

OPINION

The FDA's assessment of follow-on protein products: a historical perspective

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Abstract | The scientific and regulatory issues that are associated with the possible introduction of 'follow-on' versions of protein drug products are the topic of considerable debate at present. Because of the differences between protein drug products and small-molecule drugs, the development of follow-on versions of protein products presents more complex scientific challenges than those presented by the development of generic versions of small-molecule drugs. Here, with a view to illustrating the Food and Drug Administration's (FDA's) scientific reasoning and experience in this area, we discuss past examples of the FDA's actions involving the evaluation of various types of follow-on and second-generation protein products and within-product manufacturing changes. The FDA believes its evaluation of the safety and effectiveness of follow-on protein products will evolve as scientific and technological advances in product characterization and manufacturing continue to reduce some of the complexity and uncertainty that are inherent in the manufacturing of protein products.

There has been much discussion and debate recently about the scientific considerations related to 'follow-on' protein products (including peptides; BOX 1, Note 1). These are protein products that are manufactured using biotechnology or derived from natural sources that are intended to be sufficiently similar to a product or products already approved in the United States to permit the follow-on applicant to rely, in part, on certain scientific knowledge about the approved products to demonstrate safety and effectiveness in a marketing application (BOX 1, Note 2). This interest is due, in part, to the expiration or imminent expiration of patent protection for a number of first-generation, biotechnology-derived protein products (BOX 1, Note 3).

Unlike small-molecule generic products, follow-on protein products can exhibit a

range of structural similarities to the original product. The follow-on might be intended to be precisely identical (for example, some peptides), highly similar (for example, some recombinant proteins) or generally similar (for example, some natural products). So-called second-generation products — those with structural differences designed to improve performance while maintaining the same mechanism of action as the original product — are not conventionally considered as follow-on products. However, the evaluation of second-generation protein products raises some issues that are similar to those raised during the evaluation of follow-on products. Also, in some cases, approved protein products might undergo major manufacturing changes that introduce questions of uncertainty similar to those for a follow-on product. However, the original

manufacturer would have access to detailed information relevant to manufacturing changes, such as details of methodology and product reference standards, that would not be available to a different manufacturer aiming to develop a comparable product.

Using examples of past Food and Drug Administration (FDA) actions, this paper describes some of the factors the FDA has considered when evaluating various types of follow-on and second-generation protein products, or manufacturing changes in protein products similar in magnitude and scope to follow-ons. The examples illustrate the FDA's scientific reasoning involved in making determinations about the extrapolation of findings from one product to a similar one, and represent the FDA's reasoning with regard to follow-on proteins. We recognize that regulatory authorities in other geographical regions may approach these determinations differently, but this article limits its discussion to the FDA's perspective on this topic.

Background

Non-protein, small-molecule drugs are typically organic molecules of low molecular mass and known structure. Because the molecular structure of such a drug can usually be verified analytically, it is fairly easy for a generic-drug manufacturer to produce a duplicate product containing an active ingredient that is the same as the active ingredient in an innovator's approved drug product. The generic-drug product can generally be demonstrated to be as safe and effective as the innovator product for the approved uses by showing that it is pharmaceutically equivalent (that is, it contains the same active ingredient in the same strength, dosage form and route of administration) and bioequivalent (that is, absorbed into the body at a similar rate and extent) to the approved drug. In addition, under certain circumstances (for details see REF. 1) a manufacturer can establish the safety and efficacy of a product containing the same active moiety as an approved product that has undergone certain types of changes, such as in formulation or route of administration, by relying on certain existing information about the approved product and providing

Box 1 | Additional notes and explanations

Note 1. Peptides represent the simplest subset of proteins. Throughout this document, we use the term 'proteins' to refer to all forms of proteins, including peptides, unless otherwise specified.

Note 2. Protein and peptide drugs have been approved or licensed by the Food and Drug Administration (FDA) under the authority of Section 505 of the **Federal Food, Drug, and Cosmetic Act** (FDCA) (21 USC § 355) and under Section 351 of the **Public Health Service Act** (PHS Act) (42 USC § 262), depending on the nature of the product. Section 505 of the FDCA includes two abbreviated approval pathways: Sections 505(b)(2) and 505(j). There is no abbreviated approval pathway analogous to 505(b)(2) or 505(j) for products licensed under Section 351 of the PHS Act. However on 14 February 2007, legislation was introduced in the US House of Representatives and the US Senate that would give the FDA the authority to approve follow-on biologics using an abbreviated pathway. Under this proposal, the FDA could decide on a case-by-case basis how much testing a manufacturer would need to do to obtain approval.

Note 3. Although complex issues have been raised related to the legal framework under which protein products are regulated, this paper does not address these issues.

additional information that demonstrates that the new product remains sufficiently similar in clinical performance.

Protein products are typically much larger, more complex molecules than non-protein, small-molecule drugs and generally cannot be fully characterized using available analytical techniques. Additionally, protein products are often heterogeneous mixtures of molecules that vary slightly in molecular structure. Unlike small-molecule drugs, proteins fold upon themselves and form specific conformations that can be critical to biological activity. Many well-characterized, highly purified proteins exhibit micro-heterogeneity (that is, slight differences in structure between essentially identical molecules, such as in the saccharide portion of a glycoprotein). Recombinant products can vary slightly from lot to lot even when the same manufacturing process is used. The quality and nature of natural-source products can also vary depending on factors such as variability of the source material (for example, time of year of harvest, species) and the processes used to extract and purify the product.

A major scientific issue in evaluating follow-on protein products is determining how much and what kind of data are needed to establish whether the differences between similar — but not identical — protein products produced by different manufacturers are clinically insignificant (BOX 2, Note 1). Some of the factors relevant to evaluating this issue also arise when determining the comparability of protein products produced before and after a change in a specific manufacturer's manufacturing process, and in evaluating second-generation protein products in light of what is known about the first-generation product. As illustrated by the product examples discussed here,

a range of factors can influence the amount and type of data needed to establish similar or comparable clinical performance. The FDA has addressed the scientific challenges presented by these types of evaluations on a case-by-case basis, consistent with its statutory authority and in a manner analogous to the approach the FDA has taken in ensuring safety and effectiveness in other contexts (BOX 2, Note 2).

The FDA's experience in analysing related protein products dates back more than 20 years. In the 1980s, the FDA began to receive the first new marketing applications for biotechnology-derived protein products. These applications were for recombinant versions of the same manufacturer's marketed protein drug products derived from other sources (for example, animal-derived insulins and human growth hormone from the pituitaries of cadavers). In 1986, the FDA concluded² that new marketing applications ordinarily would be required for manufacturers who wished to produce new, recombinant DNA (rDNA) technology versions of existing products because "rDNA processes may (1) produce a product with variations in structure; (2) result in microheterogeneity (the existence of minor variations in product composition or structure); or (3) introduce new contaminants," which could influence safety and effectiveness. As a result of this policy, manufacturers of recombinant versions of approved products would usually have to submit to the FDA all the clinical testing data that would be required for any new product, including from appropriate efficacy trials.

The FDA also provided exceptions to this general principle. For example, if a product derived from rDNA technology were "virtually identical to an animal-source product," the manufacturer holding an

approved application for the animal-source product may "only need to submit a supplemental marketing application." The FDA clarified that "each case would be examined separately to determine the appropriate information to be submitted."² This approach provides flexibility in data requirements should the science support a reduction in the need for new data necessary for approval of a marketing application. This approach also reflects the FDA's long-standing policy of permitting appropriate reliance on what is already known about a drug, thereby saving time and resources in the drug development and approval processes and avoiding ethical concerns associated with unnecessary duplication of human or animal testing.

Evaluating protein products

The following examples of non-recombinant and recombinant protein products approved or licensed by the FDA illustrate some of the factors that have influenced the amount and type of data required by the FDA to support marketing approval for follow-on protein products, second-generation products and for the evaluation of major manufacturing changes to an approved protein product. Important factors include:

- Evidence of integrity and consistency of the manufacturing process.
- Conformance of manufacturing standards to existing regulations (if any).
- Demonstrations of a product's consistency with appropriate reference standards or comparators (using relevant assays), including comparative pharmacokinetic and pharmacodynamic data.
- The extent to which the existing body of clinical data and experience with the approved product can be relied on.

Non-recombinant protein products

The products described in this section are natural-source products — historically, the first type of protein products developed. When these products were initially used, technical factors limited our ability to analytically characterize them. Homogeneity that was adequate for clinical purposes was achieved by tight control of the manufacturing processes and by evaluating *in vitro* or *in vivo* pharmacodynamic assays, resulting in the demonstration of satisfactory clinical performance.

Albumin. Albumin is a naturally occurring human protein obtained from human plasma that is indicated for blood volume expansion in volume-depleted patients.

New clinical efficacy data are not ordinarily required for the approval of new therapeutic albumin (natural source) products for existing indications because the mechanism of action of therapeutic albumin in support of colloidal-oncotic pressure is well understood and albumin products are purified using well-established and consistent manufacturing methods. Albumin also has a well-established safety and efficacy profile because of our extensive clinical experience with the product. Approvals of albumin products have been based primarily on conformance to the product and manufacturing standards described in the regulations and performance of the products in small safety trials (for details see REF. 3).

Standardized allergenic extracts. Allergenic extracts are sterile aqueous extracts derived from natural sources, such as pollens or insects, and are used for the diagnosis and immunotherapy of allergic diseases. A major regulatory focus in the evaluation of standardized allergenic extracts is the integrity of the manufacturing process, including consistency in source materials and production methods. There are 19 extracts for which the approval takes into account the potency of the product as compared to established US reference standards. An application for a new allergenic extract might not require extensive clinical data when the allergenic extract product is demonstrated to be consistent with those reference standards.

Mammalian testicular hyaluronidase. Mammalian testicular hyaluronidase is a natural-source protein derived from bovine or ovine testicles that is indicated as an adjuvant to increase absorption and dispersion of injected drugs. The FDA has approved follow-on versions of hyaluronidase based on assay data showing that the product has enzymatic activity consistent with USP–NF (BOX 2, Note 3) standards (this activity is also the mechanistic basis for product effectiveness), clinical data assessing the immunogenicity of the product, and information establishing that the manufacturing process ensures consistency of the drug product. Evidence of enzymatic activity permits reliance on the existing body of clinical data and experience from other hyaluronidase products that have demonstrated similar enzymatic activity. Clinical testing of the immunogenicity is important here because products derived from different sources may be more or less immunogenic.

Box 2 | Additional notes and explanations

Note 1. “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.”¹⁰

Note 2. For example, see the Food and Drug Administration (FDA) guidance for industry *Providing Clinical Evidence of Effectiveness for Human Drug and Biological Products*, which discusses circumstances that would allow reliance on different types and amounts of data to support effectiveness. This guidance details the circumstances in which existing data, whether from an original application or other sources, can be used to support the determination of drug efficacy. The guidance also defines the circumstances necessary for the FDA to consider a database that does not contain the two adequate and well-controlled trials that the FDA generally requires as adequate for a marketing or licensing decision.

Note 3. The *United States Pharmacopeia–National Formulary* (USP–NF) contains public pharmacopeial standards for developing medicines, dosage forms, drug substances, excipients, medical devices and dietary supplements.

DigiFab. DigiFab (Protherics, Inc.) is used to treat life-threatening or potentially life-threatening overdoses with digoxin. The product consists of digoxin-specific antibody fragments obtained from sheep that were immunized with digoxin linked to keyhole limpet haemocyanin. The mechanism of action is the preferential binding of free digoxin to the antibody fragments, thus reducing the amount of digoxin available to bind to the receptor that mediates the cardiac effects of digoxin. The original product developed for this indication, Digibind (GlaxoSmithKline), was derived from sheep that were immunized with digoxin linked to albumin. The effectiveness of Digibind in reversing digoxin toxicity was demonstrated in a study of 150 subjects with life-threatening digitalis toxicity⁴. DigiFab was determined to be safe and effective in reversing life-threatening digoxin toxicity in a study of 15 subjects (digoxin toxicity was completely resolved in 14 out of 15 subjects in 20 hours). The study demonstrated that the ability of DigiFab to reverse digoxin toxicity was comparable with historical data for Digibind. In addition, a study in healthy volunteers demonstrated that pharmacodynamic and pharmacokinetic properties of DigiFab and Digibind were comparable 2 hours after digoxin administration. Thus DigiFab was approved on the basis of a small study demonstrating its safety and effectiveness in reversing life-threatening digoxin toxicity, an understanding of its

mechanism of action and data indicating that its pharmacodynamic and pharmacokinetic parameters were comparable with those for Digibind.

Recombinant protein products

Beginning in the 1980s, many of the first rDNA products were developed to replace natural-source products. Currently, manufacturers generally seek to produce follow-on products that are similar to approved rDNA products. Both types of products are described here.

Glucagon. Glucagon is an endogenous substance — a non-glycosylated peptide hormone important in the regulation of carbohydrate metabolism — used clinically to treat severe hypoglycaemia and as a diagnostic aid in gastrointestinal radiological examinations. The original marketed products were derived from bovine or porcine pancreas. The FDA has approved two recombinant follow-on versions of glucagon. The approvals were based on data that bridged the recombinant versions to the clinical data supporting the determination of safety and effectiveness for the natural-source products; they were also based on the extensive clinical experience with those natural-source products. Data included structural characterization of the recombinant product, which demonstrated an amino-acid sequence identical to human and bovine pancreatic glucagons; pharmacokinetic and pharmacodynamic data, which

demonstrated similarity to the natural-source products; immunogenicity and safety data, which showed no increase in antibody titres; and a safety profile comparable with the natural-source products.

Fortical (salmon calcitonin nasal spray). Fortical is a nasal-spray dosage form of a recombinant version of salmon calcitonin, a peptide hormone that is important in the control of calcium homeostasis and bone metabolism. Fortical was approved for use in treating post-menopausal osteoporosis in women more than 5 years after menopause with low bone mass relative to healthy post-menopausal women. The approval was based largely on comparative data indicating that Fortical was highly similar to an approved synthetic (as opposed to recombinant) version of salmon calcitonin, Miacalcin NS (Novartis). Data included physicochemical characterizations demonstrating that the amino-acid sequence and secondary structures of Miacalcin and Fortical are identical and the tertiary structures are indistinguishable within the limits of analytical detection; pharmacodynamic data from a 24-week study indicating comparable effects on bone resorption and a similar safety profile; pharmacokinetic data indicating Fortical is more bioavailable than Miacalcin, but not to a clinically significant extent; animal pharmacokinetic/pharmacodynamic and toxicology data demonstrating comparability; and immunogenicity data indicating comparability. On the basis of these data, the FDA concluded that Fortical was sufficiently similar to Miacalcin NS to permit reliance on the finding of effectiveness and safety for Miacalcin, including the finding (from a 2-year bone-mineral-density study) that Miacalcin increases lumbar-vertebral bone-mineral density in osteoporotic women who were more than 5 years post-menopausal, and findings from long-term carcinogenicity and toxicity studies.

Omnitrope (somatotropin). Omnitrope was the first recombinant human-growth hormone product approved by the FDA under an abbreviated approval pathway (BOX 3, Note 1). The approval relied on, among other things, physicochemical, pharmacokinetic, pharmacodynamic and clinical data comparing Omnitrope with Genotropin, a recombinant growth-hormone product approved in 1985. The clinical comparative data were from two controlled trials (6-month and 3-month durations) in 86 paediatric subjects (89 subjects enrolled; 86 subjects completed the 6- and 3-month

BOX 3 | Additional notes and explanations

Note 1. Omnitrope was approved according to Section 505(b)(2) of the Federal Food, Drug, and Cosmetic Act. This provision of the Act permits an applicant to rely for approval of a drug product on studies the applicant did not conduct and to which the applicant does not have a right of reference.

Note 2. “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.”¹⁰

trials) that directly compared Omnitrope and Genotropin for the treatment of growth failure due to inadequate secretion of endogenous growth hormone (paediatric growth-hormone deficiency). In addition to these comparative data, the FDA reviewed certain non-clinical pharmacology data specific to Omnitrope: an additional controlled trial supporting the safety and effectiveness of a reformulated version of Omnitrope for injection (the marketed version) and liquid Omnitrope in paediatric growth-hormone deficiency (involving the same 86 subjects as in the comparative studies), and safety data from a 24-month uncontrolled trial in 51 subjects that provided support for Omnitrope's long-term safety and confirmation of an acceptable level of immunogenicity (for further details, see the FDA response to the Omnitrope citizen petition⁵). The comparative data established that the active ingredients in Omnitrope and Genotropin have highly similar structures and Omnitrope and Genotropin have highly similar pharmacodynamic and pharmacokinetic parameters, as well as similar clinical performance (safety and effectiveness) in a growth-hormone-deficient paediatric population. The comparative data permitted the FDA to rely, in part, on its finding that Genotropin is safe and effective to support its conclusion that Omnitrope is safe and effective for the same indications, including indications (paediatric and adult) for which Omnitrope was not studied. Omnitrope has not been rated by the FDA as therapeutically equivalent (that it is substitutable) to any other approved human growth hormone product (BOX 3, Note 2).

Eprex (erythropoietin- α). Erythropoietin (EPO) is a complex protein that regulates the maturation of erythroid-precursor

cells into red-blood cells. It has multiple sites of glycosylation that are essential to its effectiveness. The original recombinant version of EPO, Epogen, is manufactured by Amgen and is indicated for the treatment of anaemia associated with chronic renal failure, chemotherapy or zidovudine therapy in patients infected with HIV and to reduce allogeneic blood transfusion in surgery patients. Eprex was developed pursuant to a licensing agreement between Amgen and Ortho Biotech that provided Ortho Biotech with access to Amgen's processes and procedures and source materials (the Master Cell bank), and the right to cross-reference Epogen clinical data in the Amgen licensing applications. The FDA approved Eprex for the same indications as for Epogen based on information indicating that the manufacturing processes for Eprex and Epogen were identical or sufficiently similar and on data indicating that the products have high structural similarity, are pharmacokinetically and pharmacodynamically similar (in terms of their effect on haemoglobin levels), and have a similar clinical safety profile (incidence of adverse effects). These comparability data permitted reliance, in part, on clinical and preclinical data in Amgen's application for Epogen to support approval of Eprex. Although approved, Eprex is not commercially marketed in the United States.

This example also illustrates the need for caution concerning the comparability of recombinant-protein products (either from different sources or from changes in manufacturing or formulation), particularly if the protein is a therapeutic homologue of an endogenous protein with a unique function. Between 1998 and 2004, the incidence of pure red-cell aplasia (PRCA) associated with the administration of EPO

products increased dramatically owing to the generation of anti-EPO antibodies that cross-reacted with endogenous EPO, thus neutralizing the biological activity of both therapeutic and endogenous EPO. One analysis concluded that of the 191 reported cases worldwide during this time period, 175 were associated with Eprex. The increase in PRCA seemed to coincide with changes in the manufacture of Eprex, including a formulation change (to a polysorbate-protein stabilizer from human-serum albumin) and use of a new packaging system (a pre-filled syringe for subcutaneous administration). An extensive investigation revealed that leachables associated with the syringe's rubber stopper were present in the product following the manufacturing changes and might have acted as an adjuvant that enhanced the immune responses⁶. The definitive cause(s) of neutralizing anti-EPO antibodies and PRCA are still being discussed^{7,8}.

Recombivax HB (hepatitis B vaccine).

Heptavax B, the original hepatitis B vaccine approved for marketing in the United States (no longer marketed), was derived from hepatitis B surface antigen (HBsAg) obtained from plasma of chronic HBsAg carriers (that is, it was a natural-source product). It was approved, in part, on the basis of two large clinical trials (involving 1,083 and 1,042 subjects) in homosexual males at risk for hepatitis B, in which it was demonstrated that Heptavax B induced high levels of antibody to HBsAg and was effective in preventing infection with hepatitis B virus.

Recombivax HB, the first recombinant hepatitis B vaccine, was developed as an alternative to Heptavax B by the same manufacturer. Physicochemical and bio-analytical testing revealed that Recombivax HB differed from Heptavax B in several ways, including whether lipids are incorporated into the antigenic particles, whether there is glycosylation or aberrant disulphide bonds, and how they perform in commercial radioimmunoassays. However, serological data from 1,200 healthy volunteers indicated that both Recombivax HB and Heptavax B induced levels of antibody to HBsAg that were known to be protective against transmission of hepatitis B virus in a high proportion of individuals. Although Recombivax HB induced lower antibody titres than Heptavax B, the titres were still above the minimum level that was associated with protection from infection. Because the Heptavax B development

programme had established that antibody titres of HBsAg of 10 mIU ml⁻¹ or greater were effective in preventing infection with hepatitis B virus (surrogate marker), approval of Recombivax HB did not require a large clinical study to demonstrate clinical effectiveness in actual prevention of hepatitis B virus infection in at-risk adults. Recombivax HB was approved on the basis of safety and immunogenicity data (efficacy data for the surrogate marker) in 1,200 healthy volunteers and clinical efficacy studies (involving a total of 289 subjects), which demonstrated the safety and effectiveness of the recombinant vaccine in preventing chronic hepatitis B infection in neonates born to mothers positive for HBsAg and hepatitis Be antigen (HBeAg; an indicator of active viral replication and high infectivity). This example also demonstrates the use of mechanistically well-understood pharmacodynamic data (for example, antibody production) together with clinical data.

Major manufacturing changes

Avonex (interferon β 1a). The case of Avonex (interferon β 1a) illustrates the major challenge associated with approvals of follow-on recombinant versions of approved recombinant products — that is, the amount and type of data needed to demonstrate that a product produced after major changes (for example, use of a new cell line) in the manufacturing process has safety and effectiveness that are comparable with the product manufactured before the change.

Avonex is a highly characterized recombinant protein approved to slow the accumulation of physical disability and decrease the frequency of clinical exacerbations of relapsing forms of multiple sclerosis. The major efficacy trial that supported the approval of Avonex used a version of interferon β 1a that was manufactured by a German company, Bioferon, which at the time was a co-developer of interferon β 1a with Biogen (now Biogen-Idex). Bioferon encountered financial difficulties and ceased production of their version of the product. To obtain approval for Avonex, Biogen had to develop its own manufacturing process for Avonex and demonstrate that the version of interferon β 1a produced by that process was sufficiently similar to the Bioferon product that the data from the clinical studies using the Bioferon product could be relied on to support approval of the Biogen version.

Production of Avonex by Biogen necessitated a change in the cell line used to

produce the recombinant product — one of the many differences in manufacturing processes that manufacturers of follow-on versions of such products are likely to face. Biogen's initial effort to develop a new cell line and produce an interferon β 1a that was comparable with the Bioferon product was unsuccessful⁹. A subsequent effort using another new cell line was successful. Physicochemical testing (for example, peptide maps and glycoform characterizations) indicated that the structures were similar. Multiple bioassays (for example, antiproliferation and enhancement of major histocompatibility complex (MHC) class I expression) indicated that the products had comparable bioactivity, and pharmacokinetic data indicated that distribution and clearance of the products were comparable. On the basis of these data, the FDA concluded that the totality of the evidence indicated that the Bioferon product and Avonex were sufficiently comparable to rely on data from the major efficacy study using Bioferon's product to support licensure of Avonex. In a subsequent immunogenicity study, the Avonex product demonstrated decreased immunogenicity. Although decreased immunogenicity is advantageous, the fact that there were differences in immunogenicity between the two products highlights the importance of immunogenicity to product evaluations.

Conclusions

Scientific and technological advances have created new opportunities for the characterization and evaluation of protein products. The examples of approved protein products described here illustrate the FDA's scientifically based, case-by-case approach to evaluating follow-on proteins and related products, and significant manufacturing alterations. In all cases, when assessing applications for protein products that were similar to prior products, the FDA has considered a number of factors, including the robustness of the manufacturing process, the degree to which structural similarity could be assessed, the extent to which mechanism of action was understood, the existence of valid, mechanistically related pharmacodynamic assays, comparative pharmacokinetics, comparative immunogenicity, the amount of clinical data available, and the extent of experience with the original product, or products. For follow-on protein products produced through rDNA technology, establishing a high degree of structural similarity between the follow-on and the original product has been a crucial

first step in enabling the FDA to consider what available existing scientific information might pertain to a follow-on product and to determine the extent of the clinical studies of safety and efficacy necessary to support approval. We expect that, as analytical technology continues to improve, the evaluation of structural similarity will become feasible for a wide range of products. As a science-based agency, the FDA will continue to integrate scientific advances and public health needs into its review of protein products.

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Competing interests statement

The authors declare no competing financial interests.

FURTHER INFORMATION

Federal Food, Drug, and Cosmetic Act:

<http://www.fda.gov/opacom/laws/fdact/fdctoc.htm>

Providing Clinical Evidence of Effectiveness for Human

Drug and Biological Products: <http://www.fda.gov/cder/guidance/1397Inl.pdf>

Public Health Service Act:

<http://www.fda.gov/opacom/laws/phsvact/phsvact.htm>

United States Pharmacopeia–National Formulary:

<http://www.usp.org/USPNF>

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