DEPARTMENT OF HEALTH & HUMAN SERVICES

Food and Drug Administration
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STATEMENT OF
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BEFORE THE

COMMITTEE ON OVERSIGHT AND GOVERNMENT REFORM

UNITED STATES HOUSE OF REPRESENTATIVES

"FOLLOW-ON PROTEIN PRODUCTS"

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INTRODUCTION

Mr. Chairman and Members of the Committee, I am Janet Woodcock, M.D., Deputy Commissioner, Chief Medical Officer at the U.S. Food and Drug Administration (FDA or the Agency). Thank you for the opportunity to testify about the scientific and regulatory background surrounding follow-on protein products.

During the past several years, there has been increasing public interest in the development of follow-on versions of approved protein products. This interest has been fostered, in part, by advances in manufacturing technology, process control, and characterization that allow greater control over, and understanding about, the physical structure of certain of these products. However, a number of important issues related to development of such follow-on products also have been identified. First, there is general recognition that the idea of *sameness*, as the term is used in the generic drug approval process under the Federal Food, Drug, and Cosmetic (FD&C) Act and applied to small molecules, will not usually be appropriate for more structurally complex molecules of the type generally licensed as biological products under the Public Health Service (PHS) Act. Additionally, as a related matter, there are clearly scientific challenges involved in determining that a molecule that is not the same as an approved or licensed version is nevertheless similar enough that the Agency's conclusions about the safety and effectiveness of the approved or licensed version could be relied on to support approval of the follow-on product. Finally, it is recognized that the PHS Act does not contain an abbreviated approval pathway analogous to the FD&C Act

section 505(b)(2) and 505(j) (21 U.S.C. 355 (b)(2) and 355 (j)), but the Agency has approved a number of biological products, such as human growth hormone, under the FD&C Act.

Background

Before I go any further, I would like to define some terms and describe the scope of my remarks, so that we can have a common understanding of the issues. I will define additional terms as needed in this testimony as I first outline the pertinent regulatory schema and then describe the scientific issues. First, I would like to recognize that the terms *biologics*, *generic biologics*, *biogenerics*, and *follow-on biologics* are often used informally to refer to certain products produced through biotechnology. Because these terms are imprecise and can be confusing, and because the use of the term *generic* inaccurately implies the same meaning as exists for generic drugs, I will try to rely instead on terms with established meanings or definitions.

For purposes of this discussion, I will use the term *protein products* to refer to certain biological products licensed under the PHS Act and to certain protein and peptide products approved under the FD&C Act. I will further use FDA's informal term *follow-on protein products* to refer to proteins and peptides that are intended to be sufficiently similar to an approved product to permit the applicant to rely on certain existing scientific knowledge about the safety and effectiveness of the approved protein product. Follow-on protein products may be produced through biotechnology or derived from natural sources.

A *biological product* is defined, in relevant part, under the PHS Act as "a virus, therapeutic serum, toxin, antitoxin, vaccine, blood, blood component or derivative, allergenic product, or analogous product . . . applicable to the prevention, treatment or cure of a disease or condition of human beings." (PHS Act §351(i), 42 U.S.C §262(i)). Many categories of biological products are defined by their clinical use, for example, vaccines and allergenic products. Vaccines can include live attenuated viruses and inactivated viruses, products made from bacteria or other microorganisms, products made from cells (human or other), and protein products made using biotechnology. Other biological products are defined by their origin (e.g., blood and blood products). Blood products may be made from human blood collections, from blood from animal species, or using biotechnology. Monoclonal antibodies are biotechnology-derived versions of certain blood proteins. Newer types of biological products include cellular therapies (beyond the traditional blood cells) and gene therapies. Many biological products are not completely characterizable using current technology.

Traditionally, some natural source proteins have been regulated as drugs under the FD&C Act, including insulin, hyaluronidase, menotropins, and human growth hormones, while other natural source proteins, such as blood factors, are regulated as biological products under the PHS Act. In the late 1970s and early 1980s, recombinant proteins and monoclonal antibodies began to be developed. Certain of these products were regulated by CDER under the FD&C Act as drugs (e.g., hormones such as insulin and human growth hormone), and others were regulated by CBER under the PHS Act (e.g., cytokines, proteins that are involved in the immune response, and blood factors, such as factor VIII for the treatment of hemophilia). In 2003, certain therapeutic proteins regulated by CBER were transferred to CDER, with no

change to the applicable regulatory authority. Currently, some proteins are licensed under the PHS Act, and some are approved under the FD&C Act.

At this point, it may also be helpful to set out certain terms that describe how certain products relate to each other.

Comparability
The current FDA use of the term "comparability" generally refers to the comparison of a biological product before and after a manufacturing change by the manufacturer. A sponsor may be able to demonstrate that a product made after a manufacturing change is comparable to a product made before implementation of the change. This may be demonstrated through different types of analytical and functional testing and might not require additional clinical studies. The Agency may determine that the two products are comparable if the results of the comparability testing demonstrate that the manufacturing change does not affect safety, identity, purity, or potency. See April 1996 FDA Guidance Concerning Demonstration of Comparability of Human Biological Products, Including Therapeutic Biotechnology-Derived Products.

The International Conference on Harmonization (ICH) guidance defines comparable as a conclusion that products have highly similar quality attributes before and after manufacturing process changes and that no adverse impact on the safety or efficacy, including immunogenicity, of the drug product occurred. See June 2005 ICH Guidance for Industry Q5E Comparability of Biotechnological/Biological Products Subject to Changes in Their Manufacturing Process.

Therapeutic Equivalents
These are approved drug products, often made by different manufacturers, that are pharmaceutical equivalents and for which bioequivalence has been demonstrated. Therapeutic equivalents can be expected to have the same clinical effect and safety profile when administered to patients under the conditions specified in the labeling. Therapeutically equivalent prescription drugs will receive an "A" equivalence evaluation code in FDA's "Approved Drug Products with Therapeutic Equivalence Evaluations" (Orange Book). This term has been applied only in the context of drugs approved under section 505 of the FD&C Act.

Interchangeability
This term is not defined by FDA and could have a number of different meanings. It could refer to products that are therapeutic equivalents, and thus could, in some circumstances, be substituted at the pharmacy level without a physician's intervention. Alternatively, the term could describe similar products that are not "substitutable" but which, under a physician's supervision, could be used to treat the same disease or condition in the same patient.

The concept of a follow-on protein product is that an applicant could obtain approval for its product through the submission of an abbreviated application. An *abbreviated application* would be one that relies, to at least some extent, on the Agency's conclusions regarding the safety and effectiveness (or safety, purity, and potency) of an approved product and also contains additional data necessary, other than the underlying clinical data supporting the approved product, to establish that the follow-on product is safe and effective. It is important to ensure that facilitating the development of follow-on products through abbreviated pathways does not discourage innovation and the development of new biological products.

Follow-on Protein Products

Generally speaking, the interest in development of follow-on protein products pertains to versions of follow-on products manufactured using biotechnology. As noted, these protein products are either approved as drugs under the FD&C Act or licensed as biological products under the PHS Act. Unlike small molecule drugs whose chemical composition can easily be determined the *same* as an approved product, the very nature of protein products makes comparisons of one protein to another, including to establish safety and efficacy, more scientifically challenging.

Statutory Framework for Drug Approval

FDA approves new drugs, as distinguished from biological products, under approval mechanisms found in section 505 of the FD&C Act and licenses biological products under section 351 of the PHS Act. Under the FD&C Act, in addition to the approval pathway

involving the submission of a full 'soup to nuts' new drug application, there are two abbreviated pathways for subsequent versions of already approved drug products.

Abbreviated Approval Pathways Under the FD&C Act

The Abbreviated New Drug Application (ANDA) process in section 505(j) was established through the 1984 Hatch-Waxman Amendments, and reflects Congress' intention to balance the need to encourage innovation with the desire to speed the availability of lower cost alternatives to approved drugs and to avoid ethical concerns associated with unnecessary, duplicative human testing. This is an abbreviated approval mechanism for duplicates of drugs already approved under section 505 of the FD&C Act. Under these statutory standards, a generic drug generally must contain the same active ingredient as an innovator product; it must be bioequivalent to the innovator drug; and it must have the same dosage form, strength, route of administration, labeling, and conditions of use. By establishing that the drug product described in the ANDA is the same as the approved innovator drug product, the ANDA applicant can rely on the Agency's finding of safety and effectiveness for the approved drug. Most drug products approved under section 505(j) are therapeutically equivalent to the referenced approved drug.[1] Therapeutic equivalents can be expected to have the same clinical effect and safety profile when administered to patients under the conditions specified in the labeling. In many jurisdictions, therapeutically equivalent drugs may be substituted at the pharmacy level, without a physician's intervention.

[1] Drug products approved pursuant to a petition submitted under section 505(j)(2)(C), which can differ in among other things, route of administration, dosage form, or strength of the drug would not be therapeutically equivalent to the referenced approved product.

The abbreviated pathway described in section 505(b)(2) of the FD&C Act permits an applicant to rely on published literature or on the Agency's finding of safety and effectiveness for a referenced approved drug product to support approval of a proposed product. The 505(b)(2) applicant must demonstrate that reliance on the previous finding of safety and effectiveness is scientifically justified and must submit whatever additional nonclinical and clinical data are necessary to establish that the proposed product is safe and effective. FDA has used this pathway to approve some follow-on protein products including human growth hormone.

Scientific Issues

Compared to many small molecule drug products, proteins are usually substantially larger, more complex molecules that may be mixtures of distinct entities. Even well-characterized, highly purified recombinant proteins may exhibit minor degrees of structural variability from lot to lot resulting from variations in the manufacturing process. The quality and nature of natural source products can vary depending on condition of the source material, processes used to extract and purify the product, and other factors.

Because of the variability and complexity of protein molecules, current limitations of analytical methods, and the difficulties in manufacturing a consistent product, it is unlikely that, for most proteins, a manufacturer of a follow-on protein product could demonstrate that its product is identical to an already approved product. Therefore, the section 505 (j) generic

drug approval pathway, which is predicated on a finding of the same active ingredient, will not ordinarily be available for protein products.

However, FDA has considerable experience with reviewing some protein products, including cases where the Agency has considered the extent to which existing conclusions about the safety and effectiveness of a protein product could be applicable to another protein product based on data and information showing the similarity of the products. One example is the situation in which a manufacturer has sought to demonstrate that a new version of its licensed biological product manufactured using a different manufacturing process is comparable to the product manufactured using the original process. Another example is the situation in which a different manufacturer has sought to demonstrate that its protein product is similar enough to a protein product marketed by another manufacturer that the finding of safety and/or effectiveness made for the approved product could be relied on to support approval of the proposed product (e.g., a 505(b)(2) application). Typically, demonstrating the similarity of a follow-on protein product to a reference product will be more complex, and thus require more new data, than assessing the similarity of products before and after manufacturing changes made by the approved product's sponsor.

In general, the amount and type of new data that will be needed to demonstrate the safety and effectiveness of a follow-on protein product, compared to the data that supported the safety and effectiveness of an already marketed product, will be influenced by the extent to which the follow-on product can be demonstrated to be sufficiently similar (structurally, functionally, and clinically) to an approved protein product to permit some degree of reliance

on the findings of safety and effectiveness for the approved product. In addition, the amount and type of new data needed will be influenced by the clinical use of the product and the amount and type of clinical experience that has been accumulated about the approved product as well as related products.

Current technologies, such as peptide mapping, protein sequencing, and mass spectroscopy enable manufacturers to determine, with certainty, the amino acid sequence of a recombinant protein. However, the amino acid sequence is the most rudimentary characteristic of a protein. Conclusive analysis of other aspects of a protein's structure requires much more sophisticated technologies and is fraught with uncertainties that are proportional to the size and complexity of the protein itself. Such complexities include: folding of the protein's amino acid chain into highly organized structures, post-translational modification of the protein with a broad range of biochemical additions (e.g., glycosylation, acetylation, phosphorylation, etc.), and association of multiple protein molecules into aggregates. It is the combination of the protein's amino acid sequence and its structural modifications that give a protein its unique functional characteristics. Therefore, the ability to predict the clinical comparability of two products depends on our understanding of the relationship between the structural characteristics of the protein and its function, as well as on our ability to demonstrate structural similarity between the follow-on protein and the reference product. Although this may be currently possible for some relatively simple protein products, technology is not yet sufficiently advanced to allow this type of comparison for more complex protein products.

Functional characterization, using *in-vitro* tests, is also of great importance in assessing the similarity of two proteins. For proteins with a well-understood mechanism of action and available functional assays, extensive functional comparisons will enhance understanding of comparability. Future scientific advances may facilitate the ability to perform more meaningful functional testing.

Protein products are used for a wide variety of indications. In some cases, there is an extensive mechanistic understanding of the role of the product in the treatment process. For example, some products are used as replacement therapies to treat a known deficiency (e.g., human growth hormone for growth hormone deficiency). For some such products, the mechanism of action and the role of replacement is well understood. In the case of other products, the primary mode of action of the product is not well understood and its role in treatment was derived, in part, by trial and error. In such cases, even very extensive structural and functional comparisons between a follow-on and a comparable innovator product may not be sufficient to allow broad reliance on conclusions regarding a prior product. When the mechanism of action is well understood and there is a significant amount of clinical experience with a product, it may be easier to make a scientific assessment of the ability to rely on conclusions about safety and efficacy from a prior application.

Immunogenicity is the ability to stimulate an immune response. An immune response to a therapeutic protein can range from development of detectable but not clinically significant antibodies, to an immune response with impact on safety or effectiveness. "Neutralizing antibody" responses can decrease the clinical effect of a protein. Adverse safety events from

an immune response could include hypersensitivity reactions such as anaphylaxis, rash, fever and kidney problems, to cross-reaction with an endogenous (naturally occurring in the body) protein (e.g., erythropoietin). Immunogenicity may be influenced by patient-related, disease-related, or product-related factors. Immune responses to administered protein products can be extremely serious or life-threatening; therefore, this issue requires significant attention.

The ability to predict immunogenicity of a protein product, particularly the more complex proteins, is extremely limited. Therefore, some degree of clinical assessment of a new product's immunogenic potential will ordinarily be needed. The extent of independent testing needed will again depend on a variety of scientific factors such as the indication, whether the product is to be administered chronically, the overall assessment of the product's immunogenic potential, and whether there is the possibility of generating a cross-reaction with an important endogenous molecule.

A finding by the Agency that a follow-on protein product may be approved as safe and effective is distinct from a determination that the follow-on protein product would be substitutable for the referenced protein product. To establish that two protein products would be substitutable, the sponsor of a follow-on product would need to demonstrate through additional clinical data that repeated switches from the follow-on product to the referenced product (and vice versa) would have no negative effect on the safety and/or effectiveness of the products as a result of immunogenicity. For many follow-on protein products -- and in particular, the more complex proteins – there is a significant potential for repeated switches between products to have a negative impact on the safety and/or effectiveness. Therefore, the

ability to make determinations of substitutability for follow-on protein products may be limited.

Examples of Approvals

Even though protein products are more complex than small molecules, FDA has applied its expertise and experience to approve certain follow-on protein products in applications described in section 505(b)(2) of the FD&C Act. Some examples of products approved in this manner are: Hylenex (hyaluronidase recombinant human), Hydase (hyaluronidase), Fortical (calcitonin salmon recombinant) Nasal Spray, Amphadase (hyaluronidase), GlucaGen (glucagon recombinant for injection), and Omnitrope (somatropin [rDNA origin]). I will discuss, in detail, two of these examples of protein products that were approved through an abbreviated approval pathway.

Omnitrope (somatropin)

Omnitrope is a human growth hormone product derived from recombinant DNA processes. Human growth hormone is a single-chain, 191 amino acid, nonglycosylated protein. Its amino acid sequence is well known and physicochemical tests are able to determine the complex folded structure of human growth hormone products. There are also clinically relevant bioassays and validated biomarkers (laboratory indicators of effect) available to assess the performance of human growth hormone products.

Human growth hormone has a long and well-documented clinical history as replacement therapy for growth failure in pediatric patients due to endogenous growth hormone deficiency,

and its mechanism of action and toxicity profile are well established. Some marketed human growth hormone products are approved for other uses, such as therapy for growth failure associated with chronic renal insufficiency and replacement of endogenous growth hormone in adults with growth hormone deficiency.

The original marketed versions of human growth hormone were derived from the pituitary glands of human cadavers. The first recombinant version was approved in 1985. Since then, several more recombinant human growth hormone products have been approved under section 505(b)(1) of the FD&C Act (i.e., each product approval relied on original clinical data developed specifically for that product, not an abbreviated pathway).

Omnitrope is the first recombinant human growth hormone product approved through the abbreviated pathway described by section 505(b)(2) of the FD&C Act. It was approved for (1) long-term treatment of pediatric patients who have growth failure due to inadequate secretion of endogenous growth hormone and (2) long-term replacement therapy in adults with growth hormone deficiency (either childhood or adult onset). The approval of Omnitrope was based on new data specific to Omnitrope (but less new data than would be needed to support an approval under section 505(b)(1)) and also relied on the approval of Genotropin (a previously approved version of rDNA-derived somatropin) for the same indications proposed. Specifically, the approval was based on the following.

- Physicochemical testing that established, among other things, that the structure of the active ingredient in Omnitrope is highly similar to the structure of the active ingredient in Genotropin;

- New non-clinical pharmacology and toxicology data specific to Omnitrope;
- Vast clinical experience and a wealth of published literature concerning the clinical effects (safety and effectiveness) of human growth hormone;
- Pharmacokinetic, pharmacodynamic, and comparative bioavailability data that established, among other things, that Omnitrope and Genotropin are highly similar based on pharmacokinetic parameters and pharmacodynamic responses;
- Clinical efficacy and safety data from controlled trials comparing Omnitrope to Genotropin and from long-term trials with Omnitrope in pediatric patients; and
- FDA's conclusions that Genotropin is safe and effective for the indications for which approval was sought in the Omnitrope application and that Omnitrope is highly similar to Genotropin.

Omnitrope has not been rated by FDA as therapeutically equivalent (that it is substitutable) to any other approved human growth hormone product.

Hyaluronidase

The hyaluronidases are enzymes that break down hyaluronic acid and chondroitin. Hyaluronidase injection is indicated for use to increase the absorption and dispersion of other injected drugs and for related uses. The enzymatic activity of this product is one of its critical quality attributes, and a method for assessing the enzymatic activity of hyaluronidase is described in the U.S. Pharmacopeia (USP). Most hyaluronidase products are natural source proteins, purified from mammalian testicles, whose amino acid sequences vary based on the species and the tissue from which it is obtained. There may also be variability within the same tissue source.

The first hyaluronidase product was approved for marketing in 1948 under the FD&C Act, based on a literature review demonstrating its safety. Hyaluronidase products containing mammalian hyaluronidase enzyme preparations were subsequently determined to be effective for their current indications. In addition, an extensive body of literature has been developed supporting the safe and effective use of mammalian testicular hyaluronidase for these indications. FDA has approved follow-on versions of mammalian testicular hyaluronidase (ovine and bovine) under section 505(b)(2) of the FD&C Act (i.e., via an abbreviated pathway) for the existing indications and has more recently approved a human recombinant hyaluronidase follow-on product. For new follow-on hyaluronidase products, the potential for allergic reactions is the primary clinical safety concern. Therefore, in addition to requiring that a given product have the necessary enzymatic activity, the Agency now requires clinical data to assess the allergenic potential of that product. In addition, an applicant is required to provide assurance that its standards for manufacturing ensure consistency of the drug substance and drug product. No hyaluronidase product is rated by FDA as therapeutically equivalent (that it is substitutable) to any other approved hyaluronidase product.

FDA Activity Related to Follow-on Protein Products

Because there are many challenging scientific and policy questions about follow-on protein products, FDA has actively promoted a public dialogue on these issues. FDA has held two public meetings (September 2004 and February 2005) and co-sponsored a workshop, in collaboration with the National Institute for Standards and Technology, and with the

New York Academy of Sciences (December 2005), to gather input on scientific and technical issues related to follow-on protein products. These meetings resulted in a large number of comments and concerns from the interested parties that have informed our considerations of these issues.

The Agency indicated its intention to issue guidance documents to specifically address human growth hormone and insulin. But, as our knowledge of this issue expanded, we reconsidered our focus and determined it would be more appropriate to initially promulgate guidance that is more broadly applicable to follow-on protein products in general. We are in the process of developing such guidance with respect to products approved under the FD&C Act. Of course, as you know, even in the absence of published guidance, a sponsor may contact the Agency to request advice on a case-specific basis regarding the development of a follow-on protein product for submission in an application under section 505 of the FD&C Act. Thus, the Agency continues to review and approve certain follow-on protein products under its current authority and works to do this as effectively and efficiently as possible. Although we currently work closely with all product sponsors to assist them through the FDA review process, as discussed earlier, the Agency plans to address scientific considerations related to the approval of follow-on protein products in a comprehensive manner through issuance of a series of guidance documents. We expect this approach will provide useful guidance to industry while ensuring that we not stifle innovation or the use of state-of-the-art technologies. We appreciate the interest that Congress has always demonstrated in working to provide safe, effective, and affordable medicines to consumers.

Conclusion

I appreciate the opportunity to provide this background information on the important issue of follow-on protein products.