

FDA Approval of Sandoz's 505(b)(2) Application for a Follow-On Recombinant Human Growth Hormone Product

On May 30, 2006, FDA approved Sandoz, Inc.'s NDA 21-426 for its follow-on recombinant human growth hormone ("rhGH") product, Omnitrope (somatotropin [rDNA origin] for injection) (the "Omnitrope NDA"). Sandoz had submitted the Omnitrope NDA pursuant to section 505(b)(2) of the Federal Food, Drug, and Cosmetic Act ("FDCA") relying in-part on FDA's prior approval of Pfizer's pioneer rhGH product, Genotropin.

In approving the Omnitrope NDA, FDA denied relevant portions of citizen petitions filed with FDA by Pfizer¹, the Biotechnology Industry Organization ("BIO")², and Genentech.³ FDA communicated this decision, and provided its reasoning in a May 30, 2006 letter to BIO, Genentech, and outside counsel for Pfizer.⁴ FDA did not address portions of these petitions that were not relevant to approval of the Omnitrope NDA. This memorandum provides a summary of FDA's decision and the accompanying statements it made in response to the citizen petitions filed by Pfizer, BIO, and Genentech.

I. Background

A. Section 505(b)(2) of the FDCA

FDA has taken the position that section 505(b)(2) permits applicants to file an NDA that does not contain full reports of clinical studies proving safety and effectiveness, and instead references a previously approved innovator product.⁵ The agency claims that it can base approval of the follow-on product on previous FDA findings of safety and effectiveness, in combination with reports of clinical studies and potentially other data to support the applicant's modifications to the innovator product. Innovator companies have argued that all applications filed under section 505(b) must be full NDAs and that section 505(b)(2) simply permits the agency to approve "paper NDAs," which rely on published studies and can be approved without any reference to safety and effectiveness data submitted by innovators. Nevertheless, in 1999 the agency approved an application filed under section 505(b)(2) for synthetic conjugated estrogens and published a guidance document that outlines the types of applications that the agency claims are permitted by section 505(b)(2).⁶ The controversy has not been resolved by the courts to date.

¹ See FDA Docket No. 2004P-0231/CP1 and SUP 1 (the "Pfizer Petition").

² See FDA Docket No. 2003P-0176/CP1 and EMC1 (the "BIO Petition").

³ See FDA Docket No. 2004P-0171/CP1 (the "Genentech Petition").

⁴ See Letter from FDA to Kathleen M. Sanzo, Esq., Stephan E. Lawton, Esq., and Stephen G. Juelsgaard, Esq. (May 30, 2006) (the "FDA Decision Letter"), available at <http://www.fda.gov/ohrms/dockets/dockets/04P0231/04P-0231-pdn0001.pdf>.

⁵ See, e.g., FDA letter to [Kathleen] M. Sanzo, Jeffrey B. Chasnow, Stephan E. Lawton, and William R. Rakoczy (October 14, 2003).

⁶ See FDA 1999 Draft Guidance: Applications Covered by Section 505(b)(2), available at <http://www.fda.gov/cder/guidance/2853dft.pdf>.

FDA has acknowledged that the 505(b)(2) approval pathway is not applicable to biological products approved pursuant to section 351 of the Public Health Service Act (“PHSA”). This includes most recombinant-DNA therapeutic proteins. For historical reasons, however, a few recombinant-DNA therapeutic proteins, such as human insulin, human growth hormone, and calcitonin were approved through NDAs under section 505 of the FDCA. In 2005, FDA approved a 505(b)(2) application for a recombinant-DNA-derived salmon calcitonin nasal spray. This approval represented the first use of section 505(b)(2) to approve a recombinant-DNA therapeutic protein.

B. The Omnitrope NDA

On July 30, 2003, Sandoz submitted its Omnitrope NDA as a 505(b)(2) application, referencing FDA’s previous approval of Pfizer’s innovator rhGH product, Genotropin. The application sought approval for two of the indications for which Genotropin is approved:

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”).⁷

The Omnitrope NDA includes CMC data, nonclinical pharmacology and toxicology data, and human pharmacokinetics and pharmacodynamic data. In addition, the Omnitrope NDA includes clinical safety and effectiveness data from three phase III original clinical trials of various Omnitrope formulations in pediatric patients with GHD over a 15-month period. Subsequently, Sandoz submitted results from a fourth phase III clinical trial in a safety update to the Omnitrope NDA.

C. The Pfizer, BIO, and Genentech Petitions

Subsequent to the filing of the Omnitrope NDA, Pfizer submitted a citizen petition requesting that FDA deny the Omnitrope NDA. Among other bases, Pfizer asserted that section 505(b)(2) does not legally permit FDA to rely on, reference, or otherwise use clinical and manufacturing information contained in Pfizer’s Genotropin NDA to approve Omnitrope, and that such reliance is also scientifically unjustified. Pfizer also argued that the data submitted with the Omnitrope NDA do not adequately assess safety, effectiveness, and manufacturing considerations for approval of rhGH products.⁸ Genentech and BIO submitted citizen petitions relating more generally to the myriad of legal and scientific issues surrounding follow-on biologics. The BIO and Genentech petitions argue, among other things, that 505(b)(2) does not permit FDA to rely on data contained in a pioneer marketing application, or FDA’s findings based on those data, to approve a follow-on product.

II. FDA’s Approval of Omnitrope

FDA approved the Omnitrope NDA on May 30, 2006.⁹ On the same day, FDA sent a 53-page letter to Pfizer, BIO, and Genentech denying the Pfizer Petition (and supplement) as well as those portions of the BIO and Genentech Petitions (and supplements) that opposed approving the Omnitrope NDA (the “Decision Letter”). FDA’s Decision Letter outlined the agency’s scientific and

⁷ See Genotropin Prescribing Information. Genotropin is also approved for two orphan indications, the treatment of pediatric Prader-Willi Syndrome and children that are small for gestational age. *Id.*

⁸ See Pfizer Petition, at 1.

⁹ This approval closely followed an April 10, 2006 order from the United States District Court for the District of Columbia compelling FDA to comply with the statutory requirements regarding timing of a decision by the agency on Sandoz’s pending NDA. See *Sandoz, Inc. v. Leavitt*, 2006 U.S. Dist. LEXIS 17549 (D.D.C. 2006).

legal basis for approval of the Omnitrope NDA and addressed FDA's reasoning for rejecting specific arguments made by the Pfizer, BIO, and Genentech petitions. The remainder of this memorandum provides a top-level summary of the Decision Letter.

A. FDA's Interpretation of Section 505(b)(2)

The FDA Decision Letter restates what the agency contends is its "long-standing" interpretation of FDCA section 505(b)(2). According to FDA, section 505(b)(2) permits an applicant to reference and rely on "the finding of safety and effectiveness that FDA made for a previously approved listed drug, a finding that is based upon studies conducted by another applicant . . . provided that such reliance is scientifically justified and the 505(b)(2) applicant complies with the applicable statutory requirements regarding patent certification."¹⁰ FDA claims that such reliance is permissible under section 505(b)(2) "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."¹¹

The Decision Letter states that although section 505(b)(2) permits FDA to rely on its previous finding of safety and effectiveness of a previous innovator product, section 505(b)(2) does not permit use or disclosure of trade secret or confidential commercial information or data contained in the innovator's NDA.¹² FDA contends, however, that its review and approval of the Omnitrope NDA did not require any such use or disclosure and, as a result, that its Omnitrope approval is consistent with the agency's interpretation of section 505(b)(2).¹³

B. Lack of Complexity of rhGH Products

The FDA Decision Letter repeatedly emphasizes that its review and approval of Omnitrope was greatly simplified because of the agency's belief that hGH is a "relatively simple recombinant protein." The Decision Letter asserts that hGH is non-glycosylated and is readily purified for structural assessments, and is therefore adequately characterized. The Decision Letter also asserts that 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. Finally, the Decision Letter claims that hGH has a long history of clinical use and its safety and effectiveness profile is thoroughly described in the literature and is well understood.¹⁴

¹⁰ FDA Decision Letter, at 5-6.

¹¹ *Id.* at 6. The FDA Decision Letter asserts that FDA's interpretation is supported by the text of section 505(b)(2), the structure of the Hatch-Waxman Amendments, the purposes of that legislation, and public policy considerations. FDA also emphasizes that its interpretation of section 505(b)(2) has been promulgated in a series of public statements including the 1989-1994 Hatch-Waxman rulemaking process, its 1999 draft guidance, and the agency's October 2003 consolidated response to various citizen petitions regarding 505(b)(2).

¹² See FDA Decision Letter, at 37.

¹³ See *id.*

¹⁴ See *id.* at 8.

According to FDA, this relative lack of complexity facilitates comparisons between two rhGH products. For example, according to the Decision Letter, the Pfizer Petition argued that protein products are defined by their manufacturing processes and thus small differences in process can result in significant changes in the product. Thus, for FDA to conclude that Omnitrope contains the same active ingredient as Genotropin, FDA would have to compare, among other things, the products' recombinant plasmids, master cell banks, and working cell banks. The only way for FDA to compare these factors would be to reference the trade secret and confidential CMC data contained in the Genotropin NDA.¹⁵

According to FDA, however, because hGH is a relatively simple recombinant protein, such reliance on Pfizer's trade secret CMC data was not necessary to review and approve Omnitrope. Rather, the agency asserts that current analytical technology permits adequate characterization of hGH, thus making it "possible to determine that the end products of different manufacturing processes are highly similar, without having to compare or otherwise refer to the processes."¹⁶

In addition, the Decision Letter asserts that because of Omnitrope's relative lack of complexity, FDA did not need to address or resolve many of the arguments raised by the BIO and Genentech Petitions (and comments thereto) relating to approval of follow-on protein products generally.¹⁷ FDA therefore chose not address important scientific issues associated with more complex protein products such as those that have unknown or multiple active ingredients, have unknown mechanisms of action, are difficult to characterize, or are glycosylated. The Decision Letter also does not address legal issues such as takings arguments under the Fifth Amendment to the United States Constitution (because FDA purportedly did not need to review or use any trade secret information from the approved Genotropin application), or arguments concerning approval of follow-on versions of protein products originally approved under section 351 of the PHSA. Because Sandoz did not seek an "A" therapeutic equivalence rating for Omnitrope (Omnitrope received a "BX" rating), the Decision Letter also does not address arguments relating to "A" therapeutic ratings and interchangeability for recombinant protein products.

C. The "Sufficient Similarity" Standard

According to FDA, the Omnitrope NDA contains data sufficient to demonstrate that Omnitrope is "sufficiently similar" to Genotropin, thus justifying reliance on FDA's previous finding of safety and effectiveness for the pioneer. Critically, the Decision Letter asserts that this "sufficient similarity" standard presents a lower bar than the "sameness" standard required for an ANDA under section 505(j). Indeed, the agency anticipates that 505(b)(2) applications will represent changes to the already approved drug product.¹⁸

¹⁵ See FDA Decision Letter, at 14 (citing the Pfizer Petition, at 6, 9-11).

¹⁶ FDA Decision Letter, at 15.

¹⁷ See FDA Decision Letter, at 3-4.

¹⁸ See *id.* at 20.

FDA does not articulate an objective standard for sufficient similarity. Instead, the Decision Letter states only that FDA will permit reliance on its finding of safety and effectiveness of the innovator product when such reliance is “scientifically justified.”¹⁹ Other than a recitation of the data that Sandoz provided in the Omnitrope NDA, FDA does not provide any guidance in the Decision Letter regarding what constitutes sufficient similarity or scientific justification. This suggests that the agency will attempt to make decisions regarding sufficient similarity and scientific justification on a case-by-case basis.

In the case of the Omnitrope NDA, the Decision Letter states that Sandoz provided ample information to establish sufficient similarity to Genotropin. According to FDA, Sandoz compared the active ingredient in Omnitrope to that in Genotropin as well as to international reference standards for somatotropin provided by the WHO and the European Pharmacopoeia. To do this, Sandoz assessed primary, secondary, and tertiary structures, molecular weight, impurities, and biological activity.²⁰ FDA approved the Omnitrope NDA even though it acknowledged that there were differences between the two products, including different impurities and molecular variants.

D. Clinical Data Submitted with the Omnitrope NDA

In addition to data from three pharmacokinetic/pharmacodynamic studies, Sandoz submitted data from four phase III studies in treatment of pediatric GHD. These studies included approximately 140 patients over more than three years. In all, the Omnitrope phase III clinical program “involved a total patient exposure to lyophilized formulations of Omnitrope . . . of 154 patient years (and to Genotropin of 33 patient years).”²¹ FDA relied upon these studies despite the fact that Sandoz used three different versions of Omnitrope (only one of which was approved by FDA). In addition, Sandoz does not appear to have submitted any original clinical data regarding the use of Omnitrope in adult GHD patients.

FDA’s Decision Letter claims that the relative lack of complexity of the hGH protein also simplified Omnitrope’s original clinical trial requirements. For example, according to FDA, the Pfizer Petition contended that because Sandoz had provided clinical studies only in pediatric patients, the study population was inadequate to establish safety and effectiveness for both pediatric and adult GHD.²² For example, comments to the Pfizer Petition suggested that inherent differences in follow-on proteins may cause differences in the safety and effectiveness profile across different indications, thus requiring clinical data for each separate indication.

According to FDA, however, these concerns are not applicable to Omnitrope because “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.” According to FDA, therefore, the clinical trials submitted with the Omnitrope NDA establish the safety and effectiveness of Omnitrope in both pediatric and adult GHD. FDA claims that these data also bridge any gaps created by modifications to Omnitrope as compared to Genotropin²³ and provide further evidence that

¹⁹ See *id.* at 13.

²⁰ *Id.* at 16.

²¹ *Id.* at 25.

²² See FDA Decision Letter, at 26 (citing Pfizer Petition at 7, 28).

²³ For example, the clinical studies provide the data FDA deemed necessary to determine that differences in immunogenicity profiles between Omnitrope and Genotropin do not adversely impact the safety and effectiveness profile of Omnitrope. See Decision Letter, at 34.

Omnitrope and Genotropin are “highly similar.” Thus FDA asserts that these clinical trials, in addition to the other nonclinical data included in the Omnitrope NDA, established that “it is scientifically appropriate to rely on [FDA’s] finding of safety and effectiveness for Genotropin to support the approval of Omnitrope.”²⁴

III. Conclusions

FDA’s decision on Omnitrope does not appear to create a direct precedent for follow-on versions of other biological products. FDA makes clear in its Decision Letter that because it believes that Omnitrope is a relatively simple protein, the agency did not have to consider many of the more complex issues that would be raised by more complex recombinant protein products. FDA also specifically acknowledged that section 505(b)(2) of the FDCA cannot be applied to biological products licensed under section 351 of the PHSA.²⁵

Moreover, despite FDA’s repeated claims that Omnitrope is a relatively simple recombinant protein, FDA required Sandoz to conduct several original clinical studies including four original phase III clinical trials. This strongly implies that any future application for a follow-on biological product would require a similar or greater amount of original data. This would seem particularly to be the case for more complex protein products. Given that FDA characterized rhGH as a relatively simple protein, it is difficult to imagine a justification for requiring less data for more complex products. This decision, therefore, may have created a sizeable scientific hurdle that will have a substantial impact on FDA’s consideration of more complex proteins regulated as drugs, and Congress’s consideration of an approval pathway for follow-on biologics.

²⁴ Decision Letter, at 17.

²⁵ See Decision Letter, at 45 n. 89.

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If you have any questions concerning the material discussed in this client alert, please contact the following members of our food & drug practice group:

Richard Kingham	202.662.5268	rkingham@cov.com
Peter Safir	202.662.5162	psafir@cov.com
Michael Labson	202.662.5220	mlabson@cov.com
Erika Lietzan	202.662.5165	elietzan@cov.com
Grail Sipes	202.662.5379	gsipes@cov.com
Scott Cunningham	202.662.5275	scunningham@cov.com
Scott Danzis	202.662.5209	sdanzis@cov.com

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