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Testifying on behalf of the Biotechnology Industry Organization
Before the Food and Drug Administration, HHS

Public Workshop on the Scientific Considerations Related to Developing Follow-On Protein Products

September 14, 2004

The Biotechnology Industry Organization (BIO) appreciates the opportunity the Food and Drug Administration (FDA) has made available to stakeholders to discuss scientific and technical issues surrounding whether and how so-called "follow-on" protein products may be approved using an abbreviated approval pathway. BIO requested open and meaningful debate on these issues in its Citizen Petition submitted to the agency last year, because of our concerns that significant risks to patients will arise if biological products are approved based on less than the full complement of data necessary to show safety and effectiveness. BIO is also concerned that any safety problems that develop as a result of such approvals could undermine the confidence of physicians and patients in all biological products.

We welcome this meeting, and we also look forward to the scientific workshop FDA is planning for January 2005. We believe, however, as we stated in our Citizen Petition and in subsequent submissions to FDA dockets on this topic, that the questions about how FDA deals with follow-on protein products go beyond the scientific and technical considerations which are the focus of this workshop and include legal and policy issues. We look forward to FDA initiating a similar process to discuss the significant legal and policy issues presented by "follow-on" protein products.

BIO represents more than 1,000 biotechnology companies, academic institutions, state biotechnology centers, and related organizations in all 50 U.S. states and 33 other nations. BIO members are involved in the research and development of healthcare, agricultural, industrial, and environmental biotechnology products. Representatives from a number of BIO member companies engaged in the research and development of novel biotechnology-derived protein products are also speaking at today's workshop. BIO will present three general scientific and technical concepts that are grounded by the specific hands-on experience of BIO member companies; experience that is crucial to understanding biological products. In addition, BIO will submit written testimony containing more detailed responses to the 13 specific questions posed by the agency in its Federal Register notice for this meeting, and BIO will be an active contributor to the January 2005 workshop. Many of the points that we will present today have also been made in our Citizen Petition and docket submissions, which are available on our website at www.bio.org.

First, protein products are more complicated and more fragile than most traditional "small-molecule" drugs. Compared with the small molecules that constitute the active ingredients of chemically synthesized drugs, proteins almost always have a much higher molecular weight and greater structural complexity. Proteins may be modified by the addition of carbohydrates (i.e., "glycosylated") and by other post-translational modifications. Also, protein products can be mixtures of many molecular species, and can have unique impurity profiles, which are invariably dependent on manufacturing process.

Second, the nature of a protein product is closely dependent on the starting materials and processes used to make that product. Protein products are typically made in living systems, which have inherent variability. 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 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. To ensure consistency in the characteristics of the final product, and to ensure consistent safety and effectiveness, the source material, manufacturing process, formulation, and storage conditions must be carefully kept within specifications and control limits that have been empirically determined by the manufacturer and presented for regulatory approval. Importantly, we mean specifications and control limits that have been functionally validated as applicable to a unique manufacturing process.

There are many steps involved in producing and purifying an active biological ingredient from starting materials, and these steps must remain consistent from batch to batch to ensure the quality of the final product. The types of cells used and any modification of those cells are crucial to the characteristics of the final product. The master cell bank is a unique entity, comprised of living cells; the cell lines and cell banks that would be used to make "follow-on" products would never be the same as those used by the innovator. The large-scale cell culture required to manufacture the necessary amounts of the desired protein is highly dependent on the vessels used, the components of the solution (including nutrients, growth factors, and sera), the type of fermentation process, and other conditions such as temperature, shear forces, phase, and enzymatic activity. Various and often sophisticated techniques are used for the isolation and purification of active moieties from cell culture, and the sequence and method of operation of these techniques are crucial to the final outcome. Purification steps necessary to remove undesired proteins and other impurities may result in altered forms of the desired protein, and this must be detected and prevented. On-going testing is essential during and after purification to rule out contamination and to confirm parameters such as amino acid sequence, glycosylation pattern, molecular heterogeneity and isoform profile, and potency – all of which may have an impact on a product's toxicology, pharmacokinetic and pharmacodynamic profiles, immunogenicity, and ultimately clinical safety and effectiveness. Changes to a protein product can not only render the product ineffective, but may also elicit an immune reaction which causes the body to attack endogenous proteins; the potential for eliciting such immune reactions is extremely difficult to predict using analytical testing or animal models.

Third, protein products are difficult to characterize. Even a relatively small and simple protein product is difficult to characterize, and the molecular structure of many proteins cannot be characterized fully with current technology. Thus, significant changes to the product that may occur through even a modest alteration in manufacturing process might be difficult or impossible to detect through end-product testing. Furthermore, improvements in our ability to characterize proteins through analytical testing may simply reveal more heterogeneity and complexity in approved protein products, rather than less.

While analytical and other non-clinical tests are becoming increasingly powerful and sophisticated, such tests remain limited in their ability to detect differences in manufacturing processes and changes in the final protein product that may affect clinical safety and effectiveness. For small-molecule drug products a straightforward dissolution assay or a bioequivalence study involving a small number of patients may be sufficient to demonstrate "sameness," but far more is required for a protein product. Demonstrating that known and unknown changes are unlikely to have impacted on the safety or effectiveness of a protein product requires substantial effort on the part of an original manufacturer that is intentionally making a minor change to its own manufacturing process. When innovator companies make changes in their own manufacturing processes, unanticipated changes in the product can and have occurred, and this is why FDA itself has regulated manufacturing changes for biologics so assiduously. Yet regardless of scrupulous oversight, the complex nature of biological manufacturing methods means that the manufacturing process used by a follow-on manufacturer will be different from the manufacturing process of the innovator. To establish with reasonable certainty that process differences and changes have not affected a protein product's safety or effectiveness, both innovator and follow-on manufacturers must rely not only on testing and characterization of the final product, but also on extensive development experience with the product, in-process testing, toxicology studies, in vivo pharmacokinetic and pharmacodynamic studies, and reagents and reference standards that are not typically available to another manufacturer.

While science is able to tell us much about some therapeutic proteins, this knowledge is inherently rooted in what is known about specific protein products. What is understood about a specific protein product's safety and effectiveness relates closely to a particular manufacturing process, and derives from the data obtained by the original manufacturer of the product. This manufacturer isolated and purified the active protein from selected cells; developed and refined a manufacturing process that provided for consistency in structure, purity, and potency; and tested the product's safety and effectiveness with substantial clinical trials. In cases where there is more than one approved product whose active component is a given therapeutic protein, each of the manufacturers separately conducted these activities and provided FDA with extensive data from clinical studies demonstrating their particular product's safety and effectiveness.

Because a follow-on manufacturer can never exactly duplicate the innovator's process, and because differences in process may result in differences in the protein product and its clinical effects, FDA must continue to apply consistent regulatory standards for all manufacturers, and FDA must insist on receiving the full complement of data necessary to demonstrate safety and effectiveness. A full complement of data is the set of data contained in the complete regulatory filing submitted by a manufacturer to the FDA (or other appropriate regulatory authority) sufficient to show safety and effectiveness. It includes all of the preclinical and clinical data needed to support the label being claimed. BIO does not support any regulatory framework that incorporates requirements for unnecessary preclinical or clinical testing. BIO believes, however, that it is only through a thorough assessment of safety and effectiveness, including clinical testing meeting all ethical standards, that patients can be assured that initiating treatment with or switching

to a newly available product will provide them with the anticipated benefits and safety of the treatment.

Conclusion

FDA regulatory policies for "follow-on" protein products must differ substantially from the policies applicable to small-molecule generic drugs. This is true because of the inherent complexity of protein products; the dependence of the final protein product's characteristics and activity on its starting materials and on the processes by which it is produced, purified, formulated, and stored; and the difficulty of characterizing products with great molecular complexity and heterogeneity. We reiterate our hope that this meeting, and the conference to be cosponsored by FDA and the Drug Information Association that will take place early next year, will constitute the beginning of a truly deliberative public dialogue on follow-on protein products. The questions about future policy surely include scientific, technical, and medical considerations that will affect the outcome for patients, as well as legal questions impacting on the biotechnology industry's ability to sustain the innovation for which it is known. As BIO has requested on multiple occasions, we again ask that FDA expand its interactions with stakeholders to deal with non-scientific issues, especially the important legal questions regarding the agency's authority to consider for approval abbreviated applications for so-called "follow-on" protein products based on the data generated by pioneer companies, and used without their consent.

We believe the principles governing the debate about follow-on protein products are simple and clear: that regulatory requirements must be based in sound science; that patients deserve access to appropriately tested and competitively-priced therapies; that industry's ability to make innovative medical products available through research and development should be promoted; and, most importantly, that the health and safety of the patients served by both FDA and the biotechnology industry are preserved.

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