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August 4, 2004

Dockets Management Branch  
Food and Drug Administration  
Room 1-23  
12420 Parklawn Drive  
Rockville, Maryland 20857

Re: Docket No. 2004P-0231/CP1: Amendment to Citizen Petition and Response to Comments Submitted by Sandoz, Inc.

Dear Madam or Sir:

This letter: (i) supplements the Citizen Petition filed on behalf of Pfizer Inc (“Pfizer”) on May 13, 2004 (“the Petition”);<sup>1/</sup> and (ii) responds to the June 25, 2004 submission by Sandoz Inc. (“Sandoz Comments”).

As discussed more fully below, the Sandoz Comments fail to address, much less refute, the many scientific issues and important chemical and formulation differences between Omnitrope<sup>®</sup> 5.8 mg (somatotropin [rDNA origin] for injection) lyophilized powder and diluent with preservative (“Omnitrope”) and Pfizer’s Genotropin<sup>®</sup> (somatotropin [rDNA origin] for injection) (“Genotropin”)—including genetic sequence of the recombinant plasmid, master and working cell banks, and composition of the drug powder and diluent.

For the reasons asserted in Pfizer’s initial Petition and supplemented herein, the Food and Drug Administration (“FDA”) should deny approval of Sandoz’ New Drug Application (“NDA”) 21-426 for Omnitrope. Pfizer suggests, however, that FDA defer such action until completion of the forthcoming hearings by the Agency on follow-on biological products and the preparation of proposed guidelines for the approval of such products. FDA should also address the issues

<sup>1/</sup> Citizen Petition filed on behalf of Pfizer Inc (May 13, 2004), Docket No. 2004P-0231/CP1 (requesting that the Food and Drug Administration immediately deny approval of NDA 21-426 because: (1) it is scientifically and legally improper for FDA to rely on, reference, or otherwise use the clinical and manufacturing information establishing the safety and effectiveness of GENOTROPIN<sup>®</sup> (somatotropin [rDNA origin] for injection) to approve Omnitrope<sup>®</sup>; and (2) the Omnitrope<sup>®</sup> data do not adequately address the safety, effectiveness and manufacturing considerations for recombinant human growth hormone (“rhGH”) products or the specific product differences between Genotropin<sup>®</sup> and Omnitrope<sup>®</sup>).

raised in this docket in the forthcoming hearings and draft guidance. The public process will enhance and inform FDA's appreciation of the significant issues raised in Pfizer's Petition, and support the Agency's denial of Sandoz' section 505(b)(2) application.

### **I. FDA Should Defer Action Until The Agency Has Defined Its Policies on Follow-On Biological Products**

Although FDA ultimately should deny Sandoz' section 505(b)(2) application, Pfizer suggests that the Agency defer that action until the Agency has completed its planned public process to delineate the pre-clinical and clinical data requirements for follow-on biological products.

Pfizer fully supports the Agency's proposal to hold public meetings and to consider public comments prior to completing draft guidance on the scientific principles underpinning follow-on biological products. In testimony before Congress on June 23, 2004, Dr. Lester Crawford, FDA Acting Commissioner, outlined plans to hold a major scientific workshop in the near-term to discuss the scientific principles to be considered in assessing the degree of similarity or identity between innovator and follow-on biological products currently regulated as drugs or biologics.<sup>2/</sup> Dr. Crawford confirmed the importance of an exchange among manufacturing experts, chemical experts, the academic community, and the medical community to consider the scientific and medical issues that must be resolved *prior* to the assessment of any specific follow-on product.<sup>3/</sup>

Dr. Janet Woodcock, Acting Deputy Commissioner for Operations, also has emphasized the importance of developing a framework that can be applied both to biological products regulated under the Federal Food, Drug, and Cosmetic Act and the Public Health Service Act,<sup>4/</sup> and Dr. Anthony Mire-Sluis, Principal Advisor for Regulatory Science and Review, Office of Biotechnology Products, has confirmed the Agency's two-step public process (*i.e.*, public meetings, followed by draft guidance) for defining the requirements for follow-on biological products.<sup>5/</sup>

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<sup>2/</sup> The Law of Biologic Medicine: Hearing Before the Senate Judiciary Comm., 108th Cong. 6 (2004) (Attachment 1).

<sup>3/</sup> Id. at 10 (Attachment 1).

<sup>4/</sup> F-D-C Reports, Inc., "The Pink Sheet" 66(24):28 (June 14, 2004). Follow-on Biologics Guidance Delayed Because of Broadened Scope (Dr. Woodcock stated that "we need to make sure we get a consistent scientific approach across these products, and that we're not making fundamentally different scientific recommendations or decisions on comparability or anything else as we move forward") (Attachment 2). Senate Health Committee Counsel Steve Irizarry has also encouraged FDA not to issue draft guidance on follow-on biological products until Congress has reviewed the proposed approval process. F-D-C Reports, Inc., "The Pink Sheet" 66(27):34 (July 5, 2004). Follow-on Biologics Delay Lauded by Senate Health Cmte. Staffer (Attachment 3).

<sup>5/</sup> F-D-C Reports, Inc., "The Pink Sheet" 66(27):33 (July 5, 2004). Follow-on Biologics Process May Allow Post-Approval Immunogenicity Tests (Attachment 4).

Pfizer agrees that it is necessary and prudent for FDA to establish its follow-on biological products policy before making any decisions about such products. If the Agency makes ad-hoc decisions pending the development of its policy, these decisions would cause confusion and result in a piecemeal and possibly incoherent policy, which will undermine the policy's acceptance by scientists, industry, and consumers. Notwithstanding the assertions in the Sandoz Comments, FDA has not already established a precedent on follow-on biological products through its approval of the section 505(b)(2) application for Novo Nordisk's GlucaGen (glucagon [rDNA origin] for injection) in June 1998. GlucaGen was the first recombinant glucagon product approved in the U.S. and, by definition, is an innovator product. Because GlucaGen was not a follow-on product, contrary to Sandoz' contentions, its approval does not serve as a precedent for approval of purported follow-on biological products such as Omnitrope.

Pfizer thus supports FDA's plans to develop a follow-on biological product policy through an inclusive public process that will allow all stakeholders to share their views on potential scientific and medical problems prior to decisions about these products. Pfizer looks forward to working with the Agency to ensure that patient reliance on safe and effective recombinant human growth hormone ("rhGH") and other biological products is not jeopardized by premature approval of follow-on products before the significant issues raised in the Pfizer Petition and by other experts are addressed. Accordingly, Pfizer suggests that FDA defer its denial of Omnitrope and its response to the Petition until the completion of the public meetings, collection of comments, and issuance of new draft guidance on follow-on biological products.

## **II. Sandoz Largely Fails to Rebut or Address the Many Significant Scientific Concerns Raised in the Petition**

The Sandoz Comments fail to rebut or even address the many significant scientific issues raised in the Petition. Specifically, Sandoz completely ignores:

- The many important differences in the biosynthetic manufacturing process between Genotropin and Omnitrope, including differences in the genetic sequence of the recombinant plasmid, and master and working cell banks (discussed at pp.6, 8, 25-26, and 30 of the Petition);
- The significant differences in the formulation of Genotropin and Omnitrope, including the lyophilized drug powder, and the diluent used to reconstitute the product for injection (discussed at pp.4 and 26-27 of the Petition);
- The important differences in the containers and reconstitution procedures (discussed at pp.8 and 26-27 of the Petition);
- The differences in the delivery systems and dosing (discussed at pp. 8, 27, and 31 of the Petition);

- The need for clinical safety data for purported follow-on versions of Genotropin, including Omnitrope, to ensure that there are no potential adverse effects resulting from molecular variants, host cell impurities, or contaminating proteins (discussed at pp.12-19 of the Petition);
- The significant efficacy concerns presented by purported follow-on versions of Genotropin, such as Omnitrope, including the potential effects on efficacy resulting from mutations below the level of detection or changes in the structures of recombinant proteins, and the failure of bioassays to adequately predict clinical efficacy (discussed at pp.12 and 20-21 of the Petition);
- The serious concerns about the lack of data supporting the de novo manufacturing process for Omnitrope, and the significant Omnitrope manufacturing process problems experienced thus far (discussed at pp.4-5, 7-10, and 34-35 of the Petition); and
- The limitations and inadequacy of the public Omnitrope data, resulting from methodological shortcomings and failure to account for the many differences between Genotropin and Omnitrope (discussed at pp.4, 7-9, and 27-31 of the Petition).

Moreover, Sandoz' attempt to address the reported molecular weight difference between Omnitrope and Genotropin is inadequate and misleading. The molecular weight of Omnitrope was given as 21,125 daltons (191 amino acids) in a Biochemie document that was labeled as a "Final Protocol."<sup>6/</sup> The molecular weight of Genotropin is 22,124 daltons (191 amino acids), and this significant difference in the reported molecular weights was given as an example of one of the many important differences between Omnitrope and Genotropin.

Although Sandoz attributes the molecular weight difference of 1001 daltons to "a significant typographical error," Sandoz fails to provide the correct molecular weight of Omnitrope, and thus, it remains unclear whether it is identical to that of Genotropin.<sup>7/</sup> Accordingly, the scientific

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<sup>6/</sup> Biochemie GmbH, Study Protocol, An Open, Multicentre Phase III Study To Demonstrate The Efficacy and Safety of Omnitrop® Lyophilised (Somatotropin) In The Treatment Of Growth-Deficient Children Due To Insufficient Endogenous Growth Hormone Secretion (10.02.2002).

<sup>7/</sup> Sandoz asserts that "a 1,001 daltons difference in molecular weight, if accurate -- which it is not -- would represent a decrease in content of at least seven (7) amino acids." Sandoz Comments, footnote 3, at 2. However, whatever the actual molecular weight difference between Omnitrope and Genotropin, it need not necessarily reflect deletions of amino acids, but would more likely arise from amino acid substitutions or other structural alterations.

For example, as discussed in Pfizer's Petition (at pp.18-19), during the production of recombinant human growth hormone ("rhGH") in bacteria, a variant is generated with a trisulfide bond at Cys182-Cys189 in addition to the native disulfide form. See, e.g., C. Andersson et al., 1996. Isolation and characterization of a trisulfide variant of recombinant human growth hormone formed during expression in Escherichia coli. International Journal of Peptide & Protein Research. 47:311-321. This variant, and other molecular weight

issues raised in Pfizer's Petition concerning molecular weight differences continue to be relevant. Moreover, notwithstanding Sandoz' unexplained assertions to the contrary, the molecular weight difference between Omnitrope and Genotropin is not the core of the long list of scientific issues that Sandoz has failed to address, or the so-called "linchpin" of Pfizer's concerns with the safety and effectiveness of Omnitrope. Rather, it is one of many scientific issues raised by Pfizer, yet the only one that Sandoz chose to address.

### **III. Sandoz' Omnitrope Study Protocol is Relevant to FDA's Assessment of Sandoz' Section 505(b)(2) Application**

Although Sandoz challenges Pfizer's reference to the Omnitrope study protocol, there is no doubt that the protocol is critically important to FDA's consideration of the Omnitrope application. Pfizer also has a legitimate interest in evaluating the scientific information included in the Omnitrope study protocol as well as other sources of information, to determine whether this product meets the NDA safety and effectiveness requirements.<sup>8/</sup> Accordingly, Pfizer carefully considered this information, presented issues of concern in the Petition, and requested that FDA take related actions, in accordance with 21 C.F.R. § 10.30.

Indeed, to do otherwise would result in an unfortunate information asymmetry, with Sandoz seeking to rely on Pfizer's proprietary data and information to support FDA approval of Omnitrope, but objecting to discussion of any of its scientific support or other information concerning its proposed product. This situation clearly would be detrimental to FDA's informed consideration of the scientific issues Pfizer has raised.

Rather than properly explaining the merits of its study, or clarifying glaring errors in the study's documentation, Sandoz seeks to suppress the study protocol by criticizing Pfizer's possession of it. Whatever dispute Sandoz may have with Pfizer over Pfizer's possession of this protocol,<sup>9/</sup> that dispute should not inhibit a full and searching assessment by FDA of the safety and efficacy of the product Sandoz seeks to market for patient use. FDA properly is not required to expend

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variants, are formed during industrial scale production of rhGH, and Pfizer has developed significant proprietary expertise and data to control the manufacturing process to generate a safe and effective rhGH product. For example, Pfizer has invented a method for the production of recombinant proteins with a low amount of trisulfides. International Patent Application PCT/SE99/01222 (filed July 5, 1999) (Attachment 5). In the absence of access to or use of these controls during the manufacturing process, Sandoz' Omnitrope may have a different molecular weight than Genotropin, with unknown effects.

<sup>8/</sup> To the extent that a less safe and effective somatotropin were made available, and particularly one that was asserted to be comparable to Genotropin, there could be damage to the reputation of Genotropin as a safe and effective therapy for growth hormone deficiency in children and adults.

<sup>9/</sup> Pfizer denies that either its receipt of the protocol, or the submission of the protocol to FDA, was improper.

its limited resources on issues not germane to Agency functions particularly where such issues can be addressed in a different forum.<sup>10/</sup>

#### **IV. The Sandoz Comments Include Many Inaccuracies and Misleading Statements**

While many of the misleading statements and inaccuracies in the Sandoz Comments are not worthy of a response, as they concern transparent attempts to have FDA consider issues outside of its statutory purview, certain issues properly need to be addressed.

Specifically, the Sandoz Comments inconsistently state that there is a “finite rhGH segment in the U.S. limited to 10 rhGH product lines, only eight (8) of which are currently marketed, produced by six (6) different manufacturers,” and that “Genotropin is not entitled to a perpetual monopoly.”<sup>11/</sup> This so-called finite market cannot constitute a monopoly (one-seller) market, because as Sandoz states, there are currently eight competing products in the market. Sandoz also misleadingly tries to put this situation in the context of typical small generic/large pharmaceutical company disagreements. Sandoz is, however, a wholly-owned subsidiary of Novartis AG. Obliquely referred to as Sandoz’ “sister company” in the Comments, Novartis is far from the typical generic drug company—it is the fifth largest pharmaceutical company in the world with pharmaceutical sales of \$16 billion in calendar 2003.<sup>12/</sup> Moreover, Sandoz itself is the world’s second largest generic drug company, also known as Novartis Generics, with \$2.9 billion in sales and \$473 million in operating income in calendar 2003.<sup>13/</sup>

Sandoz also is mistaken that Pfizer should be estopped from contesting Sandoz’ application because Pfizer did not specifically challenge prior FDA initiatives involving section 505(b)(2). Sandoz cites no authority, and there is none, suggesting that there is any such estoppel principle, or that Pfizer must police FDA’s behavior on general policy issues that may have no immediate effect on Pfizer in order to preserve its right to contest specific agency actions that do affect Pfizer’s interests.

#### **V. Conclusion**

Sandoz still has provided no basis to deny Pfizer’s Petition. Prior to granting Pfizer’s Petition and denying Sandoz’ NDA, however, FDA should address the issues raised in this docket in the forthcoming public hearings and draft guidance relating to follow-on biological products.

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<sup>10/</sup> See e.g., *A.L. Pharma, Inc. v. Shalala*, 62 F.3d 1484, 1488 (D.C. Cir. 1995) (upholding FDA decision to defer issues of data ownership to other forums)

<sup>11/</sup> Comments of Sandoz, Inc., No. 2004P-0231/CP1, at 3, 5 (June 25, 2004).

<sup>12/</sup> Novartis, About Novartis, at [http://novartis.com/about\\_novartis/en/our-businesses.html](http://novartis.com/about_novartis/en/our-businesses.html) (Attachment 6).

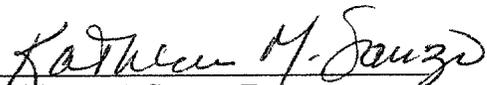
<sup>13/</sup> Sandoz, Profile: Facts & Figures, at [http://sandoz.com/site/en/company/facts\\_and\\_figures/content.html](http://sandoz.com/site/en/company/facts_and_figures/content.html) (Attachment 7); Press Release, PR Newswire, Geneva Pharmaceuticals, Inc. Renamed Sandoz, Inc. (Dec. 1, 2003) (Attachment 8).

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Thereafter, consistent with the foregoing and Pfizer's Petition, FDA should grant Pfizer's Petition requests and deny approval of NDA 21-426 for Omnitrope.

Respectfully Submitted,

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Attachments