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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) appreciates this opportunity to comment on scientific considerations related to developing follow-on protein products. BIO is the largest trade organization to serve and represent the biotechnology industry in the United States and around the world. We represent 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.

BIO applauds the Food and Drug Administration's (FDA's) decision to seek public input on relevant scientific issues before issuing any draft guidance on follow-on protein products[1] and strongly supports public participation in the process to raise, discuss, and address these and other important issues. FDA's public workshop held in September 2004, and the request for public comments under this docket, are important initial steps in this process. BIO looks forward to the release of FDA's background document on the regulatory treatment of approved natural source-derived and biotechnology protein products,[2] and to continued public discourse with FDA at the next scientific workshop on February 14-16, 2005. We also urge FDA to expand the nature and scope of this important public discourse to include important legal and policy issues.

As knowledge about protein products increases and analytical testing methods evolve, and if legal and policy issues are resolved, BIO thinks that an

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[1] The term "follow-on" refers to protein products that purport to be similar enough to the innovator's product that the follow-on manufacturer may rely on data and information developed by the innovator for approval. "Protein products" mean therapeutic protein and peptide products that are prepared from biological source materials in living systems.

[2] In October 2004, Dr. Janet Woodcock, FDA's Acting Commissioner for Operations, stated that the agency intends to release a "background document" that will "illustrate prior regulatory treatment paths of the natural source-derived and biotech protein products that are currently on the market." *FDA Follow-On Biologics Background Document to be Released by Year-End*, The Pink Sheet (Nov. 1, 2004).

abbreviated process may be possible in the future for certain protein products. BIO's comments below reflect, however, our strong belief that any such process must be grounded in sound science as well as sound policy and have a firm and adequate legal basis. The scientific unknowns are too great and the potential risks to patients too high for FDA to approve any protein product without the full complement of preclinical and clinical testing necessary to show quality, safety, and effectiveness,[3] and to support the claims in the product's labeling.

In asserting that FDA must continue to require the full complement of data necessary to show quality, safety, and effectiveness, BIO does not assert that a follow-on manufacturer would have to undertake exactly the same development and manufacturing program as that completed by the innovator. Indeed, we think the examples given below show 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. Under a future approval pathway for follow-on products, some applications may require less extensive preclinical and clinical studies than the innovator had to submit. However, the characteristics of therapeutic protein products continue to be closely dependent on the product-

[3] FDA has approved protein products under the Federal Food, Drug, and Cosmetic Act (FDCA) as new drug products and the Public Health Service Act (PHSA) as new biological products. Under the FDCA, new drug products must be high quality, safe, and effective before being approved by FDA. *See* 21 USC 355(d). This standard differs from the PHSA requirement that biological products be consistently safe, pure, and potent. *See* 42 USC 262(a)(2)(C). For purposes of these comments, any reference to "quality, safety, and effectiveness" includes the concept of "safe, pure, and potent" for biological products under the Public Health Service Act (PHSA).

specific manufacturing processes used to create them, and analytical tests – while valuable – are currently very limited in their ability to substitute for experience with a particular manufacturing process and to predict the clinical safety and effectiveness of a follow-on protein product. Therefore both preclinical safety and clinical studies are expected to be necessary for follow-on protein products in order to protect patients. As FDA leads public debate about the potential development of a process for regulatory review and approval of follow-on protein products, it is imperative that FDA not waiver in its commitment to the scientific principles underlying the review and approval process for pioneer protein products.

I. BACKGROUND

A. Innovative biotechnology therapies are critical for patients and public health

For several years, BIO has been at the forefront of the discussion on follow-on versions of protein products. This leadership position derives from the successes BIO member companies have enjoyed in pioneering innovative and life-saving treatments for patients worldwide using biotechnology processes. Due largely to the efforts of BIO members in pioneering biotechnology innovation, dozens of important therapies have entered the marketplace. These therapeutic and diagnostic products are leading to significant improvements in the care of patients

with serious diseases – in many cases providing the first approved treatment for a condition.[4]

These tremendous advances in patient care are the outgrowth of much research by government, academic, and industry scientists as well as enormous scientific effort and skill on the part of the biotechnology industry. Only by developing unique and complex manufacturing systems and establishing careful controls over those systems can biotechnology companies assure that diagnostics and therapies are consistently of high quality, safe, and effective. Throughout the drug development process, FDA plays a critical role in defining what data and information are required for approval and establishing rigorous review criteria that ensure the development of high quality, safe, and effective products.

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[4] For example, Gaucher's disease is a genetic enzyme deficiency disorder affecting approximately 30,000 people worldwide. The deficiency causes the accumulation of fatty deposits in the spleen, liver, lungs, or bone marrow, which may result symptoms that vary from minor to progressive and debilitating (such as enlarged organs, bone degeneration, anemia, easy bruising, severe disability, or even death). The first approved enzyme replacement treatment for the most common form of Gaucher's disease (Type 1) was developed by a BIO member.

BIO members have also contributed to the treatment of multiple sclerosis (MS), the most common acquired disease of the nervous system. MS is a chronic, debilitating, and unpredictable disease that affects an estimated 2.5 million people worldwide, 400,000 of them in the United States. Three BIO members developed and now market pioneering interferon products that slow both the rate of MS relapses and progression to disability – providing patients with substantial therapeutic benefits.

Similarly, BIO members have made huge strides in developing innovative biotechnology therapies to treat rheumatoid arthritis (RA), a chronic disease for which there is no known cure, that affects approximately 2.1 million Americans. Left untreated, RA can lead to painful symptoms such as irreversible joint degeneration and functional disability. Three BIO members have engineered breakthrough therapies that inhibit TNF, a naturally-occurring protein causing tissue inflammation around the joints. Compared to conventional drug treatments, anti-TNF (tumor necrosis factor) therapy has a much faster onset of action and is often recommended when other treatments are ineffective.

BIO applauds FDA's willingness to work with the biotechnology industry to foster the scientific innovation that continues to benefit patients. Science must drive any FDA decision as to whether the quality, safety, and effectiveness of protein products can be shown by abbreviated data sets (that might include less preclinical and clinical data than FDA currently requires from an innovator). Patients, FDA, and industry must be confident that scientific testing and manufacturing methods can assure high quality, safe, and effective follow-on protein products before Congress considers moving forward to create an approval process for such products.[5]

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[5] BIO has followed with great interest the development of legislation and policies on this subject in the European Union (EU). Although it is too soon to tell whether the new EU framework will result in the contemplated clarification of biosimilar regulatory pathway while protecting and enhancing innovation, a review of the new framework is informative.

In June 2003, the European Commission issued a Directive (2003/63/EC) establishing requirements for biological medicinal products including "biosimilars," the term used in the EU for biological medicinal products similar to approved innovator products. This statutory framework was carried over in EU legislation modifying the EU "community code on medicinal products. Published in April 2004, biosimilar applicants must submit pharmaceutical, chemical, biological, bioequivalence, and bioavailability data, supplemented with "the results of appropriate pre-clinical tests or clinical trials." Directive 2004/27/EC, Art. 10; *see* Directive 2003/63/EC. The type and quantity of data needed will depend on a case-by-case assessment.

In December 2003, the key EU committee responsible for product assessments, now called the Committee on Human Medicinal Products (CHMP), published two guidance documents clarifying the testing, manufacturing, and submission requirements for demonstrating the similarity of biosimilar products. For example, the CHMP states that "immunogenicity must always be addressed by clinical data, unless clinically relevant immunogenicity can be excluded by other means," and "clinical trials demonstrating equal efficacy will generally be necessary between the product to be assessed and the chosen 'reference.'" *See* Guideline on Comparability of Medicinal Products Containing Biotechnology-Derived Proteins as Active Substance: Non-clinical and Clinical Studies (Dec. 17, 2003) at 9/11. The same guideline says, "the kind of trials, the duration and type of endpoint (e.g. clinical or surrogate . . .) depend upon the experience, type of product, therapeutic area, and the availability of accepted surrogate endpoints." *Id.* The companion guidance on quality issues also states that, "comparison based on testing and characterization of active substance and finished product is not sufficient to establish all aspects pertinent to the evaluation of quality, safety, and efficacy for a biotechnology-derived protein." *Id.* As such, "the extent of pre-clinical and/or clinical bridging studies will depend on the nature of the active substance and formulation, and the complexity of its molecular structure as well as the possible differences as compared to the reference

B. FDA also must address critical legal and policy issues before proceeding further

BIO appreciates that FDA is providing an opportunity for stakeholders and scientific experts to comment on and discuss important scientific issues associated with any future regulatory pathway for approval of follow-on protein products. However, BIO thinks that discussing the scientific principles absent a full discussion and understanding of the legal framework that could govern these products may lead to inappropriate conclusions. At FDA's request, BIO is largely limiting its comments below to specific scientific issues and questions raised by the agency. However, we continue to emphasize that important legal and policy issues in this area are integrally related to the discussion of scientific issues. It is difficult to assess the practicality or validity of many suggestions made at FDA's September 2004 public workshop without first assessing the legal and policy environment in which they arise.

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product (including impurities and stability, and in some cases the finished product formulation.)" *Id.* at 8-9/11.

The EU legislation forbids reference by the European Medicines Agency (EMEA) to the innovator's file in deciding whether to approve a biosimilar. This provision coupled with the detailed data requirements detailed in the June 2003 directive and December 2003 guidelines cast doubt on whether there truly will be a reduction in the quantity of data required for approval of a biosimilar. The EU medicinal products framework also provides for considerably longer exclusivity periods for innovative pharmaceuticals as compared to U.S. law.

Finally, it is notable that, to date, no biosimilar product has been approved in Europe. The new legislation described above is not yet fully operational. Litigation is pending in the European Court of First Instance over the approvability under the EU legislation that was in effect at the relevant time of a follow-on version of human growth hormone. Thus, it is clear that, while the EU legislative experience is of great interest to American policy makers, the EU framework is very much at an embryonic stage. In November 2004 CHMP published five concept papers for comment; BIO is currently reviewing these documents.

On April 23, 2003, BIO submitted a Citizen Petition to FDA calling for meaningful public discussion of the scientific and legal issues surrounding any future approval process for follow-on protein products, including public meetings and the creation of a public docket for the submission of comments. *See generally* BIO Citizen Petition (Docket No. 2003P-0387/CP1)(Apr. 23, 2003). FDA responded in part by initiating the current public discourse concerning scientific issues. BIO appreciates this effort but believes it addresses only part of the matters raised.

In its Petition, BIO challenged the contention, set forth in FDA's 1999 draft guidance, that section 505(b)(2) of the FDCA permits FDA to approve products based on prior findings of safety and effectiveness for previously-approved products. BIO strongly disagreed with FDA's interpretation of section 505(b)(2) and continues to oppose implementing that interpretation without a public process. In addition, as BIO made clear in a supplement to the Petition submitted August 8, 2003, and in its comments to the citizen petition filed by Genentech, Inc. on April 8, 2004, FDA should not reveal or rely on any proprietary information submitted by the innovator, or findings from that information, to review or approve a follow-on product. *See* Docket No. 2004P-0171/C1 (June 16, 2004).

Under current law, FDA is prohibited from using or revealing an innovator's trade secret and confidential commercial data and information for

anything but review and approval of the particular product about which the data and information were submitted. *See* 21 USC 331(j). With respect to protein products approved under the PHSA, innovators continue to rely on long-standing regulatory policy statements that their proprietary information would not be used to approve a follow-on product based on an abbreviated data set.

Although the PHSA regulations authorize FDA to make the safety and effectiveness data and information of protein products publicly available immediately after licensure, the agency repeatedly has assured innovators that a license "is under no circumstances granted . . . to a second manufacturer based on published or otherwise publicly available data and information on another manufacturer's version of the same product." 39 FR 44602, 44641 (Dec. 24, 1974). Until the legal framework is changed by Congress and just compensation is provided for any regulatory taking, FDA must continue to protect that data and information from inappropriate disclosure and use.[6]

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[6] In a recent Canadian case, *Merck Frosst Canada & Co. v. Canada (Minister of Health)*, 2004 FC 959, the Quebec Federal Court held that all information in a drug application file (except for the approval letter and approved labeling) was exempt from disclosure under the Access to Information Act, which is the Canadian version of the US Freedom of Information Act. According to the court, non-confidential information cannot be sufficiently severed from confidential information because competitors could review excerpted information and "connect the dots and gain insight not only from what has been disclosed, but also from what has been deleted." 2004 FC 959, para. 64. This case illustrates the difficulty FDA will face in determining whether it can segregate trade secret and confidential commercial information from other public data when reviewing applications for follow-on protein products. Before proceeding to review such applications, the agency should first address these complex problems in a public process.

Therefore, three important legal and policy issues remain to be addressed before any formal action can be taken by FDA: (1) the need for public participation in the development of any approval process for follow-on protein products; (2) the lack of legal authority to approve follow-on protein products under current law; and (3) the importance of and methods for protecting innovators' trade secret and confidential commercial information. BIO urges FDA to immediately establish a public process to address these fundamental issues.

II. THE TERMS "COMPARABILITY" AND "THERAPEUTIC EQUIVALENCE" ARE NOT APPROPRIATE TO DESCRIBE THE RELATIONSHIP BETWEEN INNOVATOR AND FOLLOW-ON PROTEIN PRODUCTS

BIO urges FDA, as it proceeds with discussions on this issue, to establish more appropriate terminology to describe the relationship between innovator and potential follow-on protein products.

A. Use of the term "comparability"

BIO cautions against the use of the word "comparability" in describing the relationship between innovator and follow-on proteins, because comparability is a term of art that long has been restricted to "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 both by FDA (e.g. in its draft guidance *Comparability Protocols - Protein Drug Products and Biological Products - Chemistry, Manufacturing, and Controls Information)* and 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 FDA and ICH documents not be taken 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. Over the course of time, the innovator accumulates extensive historical data about its product. That knowledge and those data, to which the follow-on manufacturer generally would not be privy,[7] are "an integral component in determining the design of an appropriate comparability assessment program."[8] The term "comparability" assumes extensive side-by-side comparison of intra-manufacturing changes to an established process – that is, comparison of an

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[7] Historical data about protein products are not available to a follow-on manufacturer unless the information is published in scientific literature or otherwise publicly released by the innovator, or unless the innovator grants the follow-on manufacturer a license to such information.

[8] *Guidance Concerning Demonstration of Comparability of Human Biological Products, Including Therapeutic Biotechnology-Derived Products* (April 1996) (the "*April 1996 Comparability Guidance*").

innovator's protein product made after a manufacturing change with product made before the change.

Further, the "most important factor to FDA as it assesses product comparability is whether it is anticipated that any of . . . these manufacturing changes will translate into significant changes in clinical safety or effectiveness."[9] In other words, a comparability study assesses the risk that an intra-manufacturer change will have a significant impact on the quality, safety, and effectiveness profiles of the finished product. Innovators are able to assess this risk because they have access to and can control key variables – including the original product and process intermediates, assays, analytical procedures, and equipment. Even so, in some cases, innovators may be unable to detect the clinical significance of a manufacturing change without preclinical and clinical studies.

The experience of a biological products manufacturer with manufacturing a particular product provides the context within which comparability protocols – as that term is currently used by FDA – can legitimately be used. Absent such context, the impact of any changes to the product or the process by which it is produced must be assessed differently. Critical manufacturing information and data about the innovator's product, which are needed to provide to provide the proper context in which to assess "comparability,"

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[9] *Id.*

are likely to be protected trade secrets and/or difficult for another manufacturer to obtain.

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.[10]

B. Use of the term "therapeutic equivalence"

BIO also objects to the use of the term "therapeutic equivalence" as part of the current debate. "Therapeutic equivalence" is imprecise with respect to protein products because it fails to reflect the variability that inevitably exists between therapeutic protein products. "Therapeutic equivalence" is a term of art developed to describe small-molecule drug products that are pharmaceutically equivalent and that are "expected to have the same clinical effect and safety profile." *See* Introduction to *The Approved Drug Products with Therapeutic Equivalence Evaluations* (the "*Orange Book*").

Drug products meet the definition of "pharmaceutically equivalent" only if they contain an identical amount of "the identical active drug ingredient" in

[10] *See discussion of EU policies, supra,* note 6.

the same dosage form and with the same route of administration. 21 CFR 320.1(c). Because protein products are generally composed of large complex molecules (and often of mixtures of such molecules), and formulation and other key manufacturing steps often vary and lead to analytical differences among protein products that may seem alike, it is highly unlikely that a follow-on protein product will be "identical" to the product it is purporting to copy. Consequently, the terminology developed to describe chemical drugs does not reflect the scientific challenges inherent in developing requirements for therapeutic protein products.

Furthermore, according to the *Orange Book*, products that are "therapeutically equivalent" are expected to have "the same clinical effect and safety profile." *See* Introduction, *Orange Book*. Even in cases where it might be possible to establish that an innovator and follow-on product have similar clinical effect through head to head trials,[11] it is possible that two protein products manufactured using different source materials and/or different manufacturing processes will have different safety profiles. In sum, use of the term "therapeutic equivalence" to describe the relationship between two protein products erroneously may suggest that the products share the same attributes that therapeutically equivalent chemical drugs share.

[11] The difficulties associated with establishing safety and efficacy of protein products without a full complement of preclinical and clinical data is discussed below in section III.

For example, substituting insulin products in patients with diabetes could create risks for patient safety. The dosage of insulin must be individualized for each patient, because the glucose value is controlled within a narrow range of insulin dosage levels. For certain patients, glucose levels must be carefully monitored and adjusted, as needed, for optimal treatment. *See* Humalog® Label. Slight differences in potency or bioavailability could potentially result in clinically significant and harmful consequences.

Because the use of the term "therapeutic equivalence" in the context of follow-on protein products would tend to lead to inappropriate conclusions, FDA should not accept the innovator product's United States Adopted Name (USAN), or nonproprietary nomenclature, as the established name for follow-on protein products. Designating the same USAN to follow-on products may confuse or mislead health professionals, the target audience of USAN designations, about the interchangeability of protein products and could result in clinically significant events.

III. CURRENT SCIENCE DOES NOT SUPPORT THE APPROVAL OF FOLLOW-ON PROTEINS WITHOUT PRECLINICAL SAFETY AND CLINICAL DATA

A. Preclinical Safety Studies

Preclinical studies are an important component of the information and data that must be submitted by sponsors to obtain approval of pioneer products. Preclinical studies are drug studies on animals and other nonhuman test systems, and they serve a valuable function in assessing safety issues related to the clinical development of 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 preclinical studies may also provide important insight about potential long-term toxic effects in humans. *See* Guidance for Industry: S6 Preclinical Safety Evaluation of Biotechnology-Derived Pharmaceuticals (July 1997).

As FDA has articulated, protein products possess "unique and diverse structural and biological properties" that warrant preclinical testing to assess the potentially unpredictable biological activity of each new protein product. ICH Guidance for Industry: S6 Preclinical Safety Evaluation of Biotechnology-Derived Pharmaceuticals (July 1997), at 3. The type and quantity of preclinical studies will vary depending on the protein product being tested. For instance, the appropriate dosing levels for preclinical testing "may vary with each class of biotechnology-derived pharmaceutical and its clinical indication(s)." *Id.* at 6. With respect to immunogenicity, animal immune responses to the tested product are just as variable as human immune responses. *See id.* Thus, the failure to detect

antibodies in on preclinical study may not predict potential immunogenicity in humans for that or similar protein products.

The development of an appropriate preclinical testing program is a critical step to the clinical testing and eventual approval of all protein products. In recognition of the uniqueness of protein products, FDA has not established uniform guidance for preclinical studies needed to support approval. Rather, FDA has adopted a "flexible, case-by-case, science-based" approach to preclinical assessment. *Id.* at 1. In keeping with this approach, FDA should require preclinical studies for the approval of all new protein products.

B. Clinical Studies

Any FDA decision and policy concerning development of an abbreviated approval pathway for follow-on protein products must be based on sound science. BIO accepts the notion that the approval of some protein products based on data sets different from those required for the innovator product may be possible in the future as science advances. However, as set forth below, given the unique attributes of protein products, the close dependence of the nature of protein products on specific manufacturing processes, the limits of current analytical testing, the potential safety issues attendant to these products, and the lack of knowledge about the mechanism of action for both effectiveness and toxicity for

many protein products, it is extremely important that FDA continue to require all the data – including clinical studies – necessary to show the quality, safety, and effectiveness of protein products. It is also extremely important that standards be consistently applied to all manufacturers of protein products – whether innovator or follow-on.

1. Manufacturing processes significantly affect attributes of protein products

In the notice announcing its September 2004 public workshop, FDA requested comments on the aspects of manufacturing processes for protein products that are important to their characterization and that should be considered in assessing the similarity of two protein products. 69 Fed. Reg. 50386-50388 (August 16, 2004). Many aspects of the manufacturing process contribute to the clinically relevant characteristics of protein products. The adage that the "product is the process" reflects the potentially profound clinical impact of even minor process changes to a protein product.[12]

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[12] The EMEA relied upon this principle when it issued guidelines for assessing the comparability of biotechnology-derived protein products. For instance, the EMEA noted that "[w]hatever the production step at which the change occurred, there is a necessity to compare the product derived from the modified process to the one derived from the currently used process, essentially to ascertain that introduction of the change did not alter the physico-chemical and biological characteristics of the products. These characteristics . . . are of *utmost importance as they are the basis on which quality, safety and efficacy of the product are claimed. A change in these characteristics may lead to a different safety or efficacy profile of the product.*'" EMEA's Guideline on Comparability of Medicinal Products Containing Biotechnology-Derived Proteins as Active Substance: Quality Issues (Dec. 2003) (emphasis added).

The manufacture of all protein products generally involves numerous highly variable and specialized steps, which must be tightly controlled to ensure the consistent production of pure, potent, and high-quality products. Much of the knowledge and data about the manufacturing process are proprietary to the innovator and therefore would be unavailable to follow-on manufacturers. As set forth below, ensuring an appropriate and reproducible quality, safety, and effectiveness profile for a protein product involves myriad hurdles, even for the innovator who possesses the required information. The possibility exists – even for those who have the most data and experience – to alter the product profile inadvertently through process changes that are not anticipated to cause harm.

a. Source Material. The manufacturing process begins with the identification of source material (*e.g.,* viruses, microorganisms, plants, animals) that can yield a naturally occurring or biotechnology-derived therapeutic protein. The type and quality of source material used by the manufacturer helps to define the characteristics of the protein. As noted in its comments to this docket, Pfizer Inc. carefully developed source material specifications and tailored the manufacturing process for Fragmin® (dalteparin sodium injection) to take into account the high variability of the source material. *See* Pfizer Comments, Docket No. 2004N-0355/C6 (Nov. 12, 2004), at 4-5. Differences in source material quality may affect the presence of impurities and the type of process controls used by the manufacturer. *See id.* For instance, Pfizer modified successive manufacturing

processes for Fragmin® and Genotropin®, a recombinant human growth hormone replacement therapy, to accommodate differences in source material. *See id.*

b. Development of Host Cells and Cell Lines. For biotechnology products, host cells may be developed using the conventional method of isolating the DNA sequence that codes for the desired protein and then inserting the DNA sequence into suitable bacterial or eukaryotic cells (for example, by fusion of producer cells with cells containing the desired DNA sequence, or by selecting a vector to carry the DNA sequence into cells). Proteins may also be developed using technological methods such as gene activation (a protein is used to mark the start of a specific gene in a human cell, and initiate transcription). The exact DNA sequences used, the types of cells used, and cell culture conditions contribute to the characteristics of the final protein product.

Generally speaking, proteins consist of larger and more complex molecules than the active moieties of small molecule drugs. Each protein consists of a chain or chains of amino acid units, which may range from fewer than 10 to several thousand. *See, e.g.,* BIO Citizen Petition at 41. Within each such chain or peptide, amino acids are arranged linearly in a specific sequence that is fundamental to the subsequent structure and function of that protein. Alteration of a single amino acid in that sequence has the potential to affect significantly the function, pharmacokinetics, pharmacodynamics, or immunogenicity of the protein

(and by contrast, sometimes products with different amino acid sequences have similar clinical effects). Hemoglobin, for example, is a protein that delivers oxygen from the lungs to peripheral tissues in order to maintain the viability of cells. If only one of its amino acids is out of sequence, the resulting product could cause sickle cell anemia.

The functionality of a protein also may be affected by post-translational modifications, that is, certain changes to the protein that occur after the initial formation of an amino acid chain. These modifications may include the attachment of lipids, carbohydrates, and phosphates, or the removal of amino acids by enzymes. In its April 2003 Citizen Petition to FDA, BIO discussed the manner in which glycosylation, or the addition of carbohydrate molecules, may affect the effectiveness of a protein product. *See* BIO Citizen Petition at 42, n.72. We noted that even if two proteins contain the same number of amino acids, differences in the presence of carbohydrates can dramatically affect clinical outcome. *Id.*

An example of a change in cell line that affected the final product is the major cell line change that was made for Biogen Idec's Avonex® during the transition from Phase III trials to commercial manufacture. The cell line was changed because the manufacturing source that was used to produce the Phase III material became unavailable. An extensive battery of side-by-side analyses was conducted to support the change. Complete primary sequences were established by

Edman sequencing as well as by mass spectroscopic analyses. Higher order chemical structures were confirmed and included disulfide bond assignments, CD and fluorescence spectra, and denaturation profiles. Carbohydrate analyses for glycan identification and distribution were conducted by both mass spectroscopic and chemical methods. Purity was compared chromatographically and electrophoretically, and levels of aggregation, oxidation, and deamidation were determined. *In vitro* bioactivity assays showed no differences in receptor affinity, antiviral, antiproliferative, or immunomodulatory activity across a variety of cell types.

At the conclusion of the laboratory studies, Biogen (as the company was then named) concluded that neither preparation was homogeneous, but qualitatively the same species were present in both preparations though quantitative differences were noted. For example, intact, full-length glycosylated molecules represented the predominant species in both forms, but the proportion of molecules lacking an N-terminal methionine was greater in the new product, and the new product contained a small but nonetheless higher proportion of molecules with lower levels of glycosylation. Most of these minor components were purified or highly enriched and separately characterized so as to minimize issues of assay sensitivity.

Based on these assessments, a "highly comparable" product was selected for commercial manufacture.[13] Although the new product appeared, by chemical analysis, to be slightly more disperse or heterogeneous, no difference could be found using an extensive array of biological assays, including assays of the purified, minor components. Scientists at Biogen and at FDA concluded that the data showed sufficient product comparability and the new product was approved for commercial manufacture, with substantial Phase IV commitments to further assess safety and effectiveness.

Eventually and contrary to expectations, the new product was found to have a lower immunogenicity rate (< 5 percent) than the predecessor product used in Phase III trials (approximately 24 percent). In this case, the product characterization studies that were performed were not predictive of this change in the immunogenicity profile. Biogen Idec's experience with Avonex® demonstrates that even with complete and open access to all of trade secrets and confidential data about the precursor product, the comparability studies conducted by the company failed to detect clinically meaningful differences between the two products that would have predicted the large change in immunogenicity rates.

At this time, no validated laboratory or nonclinical test system is available to predict whether a molecule produced by a new or altered process will

[13] Because this comparability determination was done with full knowledge of the manufacturing scheme by both manufacturing partners, it does not represent a taking of data, but rather an agreed upon sharing of data between manufacturers.

cause adverse immunologic consequences in the clinic. As discussed more fully below in Section III.B., whether a product produced by a new or altered process will cause an adverse change in a product's immunogenicity profile often must be evaluated by clinical assessment.

c. Establishment of Master Cell Banks and Working Cell Banks. Once appropriate host cells and cell lines are identified, the manufacturer creates a master cell bank for storage of cryopreserved cell lines to maintain their integrity and quality attributes, and to assure sufficient supply. Aliquots of the master cell bank are expanded when necessary to develop a working cell bank. Before batch production is initiated from the working cell bank, the manufacturer conducts tests to ensure the potency and identity of cell lines and for microbial or viral contamination arising from the source materials, cell lines, or the cell banking process.

Biogen Idec experienced an unexpected change in pharmacological activity of a protein due to process changes made prior to Phase III trials. The product, Amevive ®, is a fusion protein produced in CHO cells, and, on the basis of *in vitro* and analytical characterizations, the new material was found to be comparable to the material that was produced previously, with minor variations in carbohydrates and aggregate levels. The product's potency was as predicted, the

data set for a product at this stage was typical, and no major concerns were identified.

In subsequent clinical studies, however, a reduction in potency was detected. The decrease in potency was also noted in tissue and peripheral blood levels in a long-term primate toxicology study. Neither of these changes was attributable to a change in pharmacokinetics. Furthermore, since this protein was essentially non-immunogenic, the reduction in potency could not be ascribed to a blocking or neutralization response. Also, a single dose human bioequivalence study was conducted and the two preparations were shown to be pharmacokinetically equivalent. In this case, both preclinical and clinical testing were required to show that there was a meaningful biologic difference between the molecules produced by the two processes.

Having a validated and stable working cell bank that is free from impurities and adventitious agents is critical, but does not necessarily prevent the introduction of impurities or adventitious agents during batch production (see section 5 below).

d. Production System. For optimal propagation of cell lines from the working cell bank, the manufacturer may modify conditions for fermentation, a common methodology for batch production and maintenance of cell line integrity. A

variety of factors can affect the growth condition of cell lines, such as protein pH, protein stability, type of culture medium used, and specifications of fermentation reactors.

Changes in fermentation vessels also may affect the nature of the protein product. For example, when tissue plasminogen activator (tPA) was produced in stirred bioreactors rather than roller bottles, the resulting protein product showed differences in its glycosylation pattern and degree of internal cleavage. The product also possessed a different pharmacokinetic profile and dose response in humans.

Production scale-ups also may affect the overall clinical safety and effectiveness of protein products. A well-known example of a problem arising out of scaling-up production is Genentech's experience with Raptiva® (efalizumab). Raptiva® was originally manufactured by XOMA Ltd. After the manufacturing process was transferred to Genentech and scaled-up for an additional clinical trial, Genentech conducted extensive analytical, biological, and animal testing, and observed what was thought to be inconsequential analytical and formulation differences between the XOMA and Genentech products. Only after Genentech conducted a human bioequivalence study did it discover that the products were significantly different in terms of pharmacokinetics and bioavailability. Because of the unexpected pharmacokinetic differences, an additional Phase III clinical study

was performed to determine the safety and effectiveness of the Genentech material. The study indicated the XOMA and Genentech materials did not have the same therapeutic effects – a lower Psoriasis Area Severity Index (PASI) response to Genentech's material despite a higher peripheral drug concentration. The study demonstrated that the formulation alone did not account for the difference.

e. Purification. The next manufacturing step is the purification of the production batches to remove or inactivate adventitious agents or impurities. Purification may involve a number of different methods, such as column chromatography, filtration, and centrifugation; the purification process is developed based on the manufacturer's extensive historical experience and knowledge of the product. Seemingly trivial changes to the purification process have the potential to alter the purity profile of the product and cause changes to its clinical safety and effectiveness.

The ability to identify impurities during the manufacturing process enables manufacturers to design a purification process that will isolate and remove the contaminants. For example, Pfizer observed the modification of a disulfide bond to a trisulfide bond in some molecules of recombinant somatropin, the active substance of Genotropin®. *See* Pfizer Comments at 5. After identifying the source of the impurity, Pfizer was able to detect and remove molecules containing trisulfide bonds during the purification process. *Id.*

f. Formulation and Filling. The manufacturing process concludes by formulating the purified substance into a finished product form, sterilizing containers and closure systems, and freeze-drying or filling the finished product into containers (e.g. ampules, vials) for commercial distribution. As with each of the process steps described above, the manufacturer performs extensive testing, using both standard and customized physicochemical and biological assays, to ensure the identity, purity, and stability of the finished product. A change in any of the equipment, the product contact materials, or methods used in these final steps may affect product integrity.

A small change in the formulation adversely affected Eprex® (epoetin alfa). Leachates from a rubber stopper were the apparent cause of the increased incidence of pure red cell aplasia (PRCA) associated with the product. The cause was identified only after several years of intensive investigations by Johnson & Johnson.

Similarly, Pfizer discovered that a geometrical change in the new stopper for Somatonorm®'s container closure system caused unintended polymer formation, which consequently affected the lyophilization process for Somatonorm®. *See* Pfizer Comments at 5.

Changes to virtually any of the steps in the manufacturing processes for protein products are capable of affecting the clinical profile of those products. Thus the impact of each step on the finished product must be considered in order to identify and remedy problems. For example, Pfizer originally attributed unintended changes in a formerly marketed product, Groliberin, to polymer formation during the lyophilization step; Pfizer later learned the changes were due to phthalate leaching during the filling process.

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As the above examples illustrate, the manufacturing process is particularly critical to the overall safety and effectiveness of protein products. Slight changes that seem inconsequential may be, in fact, clinically detrimental. Even when a manufacturer fully familiar with its own product and history of production makes a change to the manufacturing process, it may be difficult to determine the impact of that change on the resulting product. A manufacturer attempting to make a follow-on product may certainly be as technically capable as the innovator manufacturer, but often will lack critical product-specific information to evaluate the impact of using a process that is different from that of the innovator.

2. Analytical testing studies are necessary but, without preclinical and clinical studies, they are not sufficient to

determine the clinical safety and effectiveness profiles of follow-on protein products

BIO disagrees with those who think that analytical studies provide sufficient evidence to justify approval of a follow-on protein, first because such tests are often process-specific, and second because such tests are limited in their ability to detect changes that may affect a therapeutic protein's safety and effectiveness. Throughout the manufacturing process, the protein mixture is subject to various tests to ensure characteristics such as structure, and potency, as well as the absence of impurities and contaminants. However, analytical tests performed by the innovator may rely on testing limits and criteria that have been shown to be valid only with respect to a particular process, and/or may involve proprietary reagents and equipment. Thus, the analytical tests performed by the innovator may be completely irrelevant to a similar product developed through a different manufacturing process by another company. For this reason, it can be difficult to establish a "standard" or "uniform" array of analytical tests for use with particular types or classes of products.

Furthermore although testing technology is rapidly evolving, current analytical tests remain limited in their ability to detect product variations that may affect clinical safety and effectiveness. For instance, it has been Pfizer's experience that the available analytical tests for characterizing low molecular weight heparin

drugs like Fragmin® may not reliably predict a safe and effective product. *See* Pfizer Comments at 8-9. Even though hundreds of analytical tests, whether standard or specialized, may be conducted to characterize a protein, it can be difficult for a manufacturer to identify appropriate analytical technologies to detect/explain changes when the biochemical basis for the changes is unknown. Further, a high degree of analytical correlation between an innovator and follow-on product might not translate into the same degree of clinical quality, safety, or effectiveness, while analytically dissimilar products may have similar safety and effectiveness profiles.

This is not to say that analytical studies are meaningless. We recognize that biochemical analysis of the active moiety and finished product are crucial prerequisites for understanding and approving all protein products. Amino acid analysis, protein sequencing, peptide mapping, mass spectrometry, immunoassays, functional assays, and other analytical studies provide important information about the molecular structure and attributes of protein products. Technological advances continue to improve the sophistication and sensitivity of analytical methodology. Although follow-on manufacturers generally would lack access to proprietary information about the innovator's manufacturing processes, it may be possible for them to conduct certain analytical correlation assessments based upon publicly available information about the innovator product. Future

changes and improvements in analytical technology also may affect the ability of manufacturers to assess the correlation between products.

However laboratory assays, while very valuable, cannot currently be used as surrogates for establishing high quality, safety, and effectiveness of a follow-on protein. Experience demonstrates that more often than not, differences (and the absence of differences) detected using a combination of biochemical and bioassay assessments cannot fully predict clinical safety or efficacy consequences. Hence, BIO strongly disagrees with the assertion made by several speakers at FDA's September 2004 workshop that clinical studies may be unnecessary if the follow-on manufacturer can demonstrate that its protein product is analytically similar to the precursor or innovator product.

3. Safety concerns related to protein products, including immunogenicity, should be clinically studied

Safety concerns related to therapeutic proteins, particularly immunogenicity, are a critical component of any public discussion of potential follow-on protein approval pathways. FDA can move forward with follow-on approvals only if legal and policy issues are resolved and scientific principles can be applied to assure the public that follow-on protein products are safe for their intended use. Among the safety concerns that any manufacturer – innovators and

follow-on 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.

The potential immunogenicity of any therapeutic protein is an important topic for consideration by any manufacturer – innovators and follow-on manufacturers alike. Although for the vast majority of protein products immunogenic responses are not a concern, and differences in immunogenicity are not always clinically relevant, when clinically relevant immunogenic responses do occur they can have serious consequences including hypersensitivity, severe allergic or anaphylactic responses, or autoimmunity to endogenous proteins. These kinds of immunogenic responses could alter significantly the clinical safety and effectiveness of the protein product.[14]

Immunogenicity may be related to factors such as a protein's structure (defined by its unique amino acid sequence and post-translational modifications), the introduction of adjuvants during the manufacturing process, route of administration, dose frequency and duration of treatment, and/or the presence of manufacturing-related impurities or contaminants. *See* Citizen Petition at 45. Analytical studies of common immunogenic factors (*e.g.,* protein aggregation,

[14] The Citizen Petition lists several examples of such protein products, including Factor VIII, interferon-alpha2b, interferon-beta, interleukin-2, erythropoietin, thrombopoietin. *See* Citizen Petition at 45-46.

comparison of immunogenicity profiles) may be informative. The identification of differences in immunogenicity profiles in animals may also be instructive. However, clinical studies of immunogenicity would be necessary for follow-on protein products because immunogenicity is not fully understood, and because conclusions about immunogenicity of proteins are very difficult to draw from analytical and preclinical safety studies.

Because a myriad of factors can affect immunogenicity, two protein products that are similar in molecular structure and composition may not have similar immunogenicity profiles. To illustrate, Roferon-A® and Intron-A® are two alpha interferon products manufactured by two different companies but they originate from the same type of bacterial cells, contain the same number of amino acids, and have approximately the same molecular weight. Despite the similar protein characteristics, clinical studies indicate that Roferon-A® is likely to produce a greater immunogenic response, demonstrating that the absence of immunogenicity in one protein product reliably does not predict the absence of immunogenicity in a related protein product.

The difficulty of predicting immunogenicity from analytical studies alone is also demonstrated by Somatonorm®. In comments to this docket, Pfizer observed that Somatonorm® was immunogenic due to certain unidentified host cell contaminants. *See* Pfizer Comments at 10. It now appears, based on findings from

a clinical study, that the source of those contaminants were *E. coli* bacteria. Removal of the host cell proteins reduced antibody formation to very low levels. *Id.*

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. Until and unless the scientific community is more confident about the causes of immunogenicity and other safety issues, process-specific immunogenicity and safety testing will be necessary for the approval of each and every new protein product. Requiring anything less could be detrimental to patient health.

4. Preclinical or clinical data supporting one indication should not be taken automatically to support additional indications for the same follow-on product

BIO thinks that data supporting the approval of one indication for a follow-on protein product should not be automatically extended to support approval of other indications for that protein product, but that such extrapolations must be carefully considered in light of the indications involved, the nature of the product, and the data provided to support the application.[15] In addition, the clinical effect of a protein may vary in different patient populations. If a protein is indicated for two

[15] 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.

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 not be detected without clinical studies designed to detect them for each indication in each patient population.

For example, when patients treated with Intron A® (recombinant interferon alfa-2b)[16] were tested for antibody activity in clinical trials, serum anti-interferon neutralizing antibodies were detected in 0 percent (0/90) of patients with hairy cell leukemia, 0.8 percent (2/260) of patients treated intralesionally for condylomata acuminata, and 4 percent (1/24) of patients with AIDS-Related Kaposi's Sarcoma. In less than 3 percent of patients treated with higher Intron A® doses, serum neutralizing antibodies were detected in malignancies other than hairy cell leukemia or AIDS-Related Kaposi's Sarcoma. The clinical significance of the appearance of serum anti-interferon neutralizing activity in these indications is not known. Serum anti-interferon neutralizing antibodies were detected in 7 percent (12/168) of chronic hepatitis C patients either during or after treatment of Intron A®, and in 13 percent (6/48) of chronic hepatitis B patients who received Intron A®.

As this example makes clear, the clinical significance of using a product for approved uses in different patient populations is not known. FDA and

[16] Intron A® is a recombinant version of endogenous alpha interferon that has been approved by FDA for treatment of a variety of conditions, including hairy cell leukemia, condylomata acuminate, AIDS-related Kaposi's sarcoma, chronic hepatitis B, and chronic hepatitis C.

manufacturers cannot assume safety based on an imprecise testing regime. Consequently, to protect patient health, BIO could not endorse a regulatory scheme that allows a follow-on protein to be approved for the same set of indications for which the innovator protein is approved unless appropriate clinical studies are completed.

IV. CONCLUSION

Assuming that key scientific concerns can be addressed, it may be possible in the future for the quality, safety, and effectiveness of follow-on therapeutic protein products to be established using a data set that is not identical with that currently expected from innovator companies. However, as discussed above, a very broad spectrum of factors may affect the quality, safety, and effectiveness of protein products, including, among others: the molecular complexity of the protein; unique aspects of the manufacturing process; immunogenicity or other safety concerns; and the sophistication of available analytical technology.

Given the wide variability among protein products, BIO does not think that it is possible to establish a "one size fits all" approach to abbreviated approval of therapeutic protein products, and that it is essential to maintain high and appropriate regulatory standards akin to those that have applied been to date to innovator biotechnology products. The extent of analytical, preclinical, and clinical

data necessary for any follow-on product would depend on the scientific correlation between the characteristics of the follow-on and innovator products, as well as the potential risks to patients posed by the particular products under review. The greater the risk that a clinically significant effect would arise from manufacturing differences between the follow-on and innovator products, and the more serious the potential risk is to patients, the more data should be required. We think that preclinical and clinical assessment will be essential for all follow-on products but that the precise nature of the studies may vary between innovator and follow-on manufacturer.

An acceptable scientific framework for approving follow-on protein products can be created only after careful assessment – with extensive input from the public – of the risks that any manufacturer of protein products must control or eliminate and the availability of scientific tools (including preclinical and clinical testing) to control or eliminate such risks. The iterative nature of science and creativity of the biotechnology industry ensure that this process and discussion will continue to emerge and be challenging. BIO looks forward to continued opportunities to engage in thoughtful public discussion about the scientific considerations related to developing follow-on protein products.

We thank FDA again 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. We look forward to additional opportunities to discuss the matters outlined above.

Sincerely,

/s/

Sara Radcliffe
Managing Director
Science and Regulatory Affairs