separately demonstrated. *See* Directive 2003/63/EC.

for each indication in each patient population. Consequently, we ask EMEA to clarify that testing in one indication is generally not sufficient evidence to justify use in a different indication, and that supporting evidence from clinical trials is likely to be required.

We request that in this or other guidance, EMEA address content of labelling for SBMPs, and specifically what components of the labelling for the reference product should or should not be reflected in the SBMP labelling. For example, we suggest that adverse effects observed for the reference product be reflected in the SBMP labelling unless these adverse effects have been demonstrated to be inapplicable to the SBMP.

Section 3. Non-clinical studies

We ask EMEA to clarify that non-clinical studies are essential, i.e. not simply recommended, for the approval of all protein products. The development of an appropriate non-clinical testing program, involving drug studies in animals and other nonhuman test systems, is a critical step before the clinical testing and eventual approval of all protein products. These studies aid in the evaluation of safe dosing regimes for humans, identification of organs that may be susceptible to toxicity, and development of boundaries for safe use of the drug during clinical testing. Information from non-clinical studies may also provide important insights about potential long-term toxic effects in humans. Both in vitro and in vivo non-clinical data should be provided, and comparative non-clinical studies must be designed and powered to reveal differences between the claimed-similar and the reference product that are likely to affect safety and/or efficacy, if such differences exist.

Paragraph 1

We ask EMEA to state explicitly that where non-clinical testing reveals differences between the claimed-similar product and the reference product, it may be appropriate for the applicant to use the regulatory approval procedure for new active substances rather than the procedure for SBMPs. We note that the former procedure has been used to date for different manufacturers' versions of numerous existing biotechnology products (e.g., recombinant human insulin, somatropin, erythropoietin and α- and β-interferon). Going forward, standards for the approval of SBMPs must not conflict with or undermine the scientific standards applied for the approval of innovative versions of biotechnology products; indeed, approval of follow-on biotechnology products must be based on the same rigorous standards applied for the approval of innovative biotechnology products.

Paragraph 4

We agree that approaches to non-clinical testing "should be tailored to the specific product concerned on a case-by-case basis." Because of the uniqueness of protein products, it is often not possible to establish uniform guidance for non-clinical studies needed to support approval; rather a flexible, case-by-case, science-based approach to non-clinical assessment is necessary. We suggest that EMEA expand on this point by

referencing sections of ICH Guideline *S6 – Preclinical Safety Evaluation of Biotechnology-Derived Pharmaceuticals (July 1997)*. For instance, ICH S6 notes that the appropriate dosing levels for "preclinical" testing "may vary with each class of biotechnology-derived pharmaceutical and its clinical indication(s)."

Paragraph 8

We suggest inserting the phrase "and the dose of adequate strength" into the third sentence so that it reads "The duration of the studies should be sufficiently long and the dose of adequate strength to allow detection of relevant differences . . ."

Section 4. Clinical studies

Paragraph 1

BIO agrees that the types of clinical studies required will "depend on the type of the biological medicinal product and the claimed therapeutic indication(s)." We reiterate however BIO's long-standing view that, based on the current state of scientific knowledge concerning biotechnology products, clinical studies beyond PK/PD studies are essential for the evaluation of safety and effectiveness for claimed-similar 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 (please see our earlier written submissions to EMEA for substantiation of these points).

We recommend adding "product specific" to the second sentence so that it reads "Available disease specific and product specific guidelines should be followed when appropriate."

The guideline or other guidance documents should also address the issue of interchangeability. Specifically we ask EMEA to clarify that SBMPs will not be considered interchangeable unless the EMEA affirmatively finds them to be so following scientific review, and that the EMEA will require robust data, including comparative clinical studies, to justify claims of interchangeability.5 BIO notes that regardless of whether a protein product is found to be interchangeable with another, caution will always be appropriate when patients are switched from one protein product to another – whether it is an SBMP or a different innovative version of the product. Patients and their physicians should always be involved when any such switch is considered.

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5 We request that EMEA clarify its use of the term "therapeutic equivalence" in relation to SBMPs, and specifically the implications of this term for interchangeability. We note that the U.S. Food and Drug Administration has permitted interchangeability only when two products are "therapeutic equivalents" as defined in *Approved Drug Products with Therapeutic Equivalence Evaluations* (the "Orange Book," http://www.fda.gov/cder/orange/obannual.pdf), and that a "follow-on protein product" and its respective reference product would not meet the Orange Book definition of therapeutic equivalents.

Subsection 4.1. Pharmacokinetics

Paragraph 3

BIO agrees that the design of comparative PK studies should enable examination of parameters (such as difference in clearance and elimination half-life) that are not examined in standard PK studies; such studies should incorporate a full panel of PK parameters that are appropriate for biotechnology products. However we request that EMEA make clear that all requirements of the standard bioequivalence study (Cmax, AUC and Tmax) should also be met. Additional parameters may be outlined in disease-specific and product-specific guidance.

Subsection 4.3. Confirmatory pharmacokinetic/pharmacodynamic (PK/PD) studies

As we have stated above and elsewhere in our comments to EMEA, we believe that comparative PK/PD studies between the claimed-similar product and the reference product will not be sufficient to demonstrate equivalence, and that comparative clinical trials to confirm efficacy will be required.

In the first sentence of the last bullet point, we suggest that the phrase "at least one PD marker is accepted or even established as a surrogate marker for efficacy" be revised to read "at least one PD marker is validated as a surrogate marker for efficacy."

Section 5. Clinical safety and pharmacovigilance requirements

Safety concerns related to therapeutic proteins, particularly immunogenicity (as addressed below and in Section 6 of the draft guideline), are a critical component of any public discussion of potential SBMP approval pathways. Among the safety concerns that any manufacturer – innovators and SBMP manufacturers alike – must recognize and address in research and development for therapeutic protein products are potential sub- or superpotency, altered biodistribution, toxicity, neoactivity, altered therapeutic index, and immunogenicity.

With regard to the safety database, the number of patients should be at least the same as that studied by the innovator unless rare adverse events have been identified by the agency as a concern. If rare events have been identified, then a larger number of patients should be considered.

We ask EMEA to clarify that to permit effective pharmacovigilance, each SBMP will have a unique International Nonproprietary Name (INN). This will ensure that physicians and patients are informed and aware of the unique identity of each protein product. If patients receive multiple products without adequate record-keeping, it will be difficult or impossible to determine which product is responsible when rare immunological events or other adverse effects occur.

Paragraph 1

As we note above in our General Comments section, we think that in important respects all protein products are unique, that each must be treated as such; the complexity, variability, and heterogeneity of protein products demands a case-by-case approach to development and review. Therefore we believe it appropriate that EMEA's recommendations in this Section provide general guidance rather than giving specifics (e.g. any specific number of patients "sufficient to address the comparability of the adverse effect profiles" of the claimed-similar and reference products). We recommend that EMEA note that more details may be available in disease specific and product specific guidance. We also recommend that EMEA emphasize that even such specific guidance may not fully describe the amount and type of data that may be required for approval of particular protein products.

We suggest that in the last sentence of this paragraph, the phrase "claimed-similar product" should be used in place of "similar biological." It cannot be presumed in advance that the claimed-similar product is actually similar. In addition we suggest that the word "common" be deleted.

Paragraph 3

We request that EMEA expand on the nature and content of the "risk specification" required. We believe that any SBMP applicant should submit a full and detailed risk assessment for a claimed-similar product, just as innovators submit full and detailed risk information for original products.

We note that an SBMP sponsor will not be a position to provide a comprehensive description of "possible safety issues related to tolerability of the medicinal product that may result from a manufacturing process different from that of the originator" because the SBMP sponsor will not have access to critical confidential information about the innovator's manufacturing process.

Paragraph 4

We suggest that EMEA make specific reference to ICH Guideline *E2E – Pharmacovigilance Planning* in this paragraph. EMEA may also wish to note that pharmacovigilance plans and any necessary risk management plans should be updated as necessary, taking into account new information from post-marketing surveillance and other sources.

Section 6. Immunogenicity

We request that EMEA begin this section by stating explicitly that clinical studies of immunogenicity will be necessary for all SBMPs. For the vast majority of protein products immunogenic responses occur, but are not clinically relevant; however when clinically relevant immunogenic responses do occur they can have extremely serious

consequences including hypersensitivity, severe allergic or anaphylactic responses, or autoimmunity to endogenous proteins. Furthermore conclusions about immunogenicity of proteins are currently very difficult to draw from analytical and non-clinical safety studies. With respect to non-clinical studies, animal immune responses to the test product can be variable – as can human immune responses – and it is well established that human proteins are often immunogenic in animal models when they are not be immunogenic in humans. For these reasons the failure to detect antibodies in a non-clinical study may not predict potential immunogenicity in humans. Therefore although analytical correlation studies and animal studies will be useful and will provide some information about immunogenic responses in humans, they should not be substitutes for clinical studies.

We urge the EMEA/CHMP to consider procedures that discourage initiation of large-scale pivotal (phase III) clinical trials before smaller studies have been conducted to evaluate possible immunogenic reactions or other adverse effects. In practice, this will likely require that the EMEA supervise clinical development programs for follow-on protein products, because competent authorities and ethics committees in many member states lack the resources to make the required determinations. Individual member states cannot in any event ensure a consistent, Community-wide approach.

Factors affecting immunogenicity

We suggest that EMEA specify what is meant by "the nature of the active substance"; for example that this includes the protein's structure (defined by, among other things, its unique amino acid sequence and post-translational modifications).

In addition to the factors mentioned, immunogenicity may also be related to factors such the introduction of adjuvants during the manufacturing process, duration of treatment, and manufacturing-related contaminants; these factors should also be mentioned here.

This section only addresses immunogenicity issues related to antibody response. We request that EMEA expand this section to address other immune mechanisms that may be of concern.

Testing

The number of patients studied for the immunogenicity database should be at least the same as that studied by the innovator.

The requirement for one year of follow-up data in cases of chronic administration is reasonable and is in accordance with general principles set out in Guideline CHMP/3097/02. However we note that longer-term follow-up may be required in certain populations (e.g. children and pregnant women) or in cases where a product's mode of action is not well understood.

When appropriate, post-market antibody testing should be included as part of a risk management plan. The plan should include information about how antibody testing will be provided, and how physicians and patients will be informed about the need for such testing and the meaning and implications of results.

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

Respectfully submitted,

/s/

Sara Radcliffe
Managing Director
Science and Regulatory Affairs