BIOTECHNOLOGY
INDUSTRY
ORGANIZATION

March 16, 2005

Division of Dockets Management
Food and Drug Administration
5630 Fishers Lane, Room 1061
Rockville, Maryland 20852

Re: Docket No. 2004N-0355, Scientific Considerations Related to Developing Follow-on Protein Products

The Biotechnology Industry Organization (BIO) submits this letter to clarify several scientific issues raised at the Workshop on Follow-on Protein Pharmaceuticals cosponsored by the Food and Drug Administration (FDA) and the Drug Information Association (DIA) February 14-16, 2005. BIO is the largest trade organization to serve and represent the biotechnology industry in the United States and around the world. BIO represents more than 1,000 biotechnology companies, state biotechnology centers, academic institutions, and related organizations in the United States and in 33 other nations. Our members are trailblazers in the research and clinical development of innovative biotechnology therapeutic products.

The February workshop and an earlier workshop held in September provided a necessary and welcome opportunity for open and candid discussion of important scientific matters that must be deliberated thoroughly before moving forward in this area. BIO wants again to emphasize that we believe that important legal and policy issues surrounding follow-on protein products remain unaddressed. We urge that a parallel opportunity be provided for transparent discussion of those issues for the simple reason that it is difficult to assess the practicality or validity of many suggestions made at FDA's September 2004 and February 2005 public workshops without first assessing the legal and policy environment in which they arise. We therefore again urge FDA to have a similar public process to address legal and regulatory issues concerning follow-on protein products.

BIO appreciated the opportunity to participate in the FDA/DIA public workshop. We believe the majority of the participants hold the following views:

- Generic Paradigm Under the Food, Drug, and Cosmetic Act Does Not Apply: Demonstration of pharmaceutical equivalence and bioequivalence of a follow-on protein product to an innovative product would not provide sufficient assurance that the follow-on product is safe and effective clinically. The paradigm used to approve generic drugs (chemical drugs) is not applicable to protein drugs.
- Analytical Data Concerning the Protein Product: At a minimum, analytical data should be generated to show that a follow-on protein product is "similar" to the innovative product.
- Pharmacokinetics/pharmacodynamics: Follow-on manufacturers should perform appropriate PK and PD studies to demonstrate that their products are bioequivalent to the relevant innovative products.
- Nonclinical/Preclinical Toxicology Studies: Appropriate in vivo toxicology studies provide useful information on the safety of a follow-on protein product and should be submitted; head to head comparisons are most appropriate.
- Immunogenicity Studies: Follow-on manufacturers should perform appropriate immunogenicity studies in humans after performing initial screening studies in animals.
- Clinical Studies: Adequate clinical studies of a follow-on protein product should be performed in accordance with the claims sought by the follow-on manufacturer. Interchangeability would be difficult (if not impossible) to achieve without a rigorous head to head clinical comparison that applies to the specific indication studied.
- Postmarket Surveillance: The safety of follow-on protein products should be tracked through post marketing surveillance and/or registries.

BIO also appreciates FDA's re-opening of docket 2004N-0355 so we can clarify several scientific points raised in the workshop:

1. At the workshop, statements were made that manufacturers of follow-on products will make extensive use of new technologies that were not available at the time the innovative products were approved/licensed for marketing. These statements imply that innovators continue to use outdated technologies to manufacture and to analyze their marketed products. This misconception may be due partly to the fact that the scientific literature tends to lag behind the actual application of new techniques in innovator laboratories and manufacturing facilities. Far to the contrary, innovators continue to improve their processes and to characterize their products better by adopting advanced technologies and analytical tools as they become available (for some examples, please see the presentation "Use of Analytical and Characterization Technology for the Development of Follow-On Protein Products," delivered by Andy Jones, Ph.D., Genentech, Inc,. at FDA's September 14-15 Public Workshop on Scientific Considerations Related to Developing Follow-On Protein Products.) (All the presentations from this workshop are available at

http://www.fda.gov/cder/meeting/followOn/followOnPresentations.htm. Additional presentations on this topic at the subsequent (February 14-16) DIA/FDA meeting are available at http://www.fda.gov/cder/meeting/followOn/followOnPresentations2_2005.htm.) On an ongoing basis, innovators are continually adopting new methods for in-process and final product testing, and for comparability evaluation. When innovators carry out a comparability exercise, they use both current and historical analytical tools to compare the products produced before and after manufacturing process changes. In fact, the use of currently available analytical tools is mandated by FDA under the cGMP (current Good Manufacturing Practices) regulation. Consequently, innovator's applications filed with FDA are constantly updated with new information through the regulatory pathways for post-approval manufacturing changes. In addition, the innovator companies often re-evaluate their analytical approaches based on new discoveries in their research laboratories and clinical programs.

2. During the discussion regarding non-clinical in vivo toxicology studies, structural complexity was considered by some to be the only factor in determining whether an animal toxicology study provides useful information for a follow-on protein product (however, this was not the collective opinion of the expert moderators for this session). We want to point out that there are other important factors which must be considered. The purity of a chemical drug usually can reach >99% on an absolute basis and impurities can be readily quantified down to the level of 0.1% or less. On the other hand, proteins are heterogeneous, containing numerous product-related substances and product- and process-related impurities at a much higher level. Many of these substances and impurities cannot be completely structurally characterized. Some of them cannot currently be detected by available analytical tools. Moreover, while the toxicities of chemical drugs are generally intrinsic properties of the active ingredients because of the products' purity, this is often not the case for proteins. The related substances and impurities present in a protein drug, whether they are detectable or not, can also elicit known and/or unexpected toxicities. Therefore, it is prudent to evaluate all relevant factors, including structural complexity, unique manufacturing process, limitation of analytical tools, immunogenicity, known toxicity concerns, mechanisms of action, therapeutic index, and clinical experiences, in determining which toxicology studies are appropriate for a follow-on protein product. In addition, the requirements of the ICH S6 document that describe appropriate considerations for the non-clinical safety assessment of biotechnology-derived products should be met.

3. As mandated by FDA, innovators perform analytical, non-clinical toxicology, PK/PD, and/or clinical safety and efficacy testing, as scientifically justified, when making manufacturing process changes during the investigational phases of drug development or post approval. While the scope and scale for intra-manufacturer manufacturing process changes are almost always limited, the scope and scale of differences for a follow-on product necessarily would be extensive. In the latter

case, everything (cell line, raw materials, manufacturing process and process controls, test methods, reference materials, specifications, container/closure system, and manufacturing and testing facilities) would be changed. In addition, unlike innovator manufacturers, follow-on manufacturers would not have the advantage of possessing the particular extensive knowledge of a specific product's manufacturing history and critical product quality attributes to guide them through product development. (These data are trade secrets and confidential commercial information; they constitute the intellectual property of the innovator.) Thus, the manufacture of a follow-on product is not analogous to innovators making manufacturing changes. We believe that, in all cases, follow-on manufacturers would need to perform adequate clinical studies to assure safety and effectiveness of their protein products.

4. At the workshop, there was widespread consensus that follow-on manufacturers would need to perform post marketing surveillance and/or establish registries to assess immunogenicity and other safety parameters, as the innovators do. Since a follow-on protein product will never be identical to the innovator's product (for the reasons outlined in item #3, above) and may have a different adverse event profile as discussed above (item #2), it is important to ensure that any follow-on protein product can be tracked by its own unique identification system such as bar code, lot number, and/or a different United States Adopted Names (USAN) designation as appropriate. We encourage FDA to develop an identification/tracking system appropriate for follow-on protein products, before any such approvals are considered.

5. At the workshop, it was mentioned that some protein products are currently marketed abroad as copies of innovative protein products. This argument was used to suggest that it should also be possible to manufacture and market follow-on protein products in the United States. It is BIO's longstanding position that if key issues – including scientific, legal, and policy issues - can be resolved, it may be appropriate in the future to establish an approval pathway for follow-on protein products in the United States. However, we question whether the non-innovative protein products mentioned are indeed follow-on protein products as defined by FDA (i.e., identical or similar to the innovator's product). The countries mentioned at the workshop may not have the same scientific and technical approval standards required in United States or under the guidelines of the International Conference on Harmonization (ICH). Based on the very limited data presented at the September 2004 and February 2005 workshops, we believe that significant differences exist between innovator products and various products marketed abroad as alleged "copies" of innovator products and that claims concerning the similarity of such currently marketed non-innovative products would not be substantiated after careful scientific scrutiny.

6. Our understanding is that when multiple innovator "small-molecule" drug products exist, FDA will assign one product as the reference listed drug to which a generic drug must be demonstrated to be pharmaceutically equivalent and

bioequivalent. However in the case of proteins, products from multiple innovators are approved with their own unique quality standards. (It is moreover significant to note that those several innovator products may have quite different labeling, including labeling for approved indications.) Therefore, it is not clear to us what FDA's policy would be with respect to a reference protein product when multiple innovators exist. In the absence of a reference listed drug, would a follow-on manufacturer have the freedom to select a reference drug of its choice? Would FDA establish a set of selection criteria for follow-on manufacturers? We note that if similarity to one reference protein product could be established, this would not automatically imply similarity to protein products manufactured by other innovators, owing to the uniquely complex and heterogeneous nature of proteins (please see our two earlier submissions to this docket, in which we describe more fully the important scientific differences between "small-molecule" chemical drugs and protein products).

We again thank FDA for providing the public with the opportunity to comment on important scientific issues associated with any future regulatory pathway for approval of follow-on protein products. BIO looks forward to continued opportunities to engage in thoughtful public discussion about both the scientific considerations and the legal/regulatory issues concerning follow-on protein products.

Please do not hesitate to contact us if we can provide more information on any of the topics we address above.

Sincerely,

/s/

Sara Radcliffe
Managing Director
Science and Regulatory Affairs