DEPARTMENT OF HEALTH & HUMAN SERVICES

Public Health Service

Food and Drug Administration
Rockville MD 20857

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Docket Nos. 2001P-0574/CP1 and 2005P-0061/CP1

Dear Ms. Rapp and Mr. Celeste:

This letter responds to your petition dated December 14, 2001, (Ben Venue Petition) submitted on behalf of Ben Venue Laboratories (Ben Venue), asking the Food and Drug Administration (FDA) to determine that the previously approved, discontinued labeling of Sandostatin (octreotide acetate injection) was not withdrawn for reasons of safety or effectiveness. You also ask FDA to determine that (1) a generic product using the discontinued formulation of Sandostatin would not be less safe or effective than the currently marketed Sandostatin and (2) such a generic product could be found to be therapeutically equivalent to the new formulation of Sandostatin.[1] The discontinued formulation labeling for Sandostatin described a formulation using sodium chloride as the tonicity agent and a glacial acetic acid/sodium acetate buffer system. The labeling for the new formulation of Sandostatin describes mannitol as the tonicity agent and a lactic acid/sodium bicarbonate buffer system.

You amended the requests made in your original petition in an undated comment we received on July 19, 2002.[2] The comment withdraws your request that FDA permit generic applicants to refer to the discontinued labeling for Sandostatin.[3] Instead, you ask

[1] This letter also responds to the petition dated February 9, 2005, (Celeste Petition) submitted on behalf of Sun Pharmaceuticals Industries Ltd., asking FDA to determine whether the discontinued formulation of Sandostatin was withdrawn for reasons of safety or effectiveness. Although the text of this letter specifically refers to the Ben Venue Petition, this letter is responsive to both petitions because the issues are substantially the same.

[2] Ben Venue also submitted comments dated April 3, 2002, and May 14, 2003.

[3] Accordingly, FDA is not specifically addressing discontinued labeling issues in this citizen petition response. However, FDA notes that the Federal Food, Drug, and Cosmetic Act (the Act) requires the

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that FDA determine whether the discontinued formulation of Sandostatin was withdrawn for reasons of safety or efficacy. Your July 19, 2002, comment also responds to a May 3, 2002, comment submitted by Novartis Pharmaceuticals Corporation (Novartis), the holder of the new drug application (NDA) for Sandostatin.[4] Novartis contends that FDA regulations bar the approval of an ANDA for a proposed generic drug using the discontinued formulation of Sandostatin. For the reasons that follow, your petition, as amended, is granted.

I. Background

Sandostatin (octreotide acetate) Injection (NDA 19-667) was first approved in 1988 to treat symptoms of vasoactive intestinal peptide tumors and carcinoid tumors. Sandostatin was approved in 1994 for the treatment of acromegaly. The discontinued formulation of Sandostatin used sodium chloride as the tonicity agent and a glacial acetic acid/sodium acetate buffer system. Sandostatin was later reformulated to use mannitol as the tonicity agent and a lactic acid/sodium bicarbonate buffer system. FDA approved supplemental NDAs for the reformulated product in multidose vials in 1994 and in ampules in 1995.[5]

II. Safety of the Sandostatin Formulations

In your petition you assert that the discontinued and new formulations of Sandostatin are equally safe and effective, and therefore, FDA may approve generic applications that use the discontinued formulation.[6]

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applicant submitting an abbreviated new drug application (ANDA) to show that "the labeling proposed for the new [generic] drug is the same as the labeling approved for the listed drug . . . except for changes required because of differences approved under a petition filed under [section 505(j)(2)(C) of the Act] or because the new drug and the listed drug are produced or distributed by different manufacturers" (see section 505(j)(2)(A)(v) of the Act (21 U.S.C. 355(j)(2)(A)(v)); see also section 505(j)(4)(G) of the Act). FDA issued a parallel requirement, under 21 CFR 314.94(a)(8)(iv), which lists examples of permissible differences in labeling that may result because the generic drug product and the reference listed drug product are produced or distributed by different manufacturers. The plain language of the regulation includes, among other things, differences in formulation.

[4] Novartis also submitted comments dated February 14, 2002, May 3, 2002, August 22, 2002, November 19, 2002, March 26, 2003, and July 11, 2003. FDA also received three comments (dated October 3, 2002, October 16, 2002, and February 26, 2003) from two patients who use octreotide acetate injections.

[5] FDA notes that Novartis' February 14, 2002, comment (p. 1) states that the supplemental NDAs for the reformulated ampules were approved in 1996. FDA's records indicate the reformulated ampules received FDA approval on December 18, 1995.

[6] We do not need to publish a notice of our decision in the *Federal Register* because Novartis only reformulated the listed drug (NDA 19-667), and therefore the listed drug was never technically withdrawn from, and continues to be on, the market.

You point out that in Novartis' bioequivalence study comparing the discontinued and new formulations of Sandostatin no subjects dropped out because of injection site pain, and there were no reports of moderate or severe pain, only mild pain. You state that "any differences in reported pain at the injection site [between the discontinued and new formulations] are primarily associated with subcutaneous injection" (Ben Venue July 19, 2002, comment, p. 2).
You also state that:

> The level of sodium chloride in the discontinued formulation is below that of normal saline and would not present any expected therapeutic hazards to the patient. The use of mannitol in the formulation is for tonicity purposes and does not have any additional recognized therapeutic benefit. In addition, both formulations (sodium chloride vs. mannitol) produce isotonic solutions (Ben Venue Petition at 3).

Novartis asserts, however, that the new formulation of Sandostatin is safer and more effective than the discontinued formulation. To support this assertion, Novartis relies on (1) the bioequivalence study it submitted to obtain approval of the new formulation, (2) several publications concerning octreotide, and (3) a report it describes as a pharmaceutical expert report. These various sources are discussed below.

A. Novartis' Bioequivalence Study

Novartis submitted the report of a bioequivalence study, which it previously submitted to obtain approval of the new formulation of Sandostatin, in support of its conclusion that the new formulation is safer for patients than the discontinued formulation (February 14, 2002, comment, p. 2). The report contains the results of the bioequivalence study of the two formulations administered subcutaneously. The study was a single-blind crossover design in 16 healthy male subjects. FDA concluded that the discontinued formulation and the new formulation were bioequivalent in the pharmacokinetic endpoints of area under the curve of the plasma concentration over time (AUC) and the maximum drug concentration (Cmax).

During the bioequivalence study, Novartis also asked subjects to report on their pain at the injection site (February 14, 2002, comment, bioequivalence study report). Novartis states that local pain at the injection site was reported in 9 of the 16 subjects (56 %) with the discontinued formulation and in 1 subject (6 %) with the new formulation (February 14, 2002, comment, p. 2). Based on these reports in the 16 subjects, Novartis concludes that the discontinued formulation of Sandostatin is less safe than the new formulation. Novartis goes on to conclude that the new formulation is more effective than the discontinued formulation because minimizing the potential for injection site pain reduces the risk of patient noncompliance (February 14, 2002, comment, p. 2).

FDA disagrees with Novartis' conclusions. By their very nature, bioequivalence studies are designed to determine if the same doses of two different products provide the same plasma concentrations of the active ingredient over time.[7] While data on symptoms were also collected, the trial was not designed to assess safety, and the interpretation of any numerical differences between groups cannot be used alone to conclude a difference in either safety or efficacy for the two products.

The fact that Novartis also asked participants to report on injection site pain does not transform its bioequivalence study into a controlled trial adequate to compare either safety or efficacy. The trial has at least two weaknesses in this regard. First, the protocol for the study (as described in the bioequivalence study report included in Novartis' February 14, 2002, comment) does not specify that the trial was conducted in double-blind fashion, as would be necessary to assess a difference in pain. Second, the number of subjects is quite small, given the subjective and varying nature of the endpoint being assessed (pain). For instance, we note that the duration of pain reported varied considerably between 10 and 40 minutes. We also note that the pain resolved universally, and that there were no "clinically significant changes" in physical examination observed before and after the administration of the study drug (February 14, 2002, comment, bioequivalence study report, page 0051).

Most importantly, the results of controlled clinical studies reported in the currently approved Sandostatin labeling contradict the conclusions Novartis draws from its bioequivalence study. The current approved labeling for Sandostatin reports the incidence of pain on injection with the new formulation as 7.7 percent.[8] This figure is slightly higher than the incidence reported in the labeling for the discontinued formulation, which was 7.5 percent.

In sum, Novartis' bioequivalence study is not, as Novartis claims, adequate evidence that the new formulation of Sandostatin is safer or more effective than the discontinued formulation. It also does not provide evidence to suggest that Novartis discontinued the old formulation for reasons of safety or effectiveness.

B. Published Articles Concerning Octreotide

With its February 14, 2002, comment, Novartis included four published articles concerning octreotide. Novartis asserts that these articles "demonstrat[e] consistent recognition of injection site pain across clinical trials with the [discontinued] acetic acid

[7] FDA's regulation at 21 CFR 320.1(e) states: "*Bioequivalence* means the absence of a significant difference in the rate and extent to which the active ingredient or active moiety in pharmaceutical equivalents or pharmaceutical alternatives becomes available at the site of drug action when administered at the same molar dose under similar conditions in an appropriately designed study."

[8] See the labeling for Sandostatin (octreotide acetate) Injection approved January 17, 2003.

formulation" (Page 2 (footnote omitted)). The four articles are titled: (1) "Randomized Controlled Multicentre Study of the Prevention of Complications by Octreotide in Patients Undergoing Surgery for Chronic Pancreatitis"[9] (hereafter Randomized Controlled article), (2) "A Comparison of Octreotide, Bromocriptine, or a Combination of Both Drugs in Agromegaly,"[10] (3) "Randomized Double-Blind Placebo-Controlled Trial of Early Octreotide in Patients with Postoperative Enterocutaneous Fistula,"[11] (4) "Safety and Efficacy of Long Term Octreotide Therapy of Acromegaly: Results of a Multicenter Trial in 103 Patients—A Clinical Research Center Study."[12]

FDA finds these articles to be irrelevant to the point Novartis is trying to make because these publications do not compare the incidence of pain with the discontinued formulation to that with the new formulation. Accordingly, these articles do not provide persuasive evidence that the discontinued formulation was withdrawn for reasons of safety or effectiveness.

Furthermore, Novartis misstates the results of the Randomized Controlled article (at 1271) as supporting its conclusion that the excipients are the source of injection site pain (February 14, 2002, comment, p. 2). Novartis summarizes that, among patients reporting an adverse event, there was a 71 percent incidence of injection site pain upon administration of placebo and a 75 percent incidence in octreotide patients (February 14, 2002, comment, p. 2).

In fact, Novartis' calculation of the incidence rates is wrong. Incidence is the number of events divided by the number of people exposed to the test article. In the Randomized Controlled article, the incidence of patients who experienced "pain, burning, or erythema at the injection site but did not require discontinuation of the treatment" was 18 of 122 or 14.7 percent in the octreotide group and 25 of 125 or 20 percent in the placebo group. Correctly calculated, the incidence of pain, burning, or erythema at the injection site was actually greater in the placebo group than in the octreotide group. Furthermore, patients did not discontinue treatment because of injection site reactions. Thus, the Randomized Controlled article does not support Novartis' assertion that the old formulation is less effective than the new one because of patient discontinuation. These articles do not provide a sufficient basis upon which we can reasonably conclude that Novartis discontinued the old formulation for reasons of safety or effectiveness.

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[9] Friess, et al., in the *British Journal of Surgery*, vol. 82, pp. 1270-1273.

[10] Flogstad, et al., in the *Journal of Clinical Endocrinology and Metabolism*, vol. 79, pp. 461-465.

[11] Sancho, et al., in the *British Journal of Surgery*, vol. 82, pp. 638-641.

[12] Newman, et al., in the *Journal of Clinical Endocrinology and Metabolism*, vol. 80, pp. 2768-2775.

C. Novartis' Pharmaceutical Expert Report

Novartis included as Appendix 2 in its February 14, 2002, comment an excerpt from a document it describes as Novartis' Pharmaceutical Expert Reports.[13] The excerpt asserts that the new formulation produced less pain at the injection site than the discontinued formulation, although it does not provide any evidence to support this assertion. The report also states that the reduction in pain "can be explained" because "the physiological pH of about 7.2 at the injection site is more rapidly reestablished after injection of lactic acid than after injection of acetic acid" (Excerpt, p. 2).

FDA agrees that physiological pH could be more rapidly reestablished after injection of lactic acid than after injection of acetic acid. However, this fact alone does not establish that the new formulation of Sandostatin is safer than the discontinued formulation, nor does it provide sufficient evidence upon which we can reasonably conclude that Novartis discontinued its old formulation for reasons of safety or effectiveness. In fact, as discussed in section II.A above, the incidence of pain on injection is higher (7.7 percent) with the new formulation than with the discontinued formulation (7.5 percent).

III. Legal Issues Concerning Inactive Ingredients

Section 505(j)(4)(H) of the Act states that the Secretary shall approve the abbreviated new drug application (ANDA) unless, among other things,

> information submitted in the application or any other information available to the Secretary shows that (i) the inactive ingredients of the drug are unsafe for use under the conditions prescribed, recommended, or suggested in the labeling proposed for the drug, or (ii) the composition of the drug is unsafe under such conditions because of the type or quantity of inactive ingredients included or the manner in which the inactive ingredients are included.

FDA has concluded that the inactive ingredients (including the buffer system and tonicity agent) used in the discontinued formulation of Sandostatin do not make that formulation unsafe. FDA has also concluded that the discontinued formulation of Sandostatin is no less safe and effective than the new formulation. Therefore, under the statutory standard, FDA would be justified in approving an ANDA that uses the discontinued formulation of Sandostatin.

Novartis, in effect, argues that FDA's regulations prevent FDA from approving an ANDA that contains a tonicity agent that is different from the tonicity agent in the

[13] The actual title of the document is "Sandostatin Ampoules 0.1 mg/1 mL (Lactic Acid/Mannitol Formulation), Part I C: Expert Report on 1. Chemical and Pharmaceutical Documentation." The document is dated June 14, 1989, and states that it is from Sandoz Ltd., Basle, Switzerland. Sandoz was Novartis' predecessor.

reference listed drug. Because the discontinued formulation of Sandostatin uses sodium chloride as the tonicity agent, and the new formulation uses mannitol, Novartis asserts that FDA may not approve an ANDA for the discontinued formulation of Sandostatin. Novartis asserts that approval of such an ANDA is precluded by FDA's regulation at 21 CFR 314.94(a)(9)(iii) (May 3, 2002, comment, pp. 2 to 3). This regulation, *Inactive ingredient changes permitted in drug products intended for parenteral use*, provides that:

> Generally, a drug product intended for parenteral use shall contain the same inactive ingredients and in the same concentration as the reference listed drug identified by the applicant under paragraph (a)(3) of this section. However, an applicant may seek approval of a drug product that differs from the reference listed drug in preservative, buffer, or antioxidant provided that the applicant identifies and characterizes the differences and provides information demonstrating that the differences do not affect the safety or efficacy of the proposed drug product.

The regulation, which governs the content and format of an ANDA, finds its parallel in 21 CFR 314.127, which addresses the refusal to approve an ANDA. Section 314.127(a)(8)(ii)(B) provides that:

> FDA will consider an inactive ingredient in, or the composition of, a drug product intended for parenteral use to be unsafe and will refuse to approve the abbreviated new drug application unless it contains the same inactive ingredients, other than preservatives, buffers, and antioxidants, in the same concentration as the listed drug, and, if it differs from the listed drug in a preservative, buffer, or antioxidant, the application contains sufficient information to demonstrate that the difference does not affect the safety or efficacy of the drug product.

The regulations governing inactive ingredients were issued to address particular safety concerns posed by parenteral drug products. In addressing comments on proposed § 314.127 regarding changes in preservatives, buffers, and antioxidants, the Agency noted in the final rule published in the *Federal Register* that under the statute, the inquiry is whether these inactive ingredients are "safe under the conditions prescribed, recommended, or suggested in the labeling" and that the regulation "reflects this concern, which is particularly acute for parenteral drug products" (57 FR 17950 at 17970; April 28, 1992).

The regulations seem intended to address the use of excipents that could not be adequately addressed in the ANDA context (i.e., unfamiliar excipients, or excipients of a type more likely to raise safety concerns for parenteral drugs). It seems apparent that neither FDA nor commenters to the proposed rule anticipated that an ANDA applicant might seek approval to market a previous formulation of a drug product that FDA had approved as safe.

Because an ANDA for the safe discontinued formulation of Sandostatin would clearly meet the statutory standard for approval under section 505(j)(4)(H) of the Act, the Agency may rely on 21 CFR 314.99(b) to grant a waiver of the requirement that the ANDA and NDA formulations contain the same inactive ingredients and in the same concentration as the reference listed drug, with limited exceptions for preservatives, buffers, and antioxidants. This waiver provision states that "[a]n applicant may ask FDA to waive under this section any requirement that applies to the applicant under §§ 314.92 through 314.99. The applicant shall comply with the requirements for a waiver under § 314.90."[14]

Section 314.90 describes the information an applicant must submit to support a waiver request. It further states that FDA may grant a waiver if it finds that (1) compliance with the regulatory requirement is unnecessary to evaluate the application, (2) the alternative submission satisfies the purpose of the requirement, or (3) the applicant's submission otherwise justifies the waiver.[15]

The Agency's approach to approval of an ANDA for octreotide acetate injection would not involve any waiver of statutory requirements regarding inactive ingredients. FDA would not approve such an ANDA if information submitted in the application or other information showed that the inactive ingredients were unsafe. Here, experience with the innovator's own marketing of the formulation and FDA's recent analysis have shown that the inactive ingredients in the discontinued formulation of Sandostatin are safe. Therefore, when an ANDA applicant is seeking approval for a parenteral formulation that is the same as that previously marketed by the innovator, FDA believes that in appropriate circumstances it may grant waivers of the requirement that the inactive ingredients in a parenteral drug approved under an ANDA be the same as those in the reference listed drug (except for preservatives, buffers, and antioxidants). This approach is a reasonable reading of FDA regulations, is justified by the science, and is consistent with the statutory requirements for ANDA approval.

IV. Therapeutic Equivalence

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[14] Section 314.99 addresses the waiver of certain submission requirements described in § 314.94. Waiver of the parallel requirements described in § 314.127 for refusing to approve an ANDA is not explicitly stated. However, FDA interprets waiver of the submission requirement to carry with it the implicit waiver of the approval requirement. The statement in § 314.99 that an applicant may ask FDA to waive "*any* requirement that applies to the applicant" under § 314.94 would be meaningless with respect to the provisions of § 314.94 that have parallels in § 314.127 unless waiver of a submission requirement under § 314.94 permitted waiver of the corresponding approval requirement.

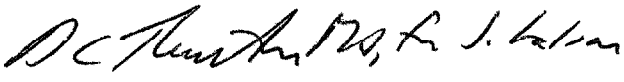
[15] FDA's discretion in waiving regulatory requirements is not unlimited. The preamble to the proposed rule adopting § 314.99 notes that FDA may not waive statutory requirements. 54 FR 28872 at 28889; July 10, 1989.

You ask that we determine whether a generic product using the discontinued formulation of Sandostatin could be found to be therapeutically equivalent to the new formulation of Sandostatin (Ben Venue Petition at 1). As stated in FDA's *Approved Drug Products With Therapeutic Equivalence Evaluations*,[16] "Drug products are considered to be therapeutic equivalents only if they are pharmaceutical equivalents and if they can be expected to have the same clinical effect and safety profile when administered to patients under the conditions specified in the labeling." FDA's scientific expertise and experience have shown that such a difference in inactive ingredients would not preclude a finding of therapeutic equivalence.

V. CONCLUSION

We have seen no scientific evidence that indicates that the discontinued formulation of Sandostatin is less safe and effective than the new formulation. The evidence presented by Novartis is both speculative in its conclusions and of doubtful relevance in evaluating the relative safety of the two formulations. FDA concludes that the discontinued formulation of Sandostatin was not withdrawn for reasons of safety or effectiveness. Furthermore, FDA's regulations do not prevent FDA from approving an ANDA for octreotide acetate injection that contains the same tonicity agent as that contained in the discontinued formulation of the reference listed drug when the discontinued formulation was not withdrawn for reasons of safety or effectiveness. Accordingly, your petition, as amended, is granted.

Sincerely,



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[16] 24th ed., 2004, p. viii.