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February 28, 2005

EMEA Comparability Working Party Secretariat
Attention: Susana Maria Soobhujhun
European Medicines Agency
7 Westferry Circus
Canary Wharf
London, E14 4HB
United Kingdom

RE: Comments on Draft Guideline on Similar Biological Medicinal Products (CHMP/437/04)

Dear Ms. Soobhujhun:

The Biotechnology Industry Organization (BIO) submits these comments on the draft Guideline on Similar Biological Medicinal Products issued by the European Medicines Agency (EMEA) on November 16, 2004 and released for public consultation on December 2, 2004. BIO members include more than 1,000 biotechnology companies (including major pharmaceutical manufacturers and emerging enterprises), academic institutions, and biotechnology centers. Our members invest heavily in research and development of biotechnology products in the European Union (EU) and employ thousands of highly skilled persons in the EU. We appreciate the opportunity to submit comments on the draft guideline.

BIO supports certain important assumptions that underlie the potential framework now being developed in Europe for follow-on protein products.[1] For example, the EU has stated 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 to identify critical changes in proteins, and more importantly it is often impossible to determine whether and how such changes 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. In addition, for many proteins, there are presently no reliable animal models for predicting effects in humans.

Recent experience in Europe and elsewhere demonstrates that these considerations merit careful attention. Minor changes made by one company in the manufacture of an erythropoietin product, for example, have been associated with an increased risk of very rare, but serious, immunological side effects. Given these risks, it is prudent to avoid a regulatory framework that relies on analytical testing alone to reach a determination about the authorization of a follow-on protein product, and we applaud the EMEA's direction toward requiring that each manufacturer provide the results of appropriate preclinical and clinical testing.

In asserting that clinical trials are necessary, BIO is not asserting that a follow-on manufacturer would have to undertake exactly the same clinical development program as that completed by the innovator. Indeed, 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 safety and effectiveness of its own product may not be relevant to a follow-on manufacturer's product. BIO believes that from a scientific perspective an integrated approach to development that includes rigorous product characterization, GMP controls, and appropriate nonclinical & clinical studies, may manage the risks associated with the development of follow on protein products. However, 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, as it leads public debate about the potential development of a process for regulatory review and approval of follow-on protein products. Any manufacturer - innovator or follow-on - that seeks to market a medicine in

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[1] BIO is using the term "follow-on protein product" to refer to a product that purports to be similar enough to an innovator product that a marketing authorization application (MAA) for 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.

the EU must expect to submit the set of data sufficient to show safety and effectiveness, including all of the preclinical and clinical data needed to support the label being claimed.

Our comments are set forth under two headings: first, the appropriate procedure for further action on the draft guideline (as well as the four product-specific concept papers released for public consultation on the same day); and second, the text of the guideline itself.

A. Procedural Comments on the Draft Guideline and Concept Papers

BIO welcomes constructive public discussion of the standards that might apply to review of follow-on protein products, including biotechnology products. The issues surrounding such standards are complex and of great importance to public health, and mechanisms for resolving such issues must permit all interested persons to discuss the data that should be required for follow-on protein products. We do not believe that 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 question whether the specific procedure EMEA plans to follow to develop the guideline and concept papers will adequately serve this purpose. The draft guideline itself provides no detail on the requirements for follow-on protein products, except to suggest that the standard generic small molecule (chemical drug) approach, based solely on bioequivalence studies, is scientifically not appropriate and will be insufficient. While we agree with this conclusion, the draft concept papers likewise provide no specifics concerning the amount or type of data that will be required for products claimed to be similar to reference products. We understand that concept papers are not intended to provide substantive information, but rather to present an overview of the subjects to be discussed in a later guideline. However it is noteworthy that specifics are missing even with respect to product categories for which EMEA might already have provided scientific advice (which may be confidential) to persons developing follow-on protein products. We understand that the Comparability Working Party of the EMEA plans to include more specific information about these requirements in draft annexes to the "Guideline on comparability of biological medicinal products containing biotechnology-derived proteins as active substance -- Non-clinical and clinical issues" (CPMP/Ad hoc group on (non)-clinical comparability of biotechnology products/3097/02), to be made available six months after the concept papers have been adopted, and that three months will be allowed for comments on these draft annexes.

BIO believes that the procedure described above is inadequate to obtain useful input on proposed requirements for follow-on protein products. First, we suggest that more valuable information could be gained by supplementing a longer written comment period with a public participatory process, described below, that involves an open workshop on each product category. Second, we believe that guidance on the demonstration of "similarity" between a follow-on and reference protein product should be kept clearly distinct from guidance on the demonstration of comparability when changes are made in the manufacturing process of approved products.

We suggest that EMEA allow at least six months for comments on any detailed proposals for requirements for protein products that claim to be similar to one already authorized. We also

suggest that representatives of the relevant Committee for Medicinal Products for Human Use (CHMP) working parties should be invited to attend open workshops on each product category, along with representatives of all segments of the biotechnology industry, the academic community, and patient organizations. Other measures which may enhance open discussion include detailed presentations about the assumptions underlying the proposals under discussion, and ample opportunities for participants to ask questions. Any comments received by EMEA should be subsequently fully addressed (either accepted, or rejected with an explanation) in relevant guidance documents. The use of such a public participatory process would be consistent with the provisions of Part II, Section 4 of Annex I of European Parliament and Council Directive 2001/83/EC, as amended by Commission Directive 2003/63/EC, which states that the "type and amount of additional data [to be required for similar biological medicinal products] shall be determined in accordance with relevant scientific guidelines."

Scientific guidelines serve to either guide applicants as to regulatory requirements for compiling a dossier prior to the filing of applications for MAAs, or alternatively, to "codify" an established regulatory practice, based on the experience gained during the approval of the medicinal products. It is thus difficult to understand how EMEA can effectively engage in the two practices at the same time, that is, to consult the stakeholders on the appropriate regulatory requirements and to review applications for the approval of follow-on protein products. We believe that the public participatory process we describe above will provide more consistent and transparent direction to potential applicants, and moreover is the best way of ensuring that applications for the approval of follow-on protein products meet rigorous requirements that assure patient safety and therapeutic value. Therefore, we respectfully request that the EMEA refrain from approving applications for follow-on protein products until all legal, regulatory, and scientific issues surrounding such products have been aired and addressed in a suitable public participatory process.

We also request that EMEA reconsider its use of the term "comparability" to apply to inter-manufacturer situations. BIO strongly cautions against the use of the word "comparability" in describing the relationship between innovator and follow-on protein products, because comparability is a term of art that has long been associated with "intra-manufacturer" situations, e.g., to describe the relationship between a manufacturer's product before and after manufacturing changes. The term "comparability" is used in this way by the International Conference on Harmonization (ICH) (e.g., in its 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 not be adopted as adequate scientific guidance for the development of follow-on protein products. 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 likely to be available to another manufacturer. In the absence of such context, the impact of any changes to the product or the process must be assessed differently. It is therefore misleading to use the term "comparability" to describe the relationship between innovator and follow-on protein products. To avoid confusion, BIO suggests that the term "comparability" not be used in

the discussion of follow-on protein products. In addition BIO requests that the applicability of EMEA guidance to inter- vs. intra- manufacturer situations be consistently, clearly, and explicitly stated.

While we are limiting our comments on the draft guideline to scientific issues, we believe that legal and regulatory issues pertaining to follow-on protein products are intrinsically linked with the scientific issues and cannot therefore be addressed separately, or at a different point in time. Such issues include the absolute need to ensure the protection of the confidentiality of the data submitted by BIO members to regulators. These issues should be addressed concurrently with scientific issues, and prior to finalization of the guidelines. For this reason, BIO urges the EMEA to expand the nature and scope of this important public discussion to include all relevant issues and stakeholders.

B. Comments on Guideline on Similar Biological Medicinal Products

1. INTRODUCTION

1.1 Regulatory framework

In this section and elsewhere, the draft guideline refers to demonstrating the "comparability" of follow-on protein products to reference (innovator) products. In this regard, please see our comments concerning use of the term "comparability" in Part A (p. 3) above. The term "comparability" should be reserved for the type of evaluation contemplated in ICH Topic Q5E, which governs changes in the manufacturing process for existing biotechnological/biological products. The requirements for demonstrating "similarity" of protein products made by two different manufacturers may be quite different from (and also more demanding than) those for demonstrating comparability.

2. BASIC PRINCIPLES

2.1 Application of "Biosimilar" approach

BIO strongly supports the findings contained in this section, which emphasize that the standard for review and approval of small molecule generic drugs is inappropriate for follow-on protein products. The scientific unknowns are too great and the potential risks to patients too high for any follow-on protein product to be approved without original preclinical and clinical testing by the manufacturer to show quality, safety, and effectiveness. While an exact duplication of the innovator's drug development program is not required, it is essential that each manufacturer provide all the data necessary to support the claims in its product's labeling.

BIO strongly agrees with the need to ensure that each indication for which biosimilarity is claimed by the follow-on applicant is supported by data obtained in appropriate comparative clinical trials.

The last indent in section 2.1 states that, in order to support pharmacovigilance monitoring, the specific product given to the patient should be clearly identified. BIO supports this statement.

We also note that rare side effects (especially side effects that may simply represent an increase above background rates of events that occur normally in a patient population) may well not be detected through ordinary pharmacovigilance, which relies on spontaneous reports from health professionals. When scientifically appropriate, formal programs of post-market evaluation, including post-approval clinical trials, should be considered. In addition, whenever the possibility exists for immunogenic effects, programs to test for antibody formation and other signals should be considered.

2.2 Choice of reference product

BIO supports the requirement that the manufacturer of a follow-on protein product choose a specific reference product and use it throughout the development process. Manufacturers should not be permitted to rely on inapplicable general information about a class of products, or pick and choose among indications, routes of administration, and other characteristics that have been approved for different reference products. Before any trials are initiated in humans, each follow-on applicant should be required to develop appropriate quality information to support its choice of reference product and specific plans for non-clinical and clinical studies.

Even when there are applicable monographs in the European Pharmacopoeia or a national pharmacopoeia, compliance with these should not necessarily be considered sufficient for approval. It is widely recognized that those monographs are almost always not sufficient in themselves to govern the full range of product quality issues for protein products; in fact, in some cases a single monograph governs two quite different products (e.g., interferon alfa 2a and 2b) that have different potencies, recommended dosages, and other characteristics.[3]

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.

The guideline should also address the issue of interchangeability. Specifically the document should clarify that follow-on protein products should 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 data) to justify claims of interchangeability or substitutability. 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 "similar" product, and patients and their physicians should

[3] This is further supported by applicable ICH guidance, which indicates that compliance with pharmacopoeial specifications is only one part of the acceptance criteria for biotechnology products, because such criteria are nearly always product-specific. See section 2.4, ICH Q6B (Specifications: Test Procedures and Acceptance Criteria for Biotechnology and Biological Products).

always be involved when any such switch is considered. It may be useful for each follow-on protein product to have a unique International Nonproprietary Name (INN) to assure that physicians and patients are informed and aware of the unique identity of each follow-on. If patients receive multiple products without adequate record-keeping, it will be difficult or impossible to determine which product is responsible if rare immunological events or other adverse effects occur.

3. RELEVANT GUIDELINES

3.2 Biological products containing biotechnology-derived proteins as active substances

This section should indicate that the EMEA/CHMP is developing further guidance on quality and non-clinical and clinical issues for follow-on protein products, which will be clearly distinguished from guidance on determining comparability when changes are made in the manufacturing process for existing 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/

Sara Radcliffe
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cc: Mr. Nils Behrndt
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