DEPARTMENT OF HEALTH & HUMAN SERVICES

Public Health Service

Food and Drug Administration
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Re: Docket Nos. 2004P-0231/CP1 and SUP1, 2003P-0176/CP1 and EMC1, 2004P-0171/CP1, and 2004N-0355

Dear Petitioners:

This responds to the citizen petition dated May 13, 2004, submitted on behalf of Pfizer Inc. (Pfizer Petition) and the supplement to the petition dated August 4, 2004 (Pfizer Supplement).[1] The Pfizer Petition requests that the Food and Drug Administration (FDA or the Agency) immediately deny approval of new drug application (NDA) 21-426 for the recombinant human growth hormone (rhGH) product Omnitrope (somatropin [rDNA origin] for injection) (the Omnitrope NDA). The Omnitrope NDA was submitted to FDA through the approval pathway described by section 505(b)(2) of the Federal Food, Drug, and Cosmetic Act (21 U.S.C. 355(b)(2)) (the Act) and references Pfizer Inc.'s (Pfizer's) listed drug Genotropin (somatropin [rDNA origin] for injection). According to the Pfizer Petition (at 1):

- "It is scientifically and legally improper for FDA to rely on, reference, or otherwise use the clinical and manufacturing information that establishes the safety and effectiveness of Genotropin . . . to approve Omnitrop[e]"; and

- Data submitted to support approval of Omnitrope "do not adequately address the safety, effectiveness, and manufacturing considerations" for approval of rhGH products or "the specific product differences between Genotropin and Omnitrop[e]."

[1] See Docket No. 2004P-0231/CP1 and SUP1. In preparing this response, FDA has considered the comments submitted to the Pfizer Petition docket.

In addressing the Pfizer Petition, this response also addresses relevant parts of citizen petitions and related supplements submitted by the Biotechnology Industry Organization (BIO)[2] and Genentech[3] regarding follow-on protein products.[4] BIO's petition, dated April 23, 2003 (BIO Petition), and supplement, dated August 8, 2003 (BIO Supplement), request, among other things, that FDA refuse to approve any application for a therapeutic protein product that relies on information contained in another approved application.[5] Genentech's petition, dated April 8, 2004 (Genentech Petition), similarly contests the Agency's interpretation of section 505(b)(2) of the Act as authority to approve applications for biotechnology-derived products that rely on a previous approval.[6] This response also addresses certain comments that were raised in FDA's separate public docket entitled *Scientific Considerations Related to Developing Follow-on Protein Products*[7] (Follow-On Proteins Docket) and related public meetings sponsored by FDA[8] that pertain to the scientific and technical issues involved in approval of the Omnitrope application.

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[2] See Docket No. 2003P-0176/CP1 and EMC1. FDA also has considered the comments submitted to this docket.

[3] See Docket No. 2004P-0171/CP1. FDA also has considered the comments submitted to this docket.

[4] Regarding the terminology *follow-on protein products*, see note 7 of this response.

[5] Many of the legal and regulatory arguments raised by the BIO Petition concerning section 505(b)(2) of the Act were addressed in FDA's October 14, 2003, consolidated response to various citizen petitions. See October 14, 2003, response to [Kathleen] M. Sanzo, Jeffrey B. Chasnow, Stephan E. Lawton, and William R. Rakoczy re: Docket Nos. 2001P-0323/CP1 & C5, 2002P-0447/CP1, and 2003P-0408/CP1 (505(b)(2) Citizen Petition Response). Other arguments not addressed in our 505(b)(2) Citizen Petition Response, but that are relevant to approval of the Omnitrope NDA, including arguments raised in comments submitted on the BIO Petition since our 505(b)(2) Citizen Petition Response, have been considered and are addressed in this response where applicable. Arguments raised by the BIO Petition (and Genentech Petition) which have not been addressed in the 505(b)(2) Citizen Petition Response or in this response, will be addressed in a subsequent response, as appropriate.

[6] The Genentech Petition requests that FDA decline to approve 505(b)(2) applications for biotechnology-derived products that seek to rely on the Agency's finding of safety or effectiveness for a Genentech product. Although the Omnitrope NDA does not rely on a finding of safety or effectiveness for any Genentech product, certain arguments in the Genentech Petition are nevertheless relevant; moreover, the Pfizer Petition incorporates the Genentech Petition by reference (Pfizer Petition at 2, note 3).

[7] See Docket No. 2004N-0355. As the *Federal Register* notice establishing this docket described, we are further considering the term *follow-on protein products* (see Scientific Considerations Related to Developing Follow-On Protein Products, Notice of Public Workshop (69 FR 50386, August 16, 2004)). We generally use the informal term *follow-on protein products* (as well as the term *follow-on protein*) to refer to proteins and peptides that are intended to be sufficiently similar to a product already approved under section 505 of the Act or licensed under section 351 of the Public Health Service Act (PHSA) 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. We note that there is no abbreviated approval pathway analogous to 505(b)(2) or 505(j) of the Act for protein products licensed under section 351 of the PHSA.

[8] These meetings were held on September 14 and 15, 2004, and February 14 to 16, 2005.

For the reasons described in detail in this response, the Agency denies the Pfizer Petition and Pfizer Supplement[9] and, to the extent they oppose approving the Omnitrope NDA, relevant portions of the Genentech Petition, the BIO Petition, and the BIO Supplement. Today, the Agency approved Sandoz' NDA for Omnitrope.

I. THE SCOPE OF THIS RESPONSE[10]

The Omnitrope NDA was submitted pursuant to section 505(b)(2) of the Act.[11] The Agency has described its interpretation and application of this provision of the Act at length in our 505(b)(2) Citizen Petition Response, and in the regulatory materials (e.g., regulations, preambles to those regulations, and draft guidance) cited in that response. In the 505(b)(2) Citizen Petition Response, the Agency reserved the scientific issues related to the use of section 505(b)(2) to approve *biologically derived products*, noting that these issues would be addressed in a later response.[12]

This response briefly reviews the 505(b)(2) drug approval pathway, describes the Omnitrope application, and then addresses specific issues raised by petitioners and others related to the review and approval in a 505(b)(2) application of the rhGH product Omnitrope. As described in detail in this response, the Omnitrope NDA relies, in part, on FDA's finding of safety and effectiveness for another rhGH product, and also is supported by preclinical and clinical data generated by its sponsor, Sandoz Inc., on behalf of Sandoz GmbH (Sandoz). As further explained below, rhGH products such as Omnitrope are distinguishable in several critical respects from other (often more complex or less well-understood) protein products. For these and other reasons, many of the more general arguments raised in the petitions and comments regarding follow-on protein products do not apply to Omnitrope; accordingly, these issues are not addressed in this response.

This response does not address, for example, the following:

- Trade secret and Constitutional law (Fifth Amendment takings clause) arguments based on the use of trade secret data and information (e.g., chemistry, manufacturing, and controls (CMC) data) in one approved application to review and approve an application for a follow-on protein product (as discussed in section III.A.2 of this response, FDA has not and does not need to review or use any trade secret information from the approved Genotropin application, or any other application, to approve the Omnitrope NDA).

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[9] To the extent that action on the Omnitrope NDA was deferred pending completion of the public meetings on Scientific Considerations Related to Developing Follow-On Protein Products, the Pfizer Supplement is granted in part.

[10] For ease of reference, an index to this response is attached as Appendix A.

[11] The text of section 505(b)(2) of the Act is set forth in section II.A of this response.

[12] 505(b)(2) Citizen Petition Response at 1, note 1. For purposes of this response, *biologically derived products* include follow-on protein products.

- Arguments concerning the legality of relying on the approval or licensing of another product to approve or license follow-on protein products under the Public Health Service Act (PHSA) or in an abbreviated new drug application (ANDA) under section 505(j) of the Act (the Omnitrope NDA was a 505(b)(2) application).

- Arguments relating to "A" therapeutic ratings and interchangeability for recombinant protein products (Sandoz does not seek an "A" therapeutic rating for Omnitrope and we will designate Omnitrope with a "BX" rating in FDA's *Approved Drug Products with Therapeutic Equivalence Evaluations* (the Orange Book)).[13]

- Scientific issues associated with protein products that have unknown or multiple active ingredients (Omnitrope and other rhGH products have one active ingredient (somatropin)).

- Scientific issues associated with proteins with an unknown mechanism of action (somatropin's mechanism of action is understood; see section III.A.6.d of this response).

- Scientific issues associated with proteins that are difficult to characterize (as discussed in section III.A.2 of this response, rhGH can be extensively and adequately characterized using currently available analytical technologies).

- Scientific issues associated with glycosylation (Omnitrope and other rhGH products are not glycosylated).

This response describes the scientific and regulatory bases for the Agency's denial of the Pfizer Petition and Pfizer Supplement and, to the extent they oppose approving the Omnitrope NDA, relevant portions of the Genentech Petition, the BIO Petition, and the BIO Supplement.

II. BACKGROUND

A. Section 505(b)(2) Applications

Section 505(b)(2) of the Act was enacted as part of the Drug Price Competition and Patent Term Restoration Act of 1984 (Public Law 98-417) (Hatch-Waxman or the Hatch-Waxman Amendments). As described in our 505(b)(2) Citizen Petition Response, the Hatch-Waxman Amendments reflect Congress' attempt to balance the need to encourage innovation with the desire to speed the availability of lower cost alternatives to approved drugs. Incentives for drug development were established in the form of marketing exclusivity and patent extensions (505(b)(2) Citizen Petition Response at 4 to 6). With passage of the Hatch-Waxman Amendments, the Act described two broad categories of drug applications: new drug applications (NDAs), for which the requirements are set out

[13] The code BX in the Orange Book refers to "[d]rug products for which the data are insufficient to determine therapeutic equivalence."

in section 505(b) and (c) of the Act, and abbreviated new drug applications (ANDAs), for which the requirements are set out in section 505(j). The NDA category described at section 505(b) of the Act includes both applications that contain full reports of investigations of safety and effectiveness that were conducted by or for the applicant or for which the applicant has a right of reference, and applications that contain full reports of investigations of safety and effectiveness, where at least some of the information required for approval comes from studies not conducted by or for the applicant and for which the applicant has not obtained a right of reference. This latter category of NDA is described in section 505(b)(2) of the Act and is referred to as a "505(b)(2) application" (505(b)(2) Citizen Petition Response at 8 to 9).

Section 505(b)(2) provides:

> An application [may be] submitted under . . . [section 505(b)(1)] for a drug for which the [safety and effectiveness] investigations . . . relied upon by the applicant for approval of the application were not conducted by or for the applicant and for which the applicant has not obtained a right of reference or use from the person by or for whom the investigations were conducted [and] shall also include . . . a certification . . . to each patent which claims the drug for which such investigations were conducted or which claims a use for such drug for which the applicant is seeking approval. . .

FDA has described its interpretation of section 505(b)(2), as promulgated by the Hatch-Waxman Amendments, in a series of public statements and proceedings beginning in 1987, including the 1989-1994 Hatch-Waxman rulemaking process, a 1999 draft guidance, and the comprehensive 505(b)(2) Citizen Petition Response. As explained in detail in our 505(b)(2) Citizen Petition Response, 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.[14] A 505(b)(2) applicant may rely on such studies either by submitting as part of the application published literature that describes the study results or by referencing in the application the finding of safety and effectiveness that FDA made for a previously approved listed drug,[15] a

[14] As defined at 21 CFR 314.3, "*Right of reference or use* means the authority to rely upon, and otherwise use, an investigation for the purpose of obtaining approval of an application, including the ability to make available the underlying raw data from the investigation for FDA audit, if necessary."

[15] As defined at 21 CFR 314.3:

> *Listed drug* means a new drug product that has an effective approval under section 505(c) of the act for safety and effectiveness or under section 505(j) of the act, which has not been withdrawn or suspended under section 505(e)(1) through (e)(5) or (j)(5) of the act, and which has not been withdrawn from sale for what FDA has determined are reasons of safety or effectiveness. Listed drug status is evidenced by the drug product's identification as a drug with an effective approval in the current edition of FDA's "Approved Drug Products with Therapeutic Equivalence Evaluations" (the list) or any current supplement thereto, as a drug with an effective approval. A drug product is deemed to be a listed drug on the date of effective approval of the application or abbreviated application for that drug product.

finding that is based upon studies conducted by another applicant. FDA's long-standing interpretation of section 505(b)(2) permits the Agency to approve NDAs that rely on published literature or on the Agency's finding of safety and effectiveness for another drug product, provided that such reliance is scientifically justified and the 505(b)(2) applicant complies with the applicable statutory requirements regarding patent certification.

For 505(b)(2) applications that rely not on literature but on the Agency's finding of safety and effectiveness for a listed drug, a key consideration is that the 505(b)(2) applicant may rely on FDA's finding only to the extent that the proposed product in the 505(b)(2) application shares characteristics (e.g., active ingredient, dosage form, strength, route of administration, indication, conditions of use) in common with the listed drug. The 505(b)(2) application must include data and information (including bioavailability and/or comparative bioavailability studies) sufficient to establish that it is appropriate for the applicant to rely on the Agency's finding of safety and effectiveness for the listed drug. To the extent that the listed drug and the drug proposed in the 505(b)(2) application differ, the 505(b)(2) application must include sufficient data, including clinical or nonclinical data, as appropriate (21 CFR 314.54(a)), to demonstrate that the proposed drug meets the statutory approval standard for safety and effectiveness.[16] As is the case with ANDAs under section 505(j), approval of a section 505(b)(2) application is subject to the patent and exclusivity protections that apply to the listed drug (505(b)(2) Citizen Petition Response at 7 to 8).

Reliance on FDA's *finding* or conclusion that an approved drug is safe and effective does not involve disclosure to the ANDA or 505(b)(2) applicant — or to the public — of the data in the listed drug's NDA. Instead, it permits the ANDA or 505(b)(2) applicant to rely on the fact that FDA found a drug product with certain characteristics to be safe and effective and, in the case of a 505(b)(2) applicant, to target its studies to establish that the modified drug product also meets FDA's safety and effectiveness standards.

As described in detail in the 505(b)(2) Citizen Petition Response, FDA's interpretation is supported by the text of section 505(b)(2), the structure of the Hatch-Waxman Amendments, and the purposes of that legislation. The interpretation is also supported by sound policy considerations. By permitting appropriate reliance on what is already known about a drug, FDA's interpretation allows the pharmaceutical industry to target investment on innovative drug development and to avoid ethical concerns associated with unnecessary duplicative human testing, saving time and resources in the drug

[16] Our regulations, which expressly provide that we may refuse to review duplicates under section 505(b)(2) of the Act (see 21 CFR 314.101(d)(9)), reflect an intended use of the 505(b)(2) approval pathway for products that include changes from a listed drug. Section 505(j) permits approval of ANDAs that are either for duplicates of the listed drug or for drug products that differ from the listed drug in specified ways and for which approval would be warranted without additional clinical safety and effectiveness data (505(b)(2) Citizen Petition Response, at 7). The informal term *duplicate* is used in this response, as it was in the 505(b)(2) Citizen Petition Response, to refer to an application under section 505(j) describing a product that is the same as the listed drug with respect to active ingredient, dosage form, route of administration, strength, labeling, and conditions of use, among other characteristics.

development and approval process (505(b)(2) Citizen Petition Response at 14). Since 1987, the Agency has approved over 178 applications submitted through the 505(b)(2) pathway.

Sandoz has used the 505(b)(2) pathway to obtain approval of the Omnitrope NDA, which is for a drug product that has a recombinant protein as its active ingredient. As this petition response explains, rather than being a substantial expansion of the use of section 505(b)(2), the approval of Omnitrope reflects the application of a reasonable and well-established drug approval process to a drug product with a well-characterized and well-understood recombinant DNA-derived active ingredient for which the sponsor submitted an application containing adequate data and information to establish safety and effectiveness for the labeled indications.

B. Human Growth Hormone Products

Human growth hormone (hGH) has a long history of clinical use as replacement therapy for endogenous growth hormone deficiency (GHD). Treatment with pituitary-derived hGH first was reported in 1958,[17] and subsequently was facilitated by the National Hormone and Pituitary Program (1963-1985) and approval under section 505 of pituitary-derived hGH for commercial distribution beginning in 1976.[18] The approval of a recombinant hGH (rhGH), Protropin (somatrem), in 1985 ensured a stable supply of the hormone and obviated concerns regarding the risk of Creutzfeldt-Jakob Disease associated with pituitary-derived hGH.[19] Since the approval of Protropin (somatrem), FDA has approved seven recombinant hGH (somatropin) product lines for a variety of indications.[20]

As a general matter, hGH has several characteristics that facilitate comparisons between two rhGH products. These characteristics include the following:

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[17] Raben MS. Treatment of a pituitary dwarf with human growth hormone. J Clin Endocrinol Metab. 1958;18(8):901-903.

[18] Two pituitary-derived human growth hormone products (Asellacrin and Crescormon) were approved under section 505 of the Act in 1976 and 1979, respectively. The approval of these somatropin applications for pituitary dwarfism was described as being "based almost exclusively on reports from the published literature" (Response to Petition Seeking Withdrawal of the Policy Described in the Agency's "Paper" NDA Memorandum of July 31, 1978; Notice (45 FR 82052 at 82055, December 12, 1980)).

[19] See, e.g., National Institute of Diabetes & Digestive & Kidney Diseases, Information for People Treated with NHPP Human Growth Hormone (hGH), available at http://www.niddk.nih.gov/health/endo/pubs/creutz/updatecomp.htm; Parker KL, Schimmer BP. Pituitary Hormones and Their Hypothalamic Releasing Factors. In *Goodman & Gilman's The Pharmacological Basis of Therapeutics*. 10th ed. New York: McGraw-Hill, 2001, at 1546.

[20] It should be noted that Protropin (somatrem) contained an additional amino acid residue (methionine) at the N-terminal of the molecule. Subsequent rhGH products approved by FDA were methionyl-free and contained an amino acid sequence identical to pituitary-derived hGH (somatropin) (see, e.g., *Genentech, Inc. v. Bowen*, 676 F. Supp. 301, at 306 (D.D.C. 1987)).

- hGH is a single-chain, 191 amino acid, non-glycosylated protein with two intramolecular disulfide bonds.

- hGH is readily purified for structural assessments. The primary structure of hGH is known, and physicochemical tests exist for the determination of an hGH product's secondary and tertiary structures (see discussion in section III.A.2 of this response regarding structural characterization techniques).

- Clinically relevant bioassays and qualified biomarkers are available for hGH. The mechanism of drug action is known and the human toxicity profile is well understood (see discussion in sections III.A.2, III.A.6.a, and III.A.7 of this response).

- hGH has a long history of clinical use as replacement therapy for endogenous GHD and its safety and efficacy profile is thoroughly described in the literature and well understood.

C. The Omnitrope NDA

The Omnitrope NDA was submitted to FDA as a 505(b)(2) application on July 30, 2003. Originally submitted by Biochemie U.S., Inc., this NDA is currently sponsored by Sandoz.[21] The Omnitrope NDA sought approval of rhGH for the following indications: (1) long-term treatment of pediatric patients who have growth failure due to an inadequate secretion of endogenous growth hormone (pediatric GHD), and (2) long-term replacement therapy in adults with GHD of either childhood or adult-onset etiology (adult GHD). Sandoz relied for approval, in part, on data generated by Sandoz and, in part, on FDA's finding of safety and effectiveness for Genotropin, which is approved for the same indications that Sandoz sought, and has now obtained, approval of Omnitrope.[22]

Sandoz submitted data and information, as required by §§314.50 and 314.54 and section 505(b) of the Act, to support the safety and effectiveness of Omnitrope for GHD. As further described in this response, Sandoz has established that Omnitrope is sufficiently similar to Genotropin to warrant reliance on FDA's finding of safety and effectiveness for Genotropin to support the approval of Omnitrope. Sandoz also has submitted extensive original clinical data supporting approval of Omnitrope for pediatric GHD. These data, when considered in conjunction with relevant literature and FDA's finding of safety and effectiveness for Genotropin, support the approval of Omnitrope in 1.5-milligram (mg) and 5.8-mg dose strengths for use in pediatric and adult GHD. The

[21] References to Sandoz in this response should be interpreted to include Biochemie U.S., Inc., as appropriate.

[22] Genotropin is indicated for pediatric GHD and adult GHD, as well as "[l]ong-term treatment of pediatric patients who have growth failure due to Prader-Willi syndrome (PWS)," "[l]ong-term treatment of growth failure in children born small for gestational age (SGA) who fail to manifest catch-up growth by age 2," and "[l]ong-term treatment of growth failure associated with Turner Syndrome in patients who have open epiphyses" (Genotropin product labeling (approved April 27, 2006), available at http://www.fda.gov/cder/foi/label/2006/020280s049lbl.pdf).

Omnitrope NDA, which includes CMC, nonclinical pharmacology and toxicology, human pharmacokinetic and pharmacodynamic, and clinical safety and effectiveness data, is described in the following subsections of this response.

1. CMC Data

CMC data submitted by Sandoz established, among other things, that the active ingredient in Omnitrope is somatropin and is highly similar,[23] physicochemically, to the active ingredient in Pfizer's Genotropin. As further discussed in section III.A.2 of this response, these conclusions derive from comparative analyses performed by Sandoz of Omnitrope, commercially available samples of Genotropin, and internationally available reference standards for somatropin obtained from the World Health Organization (WHO) and the European Pharmacopoeia. These analyses were performed using generally recognized analytical methods for characterizing proteins and in no way necessitated reference to, or reliance by Sandoz or the Agency on, trade secret CMC data in the Genotropin NDA.

2. Nonclinical Pharmacology and Toxicology Data

Nonclinical pharmacology and toxicology data submitted by Sandoz in support of the Omnitrope NDA included data from bioassays in hypophysectomized (and thus growth hormone deficient) rats, a subacute 14-day rat toxicology study, and a local (skin) tolerance study in rabbits. Sandoz assessed the bioactivity of Omnitrope using a hypophysectomized rat weight-gain bioassay, which is widely used and specific to hGH. As explained in section III.A.6.a of this response, minimal toxicity data are needed to support Omnitrope's approval because the clinical effects of hGH excess are well established and understood based on study of the clinical syndrome known as acromegaly (endogenous hGH excess due to a pituitary somatotroph tumor). In addition, historical experience with growth hormone replacement therapy is vast and extensively documented in general reference texts and other published literature.[24]

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[23] In the context of review of a 505(b)(2) application, an assessment of similarity between a proposed drug (in this case, Omnitrope) and a listed drug (in this case, Genotropin) may include comparative physicochemical tests, bioassay, preclinical data, pharmacokinetic data, pharmacodynamic data, and/or clinical data, considered with any information regarding differences between the proposed drug and the listed drug to determine whether it is scientifically appropriate for the Agency to rely on its finding of safety and effectiveness for the listed drug to support approval of the proposed drug. We use the term *highly similar* in this response to describe the degree to which certain properties of Omnitrope resemble properties of Genotropin, as shown by the above-referenced methods. In this case, FDA has determined that the degree of similarity between Omnitrope and Genotropin is sufficient to make it scientifically appropriate to rely on FDA's finding of safety and effectiveness for Genotropin to support approval of Omnitrope. This does not imply that a finding that two products are highly similar with respect to any specific property or set of properties is always necessary to support reliance in the 505(b)(2) context. Further, a finding of *similarity* in the context of a 505(b)(2) application does not imply a finding of *sameness* as that term is used in section 505(j) of the Act.

[24] The Omnitrope NDA references more than 230 published articles about hGH.

3. Human Pharmacokinetic and Pharmacodynamic Data

The Omnitrope NDA contains human pharmacokinetic, pharmacodynamic, and comparative bioavailability data which, among other things, substantiated with bridging across drug substance and formulation changes that Omnitrope and Genotropin are highly similar based on pharmacokinetic parameters and pharmacodynamic responses.

4. Clinical Safety and Effectiveness Data

As further detailed in sections III.A.6.f and III.A.7 of this response, in support of the Omnitrope NDA, Sandoz submitted data from original clinical trials of Omnitrope formulations in pediatric patients with GHD. These trials involved three formulations of the drug:

- *Early Omnitrope* — A lyophilized formulation that differs from Omnitrope in its manufacturing process and drug substance manufacturer (changes were made to address high levels of host cell proteins and related immunogenicity associated with Early Omnitrope).

- *Omnitrope* — The lyophilized formulation approved in the NDA.[25]

- *Liquid Omnitrope* — A liquid formulation that contains the same drug substance (made at the same manufacturing site and by a substantially similar manufacturing process) as Omnitrope.

Sandoz conducted three[26] sequential, multicenter, phase 3 pivotal trials in pediatric patients with GHD over a 15-month period in which it demonstrated the clinical comparability of Early Omnitrope and Genotropin in head-to-head trials, and the clinical comparability of the three Omnitrope formulations (Early Omnitrope, Omnitrope, and Liquid Omnitrope, as defined above).

In the first phase 3 trial, 89 pediatric patients with GHD were randomly assigned to treatment with Early Omnitrope (44 patients) or Genotropin (45 patients) for a 6-month

[25] The lyophilized Omnitrope formulation used in part A of the third phase 3 clinical trial differs slightly from the to-be-marketed Omnitrope formulation in that there was a minor modification to the ratio of two excipients. The to-be-marketed Omnitrope formulation was studied in the fourth phase 3 trial, which is discussed in further detail in this section of the response.

[26] It should be noted that the phase 3 component of the Omnitrope clinical program alternately could be described as two clinical trials (corresponding with months 0 to 9 and 9 to 30 of the study sequence, of which months 0 to 15 are considered pivotal) or even as a continuous study in which two cohorts of rhGH-treatment naïve patients were exposed sequentially to different pairs of rhGH products. For clarity of reference, we describe the phase 3 program as comprising three sequential trials. In addition, as discussed in further detail in sections II.C.4 and III.A.7 of this response, Sandoz submitted the results from a separate multicenter phase 3 clinical trial with its safety update to the application. Accordingly, we refer to this study as the fourth phase 3 trial.

period (months 0 to 6 of the study sequence). The second phase 3 trial was a 3-month extension study comprised of the 86 pediatric patients who completed the first phase 3 trial, without modification of the assigned treatment regimen with Early Omnitrope or Genotropin.[27] Together, the first and second phase 3 clinical studies evaluated the short-term safety and efficacy of Early Omnitrope as compared to Genotropin over a combined period of 9 months and demonstrated that these rhGH products have a similar clinical safety and efficacy profile, except for relatively more immunogenicity associated with Early Omnitrope. Immunogenicity associated with Early Omnitrope was addressed by changes in the drug substance manufacturer and manufacturing process to decrease host cell protein content; these changes are encompassed in Omnitrope.

The third phase 3 trial consisted of two parts (Part A, which is considered pivotal, and Part B, discussed in the next paragraph, which contributed supporting data), and provided further evidence of Omnitrope's safety and effectiveness for treatment of pediatric GHD. Part A of the third phase 3 trial was a 6-month extension study (months 9 to 15 of the study sequence) that involved 86 patients who had completed the first and second phase 3 studies and compared the lyophilized formulation of Omnitrope approved in the NDA (42 patients) to Liquid Omnitrope (44 patients). In this extension study, patients from the two treatment arms in the first and second phase 3 trials were not re-randomized: patients who previously had received Early Omnitrope in the first and second phase 3 trials (months 0 to 9 of the study sequence) were administered Omnitrope, while patients who previously had received Genotropin were administered Liquid Omnitrope. The effects on growth-related endpoints for patients within each study arm were compared to those for the same patients in the earlier clinical trials; in addition, this data was compared to historical data in the public domain regarding rhGH administration in pediatric patients with GHD. Part A of the third phase 3 trial demonstrated, among other things, that both patient groups (Omnitrope and Liquid Omnitrope) maintained the rates of growth and the effects on hGH-related pharmacodynamic variables that were demonstrated in the first and second phase 3 trials.

In addition, Sandoz provided supportive long-term safety and efficacy data from Part B of the third phase 3 trial,[28] in which patients from both treatment arms of the earlier phase 3 trials were administered Liquid Omnitrope during a subsequent 15-month period (months 15 to 30 of the study sequence). Results from Part B of the third phase 3 trial demonstrate that Liquid Omnitrope (which contains the same drug substance as the lyophilized formulation of Omnitrope approved in the NDA) had a sustained effect on height-related variables and insulin-like growth factor 1 (IGF-1) (a key marker of hGH pharmacodynamic action). Further, data from Part B of the third phase 3 trial support the conclusion that Omnitrope has a low and acceptable level of immunogenicity, consistent with rates of positive antibody formation in the published literature for approved rhGH products.

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[27] Three patients were withdrawn from the first phase 3 study after enrollment: two patients in the Early Omnitrope group and one patient in the Genotropin group; none of the withdrawals was due to adverse events.

[28] Part B of the third phase 3 trial is not considered a pivotal study.

Finally, Sandoz submitted the results from a separate multicenter phase 3 clinical trial with its safety update to the application. In this fourth phase 3 trial, 51 pediatric patients with GHD were treated with Omnitrope for a 24-month period.[29] This study provided supportive evidence of Omnitrope's safety and confirmed that Omnitrope has a low and acceptable level of immunogenicity: none of the patients developed anti-GH antibodies during the 24-month study, and only one patient developed anti-host cell protein antibodies, which were of no detectable clinical consequence. This study also provided supportive data regarding the efficacy of Omnitrope on height-related variables and secondary endpoints, consistent with the earlier clinical trials.

Thus, Sandoz has demonstrated a high degree of similarity of the active ingredient in Omnitrope, Early Omnitrope, Liquid Omnitrope, and Genotropin physicochemically and in terms of bioactivity (biologically), and also has shown a high degree of similarity of Early Omnitrope, Liquid Omnitrope, and Genotropin pharmacokinetically and pharmacodynamically, such that Omnitrope's reliance on FDA's previous finding of safety and effectiveness for Genotropin is justified.[30] In addition, Sandoz has provided extensive data supporting the safety and effectiveness of Omnitrope for use in treating pediatric GHD. Based on this data and information, Sandoz established an appropriate scientific basis upon which FDA was able to apply the Agency's finding of safety and effectiveness for Genotropin to approve Omnitrope for pediatric and adult GHD.[31]

Approval of the Omnitrope NDA for adult and pediatric GHD is scientifically justified and is a legally sound application of the approval pathway described in section 505(b)(2) of the Act.

III. DISCUSSION OF ISSUES RAISED BY PETITIONERS AND IN THE COMMENTS

The Petitions submitted by Pfizer, Genentech, and BIO, and comments submitted to the corresponding petition dockets and to the Follow-on Proteins Docket, raise a number of scientific, legal, and regulatory arguments opposing approval of Omnitrope and other follow-on protein products through the 505(b)(2) approval pathway. These arguments and the Agency's responses, to the extent relevant to the approval of the Omnitrope NDA, are discussed in this section of the response, beginning with the specific scientific challenges to approval of the Omnitrope NDA.

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[29] One patient withdrew from the study after 12 months; thus, 24-month data is available for 50 patients.

[30] Section III.A.6.f of this response further describes the specific comparisons made between the various Omnitrope formulations and Genotropin.

[31] FDA approved the 505(b)(2) application for Omnitrope in 1.5-mg and 5.8-mg dose strengths. Approval of the 1.5-mg strength, the composition of which is not proportional to the 5.8-mg strength, is supported by published literature on factors affecting the bioavailability of proteins and our finding of safety and effectiveness for Genotropin.

A. Scientific Issues

1. Determination of "Sameness" Not Required for 505(b)(2) Approval Pathway

BIO asserts that it is not scientifically feasible to demonstrate that the active ingredients of two rhGH products are sufficiently similar to be deemed the *same* under section 505(j) of the Act, and thus, one rhGH product cannot be approved in reliance on another under section 505(b)(2) of the Act (BIO Petition at 29). According to BIO, "[b]ecause therapeutic proteins' effects in the body are often difficult to predict or explain, *i.e.*, immunogenicity incidents, . . . bioequivalence determinations . . . would . . . prove to be of little relevance" in assessing sameness (BIO Petition at 11).

Genentech contends that the *sameness* of the active substances in two recombinant proteins cannot be established, because the process of isolating the therapeutic substance from an innovator's product to compare it to the follow-on manufacturer's active substance can itself change the characteristics of the innovator's substance. Therefore, the comparison would not be against the true innovator substance (Genentech Petition at 19; see also Pharmaceutical Research and Manufacturers of America (PhRMA) comments on Genentech Petition[32] (PhRMA Comments) at 13).

FDA Response:

Sandoz need not establish that Omnitrope has the *same* active ingredient as Genotropin in order for the Omnitrope NDA to be approved through the 505(b)(2) approval pathway. Although section 505(j) of the Act specifies that a product approved under that section must have the *same* active ingredient as that of the listed drug relied upon (see section 505(j)(2)(A)(ii)(I) of the Act), section 505(b)(2) includes no such requirement. As we explained in our 505(b)(2) Citizen Petition Response, the lack of a *sameness* requirement under section 505(b)(2) of the Act reflects this section's role in:

> fill[ing the] specific gaps left by the other [drug] approval pathways: a 505(b)(2) application can be used for approval of those changes [from a listed drug relied upon] that are not so significant that they require a stand alone NDA, but that are significant enough that they may require additional safety or effectiveness data (and, therefore, are not eligible for approval under section 505(j))

(505(b)(2) Citizen Petition Response at 16). Accordingly, as we also explained in the 505(b)(2) Citizen Petition Response, rather than requiring a showing of sameness, "FDA has long interpreted section 505(b)(2) to permit approval of NDAs that rely on the finding of safety or effectiveness of an approved drug to the extent such reliance is scientifically justified" (505(b)(2) Citizen Petition Response at 29).

[32] 2004P-0171/C6.

For the reasons discussed elsewhere in this response (see sections III.A.2 and III.A.6), we have determined that the active ingredients of Omnitrope and Genotropin are highly similar with regard to their physicochemical, biological, pharmacokinetic, pharmacodynamic, and clinical characteristics. We also recognize that there are differences between Omnitrope and Genotropin in certain respects (e.g., impurities). After review of the data and information in the Omnitrope NDA that describe the similarity of Omnitrope to Genotropin, we have determined that, consistent with our interpretation of section 505(b)(2) of the Act, it is scientifically justified for the Omnitrope NDA to rely in part on our finding of safety and effectiveness for Genotropin to support the safety and effectiveness of Omnitrope. Moreover, Sandoz has submitted adequate information to show that, to the extent that Omnitrope differs from Genotropin, it is nevertheless safe and effective for pediatric and adult GHD.

With regard to Genentech's argument, Sandoz isolated the active ingredient, somatropin, from Pfizer's Genotropin for certain comparisons with somatropin in Early Omnitrope and Omnitrope. For the isolation and characterization of somatropin, Sandoz used chromatographic procedures directly coupled to analytical instruments (e.g., reverse phase-high pressure liquid chromatography mass spectrometry (RP-HPLC MS)). These analytical procedures constitute continuous processes of separation and analysis of the protein, and are accepted methods for isolation and characterization of somatropin, as well as other proteins. In support of the reliability of Sandoz' procedure, the analytical results obtained for somatropin isolated from Genotropin by this procedure were consistent with analytical results obtained by Sandoz for the WHO and European Pharmacopoeia reference standards for somatropin. Thus, the isolation procedure used by Sandoz is considered an acceptable procedure for obtaining the somatropin active ingredient for further characterization.

2. Assessment of Degree of Similarity Between Omnitrope and Genotropin

Pfizer and others contend that FDA has historically considered proteins to be substantially defined by their manufacturing processes (Pfizer Petition at 9 to 11; Genentech Petition at 4, 6 to 9, and 17 to 19; PhRMA Comments at 11 to 15; see also BIO Petition at 20, 42 to 45, and 50). As such, "the only way for FDA to determine the similarity of the Omnitrop[e] structure and characteristics would be for the Agency to reference the nonpublic, proprietary [CMC] information in the Genotropin NDA and supplements," which is prohibited by law (Pfizer Petition at 1 to 2; see also Genentech Petition at 16 to 17; PhRMA Comments at 11, 15, and 17; Novo Nordisk Inc. comments on Genentech Petition[33] (Novo Nordisk Comments) at 2 to 4). Pfizer submits that "FDA would need to compare, among other factors, the products' recombinant plasmids, master cell banks, and working cell banks" (Pfizer Petition at 6), as differences among them could result in differences in the products' impurity profiles and molecular variants (Pfizer Petition at 25 to 26).

Pfizer further argues that FDA must access proprietary information about the purification processes used in Genotropin's manufacturing process to compare the impurities in

[33] 2004P-0171/EMC5.

Omnitrope and Genotropin (Pfizer Petition at 11). According to Pfizer, an assessment of comparability between these products cannot be based on the quantity and quality of the products' impurities, because "assays for process and product-related impurities in recombinant protein products do not necessarily provide absolute quantitative levels of specific impurities and are often measured against standards that are relatively heterogeneous and incompletely defined" (*Id.*).

Genentech and Johnson & Johnson (J&J) also contend that FDA must reference trade secret CMC data to approve a follow-on protein. In Genentech's view, to even determine which analytical tests for a follow-on protein would be important, reviewers would have to know detailed information about the processes used to produce both the listed drug relied on and the follow-on product proposed (Genentech Petition at 16 to 17). J&J asserts that FDA would need to rely on an innovator's CMC data to determine the appropriate range of batch-to-batch variability for a follow-on protein that references the innovator's product (Johnson & Johnson comments on Genentech Petition[34] (J&J Comments) at 4 to 5).

FDA Response:

Sandoz has established that Omnitrope is highly similar to Genotropin without reference to proprietary CMC data in Pfizer's Genotropin NDA. Each biotechnology manufacturer, whether producing a new molecular entity or a follow-on product, must independently develop its own cell expression, fermentation, isolation, and purification systems for the active ingredient in its product. Thus, the manufacturing process for each active ingredient is unique to each manufacturer. Nevertheless, as Sandoz has demonstrated in its Omnitrope application, for this relatively simple recombinant protein, it is possible to determine that the end products of different manufacturing processes are highly similar, without having to compare or otherwise refer to the processes. This determination of similarity may not have been possible in the past, in large part because of a lack of, or limitations in, technologies available to identify and characterize the active ingredients in protein products. However, improvements in the availability and sophistication of analytical techniques have allowed some relatively simple proteins like somatropin to be adequately identified and characterized irrespective of the product's manufacturing process.

Genotropin and other "innovator" rhGH products (i.e., those products approved based on a stand-alone application submitted under section 505(b)(1) of the Act) are known — based on analytical and biological assessments conducted without reference to proprietary data about any other such product — to have a common active ingredient, somatropin,[35] even though they may have different manufacturing processes. Currently

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[34] See 2004P-0171/C2.

[35] Although they may differ in some respects, all products with the established name *somatropin* share relevant, identifying characteristics of their active ingredients. Accordingly, each of the seven rhGH product lines approved by FDA has the international nonproprietary name *somatropin*. These products are BX rated in the Orange Book (see note 13 of this response).

available analytical techniques and bioassays enable the active ingredient in rhGH products to be identified and thoroughly characterized with respect to key criteria such as mass (molecular weight),[36] primary structure (linear number and order of amino acids present), secondary structure (protein structure characterized by folding of the peptide chain into an alpha helix, beta pleated sheet, or random coil), tertiary structure (three-dimensional structure of somatropin), impurities, and biological activity, without reference to the product's (or any other product's) manufacturing process. Moreover, the WHO, European Pharmacopoeia, and other standard-setting bodies[37] have made available general reference standards for somatropin and established accepted biological activity values for these standards, which can be used to assess the characteristics of a particular preparation of somatropin.

Sandoz compared the active ingredient in Omnitrope to both international reference standards for somatropin provided by the WHO and European Pharmacopoeia, as well as to the active ingredient in Genotropin.[38] For these comparisons, Sandoz used various established analytical methods for assessing the characteristics discussed in the previous paragraph (e.g., primary, secondary, and tertiary structures, molecular weight, impurities, biological activity) to confirm that the active ingredient in Omnitrope is somatropin. Among others, Sandoz used the following analytical methods: RP-HPLC MS, DNA sequencing, N-terminal and C-terminal sequencing, peptide mapping, circular dichroism (CD) analysis, UV spectroscopy, one-dimensional nuclear magnetic resonance spectroscopy (1-D NMR), two-dimensional (2-D) NMR, size exclusion chromatography, isoelectric focusing (IEF), sodium dodecyl sulfate polyacrylamide gel electrophoresis (SDS-PAGE), capillary zone electrophoresis, and a hypophysectomized rat weight-gain bioassay.[39] Except for the hypophysectomized rat weight-gain bioassay, which is widely used but specific to hGH, the methods employed by Sandoz are in widespread use for the characterization of proteins generally and are appropriate to establish that the active ingredient in Genotropin and other rhGH products is somatropin. In addition, commonly used analytical methods for recombinant DNA technology (e.g., DNA sequencing) were used to verify that the DNA material in cell banks and end-of-production cells (cells after the longest fermentation run) coded for somatropin. As noted earlier, it is not necessary for either Sandoz or FDA to reference any information about Pfizer's (or any other manufacturer's) manufacturing process to perform the analyses listed in this subsection or to assess Omnitrope and Genotropin's physicochemical and biological similarity.

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[36] A specific argument raised by Pfizer concerning Omnitrope's molecular weight is addressed in section III.A.4 of this response.

[37] The United States Pharmacopeia (USP) issued its first formal monographs on somatropin on April 1, 2005 (see *First Supplement of the United States Pharmacopeia 28 and National Formulary 23* (USP 28-NF 23)), and made available a reference standard on August 22, 2005.

[38] Because of inadequate supplies of Genotropin obtained in the United States, some of the tests Sandoz performed on Genotropin used Genotropin purchased in Europe. However, Sandoz conducted multiple comparative characterization studies that establish the high degree of similarity of Genotropin sourced in Europe and Genotropin from the United States. These studies confirm that the results of testing performed using European-sourced Genotropin are applicable to Genotropin sourced in the United States.

[39] Other bioassays are also available to confirm the biological activity of somatropin products (e.g., rat tibia width assay).

There is also no need for FDA to reference the Genotropin NDA (or the NDA for any other approved rhGH product), as Pfizer asserts, to compare the impurities or molecular variants[40] in Omnitrope and Genotropin. Recombinant hGH products made by different manufacturers according to different processes generally differ in these regards. Although FDA must assess the manufacturing and purification processes for each particular rhGH product to identify any impurities or molecular variants in the product and ensure that they are adequately controlled or removed, we need not compare the impurities or molecular variants in one product to those in another to determine the products' similarity for purposes of approval under section 505(b)(2) of the Act. Pfizer's implied contention that Omnitrope must share Genotropin's impurity and molecular variant profiles to rely on Genotropin's approval is incorrect. As further discussed in section III.A.1 of this response, section 505(b)(2) of the Act does not require that a follow-on protein product be the same as the listed drug for the follow-on product to be able to rely for approval, in part, on the finding of safety and effectiveness made by the Agency for the listed drug. Instead, "FDA may rely on its earlier conclusions regarding safety and effectiveness to whatever extent the conclusions are appropriate for the drug under review in the 505(b)(2) application" (505(b)(2) Citizen Petition Response at 10, note 14).

Because Omnitrope and Genotropin are highly similar in terms of their key physicochemical and biological characteristics (and, as explained in sections II.C. and III.A.6 of this response, in their pharmacokinetic, pharmacodynamic, and clinical properties as well), it is scientifically appropriate to rely on our finding of safety and effectiveness for Genotropin to support the approval of Omnitrope. Differences in the impurities and molecular variants for these products do not preclude the approval of Omnitrope under section 505(b)(2) of the Act. As detailed in section III.A.7 of this response, Sandoz has adequately characterized, quantified, and evaluated the variants and impurities in Omnitrope and established that they do not negatively affect Omnitrope's safety or effectiveness.[41] Thus, these factors do not create a barrier to Omnitrope's approval.

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[40] Molecular variants of the desired product formed during manufacture and/or storage consist of product-related substances (variants "which are active and have no deleterious effect on the safety and efficacy of the drug product") and product-related impurities (variants such as precursors and "certain degradation products arising during manufacture and/or storage . . . which do not have properties comparable to those of the desired product with respect to activity, efficacy, and safety") (International Conference on Harmonisation of Technical Requirements for Registration of Pharmaceuticals for Human Use (ICH) guidance for industry entitled *Q6B Specifications: Test Procedures and Acceptance Criteria for Biotechnological/Biological Products* (August 1999), at 5 to 6 and 16). Depending on the manufacturing process, there may be differences in product-related substances, product-related impurities, and process-related impurities (impurities "derived from the manufacturing process, i.e., cell substrates (e.g., host cell proteins, host cell DNA), cell culture . . . , or downstream processing") between drugs (*Id.*).

[41] We note that analytical testing performed by Sandoz has established that Omnitrope and commercially available samples of Genotropin are highly similar, qualitatively and quantitatively, with regard to their high molecular weight protein impurities. As discussed in section III.A.6.a of this response, the two impurities found in Omnitrope that were not present in Genotropin were adequately characterized by nonclinical and clinical studies and found not to have a negative impact on safety or effectiveness.

As to Genentech's argument, it is not necessary for FDA or any sponsor of a 505(b)(2) application for a follow-on rhGH product, which relies, in part, on our prior approval of a listed drug, to refer to information in the listed drug's NDA to determine what analytical tests to perform. Rather, the follow-on manufacturer (and, in fact, any innovator) can use publicly available literature, as well as tests and values established by relevant standard-setting bodies, to guide its analyses. Moreover, the follow-on manufacturer can purchase the relevant reference standards, as well as the approved, commercially available product (as Sandoz did), to use as comparators in analytical testing to characterize its product.

Nor is it necessary for Sandoz or FDA to rely on trade secret CMC data for Genotropin to determine the appropriate range of batch-to-batch variability for Omnitrope. The batch-to-batch variability for Genotropin, as determined by Pfizer, is not germane to evaluating Omnitrope and Genotropin's similarity for purposes of section 505(b)(2) of the Act. Sandoz performed comparative characterization analyses of Omnitrope, commercially available lots of Genotropin, and internationally available reference standards for somatropin obtained from the WHO and European Pharmacopoeia to establish the identity of somatropin. Comparative characterization of Omnitrope with Genotropin also was performed to determine levels of anticipated impurities in Omnitrope and to identify any new impurities in Omnitrope. As with any rhGH product (innovator or follow-on), batch-to-batch variability is dependent on the consistency of the specific manufacturing process, and evaluated by FDA independently of the batch-to-batch variability for other products that may have been manufactured according to different processes. The Omnitrope specifications were established based on lots used to demonstrate manufacturing consistency and drug substance and drug product stability, and lots used in nonclinical and clinical trials.

3. Compliance with Current Good Manufacturing Practice (cGMP) Principles

Pfizer states that, consistent with cGMP requirements, it has used proprietary, historical information about the Genotropin manufacturing process (including information about in-process and final product assays and reagents, as well as historical preclinical and clinical safety and effectiveness data) to evaluate changes it has made to this process (Pfizer Petition at 8). By contrast, Pfizer notes that "Sandoz has developed a wholly new manufacturing process for Omnitrop[e] without access to or use of the Genotropin in-process and final product assays or historical pre-clinical and clinical data" (Pfizer Petition at 9). According to Pfizer, "Sandoz asserts . . . that its product [Omnitrope] is safe and effective based exclusively on final product characteristics, despite the absence of adequate process information" (*Id.*). Pfizer contends that approving Omnitrope under these circumstances "would be a dramatic reversal of longstanding FDA policy, and would be arbitrary and capricious in violation of the APA [Administrative Procedure Act]" (*Id.*). Pfizer suggests that the Agency must compare Genotropin's manufacturing process as described in its NDA to the Omnitrope manufacturing process to determine whether Genotropin and Omnitrope are sufficiently similar to justify reliance on FDA's

finding of safety and effectiveness for Genotropin to support approval of the Omnitrope NDA.

FDA Response:

Nothing in section 505(b)(2) of the Act, the Act's cGMP provisions, or our regulations implementing these portions of the Act suggests that Sandoz could comply with cGMP requirements only if it could reference historical, proprietary manufacturing data about Genotropin.[42] As noted above, each rhGH manufacturer has a unique manufacturing process, and each such process must be shown to meet prevailing cGMP standards, which, despite Pfizer's assertions, Sandoz has done. The cGMP standards are designed to help ensure that each manufacturing process will consistently achieve and maintain the appropriate identity, strength, quality, and purity of the drug product produced through that process (see 21 CFR 210.1(a)). This showing does not require or depend on reference to any other sponsor's manufacturing process.

Moreover, as detailed in sections III.A.2 and III.A.6.f of this response, Omnitrope can be and has been shown to be sufficiently similar to Genotropin for purposes of section 505(b)(2) of the Act without comparing, and despite possible differences in, these products' manufacturing processes. This has been accomplished through analytical techniques that permit somatropin, a relatively simple protein, to be adequately identified and characterized without reference to the product's manufacturing process, as well as through biological activity testing, pharmacokinetic and pharmacodynamic studies, and clinical investigation. The Omnitrope NDA is supported by the foregoing data, as well as appropriate cGMP information.

4. Reliance on FDA's Finding of Safety and Effectiveness for Genotropin in Light of Differences Between Omnitrope and Genotropin

Pfizer contends that it is scientifically inappropriate for FDA to rely on public or nonpublic data about Genotropin to approve Omnitrope because these products differ in various ways. Specifically, Pfizer asserts that the molecular weights of the rhGH in Omnitrope and Genotropin differ substantially (Pfizer Petition at 4 and 24). According to

[42] Various commenters have made reference to the (nonbinding) *FDA Guidance Concerning Demonstration of Comparability of Human Biological Products, Including Therapeutic Biotechnology-derived Products*. This and related guidances (e.g., the ICH guidance for industry entitled *Q5E Comparability of Biotechnological/Biological Products Subject to Changes in Their Manufacturing Process*) discuss using historical information about a particular manufacturing process to assess the comparability of products made before and after a change to that manufacturing process is implemented. These guidances are intended to address changes made by a manufacturer of a biotechnology-derived product to its own manufacturing process, and we have reserved the term *comparable* for such assessments in the CMC context, consistent with the definition set forth in ICH Q5E ("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. This conclusion can be based on an analysis of product quality attributes. In some cases, nonclinical or clinical data might contribute to the conclusion"). The referenced guidances do not set forth recommendations for, or in any way limit, the data and information that may be considered in an application submitted under section 505(b)(2) of the Act that relies in part on the approval of a similar product.

Pfizer, Omnitrope has a molecular weight of 21,125 daltons, while Genotropin has a molecular weight of 22,124 daltons. Pfizer notes that various other approved rhGH products have molecular weights of 22,125 daltons, which is also the theoretical molecular weight of rhGH as reported in the European Pharmacopoeia (Pfizer Petition at 4). Pfizer further notes that Omnitrope and Genotropin differ in their manufacturing processes (recombinant plasmid genetic sequences and master and working cell banks), formulations (different preservatives), containers, reconstitution methods, and delivery/dosing systems (Pfizer Petition at 2, 4, 8, 24 to 27, and 31; Pfizer Supplement at 3).

FDA Response:

Despite the differences Pfizer asserts, Omnitrope and Genotropin are highly similar in several respects. First and critically, as explained in section III.A.2 of this response, Sandoz has conducted extensive analyses and comparisons of these products which confirm that the active ingredient in both is somatropin. Pfizer's contention that the molecular weights of the Omnitrope and Genotropin active ingredients vary significantly is mistaken.[43] The molecular weight (MW), as empirically determined by Sandoz, of the active ingredient in Omnitrope is 22,125 daltons. This is the same as the MW of the active ingredient in Genotropin, within the expected experimental error of the methodology, and conforms to the theoretical MW of somatropin. Moreover, Omnitrope also shares other key characteristics with Genotropin, in particular, its proposed strengths, indications, route of administration, and conditions of use.[44]

Differences between Omnitrope and Genotropin do not preclude us from relying in part on our prior finding of safety and effectiveness regarding Genotropin to approve Omnitrope. As explained in our 505(b)(2) Citizen Petition Response (at 11 and 17), section 505(b)(2) of the Act does not require that products approved under this section be duplicates of already approved drugs. In fact, FDA's implementation of section 505(b)(2) of the Act specifically contemplates that drug products (including protein products regulated under the Act) that are submitted in 505(b)(2) applications will, like Omnitrope, represent "a change in an already approved drug [that is] supported by a combination of literature or new clinical investigations and the agency's finding that a previously approved drug is safe and effective."[45]

Notwithstanding differences between a proposed and listed drug, when reviewing a 505(b)(2) application, it is appropriate for us to rely on our previous finding of safety and effectiveness for the listed drug referenced (and any literature-based information about that drug) "to the extent that the proposed product . . . shares characteristics (active

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[43] Sandoz notes that Pfizer does not explain how it obtained the confidential Omnitrope study protocol upon which Pfizer reportedly based statements regarding the molecular weight of Omnitrope (see Pfizer Supplement at 5, note 9; Sandoz comments on Pfizer Petition (2004P-0231/C1), at 8 to 9).

[44] There are differences in excipients between the two products; however, these differences have been adequately addressed (see section III.A.5 of this response).

[45] Abbreviated New Drug Application Regulations; Proposed Rule (54 FR 28872 at 28891, July 10, 1989).

ingredient, dosage form, strength, route of administration, indications, and conditions of use) in common with the listed drug" (505(b)(2) Citizen Petition Response at 14). As made clear in our earlier response and not disputed in the Pfizer Petition, this approach is consistent with the language and structure of the Act and promotes its underlying policy objectives, including avoiding unnecessary and duplicative research and review (see 505(b)(2) Citizen Petition Response at 3 to 4, 14, and 32).

Based on our determination that Omnitrope and Genotropin share key characteristics, it is appropriate and consistent with our long-standing interpretation of section 505(b)(2) of the Act for us to consider, together with other data, the fact of our prior approval of Genotropin in evaluating the Omnitrope NDA. This is not to say, however, that our prior finding of safety and effectiveness for Genotropin, alone, would be sufficient to support Omnitrope's approval. As reflected in our regulations (21 CFR 314.54) and detailed in our 505(b)(2) Citizen Petition Response, a 505(b)(2) application must include information to demonstrate that the proposed drug, to the extent that it differs from the listed drug referenced in the application, is safe and effective. We reiterate that the Omnitrope NDA includes, and we have relied upon, preclinical, clinical, pharmacokinetic, pharmacodynamic, and CMC information specific to Omnitrope, as well as information documenting Sandoz' cGMP compliance status with respect to Omnitrope, to support Omnitrope's approval. As further discussed in section III.A.5 of this response, these data adequately demonstrate the safety and effectiveness of Omnitrope in light of the differences between Omnitrope and Genotropin.

5. Evaluation of Product Differences Between Omnitrope and Genotropin

Pfizer suggests that certain differences between Omnitrope and Genotropin may impair Omnitrope's safety and effectiveness, as summarized below:

- **Differences in formulations.** Unlike Omnitrope, Genotropin includes mannitol (in both its powder and diluent), which Pfizer describes as being important to the stability of the Genotropin rhGH. In addition, Genotropin's diluent contains the preservative m-cresol, while Omnitrope's diluent is formulated with benzyl alcohol instead (Pfizer Petition at 4 and 26). According to Pfizer, these formulation differences "have the potential to increase changes in the higher order structures of recombinant proteins, including aggregates, that can generate immunogenic products and cause significant adverse reactions" (Pfizer Petition at 26).

- **Differences in containers.** Omnitrope and Genotropin use different containers; container materials can affect the stability of rhGH (Pfizer Petition at 26).

- **Differences in reconstitution methods.** Genotropin is reconstituted semi-automatically, while Omnitrope is reconstituted manually. According to Pfizer, Omnitrope's reconstitution process is less controlled and has the potential to increase protein aggregation and immunogenicity (Pfizer Petition at 27).

- **Differences in delivery/dosing systems**. Genotropin is delivered by a closed-system injection pen; in contrast, Omnitrope is manually reconstituted and delivered. Pfizer contends that the dose of Omnitrope administered is subject to greater variability (Pfizer Petition at 27).

  FDA Response:

Omnitrope has been shown to be safe and effective, despite various differences between Omnitrope and Genotropin in formulations, containers, reconstitution methods, and delivery/dosing systems. Pfizer provides no actual evidence that these variations between Omnitrope and Genotropin render Omnitrope unsafe or ineffective or create material differences in its safety or effectiveness relative to Genotropin. By contrast, Sandoz has conducted extensive testing that demonstrates that, despite their differences, Omnitrope and Genotropin are highly similar in their clinical effects.

Pfizer asserts that mannitol, which is included in the 5.8-mg formulation of Genotropin but not in Omnitrope, is a key factor in Genotropin's stability. However, CMC data submitted by Sandoz show that Omnitrope, which does not contain mannitol, remains sufficiently stable to support its labeled expiration period.

Pfizer also questions the use of benzyl alcohol in Omnitrope's diluent[46] (instead of m-cresol, which is used in Genotropin). Characterization, release, and stability data generated by Sandoz show that the use of this ingredient does not adversely affect the quality of Omnitrope. In addition, we note that benzyl alcohol has been shown to be an acceptable preservative used in the diluent for other approved drug products (including other approved rhGH products), and numerous parenterally administered drugs for chronic use contain benzyl alcohol at concentrations equal to or greater than Omnitrope.

Pfizer maintains that the differences in formulation that distinguish Omnitrope from Genotropin present a potential for Omnitrope to be associated with increased immunogenicity. However, as further discussed in section III.A.7 of this response, clinical data generated by Sandoz demonstrate that Omnitrope and Liquid Omnitrope both have a low and acceptable level of immunogenicity. We note that these levels are consistent with immunogenicity levels for other approved rhGH products, including Genotropin.

Stability studies conducted by Sandoz demonstrate that Omnitrope is chemically, physically, and biologically compatible with its container materials. These studies show that use of a container system different from Genotropin's does not impair the stability of Omnitrope, and thus the differences in containers are not material.

Pfizer alleges that Omnitrope's manual reconstitution method presents an increased risk of protein aggregation and immunogenicity. As previously noted, Omnitrope and Liquid

[46] Benzyl alcohol is used as a preservative in the diluent for the 5.8-mg dose strength of Omnitrope. The diluent used for the 1.5-mg dose strength of Omnitrope, a single-use product, does not contain a preservative.

Omnitrope have been shown to be acceptably low in immunogenicity and, in fact, are similar to Genotropin in this regard. In addition, data submitted by Sandoz evaluating aggregates in both the Omnitrope drug substance and finished product according to standardized methods (i.e., size exclusion chromatography and RP-HPLC) establishes that aggregates are present in Omnitrope at acceptably low levels.

Although Pfizer theorizes that Omnitrope's manual delivery/dosing system presents a greater likelihood of variability in dose delivered than Pfizer's Genotropin, there are no data to support this assertion. Sandoz has conducted clinical testing which demonstrates that, despite the fact that its delivery/dosing system differs from Genotropin's, Omnitrope is dosed and delivered safely and effectively and, with bridging across drug substance and formulation changes, is highly similar to Genotropin in its pharmacokinetic/pharmacodynamic, safety, and efficacy profiles.

6. Adequacy of Preclinical and Clinical Study Data

Pfizer contends that available information about Omnitrope reveals that the body of data about this product is lacking in the ways listed in sections III.A.6.a through III.A.6.f of this response. Pfizer's analysis references only that information in the Omnitrope NDA of which it is aware, and Pfizer is incorrect in assuming that Sandoz relies entirely upon such information to support approval of Omnitrope. The Omnitrope NDA includes information other than what Pfizer has represented. We have based our response (as well as our review of this NDA) on all of the data and information that Sandoz has submitted. As detailed in this response, we disagree with Pfizer's assertion that insufficient data exist to establish the safety and efficacy of Omnitrope.

a. Adequacy of preclinical studies

According to Pfizer, Sandoz appears to have failed to conduct adequate pharmacological and toxicological studies in animals and cell lines. With reference to a 14-day toxicology study in rats, Pfizer argues that the species used is inadequate "because rats develop antibodies to human growth hormone [hGH] in ten days, and [h]GH exerts a lactogenic effect in rats, which can complicate the interpretation of the test results" (Pfizer Petition at 31). In contrast, Pfizer claims that Genotropin's approval is supported by 3-month and 12-month monkey toxicity studies (*Id.*).

FDA Response:

In arguing that the 14-day rat preclinical study supporting the Omnitrope NDA is not adequate, Pfizer assumes that rat preclinical studies are needed to assess the toxicity of rhGH *per se*. This in fact is not the case. The clinical toxicities of excess hGH are widely known, documented in medical textbooks and published literature, and constitute common medical knowledge. These toxicities have been thoroughly characterized based in large part on studies of the natural (untreated) history of acromegaly (endogenous hGH excess due to a pituitary somatotroph tumor). The clinical hallmarks of acromegaly are well known and described extensively in standard textbooks of medicine and

endocrinology.[47] Furthermore, toxicities associated with the clinical use of rhGH are also well understood from general (non-product-specific) textbooks, review articles, and other published information describing the vast clinical experience with growth hormone replacement therapy. This information documents, among other effects, abnormalities in glucose homeostasis, salt and water balance, and connective tissue leading to joint and tendon-sheath symptoms, as well as rare benign intracranial hypertension (in children treated with hGH), all of which are known to be related to the dose and mechanism of action.[48]

Given the state of current medical knowledge and analytical technologies, animal testing is not needed to understand the actual or potential toxicities of rhGH in humans (either acute or chronic) *per se*. Instead, animal testing is focused on understanding the potential toxicities of any (not previously investigated) excipients and/or impurities in rhGH products. Omnitrope does not contain any novel excipients. Although chemical and physical analyses of Omnitrope revealed the presence of certain impurities not found in Genotropin, these impurities were adequately qualified by the 14-day rat toxicity study, which confirmed the absence of any novel toxicological findings associated with Omnitrope. The limitations of the rat study alleged by Pfizer are not relevant in the context of characterizing novel impurities and, thus, do not diminish the study's validity for this purpose. The results of the rat toxicity study confirmed that Omnitrope is similar to other rhGH products.

Pfizer observes that the Genotropin NDA included data from studies in monkeys that lasted 3 months or longer. However, such studies are not, and have not been, needed to characterize the growth hormone-related toxicity of rhGH products (as previously noted in this subsection, the effects of hGH excess are well known).[49] Rather, monkey studies have been used historically as screens to evaluate the potential immunogenicity of rhGH products in humans, before the initiation of human studies.[50] However, monkey immunogenicity data do not obviate the need for immunogenicity assessments in humans

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[47] See, e.g., Melmed S, Kleinberg D. Anterior Pituitary. In *Williams Textbook of Endocrinology*, 10th ed. Philadelphia: Saunders, 2003, at 230-243; Melmed S, Jameson JL. Disorders of the Anterior Pituitary and Hypothalamus. In *Harrison's Principles of Internal Medicine*, 16th ed. New York: McGraw-Hill, 2005, at 2076-2096.

[48] See, e.g., Melmed S, Kleinberg D. Anterior Pituitary. In *Williams Textbook of Endocrinology*, 10th ed. Philadelphia: Saunders, 2003, at 226-228; Parker KL, Schimmer BP. Pituitary Hormones and Their Hypothalamic Releasing Factors. In *Goodman & Gilman's The Pharmacological Basis of Therapeutics*. 10th ed. New York: McGraw-Hill, 2001, at 1546-1547; Vance ML, Mauras N. Drug therapy: Growth hormone therapy in adults and children. N Engl J Med. 1999; 341:1206-1216.

[49] Sponsors of approved rhGH products who conducted such monkey studies in support of their NDAs conducted these studies on their own initiative.

[50] The utility of monkey studies as a screening test for potential immunogenicity in humans was first realized with the finding that the immunogenicity in humans of methionyl-GH (the first approved recombinant GH product from Genentech) carried over to rhesus monkeys, whereas native-sequence hGH, which was relatively nonimmunogenic in humans, was similarly nonimmunogenic in rhesus monkeys. Based on this finding, studies in monkeys were posited to have the capacity to distinguish more generally between hGH products with potentially greater human immunogenicity and those expected to be less immunogenic in humans.

and are superseded by human studies. The Omnitrope NDA does not include monkey immunogenicity data because the sponsor completed human immunogenicity studies (further discussed in section III.A.7 of this response) without developing monkey data. The Omnitrope NDA includes adequate human data to establish that the drug product proposed for approval is not unacceptably immunogenic; monkey data are not otherwise needed to assess the product's toxicity.

b. Adequacy of human safety testing

Pfizer asserts that a crossover study comparing [Early] Omnitrope and Genotropin with regard to pharmacokinetics and pharmacodynamics followed 24 healthy subjects for 2 weeks. Pfizer alleges that this time period is inadequate, "given the many known adverse events [associated with] . . . rhGH identified over the long course of therapy, and because the only other safety information [about Omnitrope] apparently was provided indirectly through the efficacy studies" conducted by Sandoz (Pfizer Petition at 29).

FDA Response:

Sandoz' three pharmacokinetic/pharmacodynamic studies, including the double-blind, randomized, two-way crossover study comparing Early Omnitrope and Genotropin that is referenced by Pfizer in the previous paragraph, were not the only or primary source of clinical safety data about the Omnitrope formulations. The Omnitrope clinical program also included a phase 3 component. Pfizer's concern regarding indirect derivation of safety data from efficacy studies is misplaced — phase 3 trials "are intended to gather the additional information about effectiveness and safety that is needed to evaluate the overall benefit-risk relationship of the drug and to provide an adequate basis for physician labeling" (21 CFR 312.21(c)). As with phase 3 studies conducted by sponsors of other currently approved rhGH products, the phase 3 studies conducted by Sandoz provide direct evidence of the safety of Omnitrope. Patient exposure in these studies was significant. As previously discussed in section II.C.4 of this response, the two phase 3 studies that compared Early Omnitrope and Genotropin[51] extended over a 9-month period in total and involved 89 patients (44 treated with Omnitrope and 45 with Genotropin). The third phase 3 study provides further evidence of Omnitrope's safety. Part A of this study involved 86 patients who had completed the first and second phase 3 studies and compared Omnitrope (42 patients) to Liquid Omnitrope (44 patients). Finally, the fourth phase 3 trial, submitted with the safety update to the application, involved 51 patients treated with Omnitrope over a 24-month period.

On the whole, these phase 3 studies for Omnitrope involved a total patient exposure to lyophilized formulations of Omnitrope (Early Omnitrope and Omnitrope) of 154 patient years[52] (and to Genotropin of 33 patient years). Taken together with the large body of

[51] As discussed in section III.A.6.f of this response, Sandoz conducted appropriate studies to establish that Early Omnitrope and Omnitrope are substantially similar in ways that permit the study results obtained with Early Omnitrope to be applied to Omnitrope.

[52] The total patient exposure to lyophilized formulations of Omnitrope includes patients exposed to Early Omnitrope in the first two phase 3 studies (32 patient years), and patients exposed to Omnitrope in Part A

general knowledge about rhGH's toxicity, including published studies, as well as the pharmacodynamic and pharmacokinetic studies conducted by Sandoz and mentioned earlier in this section of the response, the phase 3 studies are adequate to establish Omnitrope's safety for human use.

c. Absence of need for phase 2 dosing studies.

Pfizer contends that Sandoz appears not to have conducted phase 2 dosing studies, even though Omnitrope has a different delivery system than Genotropin that likely results in the administration of a different dose of rhGH (Pfizer Petition at 8 and 31).

FDA Response:

Phase 2 dosing studies are not needed to support Omnitrope's approval because the appropriate doses of rhGH for specific indications, including those approved in the Omnitrope NDA, are well-established and available from general publications (textbooks and review articles). Moreover, although Pfizer asserts that Omnitrope's delivery system likely results in the administration of a different dose of rhGH than Genotropin's, as described in section III.A.5 of this response, clinical studies conducted by Sandoz confirm that the appropriate dose of Omnitrope is consistently delivered and demonstrate that Omnitrope is safe and effective.

d. Study population

Pfizer contends that Omnitrope has been clinically tested only in children with growth hormone deficiency (GHD) and therefore cannot be approved for other indications (Pfizer Petition at 7 and 28; see also Roche comments on Follow-On Proteins Docket[53] at 10). PhRMA maintains that the safety and effectiveness of two protein products may not be the same across different indications because of inherent product heterogeneity, mechanisms of action that are unknown or that vary for different indications, and variations in clearance and impurities that may exist even if the products are otherwise similar and that may result in different impacts when the products are used in different indications (PhRMA comments on Follow-On Proteins Docket[54] at 4).

FDA Response:

Although Pfizer asserts that Omnitrope has been tested clinically only in children with GHD, in fact, Sandoz has submitted data from clinical studies conducted on Omnitrope in both healthy adults (phase 1 studies) and children with GHD (phase 3 studies). The results of the phase 3 studies performed in children with GHD, together with other data

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of the third phase 3 study (21 patient years) and the fourth phase 3 study (101 patient years), resulting in a total exposure of 154 patient years.

[53] 2004N-0355/C12.

[54] 2004N-0355/SUP 1 & EC13.

submitted in the Omnitrope NDA and FDA's finding of safety and effectiveness for Genotropin, support Omnitrope's use for both pediatric and adult GHD. (Genotropin has been approved for both these indications, among others.)

As explained above and in our 505(b)(2) Citizen Petition Response, 505(b)(2) applications such as the Omnitrope NDA may rely on FDA's finding of safety and effectiveness for an approved (listed) drug to the extent the proposed product and the listed drug have similar characteristics (e.g., active ingredient, strength, indications), and such reliance is scientifically appropriate. Sponsors who submit 505(b)(2) applications need not undertake duplicative research that would otherwise be required to independently document the safety and effectiveness of the shared characteristics. In approving Genotropin, FDA found an rhGH product with certain characteristics to be safe and effective for certain indications. As detailed previously in this section and section II.C of this response, various data submitted in the Omnitrope NDA confirm that Omnitrope and Genotropin share common characteristics (e.g., active ingredient, strengths, and indications). Moreover, as discussed subsequently in this section of the response, Sandoz has submitted extensive clinical data supporting Omnitrope's use in patients with pediatric GHD. Based on the Omnitrope clinical data and on data supporting reliance on FDA's finding of safety and effectiveness for Genotropin (i.e., data demonstrating that Omnitrope and Genotropin are highly similar; see sections III.A.2 and III.A.6.f of this response), we have concluded that indication-specific studies are not needed to support Omnitrope's approval for use in adult GHD.

PhRMA maintains that, as a general matter, a follow-on protein may perform differently in different indications than another protein product because of inherent product heterogeneity, impurities, and potential differences in product clearances, and to the extent that indications for the products implicate unknown or different mechanisms of action. These concerns, however, are not applicable to Omnitrope. First, the rhGH in Omnitrope was encoded by a single gene and expressed as a single protein in a bacterial cell. Like other approved rhGH products, the active ingredient in Omnitrope is nearly homogeneous, highly purified, and structurally and functionally consistent, in vitro and in vivo, with hGH (see sections III.A.2 and III.A.6.f of this response). Second, while PhRMA notes that certain biological products may have varying or undetermined mechanisms of action for their approved indications, this is not the case for rhGH. All rhGH action related to rhGH's efficacy for pediatric and adult GHD occurs via rhGH's binding to a single, specific cognate cell surface receptor (the growth hormone (GH) receptor), the activation of which mediates (both directly and indirectly via IGF-1) each of the well-described effects of rhGH. Thus, an rhGH product that is shown to be effective for pediatric GHD can be presumed to be effective for adult GHD.[55] Third,

[55] Notably, consistent with this reasoning and in contrast to Pfizer's argument, in May 2005, the European Medicines Agency's Committee for Medicinal Products for Human Use released its *Annex Guideline on Similar Biological Medicinal Products Containing Biotechnology-Derived Proteins as Active Substance: Non-Clinical and Clinical Issues; Guidance on Similar Medicinal Products Containing Somatropin* which states in part (at 5): "Appropriate demonstration of efficacy and safety in one indication may allow extension to other indications of the reference product if the mode of action is the same and if appropriately justified by current scientific knowledge."

with regard to impurities and potential differences in product clearances, Omnitrope is highly pure, and pharmacokinetic comparisons of Early Omnitrope to Genotropin show no evidence of differences in product clearances. Furthermore, the demonstrated activity of Omnitrope in animal assays of GH potency and the efficacy of Early Omnitrope, Omnitrope, and Liquid Omnitrope established in studies in children with GHD clearly refute concerns that these factors, even if present, might result in a product with different activity than Genotropin. Therefore, PhRMA's concerns do not apply to Omnitrope.

In summary, Omnitrope has been shown in clinical trials to be effective in treating pediatric GHD, and through various data to be highly similar to Genotropin physicochemically, biologically, pharmacokinetically, pharmacodynamically, and clinically. Genotropin is effective in treating pediatric GHD and adult GHD. Based on the considerations discussed in this subsection, and the well-described mechanism of action by which the effects of rhGH in treating both pediatric and adult GHD are mediated, approval of Omnitrope for adult as well as pediatric GHD is appropriate under section 505(b)(2) of the Act.

e. Clinical study design

Pfizer alleges that the Omnitrope efficacy studies were poorly designed and do not comply with FDA standards for avoiding bias in clinical trials. Specifically, Pfizer notes that the "initial" Omnitrope efficacy study was unblinded, and the "second" efficacy study was unblinded and uncontrolled. FDA has emphasized the use of blinding and randomization, as well as the use of an appropriate control group (such as comparison to an active drug), in clinical trial design (Pfizer Petition at 29).

FDA Response:

FDA agrees that blinding, randomization, and active controls are effective techniques for minimizing the potential for bias in clinical trials and fortifying the demonstration of efficacy (Pfizer Petition at 29). However, neither the Act nor our implementing regulations require that these methods be employed in all clinical trials; they are also not always scientifically necessary or preferable.[56] Trials for other approved rhGH products that, like Omnitrope, have been studied in children with GHD, have been neither blinded,

[56] Consistent with their status as guidances, the two documents Pfizer cites on these points, *ICH E8 General Considerations for Clinical Trials* and *ICH E9 Statistical Principles for Clinical Trials* (E9 Guidance), do not set forth requirements. Instead, both state that they do "not create or confer any rights for or on any person and do[] not operate to bind FDA or the public." They further state that "[a]n alternative approach may be used if such approach satisfies the requirements of the applicable statute, regulations, or both." With regard to blinding and randomization, the E9 Guidance observes that "these should be normal features of *most* controlled clinical trials intended to be included in a marketing application" (E9 Guidance at 10)(emphasis added). The E9 Guidance also acknowledges the use of open-label trials, which are unblinded (E9 Guidance at 11 and 12). With regard to the need for active controls, we note that our regulations expressly sanction the use of other types of controls, including historical controls (see 21 CFR 314.126(b)(2)).

randomized, nor conducted with an active control.[57] Thus, these methods are not necessary to ensure consistency with the standards applied in the approval of previous rhGH products; nor are they necessary to ensure the soundness of Omnitrope's phase 3 study design.

Although not essential in all situations,[58] blinded studies are preferred in many instances because they minimize the potential for bias that could arise as a result of patient or physician knowledge of treatment allocation. For example, if the patient and the investigator in a trial of a new diabetes drug know whether a patient is receiving drug or placebo, presumptions about the safety and efficacy of the drug may dictate behavior (e.g., diet, hygienic measures, compliance, use of concomitant therapies) that conceivably could systematically influence the course of an individual patient's condition during the trial and therefore the outcome of the study itself. Blinded studies also would be preferred when knowledge of treatment allocation may influence patient or physician assessment of a subjective outcome, such as reduction in pain. However, we do not believe that, in the specific context of rhGH treatment for pediatric GHD, such knowledge would likely influence the growth response differentially across treatment groups of pediatric patients living at home who are administered different rhGH products, because patients with GHD, if appropriately diagnosed, will not grow spontaneously. Thus, any acceleration of linear growth with an rhGH product would be attributed to the therapy. Likewise, potential knowledge of treatment allocation appears unlikely to systematically affect immunogenicity results. To ensure an appropriate patient population for Sandoz' Omnitrope studies, children were selected based on an extensive list of inclusion and exclusion criteria. In these studies, patients treated with Omnitrope formulations and Genotropin grew to a degree consistent with the historical experience with hGH administration in children with GHD (see section III.A.6.f of this response). In addition, rates of growth induced by both the Omnitrope formulations and Genotropin were in marked excess of what is predicted in children with GHD who are left untreated, regardless of other factors, such as diet.

Pfizer's allegation that the third phase 3 study for Omnitrope was uncontrolled appears to have been based on a study abstract that reported data from only one arm (Liquid Omnitrope) of the parallel group study (Pfizer Petition at 29, note 112). Indeed, Pfizer's critique of the design of the entire Omnitrope phase 3 program appears to have been based primarily on two study abstracts, which do not completely describe the phase 3 program (Pfizer Petition at 29, notes 111 and 112). As discussed in section II.C.4 of this response, the Omnitrope phase 3 program consisted of three sequential, multicenter clinical trials, and a fourth multicenter clinical trial, submitted with Sandoz' safety update to the application, that involved a separate cohort of children with GHD. The first phase 3 trial was an open-label (unblinded), randomized, parallel group study that evaluated

[57] Historical controls are permitted by our regulations, as mentioned at note 56 of this response. Trials using historical controls may be particularly appropriate when, as with pediatric GHD, the study involves pediatric patients with a medical condition for which there is established treatment.

[58] For example, the E9 Guidance recognizes that "[i]n some cases only an open-label trial [i.e., one in which the identity of treatment is known to all] is practically or ethically possible" (E9 Guidance at 11).

Early Omnitrope compared with Genotropin as an active treatment concurrent control. The second phase 3 trial was a 3-month extension study with the same study design. Part A of the third phase 3 trial was an open-label (unblinded) parallel group study comprised of patients who had completed the first and second phase 3 trials. In this follow-up study, patients from the two treatment arms in the first and second phase 3 trials were not re-randomized: the group assigned to treatment with Omnitrope previously had been treated with Early Omnitrope, while the group assigned to treatment with Liquid Omnitrope previously had received Genotropin. The effects on growth-related endpoints for patients within each study arm were compared to those for the same patients in the earlier clinical trials; in addition, this data was compared to historical data in the public domain regarding rhGH administration in pediatric patients with GHD. Although subjects in the third phase 3 clinical trial were not re-randomized prior to the trial's initiation, this does not affect the comparisons made within each treatment arm between pre-treatment and treatment effects on growth-related endpoints.[59] Part A of the third phase 3 trial did not include an active treatment concurrent control; however, analyses were performed between study arms to demonstrate, for bridging purposes, the clinical comparability of Omnitrope and Liquid Omnitrope.

f. Adequacy of comparative clinical testing

Pfizer opines that Sandoz has failed to adequately test the version of Omnitrope proposed for approval. Pfizer alleges that Sandoz appears to have conducted only one study comparing Omnitrope to Genotropin, which is inadequate to satisfy FDA's requirement for two controlled clinical studies (Pfizer Petition at 5, 7, and 30). Moreover, Pfizer contends that the only known clinical trial comparing Omnitrope to Genotropin is invalid because it was conducted before changes were made in Omnitrope's manufacturing process. According to Pfizer, these changes have not been adequately tested in a clinical setting (*Id.*).

FDA Response:

Under section 505(d) of the Act, applicants submitting NDAs are required to provide "substantial evidence" of a product's efficacy. As described in our guidance for industry entitled *Providing Clinical Evidence of Effectiveness for Human Drug and Biological Products* (Effectiveness Guidance), this showing is generally, but not always, met

[59] In Part B of the third phase 3 trial, patients from both treatment arms of the earlier studies were administered Liquid Omnitrope during a subsequent 15-month period. Although Part B of the third phase 3 trial was uncontrolled and is not considered a pivotal clinical trial, as noted earlier in section II.C.4 of this response, Part B of the third phase 3 trial provides supportive long-term safety and effectiveness data. While our regulation at 21 CFR 314.126(e) states that an uncontrolled study "[is] not acceptable as the sole basis for the approval of claims of effectiveness," the regulation provides that such a study nevertheless "may provide corroborative support of well-controlled studies regarding efficacy and may yield valuable data regarding safety of the test drug." Similarly, although uncontrolled, the fourth phase 3 trial, submitted with Sandoz' safety update to the application, provided supportive evidence of Omnitrope's safety and efficacy and confirmed that Omnitrope has a low and acceptable level of immunogenicity.

through the submission of two adequate and well-controlled investigations.[60] Omnitrope's efficacy is supported by a phase 3 clinical program that included a direct comparison of Early Omnitrope to Genotropin and by data establishing that the clinical data derived from those studies support the effectiveness of the approved Omnitrope product.

Further, as specifically provided for by section 505(b)(2) of the Act, the adequate and well-controlled clinical studies that support a 505(b)(2) application need not be ones conducted by or for the applicant, or for which the applicant has a right of reference. Indeed, applications submitted under section 505(b)(2) of the Act are expressly permitted to identify (as did the Omnitrope NDA) a listed drug "for which FDA has made a finding of safety and effectiveness and on which finding the applicant relies in seeking approval of its proposed drug product" (21 CFR 314.54(a)(1)(iii)). As we noted in our 505(b)(2) Citizen Petition Response, reliance on FDA's finding of safety and effectiveness for a listed drug is indirect reliance on the data (including controlled clinical trials and other data constituting substantial evidence) underlying that finding (505(b)(2) Citizen Petition Response at 10, note 14, and 15). By referencing Genotropin (and providing adequate data to demonstrate that Omnitrope and Genotropin are sufficiently similar to warrant the former's reliance on the finding of safety and effectiveness for the latter), the Omnitrope NDA is supported not only by the adequate and well-controlled efficacy studies that Sandoz has conducted, but also by FDA's finding of safety and effectiveness for Genotropin, which is, in turn, based upon additional adequate and well-controlled studies.

Pfizer's second assertion is that the comparative clinical trial conducted by Sandoz does not support Omnitrope's approval because the version of Omnitrope to be approved (Omnitrope lyophilized powder with drug substance manufactured by Biochemie GmbH) is different from the version of Omnitrope (Early Omnitrope) that was tested against Genotropin in Omnitrope's first and second phase 3 pivotal trials (Pfizer Petition at 5, 7, and 30). Pfizer contends that differences between Early Omnitrope and Omnitrope could affect the drug's structure and stability (Pfizer Petition at 7 and 30). Pfizer's concerns have been adequately addressed by various data in the Omnitrope NDA, as further described below; therefore, we do not agree that they preclude Omnitrope's approval.

As discussed above, the phase 3 clinical program for Omnitrope consists of three clinical trials (in pediatric patients with GHD) that were conducted in an unbroken sequence between 0 and 30 months using the same patient cohorts. The first and second phase 3 trials involved a direct head-to-head comparison of Early Omnitrope and Genotropin. Early Omnitrope included drug substance manufactured at a site different from the one that manufactures the drug substance in Omnitrope. Because Early Omnitrope was observed to be relatively more immunogenic,[61] the manufacturer of the drug substance

[60] The Effectiveness Guidance explains that section 505(d) of the Act expressly permits FDA to consider data from one adequate and well-controlled clinical investigation, plus confirmatory evidence, to satisfy the Act's requirement for substantial evidence demonstrating efficacy (Effectiveness Guidance at 3 to 4).

[61] Early Omnitrope's immunogenicity is further discussed in section III.A.7 of this response. The observed level of immunogenicity was not associated with an increased incidence of allergenic adverse events compared to Genotropin.

was changed, and the drug substance manufacturing process was modified to decrease host cell protein content, which was determined to be related to the observed immunogenicity. Omnitrope, as manufactured with these changes, was subject to clinical testing in the third phase 3 trial and the fourth phase 3 trial, submitted with the safety update to the application, supporting the approval of this product.

The results from Part A of the third phase 3 trial, together with chemical characterization data and data from bioassays, bioavailability studies, and pharmacodynamic studies submitted in the Omnitrope NDA, collectively establish that Omnitrope is, in all relevant respects, highly similar to Genotropin. Specifically, the Omnitrope NDA includes data demonstrating that:

- Omnitrope is highly similar clinically to Early Omnitrope, as well as to Liquid Omnitrope (which contains the same drug substance as the lyophilized formulation approved in the NDA).
- Liquid Omnitrope is highly similar pharmacokinetically and pharmacodynamically to Early Omnitrope.
- Early Omnitrope is highly similar clinically, pharmacokinetically, and pharmacodynamically to Genotropin.
- Omnitrope and Early Omnitrope are highly similar physicochemically, and both are highly similar physicochemically to Genotropin and established reference standards.
- Omnitrope and Early Omnitrope are highly similar in bioactivity to Genotropin and established reference standards.

Because Omnitrope, Early Omnitrope, and Genotropin have been adequately bridged (physicochemically, pharmacokinetically, pharmacodynamically, biologically, and clinically), the results from the clinical trials conducted on Early Omnitrope, including its head-to-head comparison with Genotropin (as well as FDA's finding of safety and efficacy for Genotropin), are appropriately applied to Omnitrope.

The Act does not require that applications submitted under section 505(b)(1) of the Act, either as stand-alone NDAs or as 505(b)(2) applications,[62] contain data from a clinical trial conducted using an active comparator. As previously noted, other rhGH products have been approved in stand-alone NDAs for pediatric GHD based on clinical trials using historical controls (i.e., trials without an active comparator). Consistent with that experience, Omnitrope also might reasonably have relied upon an open-label clinical trial using historical controls to establish Omnitrope's efficacy for pediatric GHD. (As explained earlier in section III.A.6.e of this response, we also evaluated the results of Omnitrope's phase 3 clinical trials against historical controls; these results support Omnitrope's efficacy.)

[62] See discussion in section III.B.6 of this response.

For all the reasons previously discussed in this subsection, we do not concur with Pfizer's characterization of the comparative clinical testing conducted by Sandoz as inadequate to support approval of Omnitrope.

7. Immunogenicity and Other Clinical Considerations

According to Pfizer and others, Omnitrope must be tested in clinical trials to assess the following concerns:

- **Immunogenicity.** Pfizer and others submit that clinical studies are necessary, in part, because it is not possible to determine whether a particular version of rhGH will be immunogenic without conducting clinical trials (Pfizer Petition at 13 to 17; BIO Petition at 42 and 48; PhRMA Comments at 14). Pfizer also alleges that clinical studies have in fact linked (Early Omnitrope and Liquid) Omnitrope to a higher rate of antibody formation than Genotropin and other approved rhGH products (Pfizer Petition at 7 and 30).

  BIO argues that immunogenicity should be clinically assessed in each population for which a follow-on protein is proposed for approval (BIO comments on Follow-On Proteins Docket, Genentech Petition, and BIO Petition[63] (BIO Comments) at 35 to 37). BIO and PhRMA cite Intron A (recombinant interferon alfa-2b) and Eprex (recombinant human erythropoietin), respectively, as examples of products that induced different immunogenic responses in different patient groups (BIO Comments at 36 and PhRMA comments on Follow-On Proteins Docket at 4).

- **Potential adverse events from interaction between molecular variants of Omnitrope and cell proteins or protein contamination.** According to Pfizer, aberrant forms of rhGH that exist at levels below the limits detected by chemical and physical tests can interact abnormally with other human proteins and disrupt normal metabolic functions (Pfizer Petition at 17 to 19). Similarly, a follow-on protein like Omnitrope may contain uncharacterized impurities at low levels that can produce adverse clinical effects (*Id.* at 19 to 20).

- **Diminished efficacy due to mutations below the level of detection.** Pfizer contends that mutations related to errors in translation or in the recombinant plasmid can occur at levels that are below detection by standard assays, but that can nevertheless reduce a rhGH product's efficacy after repeated injections (Pfizer Petition at 20). Likewise, changes in an rhGH product's structure or incorrect folding of an rhGH protein can result in a loss of biological activity that may not be detected by existing analytical methods (*Id.* at 20 to 21).

[63] 2004N-0355/EMC5, 2004P-0171/EMC3, and 2003P-0176/EMC3.

- **Potential differences in efficacy and immunogenicity based on differences in terminal elimination half-life.** Amgen states that clinical testing is important to assess the half-life and clearance of follow-on proteins, which can affect a product's effectiveness and a patient's potential immune response. Amgen observes that, although all currently marketed rhGH products "ha[ve] the same number of amino acids and very similar molecular weights, the terminal elimination half-life of each product varies tremendously, from 1.75 to 10 hours" (Amgen comments on Follow-on Proteins Docket[64] at 5 to 6).

- **Limitations of bioassays in predicting clinical efficacy.** Pfizer states that clinical studies on Omnitrope are essential because bioassays are not designed to predict clinical efficacy but, rather, are used to "ensure product potency, stability, and batch-to-batch consistency" (Pfizer Petition at 21). Pfizer also contends that assays cannot measure all effects of rhGH and have other theoretical and practical limitations, including limitations due to use of a heterologous species to test a human protein and inadequate sensitivity and specificity (*Id.* at 12 and 21 to 24).

  FDA Response:

The Omnitrope NDA contains substantial clinical data establishing that Omnitrope is a safe and effective rhGH product. With regard to immunogenicity and safety, clinical studies of Omnitrope and Liquid Omnitrope show a favorable profile that is similar to Genotropin's. In particular, clinical data establish that the active ingredient in Omnitrope and Liquid Omnitrope is not unacceptably immunogenic and has an immunogenicity level that is similar to Genotropin or other approved rhGH products. Although a significant number of patients who were administered Early Omnitrope developed anti-GH antibodies during the first and second phase 3 clinical trials, Sandoz implemented changes to the drug product to address this immunogenicity. (We note that the anti-GH antibodies associated with the Early Omnitrope formulation were attributed to high levels of host cell proteins but did not reduce the growth-promoting effects observed with this formulation or result in any clinical toxicities.) The third phase 3 clinical trial (months 9 to 30 of the study sequence, with immunogenicity data through month 66 of this ongoing study) evaluating Omnitrope and Liquid Omnitrope involved patients who were antibody positive in the earlier clinical studies. Over an additional 57 months of treatment, this trial showed a progressive decline, which leveled off by month 42, in the percentage of patients from the Early Omnitrope arm of the first and second phase 3 trials who were previously antibody positive. Also, patients who had been administered Genotropin in the first and second phase 3 trials did not experience any meaningful increase in the incidence of positive antibody formation over the subsequent 57 months of treatment with Liquid Omnitrope.[65] Indeed, at any given time over those 57 months, no more than

[64] 2004N-0355/C3.

[65] The patients who were administered Genotropin in the first and second phase 3 trials received Liquid Omnitrope in the third phase 3 clinical trial. Liquid Omnitrope contains the same drug substance as that in the Omnitrope lyophilized powder approved in the NDA. Bridging between Liquid Omnitrope and Omnitrope (lyophilized powder) is addressed in section III.A.6.f of this response.

one or two such patients (2 to 6 percent) were antibody positive. This rate is consistent with rates of positive antibody formation in the published literature for approved rhGH products.

The low immunogenicity of Omnitrope was confirmed by the fourth phase 3 trial, submitted with Sandoz' safety update to the Omnitrope application. In this separate multicenter study, 51 rhGH treatment-naïve pediatric patients with GHD were treated with Omnitrope for a 24-month period.[66] None of the patients developed anti-GH antibodies during the 24-month study, and only one patient developed anti-host cell protein antibodies, which were of no detectable clinical consequence. These data demonstrate that Omnitrope has a low and acceptable level of immunogenicity that is consistent with other approved rhGH products, including Genotropin.

BIO's assertion that immunogenicity should be clinically assessed in each population for which a follow-on protein is proposed for approval because of the possibility of differential effects on various populations does not apply to Omnitrope. Even though a small percentage of patients develop nonclinically significant antibodies to Omnitrope as well as to Genotropin and other rhGH products, these results may be extrapolated to all other populations (with normal immune systems) in which hGH is indicated. The only known clinical instance in which administration of hGH is ineffective due to immunogenicity is in patients with GHD due to hGH gene deletions such that their immune systems recognize any hGH as foreign and develop neutralizing antibodies to it. (Rarely, neutralizing antibodies have been described in patients with GHD treated with somatrem (methionyl-GH), and these patients continue to respond to treatment when switched to somatropin (i.e., native GH)). While the development of neutralizing antibodies does not pose a danger to these individuals, in these patients hGH is not indicated for obvious reasons (i.e., hGH becomes ineffective because the antibodies developed in response to it, bind to it, and prevent it from binding to its receptors or exercising its physiological role).

With respect to other safety considerations, despite Pfizer's speculation regarding the potential existence and adverse impact of molecular variants, no deaths, drug-related serious adverse events, patient withdrawals due to adverse events, or unusual patterns of treatment-emergent adverse events were observed in the pivotal clinical trials with Omnitrope formulations.

The clinical studies conducted by Sandoz fully support Omnitrope's efficacy, as evidenced by changes in height-related variables achieved with Omnitrope that are highly similar to those achieved with Genotropin in head-to-head studies. Whether or not any mutations or variants of rhGH or uncharacterized impurities that have not been detected by analytical testing are present in Omnitrope, data from animal studies (hypophysectomized rat weight-gain assay) and clinical trials in children with GHD conclusively demonstrate Omnitrope's growth-promoting activity by binding to and

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[66] One patient withdrew from the study after 12 months; accordingly, 24-month data is available for 50 patients.

activation of the GH receptor. Moreover, pharmacokinetic studies conducted by Sandoz show that the half-life and clearance of Early Omnitrope, Liquid Omnitrope, and Genotropin are highly similar, which further supports Omnitrope and Genotropin's clinical comparability.

Finally, Pfizer's claims concerning the limitations of bioassays in predicting clinical efficacy are irrelevant with regard to Omnitrope. The hypophysectomized rat weight-gain bioassay used by Sandoz is an internationally accepted assay for assessing the biological activity of rhGH. Studies conducted by Sandoz using this assay showed that the biological activity of Omnitrope is highly similar to the biological activity of Genotropin, and that the activity predicted by the sequence and structure of somatropin was demonstrated for both Omnitrope and Genotropin. Moreover, the growth-promoting effects of Omnitrope and Genotropin observed using this bioassay were confirmed in clinical trials of pediatric GHD patients. Thus, any potential limitations of this bioassay are immaterial.

B. Legal and Regulatory Issues

The petitions submitted by Pfizer, Genentech, and BIO, and comments submitted to the corresponding dockets also raised a number of legal and regulatory arguments opposing approval of Omnitrope and other follow-on protein products through the 505(b)(2) approval pathway. To the extent these arguments are relevant to the Omnitrope approval, they are addressed in this subsection.

1. Reliance on a Prior Finding of Safety or Effectiveness by FDA in Support of Approval of a Follow-On Protein Product

Genentech and PhRMA assert that FDA is legally prohibited from relying on nonclinical or clinical safety or effectiveness data contained in a marketing application for one biotechnology-derived product (or, these parties imply, FDA's finding based on such data) to approve another. These parties contend that the data constitute confidential commercial information under §20.61(b) (21 CFR 20.61(b)) that generally are not disclosed by FDA (Genentech Petition at 22; PhRMA Comments at 16 to 17). Genentech cites section 301(j) of the Act (21 U.S.C. 331(j)) and asserts that it "do[es] not believe that the FDA can legitimately distinguish between use and disclosure of trade secret or confidential commercial information" (Genentech Petition at 26, note 29). Genentech and PhRMA further note that in the preamble to a 1974 rulemaking (39 FR 44602 at 44641), FDA assured innovators that it would not use data in one biologics application to approve another (Genentech Petition at 22 to 24; PhRMA Comments at 17).

BIO contends that cases decided after enactment of the Hatch-Waxman Amendments — specifically, the opinion and government briefs filed in *Tri-Bio Laboratories v. FDA*, 836 F.2d 135 (3rd Cir. 1987), as well as language in *Burroughs Wellcome Co. v. Bowen*, 630 F. Supp. 787 (E.D.N.C. 1986), and *Eli Lilly & Co. v. Medtronic Inc.*, 496 U.S. 661 (1990) — confirm that section 505(b)(2) of the Act (1) permits applicants to rely on data they do not own and for which they do not have a right of reference only if such data are

described in published literature and (2) does not authorize FDA to rely on proprietary data in one application to support the approval of another (BIO Petition at 18 to 20). BIO also maintains that no case law authorizes the approval of a recombinant follow-on protein absent a full complement of product-specific data (BIO Petition at 38 to 40).

FDA Response:

We have considered the Petitioners' contentions regarding prohibitions on the use of trade secret and confidential commercial information, and we do not believe they preclude approval of the Omnitrope application. As evidenced by the preceding discussion in section III.A of this response, use of the 505(b)(2) pathway does not entail disclosure of trade secret or confidential commercial information, nor does it involve unauthorized reliance on such data.[67] In addition, the review and approval of the Omnitrope 505(b)(2) application did not require use or disclosure of trade secret or confidential commercial information, and therefore is consistent both with the appropriate use of section 505(b)(2) of the Act and with the protection of trade secret and confidential commercial information.

As described in section II.A of this response, the Hatch-Waxman Amendments established two types of applications that permit reliance on the Agency's finding of safety and effectiveness for a listed drug: NDAs described in section 505(b)(2) of the Act and ANDAs described in section 505(j) of the Act. A 505(b)(2) applicant may rely on the Agency's finding that a drug is safe and effective (a finding which is based on data and information submitted by the NDA holder) to the extent the proposed drug shares certain characteristics with the previously approved drug. As we stated in the 505(b)(2) Citizen Petition Response:

> Reliance on FDA's conclusion that an approved drug is safe and effective does not involve disclosure to the ANDA or 505(b)(2) applicant — or to the public — of the data in the listed drug's NDA. Instead, it permits the ANDA or 505(b)(2) applicant to rely on the fact that FDA found a drug product with certain characteristics to be safe and effective and, in the case of a 505(b)(2) applicant, to target its studies to prove how changes from this previously approved drug product also meet the FDA's safety and effectiveness standards.

(505(b)(2) Citizen Petition Response at 15).[68] The extent and timing of reliance by a 505(b)(2) or ANDA applicant on the Agency's finding of safety and effectiveness for a drug product is governed by the patent and marketing exclusivity protections accorded to the listed drug by the Hatch-Waxman Amendments.[69]

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[67] See also 505(b)(2) Citizen Petition Response at 15, 17 to 18, and 24 to 26.

[68] See also 505(b)(2) Citizen Petition Response at 25 ("The Agency need not disclose proprietary data for an applicant or FDA to rely on the fact that a particular drug with particular characteristics has been found safe and effective").

[69] See 21 U.S.C. 355(b)(1), (b)(2), (c)(3), (j)(2)(A), and (j)(5)(B).

Because, under the Hatch-Waxman Amendments, the Agency's finding of safety and effectiveness for a listed drug may be relied upon for approval of an ANDA or a 505(b)(2) application, the finding of safety and effectiveness is not confidential commercial information that must be protected. Confidential commercial information is "of a type customarily held in strict confidence or regarded as privileged and not disclosed to any member of the public by the person to whom it belongs" (21 CFR 20.61(b)). An applicant submitting data and information to FDA to support approval of a drug product should be well aware that, once the Agency finds that the drug is safe and effective, it will make public the fact and conditions of approval (see 21 U.S.C. 355(b)(1) and 21 CFR 314.430). The applicant also should be aware that an Agency finding of safety and effectiveness for a drug approved under section 505 of the Act may be relied upon for approval of another application in certain circumstances, as the Agency's interpretation of the ANDA and 505(b)(2) approval pathways is, as described in section II.A of this response, well-established.[70]

Although a sponsor whose NDA has been approved under section 505 of the Act may not reasonably consider the fact or conditions of the approval to be confidential commercial (or trade secret) information, the applicant is entitled to expect that information in the application will be protected as described in 21 CFR 20.61 and 314.430, when that information falls within the definition of trade secret and confidential commercial information.

Pfizer's data and information have been appropriately protected during FDA's consideration of the Omnitrope application. The review and approval of Omnitrope, as previously addressed in section III.A of this response, did not entail the disclosure of, or reliance on, trade secret data from any applicant other than Sandoz; neither Sandoz nor FDA referenced any information concerning Pfizer's (or any other applicant's) manufacturing process or other proprietary data.[71] Nor has the Agency's consideration of Genotropin in its review of the Omnitrope 505(b)(2) application extended beyond the reliance on the finding of safety and effectiveness permitted under the law. Thus, in reviewing Sandoz' rhGH product, FDA has not compromised the protections afforded under the law to Pfizer's data and information regarding its rhGH product.

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[70] Because approval of Omnitrope has been accomplished without reference to trade secret or confidential commercial information belonging to other applicants, we need not address the argument made by Genentech that reliance by FDA on trade secret or confidential commercial information would constitute a *taking* under the Fifth Amendment to the Constitution (Genentech Petition at 24 to 25). We also do not find that takings concerns are implicated by reliance on the finding of safety and effectiveness for Genotropin to approve the Omnitrope 505(b)(2) application. In the 505(b)(2) Citizen Petition Response, the Agency addressed *takings* considerations as they relate to 505(b)(2) applications that rely on the Agency's finding of safety and effectiveness for an approved NDA (505(b)(2) Citizen Petition Response at 30 to 31).

[71] Based on its petition and supplemental comment, a major premise of Genentech's argument against FDA's approval of a follow-on protein under the Hatch-Waxman provisions of the Act appears to be the contention that FDA must reference an innovator's trade secret manufacturing data to assess the degree of similarity between a follow-on and innovator protein product (see, e.g., 2004P-0171/RC1 at 6). This contention is unfounded with respect to Omnitrope, as is described in section III.A.2 of this response.

Genentech's and PhRMA's reference to FDA's 1974 rulemaking as relevant to the approval of Omnitrope is misguided. The portion of the preamble that these parties reference[72] pertains expressly to biologic products that are licensed under the PHSA, rather than to drug products approved under the Act, and thus is facially inapplicable to Omnitrope.[73] In contrast, as our 505(b)(2) Citizen Petition Response explains, that section 505(b)(2) "permit[s] a[n] . . . applicant to rely on the finding of safety and effectiveness for an approved NDA" is evident:

> not only [from] . . . the broad statutory language first enacted in 1984, but also [from] . . . the Agency's subsequent publicly announced interpretation and application of section 505(b)(2). FDA's written pronouncements on the statute's scope embodied, among other places, in proposed and final regulations [implementing the Hatch-Waxman Amendments] have further provided public notice of that broad scope. Consequently, any purported expectation that the Agency would not permit a 505(b)(2) applicant to rely on the finding of safety and effectiveness for an approved NDA is unreasonable. . . .

(505(b)(2) Citizen Petition Response at 31).

Finally, nothing in the *Tri-Bio Labs*, *Bowen*, or *Medtronic* cases cited by BIO compels us to change our existing interpretation of section 505(b)(2) of the Act, or to refrain from applying this interpretation to permit approval of the Omnitrope NDA. The issues posed for court resolution in these cases did not require a determination regarding the proper

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[72] See, e.g., Genentech Petition at 23, quoting from Public Information; Final Rule (39 FR 44602 at 44641, December 24, 1974). The preamble of the final rule reads in part as follows:

> Under section 351 [of the PHSA], a biologic must be licensed by [FDA] before it may lawfully be shipped in interstate commerce. Unlike the regulation of human and animal drugs, all biological products are required to undergo clinical testing in order to demonstrate safety, purity, potency, and effectiveness prior to licensing, regardless whether other versions of the same product are already marketed or standards for the product have been adopted by rulemaking. . . . This is required because all biological products are to some extent different and thus each must be separately proved safe, pure, potent, and effective. . . . [A BLA] is under no circumstances granted by [FDA] to a second manufacturer based upon published or otherwise publicly available data and information on another manufacturer's version of the same product. . . . There is no such thing as a "me-too" biologic.

[73] The referenced section of the preamble explained final rules that the Agency issued regarding disclosure of safety and effectiveness data and information in applications for biological products licensed under the PHSA, which differ from regulations that govern the disclosure of like information for products approved as drugs under section 505 of the Act. Largely because safety and effectiveness data about one biologic licensed under the PHSA were not thought to be capable of supporting licensure of another product, such data were deemed not to be protected trade secrets, and routine publication of such data in the scientific literature precluded application of the confidential commercial information exemption (see 39 FR 44602 at 44641). Accordingly, the rules issued in 1974 permitted safety and effectiveness data and certain other information about a licensed biologic to be publicly disclosed immediately after issuance of the biologic's license (see 21 CFR 601.51(e) (1974) (as printed at 39 FR 44602 at 44656)).

scope of section 505(b)(2) of the Act and, in particular, whether it includes applications that rely on a prior FDA finding of safety or effectiveness for a listed drug. *Tri-Bio Labs* involved FDA's approval requirements for a generic duplicate of an approved animal drug and did not implicate section 505(b)(2) of the Act. As the *Tri-Bio Labs* court observed, the Hatch-Waxman provisions of the Act (which include section 505(b)(2)) "applied only to human drugs" (*Tri-Bio Labs.*, 836 F.2d 135, at 139). Notably, the court made no specific reference to section 505(b)(2) of the Act and briefly discussed the Hatch-Waxman Amendments as "general background" only (*Id.*). It is also important to note that the animal drug approval regulations and statutory provisions at issue did not include provisions analogous to section 505(b)(2) of the Act.[74] In this context, although BIO cites language in FDA's briefs in this case, these briefs cannot be construed as interpreting the scope of section 505(b)(2) of the Act. Moreover, nothing in BIO's discussion of *Tri-Bio Labs* negates our interpretation of this section, as described in our 505(b)(2) Citizen Petition Response.[75]

BIO's reliance on the *Bowen* and *Medtronic* cases is similarly unavailing. The court opinions in these cases did not address the scope or nature of section 505(b)(2) of the Act and paper NDAs. Instead, the *Bowen* court was presented with the issue of whether an NDA submitted by Lederle for a leucovorin drug product was subject to the exclusivity attached to an NDA held by Burroughs Wellcome (Burroughs) for another leucovorin product (*Bowen*, 630 F. Supp. 787, at 789). Plaintiff Burroughs argued that Lederle's application was subject to Burroughs' exclusivity rights as either an ANDA or a paper NDA (*Id.*). In considering this issue, the court reasoned that:

> "Paper" NDAs and ANDAs are subject to the FDC [Food, Drug, and Cosmetic] Act's exclusivity provisions only if they "*refer to*" a previously approved drug. Thus, Lederle's application, even if properly termed a "paper" NDA or ANDA, is clearly not subject to Burroughs' exclusivity rights. Burroughs has submitted no evidence whatsoever that Lederle's application referred to Burroughs' oral leucovorin product or to any investigations which were conducted by or for Burroughs.

Bowen, 630 F. Supp. 787, at 790 (emphasis in original). It is evident that the court did not need to determine the scope of section 505(b)(2) of the Act to resolve the issue at hand.

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[74] The animal drug approval scheme in effect at the time of *Tri-Bio Labs* was quite distinct from the human drug approval scheme. Not only did the animal drug approval scheme not include a pathway analogous to section 505(b)(2), it also did not include a pathway comparable to the ANDA approval scheme for generic duplicates of human drugs (see *Tri-Bio Labs.*, 836 F.2d 135, at 139 ("The 1984 Act [Hatch-Waxman] provides an abbreviated application procedure for generic human drugs demonstrating bioequivalency with pioneer drugs. . . . As noted earlier, the 1984 Amendments applied only to human pharmaceuticals. The FDA's no-abbreviated application policy remained in effect for animal drugs")).

[75] See BIO Petition at 18, note 34, and 19. As discussed in our 505(b)(2) Citizen Petition Response, section 505(b)(2) of the Act, which applies to only human drugs, is broader in scope than the literature-based paper NDA policy for duplicate drugs that was in effect prior to Hatch-Waxman and addressed in *Burroughs Wellcome Co. v. Schweiker*, 649 F.2d 221 (4th Cir. 1981). See 505(b)(2) Citizen Petition Response at 15 to 16.

Likewise, the *Medtronic* court was not required to define the limits of section 505(b)(2) of the Act to decide the question presented in that case (i.e., "whether 35 U.S.C. 271(e)(1) renders activities that would otherwise constitute patent infringement noninfringing if they are undertaken for the purpose of developing and submitting to . . . [FDA] information necessary to obtain marketing approval for a medical device under [section] 515 of the . . . [Act] [21 U.S.C. 360e]. . . . ") (*Medtronic*, 496 U.S. 661, at 663 to 664). In analyzing whether the statutory provision at issue (35 U.S.C. 271(e)(1)) applied to FDA-regulated products other than drugs, the court considered an argument that this provision's scope paralleled that of 35 U.S.C. 271(e)(2) and (e)(4), which concerns acts of patent infringement specific to drugs (*Id.* at 675 to 676). The court related these provisions to the patent certification requirements in section 505(b) and (j) of the Act (which are specific to drugs) to dismiss the argument that 35 U.S.C. 271(e)(2) and (e)(4) define the limits of 35 U.S.C. 271(e)(1) (*Id.* at 676 to 678). Although the court provided some background discussion of section 505(b) and (j) of the Act in the context of this analysis, it was in no way incumbent upon the court to decide the breadth of section 505(b)(2) of the Act and, specifically, whether this section encompasses applications that seek to rely on a prior FDA finding of safety and effectiveness for a listed drug.

In sum, statements in the above-referenced cases do not govern the interpretation of the scope and effect of section 505(b)(2) of the Act.

2. Application of Section 505(b)(1) Requirements Regarding Investigations to Section 505(b)(2) of the Act

Pfizer asserts that section 505(b)(2) of the Act limits any approval of Omnitrope to specific indications that are fully supported by clinical trials conducted on this product. According to Pfizer, "Th[is] is because section 505(b)(2) . . . incorporates section 505(b)(1), which requires that the 'investigations . . . show . . . such drug is effective *in use*.' . . . In the absence of an indication-specific clinical trial . . . there is no investigation showing the drug to be effective 'in use' for that particular indication" (Pfizer Petition at 7 to 8, note 17) (emphasis in the original).

BIO states that section 505(b)(2) of the Act, through its incorporation by reference of section 505(b)(1), provides that an application submitted thereunder must contain "full reports of investigations" conducted on the drug proposed for approval (BIO Supplement at 2). BIO argues that this language prohibits the Agency from approving a 505(b)(2) application based on a prior approval of another product, because the Agency's finding of safety and effectiveness does not constitute "full reports" (BIO Supplement at 3). Finally, BIO argues that summaries of safety and effectiveness data that are made public by FDA upon approval of an NDA do not qualify as full reports of investigations (BIO Supplement at 3).

FDA Response:

Omnitrope can be approved for an indication for which Sandoz has not conducted clinical studies. Although a 505(b)(2) application must (like stand-alone NDAs submitted under

section 505(b)(1) of the Act)[76] incorporate adequate data and information to establish the safety and effectiveness of the drug for each indication for which approval of the 505(b)(2) application is sought,[77] there is no statutory or regulatory requirement that the application necessarily include product-specific clinical studies conducted for each proposed indication for which approval is desired.[78] Instead, as section 505(b)(2) of the Act expressly permits, an applicant may support one or more indications for which it seeks approval with investigations that "were not conducted by or for the applicant and for which the applicant has not obtained a right of reference or use from the person by or for whom the investigations were conducted. . . ." These include investigations conducted on another listed drug (e.g., as reported in published literature) or that form the basis for FDA's finding of safety and effectiveness for a listed drug. Implicit in this provision is the understanding that the drug product on, or for, which the studies were conducted would not be the same drug product for which approval is sought in the 505(b)(2) application, but would be a drug product that is sufficiently similar to the drug proposed in the 505(b)(2) application to justify the reference.

As discussed elsewhere in this response (see sections III.A.2 and III.A.6.f), we have determined that Omnitrope and Genotropin are sufficiently similar in certain attributes (including in their active ingredients, strengths, and intended uses) to permit the Omnitrope NDA to rely in part on FDA's prior approval of Genotropin to support Omnitrope's safety and effectiveness for its pediatric and adult GHD indication. Also, as we have previously discussed (see section III.A.6.d of this response), because of the appropriateness of this reliance, as well as for other scientific reasons, product-specific studies on every proposed indication for Omnitrope are not scientifically necessary. Accordingly, Pfizer's argument that Sandoz must support each indication it proposes with investigations conducted on Omnitrope is not legally or scientifically persuasive. To accept Pfizer's argument would be to render section 505(b)(2) of the Act essentially superfluous and redundant of section 505(b)(1).[79]

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[76] As discussed in section III.B.6 of this response, a 505(b)(2) application, like a stand-alone NDA, is submitted under section 505(b)(1) of the Act and approved under section 505(c) of the Act.

[77] See section 505(d) of the Act, which requires that applicants seeking approval of an NDA (including a 505(b)(2) NDA) establish a drug's effectiveness for each "condition[] of use prescribed, recommended, or suggested in the proposed labeling" for the drug by "substantial evidence," and which also defines substantial evidence to mean "evidence consisting of adequate and well-controlled investigations, including clinical investigations."

[78] We also note that to support approval of an NDA for which the sponsor submits all of its own data, a sponsor may rely, where scientifically appropriate, on studies of an active ingredient other than the active ingredient in the drug product for which approval is sought (see *Abbott Laboratories v. Young*, 920 F.2d 984, at 986 (D.C. Cir. 1990) (drug product containing divalproex sodium as active ingredient approved based upon studies conducted with valproic acid)).

[79] We are aware that in previous citizen petitions (see 2001P-0323/CP1 at 10 to 14 and 2002P-0447/CP1 at 8), Pfizer has opined that the scope of section 505(b)(2) of the Act exceeds that of section 505(b)(1) in one way: by permitting applicants to rely on reports of investigations in published literature to support the safety or efficacy of a duplicate product offered for approval in an application described by section 505(b)(2). In those petitions, Pfizer argued that section 505(b)(2) should be interpreted as being limited in its scope to applications that rely on such published reports. For reasons articulated in our 505(b)(2) Citizen Petition Response and in section III.B.1 of this response, we disagree. We note, however, that interpreting section 505(b)(2) even in the limited way Pfizer previously has proposed acknowledges that

In addition, relying on FDA's finding of safety and effectiveness for a listed drug in the context of a 505(b)(2) application is fully consistent with language in section 505(b)(1) of the Act calling for the submission of "full reports of investigations. . . ." To implement section 505(b)(2) of the Act, FDA's regulation at § 314.54(a)(1)(iii) permits a 505(b)(2) applicant to "[i]dentif[y] . . . the listed drug for which FDA has made a finding of safety and effectiveness and on which finding the applicant relies in seeking approval of its proposed drug product. . . ." [80] To the extent that approval of the listed drug — which was supported by data such as full reports of clinical investigations demonstrating the listed drug's effectiveness for a particular indication — is scientifically relevant to the drug proposed in the 505(b)(2) application, § 314.54(a)(3) provides that the requirement that full reports be included in the 505(b)(2) application "shall be satisfied by reference to the listed drug" under § 314.54(a)(1)(iii). To avoid unnecessary duplication of research, the 505(b)(2) applicant need only provide "th[e] information needed to support the modification(s) of the listed drug" (i.e., data to support the safety and effectiveness of differences between the listed drug and the drug proposed in the 505(b)(2) application) (21 CFR 314.54(a)).

Finally, we agree with BIO that, although FDA may make summaries of safety and effectiveness data in an NDA available to the public upon approval of the application, these summaries "do not constitute the full reports of investigations under section 505(b)(1) of the act . . . on which the safety or effectiveness of the drug may be approved" (21 CFR 314.430(e)(2)). A 505(b)(2) applicant does not rely on a summary or description of data in the NDA, but, as with an ANDA applicant, on the Agency's finding of safety and effectiveness for the approved drug, to the extent that finding is applicable to the product for which approval is sought.

3. Legislative History Regarding Application of Hatch-Waxman Amendments to Protein Products Regulated Under Section 505 of the Act

BIO argues that Congress did not intend to permit the approval of follow-on biologics. Specifically, BIO contends that while Congress expressly included the term *human biological product* in the Hatch-Waxman Amendments' provisions on patent term extension (amending Title 35 of the U.S. Code), it applied section 505(b)(2) and (j) of the Act to *drugs* only, thus evincing its intent that biological products not be approved through abbreviated procedures (BIO Petition at 64).

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this provision of the Act does not, as Pfizer argues here, mandate that original efficacy trials be conducted on the specific product described in a 505(b)(2) application to support each indication for which approval is sought.

[80] As we noted in our 505(b)(2) Citizen Petition Response, "reliance on an FDA finding of safety and effectiveness for an NDA is certainly indirect reliance on the data submitted in the original NDA" for the listed drug (505(b)(2) Citizen Petition Response at 10, note 14).

FDA Response:

Congress did not exclude protein products such as rhGH, which have long been regulated under section 505 of the Act, from the approval pathway provided by section 505(b)(2) (or that provided by section 505(j)) of that statute.

As BIO notes, section 505 of the Act applies by its terms to *drugs*. Human growth hormone (somatropin) falls within the definition of a drug[81] and hGH products have been regulated as drugs under section 505 of the Act since before the enactment of the Hatch-Waxman Amendments.[82]

Congressional activity supports our conclusion that protein products regulated as drugs under section 505 of the Act, including recombinant DNA-derived protein products, are subject to the abbreviated approval pathways described in the Hatch-Waxman Amendments. The legislative history of Hatch-Waxman reveals that Congress considered application of the legislation, including Title I, to products created through rDNA technology. The House Report references the testimony of Dr. Ronald Cape, Chairman (and Chief Executive Officer) of Cetus Corporation, before the Judiciary Committee in which Dr. Cape "urged expanded protection from the abbreviated new drug application process for biotechnology which uses recombinant DNA."[83] Dr. Cape's prepared statement indicated a concern with ANDA competition and patent challenges in light of the absence of legal precedent regarding patent infringement of rDNA-derived products at that time.[84] Dr. Cape proposed an exception to the legislation for

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[81] As defined in section 201(g)(1) of the Act (21 U.S.C. 321(g)(1)):

> The term "drug" means (A) articles recognized in the official United States Pharmacopeia, official Homoeopathic Pharmacopeia of the United States, or official National Formulary, or any supplement to any of them; and (B) articles intended for use in the diagnosis, cure, mitigation, treatment, or prevention of disease in man or other animals; and (C) articles (other than food) intended to affect the structure or any function of the body of man or other animals; and (D) articles intended for use as a component of any articles specified in clause (A), (B), or (C).

The definition of *drug* in existence at the time the Hatch-Waxman Amendments were enacted was identical, in all relevant respects, to this definition.

[82] Other proteins such as insulin, hyaluronidase, menotropins, and glucagon also meet the statutory definition of drug and also were approved as drugs under section 505 of the Act before the Hatch-Waxman Amendments. For example, a naturally sourced menotropins protein was approved under the Act in 1969 (see *Serono Laboratories, Inc. v. Shalala*, 158 F.3d 1313, at 1316 (D.C. Cir. 1998)). Humulin R, a recombinant DNA-derived human insulin product, was approved under section 505 of the Act in 1982. As discussed in note 18 of this response, two pituitary-derived human growth hormone products (Asellacrin and Crescormon) were approved under section 505 of the Act in 1976 and 1979, respectively, and were described as being "based almost exclusively on reports from the published literature" (Response to Petition Seeking Withdrawal of the Policy Described in the Agency's "Paper" NDA Memorandum of July 31, 1978; Notice (45 FR 82052 at 82055, December 12, 1980)).

[83] House Report No. 98-857, part 2, at 7 (1984), reprinted in 1984 U.S.C.C.A.N. 2686 at 2691.

[84] See Statement of Dr. Ronald E. Cape, Hearing on H.R. 3605 Before the Subcommittee on Courts, Civil Liberties and the Administration of Justice of the House Committee on the Judiciary, reported in Drug Price Competition and Patent Term Restoration Act of 1984, Hearing on S. 2748 Before the Senate

biotechnology products at least as extensive as the freedom from ANDA competition for 10 years accorded to certain drugs approved between January 1, 1982, and the date of enactment of the Hatch-Waxman Amendments.[85] However, the Hatch-Waxman Amendments do not contain such an exception, and thus drugs created through rDNA technology and approved under section 505 of the Act may be the subject of an application submitted under an abbreviated approval pathway.

We note that in the over 20 years since passage of Hatch-Waxman, the Agency has continued to regulate rhGH and certain other protein products as drugs under the Act. In 1998, we used the 505(b)(2) pathway to approve GlucaGen, which, like rhGH, is a recombinant protein,[86] and on August 12, 2005, we approved a 505(b)(2) application for a recombinant salmon calcitonin product. Most recently, on December 2, 2005, we approved a 505(b)(2) application for a recombinant human hyaluronidase drug product. We also have articulated our view that section 505(b)(2) of the Act may be an appropriate abbreviated pathway for approval of certain products which contain a naturally-derived or recombinant active ingredient and are regulated as drugs under section 505 of the Act.[87] During this period, Congress has amended sections 201(g)(1) (definition of *drug*) and 505(b) of the Act, but has not altered these sections to preclude their application to protein products such as rhGH, or to otherwise narrow their scope and application.[88]

In light of the above, it is reasonable to conclude that applying section 505(b)(2) of the Act to Omnitrope is consistent with the statutory language, Congressional intent, and our historical regulatory interpretations. Nothing in the Hatch-Waxman Amendments precludes approval of applications described by section 505(b)(2) of the Act[89] (or section

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Committee on Labor and Human Resources, 98th Cong., 2d Sess. (June 28, 1984), at 171 (Statement of Dr. Cape).

[85] See Statement of Dr. Cape, note 84 of this response, at 175-176.

[86] We disagree with Pfizer's contention that our approval of a 505(b)(2) application for GlucaGen, a recombinant glucagon product, does not constitute precedent for other follow-on protein products (see Pfizer Supp. at 3). The approval of Novo Nordisk Pharmaceuticals, Inc.'s GlucaGen through the 505(b)(2) pathway relied, in part, on the finding of safety and effectiveness for Eli Lilly and Company's animal-source glucagon product.

[87] See draft guidance for industry on *Applications Covered by Section 505(b)(2)* at 5.

[88] Section 201(g)(1) of the Act was amended as part of the Safe Medical Devices Act of 1990 (Public Law 101-629), the Nutrition Labeling and Education Act of 1990 (Public Law 101-535), and the Dietary Supplement Health and Education Act of 1994 (Public Law 103-417). Section 505 of the Act was amended in 1992 as part of the Generic Drug Enforcement Act of 1992 (Public Law 102-282); in 1993 as part of the Nutritional Labeling and Education Act Amendments of 1993 (Public Law 103-80); in 1997 as part of the Food and Drug Administration Modernization Act of 1997 (Public Law 105-115) (FDAMA); in 2002 as part of the Best Pharmaceuticals for Children Act (Public Law 107-109); and in 2003 as part of the Medicare Prescription Drug, Improvement, and Modernization Act of 2003 (Public Law 108-173).

[89] As BIO observes, section 351(j) of the PHSA exempts biological products for which a license has been granted under section 351(a) of the PHSA from the approval requirements at section 505 of the Act. We reiterate, however, that there is no prohibition in either the PHSA or the Act against use of the 505(b)(2) pathway to approve protein products, such as rhGH, that originally were approved under the Act (rather than licensed under the PHSA). Indeed, as BIO is aware, Genotropin and other innovator rhGH products

505(j) of the Act[90]) for proteins like rhGH that originally were approved under section 505 of the Act, as long as the current state of science allows the evaluation necessary to support approval under these provisions to be made within the bounds of applicable law.[91]

4. Implications of Patent Listing Requirements for Scope of Section 505(b)(2) of the Act

PhRMA notes that patents claiming a drug manufacturing process (other than product-by-process patents, which claim a product that is defined by the process used to make it) are not eligible for listing in FDA's *Approved Drug Products with Therapeutic Equivalence Evaluations* (the Orange Book). Because, PhRMA contends, biological products are defined by their manufacturing processes, and one of the functions of section 505(b)(2) is to protect innovator patent rights, PhRMA submits that this section is not an appropriate approval pathway for biological products (PhRMA Comments at 11 to 12).

FDA Response:

Recombinant hGH (somatropin) products are not necessarily defined by their manufacturing processes (see section III.A.2 of this response). Rather, through improved analytical techniques and other testing, we have been able to determine that two rhGH products, Omnitrope and Genotropin, are highly similar even though they may be produced through different processes.

Moreover, even if PhRMA's premise were scientifically correct, we note that (as PhRMA acknowledges) product-by-process patents are permitted to be listed in the Orange Book. As we have explained, "a product-by-process patent claims a product by describing or listing process steps to wholly or partially define the claimed product. In a product-by-process patent, the patented, novel invention is the product and not the process that is

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were submitted for approval under section 505(b)(1) of the Act (and approved under section 505(c) of the Act), and have been regulated as drug products under the Act since 1985.

[90] See *Abbreviated New Drug Application Regulations*; Final Rule (57 FR 17950 at 17953, April 28, 1992) (noting that "an ANDA would only be permitted for a drug product with 'tight specifications' or a biotechnology-derived drug product only if such a product is the same as a product previously approved under section 505 of the act or if FDA has approved submission of an ANDA under a petition filed under section 505(j)(2)(C) of the act."). See note 91 of this response regarding a menotropins protein product approved under section 505(j) of the Act.

[91] As a scientific matter, in determining whether the statutory and regulatory standards for approval of a protein product have been met, "FDA's policies and its interpretation of its own regulations will be paid special deference because of the breadth of Congress' delegation of authority to FDA and because of FDA's scientific expertise" (*Berlex Laboratories, Inc. v. Food and Drug Administration*, 942 F. Supp. 19, at 25 (D.D.C. 1996)). See also *Serono*, 158 F.3d 1313, at 1320 ("The FDA's determination of what is required to establish 'sameness' for purposes of the Act rests on the 'agency's evaluations of scientific data within its area of expertise,' and hence is entitled to a 'high level of deference' from this court [internal citations omitted]"). *Serono* involved FDA's interpretation of the "sameness" standard for approval under section 505(j) of the Act, as applied to a menotropins protein product (*Id.*).

used to make the product."[92] Thus, the listing of these product-by-process patents may protect innovator rights with respect to the very patents with which PhRMA is most concerned (i.e., those that define a product). In addition, holders of NDAs for both protein and non-protein drug products approved under the Act may, as described at 21 CFR 314.53(b), list formulation, composition and method-of-use patents that claim the approved drug product.

Finally, the prohibition on listing patents that claim a drug manufacturing process, as opposed to a drug product, should not preclude the use of the 505(b)(2) pathway for recombinant protein products such as rhGH. This prohibition pertains not only to protein drugs regulated under section 505(b) of the Act but also to other, non-protein drugs regulated under this section as well, even though such drugs also may be the subject of process patents. As PhRMA does not dispute, 505(b)(2) applications are nevertheless appropriate for certain of these other drugs.

5. *Scientific Review Requirements for Biological Products Approved Under the Act or Licensed Under the PHSA*

BIO and PhRMA state that the PHSA does not permit biological products regulated under that statute to be licensed in reliance on data about another product; rather, each product must be supported by original, product-specific data. BIO and PhRMA contend that there is no reason why the requirement for original, product-specific data to support the licensure of a biological product under the PHSA should not apply equally when a protein product is being considered for approval under the Act (BIO Petition at 7; PhRMA Comments at 5).

FDA Response:

In recent years, FDA has endeavored to harmonize the scientific review process for products licensed under the PHSA and those approved as drugs under the Act.[93] Although the safety and effectiveness standards under the PHSA and the Act are essentially the same,[94] the Act (at section 505(b)(2)) differs from the PHSA in that the

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[92] Applications for FDA Approval to Market a New Drug: Patent Submission and Listing Requirements and Application of 30-Month Stays on Approval of Abbreviated New Drug Applications Certifying That a Patent Claiming a Drug Is Invalid or Will Not Be Infringed; Final Rule (68 FR 36676 at 36679, June 18, 2003).

[93] See FDAMA section 123(f) ("[FDA] shall take measures to minimize differences in the review and approval of products required to have approved biologics license applications under section 351 of the Public Health Service Act (42 U.S.C. 262) and products required to have approved new drug applications under section 505(b)(1) of the Federal Food, Drug, and Cosmetic Act (21 U.S.C. 355(b)(1)").

[94] See, e.g., Application of Current Statutory Authorities to Human Somatic Cell Therapy Products and Gene Therapy Products; Notice (58 FR 53248 at 53248, October 14, 1993):

> Section 351(a) of the [PHSA] . . . requires premarket approval for biological products. Licenses are to be issued upon a showing that the establishments and products "meet standards, designed to insure the continued safety, purity, and potency of such products * * *." (42 U.S.C. 262(d)). A biological product's effectiveness for its intended uses must be shown as part of the statutory requirement for potency (21 CFR 600.3(s)).

Act explicitly permits applicants to rely for approval on data from investigations "not conducted by or for the applicant and for which the applicant has not obtained a right of reference or use from the person by or for whom the investigations were conducted" (21 U.S.C. 355(b)(2)). Thus, the investigations used to support the approval of a protein product through the 505(b)(2) pathway need not have been conducted on the particular product to be approved, as long as appropriate data and information are submitted to warrant reliance on those investigations. As discussed in section III.A, appropriate data and information have been provided in the Omnitrope NDA to support its partial reliance on FDA's finding of safety and effectiveness for Genotropin.

Moreover, as detailed in section III.A of this response, the Omnitrope NDA in fact includes extensive Omnitrope-specific clinical data supporting approval of one of the two indications (pediatric GHD) for which this product is now approved. In addition, as discussed elsewhere in this response (see section III.A.6.d), appropriate data establish that Omnitrope-specific trials are not scientifically necessary to support approval of the second indication (adult GHD) for which approval has been granted.

Finally, we disagree with BIO and PhRMA's assertion that there is no reason not to require original, product-specific trials on protein products approved under the Act (such as rhGH). Important statutory and public policy objectives are served by the use of the 505(b)(2) pathway for products for which this pathway is available and scientifically appropriate. As we explained in the 505(b)(2) Citizen Petition Response:

> The Agency's approach is to use the 505(b)(2) drug approval pathway to avoid requiring drug sponsors to conduct and submit studies that are not scientifically necessary. The conduct and review of duplicative studies would (1) divert industry resources that could be used to undertake innovative research, (2) increase drug costs, (3) strain FDA review resources, and (4) slow the process for drug approval with no corresponding benefit to the public health. In addition, the conduct of duplicative studies raises ethical concerns because it could subject human beings and animals to medically or scientifically unjustified testing.

(505(b)(2) Citizen Petition Response at 3 to 4 (internal citation omitted)).

6. Effect of FDA's Approval of Omnitrope on the Rigorousness of Approval Standards for rhGH Products

Pfizer contends that several rhGH products are already approved and available, and that an unsafe or ineffective Omnitrope would threaten the public health. According to Pfizer, FDA should thus "require that all rhGH applicants demonstrate the safety and effectiveness of their products through full reports of rigorous, population-specific clinical testing and manufacturing processes" (Pfizer Petition at 3). Pfizer maintains that,

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This standard is comparable to the requirement that drug products approved under the Act must be shown to be safe and effective (see section 505(b)(1) of the Act). See also Effectiveness Guidance at 2 to 4.

absent such requirements, FDA would unjustifiably lower the approval standards for rhGH products (Pfizer Petition at 2 and 28).

FDA Response:

The Omnitrope NDA has been approved through the 505(b)(2) approval pathway and relied in part on our prior finding of safety and effectiveness for Genotropin, while earlier rhGH products were approved based on stand-alone applications submitted under section 505(b)(1) of the Act. This distinction, however, does not lower the approval standard for rhGH products. Although an application described by section 505(b)(2) of the Act differs from other applications described in section 505(b)(1) of the Act in the source of information used to support approval of the product proposed, a 505(b)(2) application is, by the express terms of that section, "submitted under [section 505(b)(1)]." Accordingly, a 505(b)(2) application is held to the same standards for approval as a 505(b)(1) application (see section 505(b) and (c) of the Act). Pfizer's concern has been addressed in our 505(b)(2) Citizen Petition Response: "Like a stand alone NDA [i.e., a 505(b)(1) application], a 505(b)(2) application . . . must satisfy the requirements for safety and effectiveness information" (505(b)(2) Citizen Petition Response at 3).

As previously discussed in more detail in sections III.A.6.d and III.A.7, product-specific testing was determined not to have been necessary to establish Omnitrope's safety and effectiveness for each proposed indication. The safety and effectiveness of an rhGH product may, as for rhGH products approved based on stand-alone 505(b)(1) applications, be demonstrated through product-specific clinical trials conducted by or for the applicant, or for which the applicant has a right of reference or use. However, as described in section III.A, safety and effectiveness for an rhGH product also may be demonstrated, as in the Omnitrope NDA, through a combination of FDA's prior finding of safety and effectiveness for a similar listed drug as well as product-specific data generated by the applicant, including data demonstrating the safety and effectiveness of the proposed drug as it differs from the listed drug.

As authorized by section 505(b)(2) of the Act, the Omnitrope NDA relies in part on our finding that Genotropin is safe and effective for the same indications proposed for Omnitrope, as well as on data demonstrating that, among other things, the active ingredients of Omnitrope and Genotropin are highly similar. These data, together with other Omnitrope-specific information and clinical testing data submitted by Sandoz (discussed in section III.A of this response) and published literature, establish Omnitrope's safety and effectiveness for both of its proposed indications and satisfy the standards for approval that are set forth in section 505(b) and (c) of the Act.

7. *Public Process Regarding Scientific and Legal Issues Relevant to Approval of Follow-On Protein Products*

BIO, Pfizer, PhRMA, and others have requested that the Agency conduct a comprehensive public process before approving any application for a follow-on protein, to allow for a full exchange of ideas on the scientific and legal merits of approving this

type of application (BIO Petition at 1, 29 to 30, and 52 to 55; Pfizer Supplement at 2 to 3; PhRMA Comments at 18 to 20; see also Genentech Petition at 2).

FDA Response:

FDA has granted petitioners' requests regarding a public process to discuss issues relevant to the approval of follow-on protein products. This response, and final FDA action on the Omnitrope NDA, follow an extended public process through which we have received and considered significant public comment addressing both the regulatory and legal issues related to 505(b)(2) approvals, and the scientific issues associated with the approval of follow-on protein products in general, and Omnitrope in particular. The dockets for the Pfizer Petition, BIO Petition, and Genentech Petition have facilitated the submission, over a period of more than 2½ years, of vigorous public comment. Two sets of public meetings (held on September 14 to 15, 2004, and February 14 to 16, 2005) that were well-attended have provided an opportunity for the presentation and consideration of a range of scientific information. In addition, these meetings were preceded by the creation of a public docket on August 16, 2004 (2004N-0355[95]), to which 28 sets of written comments have been submitted.

The range of the commenters from whom we have heard through the meetings, and the breadth of the comments submitted to the dockets, underscore the transparency and robustness of this process in addressing considerations regarding the regulation of follow-on protein products. This process also has enhanced the Agency's consideration of the specific issues raised by the submission and review of the Omnitrope NDA under section 505(b)(2) of the Act. We noted in correspondence with Sandoz that, because of the nature and complexity of the issues raised by the Omnitrope application and because the public process might bring to light the need for additional data to support approval of the NDA, action on the Omnitrope NDA would be deferred until information derived from the public process could be considered.

The comments submitted to the public docket (2004N-0355) and presented at the public meetings raised the following scientific issues:

- Whether different manufacturing processes can yield the same product or whether the manufacturing process defines the product.

- Whether available analytical techniques are adequate to characterize most, if not all, protein products and are sufficiently precise to detect subtle differences between an innovator product and a follow-on protein product.

- The range of data required to demonstrate similarity between a particular follow-on protein product and an innovator product (e.g., physicochemical, pharmacokinetic/pharmacodynamic (PK/PD), preclinical and clinical data, or analytical testing alone with confirmatory clinical studies in limited cases).

[95] See note 7 of this response and accompanying text.

- The clinical relevance and potential limitations of bioassays, including assay sensitivity, species specificity, and availability of standards.

- The role of PK studies in supporting physicochemical and biological characterization in the assessment of similarity, and the use of PD studies as an adjunct to PK data.

- The nature and design of the clinical development program appropriate for follow-on protein products — ranging from PK/PD studies alone to an abbreviated development program to indication-specific clinical trials — based on considerations related to the complexity of the protein, the potential effects of differences in manufacturing processes, and the ability to determine the degree of similarity between the innovator product and the follow-on protein product.

- Whether it is possible to demonstrate therapeutic equivalence (for an "A" therapeutic rating in the Orange Book) between innovator and follow-on protein products of varying complexity, and the range of data needed to support such a determination (e.g., analytical studies, bioassays, PK/PD, surrogate markers, and/or clinical outcomes).

- The adequacy of assessing potential immunogenicity through methods ranging from analytical testing and characterization (with respect to factors that may influence immunogenicity) to preclinical screening to clinical studies of varying designs pre-approval and/or postmarketing.

- The importance of adequate characterization of the immune response to interpret biological significance, given that the development of antibodies to a biotechnology-derived product may not have clinical consequences. Consideration of potential population differences in immune response.

- Factors that may be considered in determining a need for postmarketing risk assessment beyond routine pharmacovigilance.

- The nomenclature used to describe follow-on protein products, and their relationship to an innovator product.

Several of these issues were presented in the context of proteins that are more complex than rhGH (e.g., high molecular weight, multiple sub-unit proteins with post-translational modifications), cannot be adequately characterized, or have unknown active ingredients or mechanisms of action. This response addresses those issues raised through the public process that are pertinent to the Omnitrope NDA. After full consideration of these issues, the Agency determined that the data and information in the Omnitrope NDA are sufficient to support approval of Omnitrope for pediatric and adult GHD. Action on the Omnitrope NDA under section 505(c) of the Act did not need to await resolution of the scientific and regulatory issues that are associated with either approval of more complex

proteins under section 505 of the Act or approval of follow-on versions of protein products licensed under the PHSA.

IV. CONCLUSION

FDA's approval of the 505(b)(2) application for Omnitrope is based upon the strength of the data in the application, the assessment of which reflects understanding of rhGH and advances in manufacturing technology, process control, and protein characterization. In addition to demonstrating, with bridging across drug substance and formulation changes, that Omnitrope is highly similar to Genotropin physicochemically, pharmacokinetically, pharmacodynamically, biologically, and clinically, Sandoz has provided extensive independent evidence of the safety and effectiveness of Omnitrope for use in pediatric GHD. Based on this data and information, Sandoz has established an appropriate scientific basis upon which to apply our finding of safety and effectiveness for Genotropin to support approval of Omnitrope for pediatric and adult GHD.

Accordingly, the Agency denies the Pfizer Petition and Pfizer Supplement and, to the extent they oppose approving the Omnitrope NDA, relevant portions of the Genentech Petition, the BIO Petition, and the BIO Supplement.

The approval of Omnitrope does not signal that the Agency has concluded that — regardless of the nature and complexity of the active ingredient and the indications for use — every protein product approved under section 505 of the Act is an appropriate candidate for reference by an applicant seeking approval of a follow-on protein product through an abbreviated pathway. Further, this decision does not address the distinct legal and regulatory issues related to approving follow-on versions of products licensed under the PHSA or the scientific challenges that may be posed by more complex and less well-understood licensed biological products.

Sincerely,

Steven K. Galson, M.D., M.P.H.
Director
Center for Drug Evaluation and Research

APPENDIX A: INDEX