



Dockets Management Branch  
Food and Drug Administration (HFA-305)  
5630 Fishers Lane  
Room 1061  
Rockville, MD 20852

2002 JUL 19 A7:00

**Re: Docket 01P-0574/CP1**

Dear Sir or Madam:

The undersigned submits comments to the above referenced petition. The original petition was submitted on December 14, 2001. The purpose of this submission is two-fold. First, Ben Venue wishes to respond to comments to this petition submitted by Novartis on May 3, 2002. The second objective of this submission is to withdraw one action requested by Ben Venue in the original petition. Specifically, Ben Venue wishes to withdraw its request that FDA permit reference to discontinued labeling that was previously approved.

**Response to Novartis Pharmaceutical Corporation's May 3, 2002 Comments**

The following comments are provided in response to a submission by Novartis Pharmaceutical Corporation (Novartis) to this petition dated May 3, 2002. In that letter, Novartis raises numerous reasons why Ben Venue Laboratories' (Ben Venue) request for a determination that an identical formulation of Sandostatin Injection, which was marketed for eight years by Novartis, should now not be used in a lower cost generic version of that product. It appears that Novartis has taken a position that the previous formulation raises safety concerns if used by a generic manufacturer in spite of the fact that Novartis has never made claims that its original formulation was unsafe nor was this formulation ever removed from the marketplace by Novartis. Ben Venue is merely requesting that FDA make a determination on the facts whether the original formulation of Sandostatin® Injection was withdrawn for reasons of safety or efficacy.

The following discussion of the issues raised in the May 3, 2002 letter from Novartis is listed in order of appearance in the Novartis correspondence. Ben Venue's comments follow the restatement of each relevant issue.

1. The new formulation of Sandostatin Injection is a safer formulation.

Comment:

Novartis claims the new formulation to be safer than the formulation for which Ben Venue is seeking approval. At least part of their claim is based on their own study report which states that "In order to *eliminate* (emphasis added) the local

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pain, a new preparation (herein after called ‘test preparation’) was developed, using lactic acid in place of acetic acid.”

The firm claims that the new formulation was developed to eliminate pain. Pain is associated with all subcutaneous injections due to penetration of intact skin. Therefore, Novartis’ claim to *eliminate* pain is clearly not an assertion that reasonably can be made. Even Novartis’ own data indicates reporting of pain at the injection site. (See p. 50 of original petition) in spite of the firm’s assertion that the new formulation eliminates pain. The firm then goes on to correctly state that the new formulation may cause less pain (p. 2 of Novartis’ May 3 submission). Hence, it is not reasonable to believe that pain at the injection site is eliminated by the introduction of the lactic acid containing formulation. To make the claim of reduced pain at the injection site, Novartis apparently relies on a bioequivalence study entitled “Bioequivalence Study of the Two Parenteral Preparations of SMS 201-995.” This study was performed in 1988. The study included 16 subjects who received a test formulation (lactic acid/mannitol) and control formulation (acetic acid/sodium chloride). All reports of pain at the injection site were classified as mild. While reports of mild pain for the control group were higher than the test group, there were no reports of moderate or severe pain in either group. This data certainly indicates when pain did occur at the injection site, that it was mild and no subject in this study left the study due to pain at the injection site. The study suggests that there are essentially no safety concerns regarding pain at the injection site for the study group receiving the acetic acid/sodium chloride formulation.

Additionally, any differences in reported pain at the injection site are primarily associated with subcutaneous injection. There is no data presented to suggest that there is any difference in irritation at the injection site for intravenous administration. Although there was no data presented, it is unlikely that the two formulations would exhibit a difference in injection site pain due to the rapid dilution of drug products when administered by intravenous injection.

2. The Regulations Do Not Permit the Formulation Changes Ben Venue Seeks to Re-introduce in Their Generic Octreotide Acetate Product

Comment:

Ben Venue wishes to explain its rationale for submitting a petition to request that the Agency make a determination that the original Sandostatin formulation was not withdrawn for reasons of safety or efficacy. Novartis has attempted to misconstrue the regulations in its May 3 submission and incorrectly interpreted the regulations in regard to formulation changes that are permitted for drug



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products submitted pursuant to section 505(j) of the Federal Food, Drug and Cosmetic Act.

The original formulation of Sandostatin was approved in 1988. The new formulation was approved for multiple-dose vials in 1994 and for ampoules in 1996. This new formulation included a change in buffer system and tonicity agents. The regulations (21 CFR 314.94(a)(9)(iii) clearly permit ANDA applicants to seek approval for parenteral products that differ in buffer system. However, because Novartis changed the tonicity agent from sodium chloride to mannitol in the reformulated product, Ben Venue submitted a petition to seek the Agency's determination that the formulation containing sodium chloride was not withdrawn for reasons of safety or efficacy. Had the buffer system been the only change to the formulation, it would not be necessary to submit a petition to the Agency. Rather, the difference in buffer system between the proposed product and the reference-listed drug would have been identified and characterized in the ANDA as required by the regulations. The technical review of the buffer system proposed by Ben Venue would be based entirely on FDA assessment without public debate by Novartis. Novartis expends considerable effort in an attempt to dissuade the Agency from considering a buffer system that had been previously approved and marketed by the firm for several years. In fact, except for the change in tonicity agents, the Ben Venue ANDA would not be subject to overt attempts to prevent approval of a lower cost product that is essentially the same to the product marketed by Novartis for years. Therefore, the only reason to address the formulation in the petition was to clarify the change in tonicity agents.

Novartis also attempts to confuse the issue by citing the refuse to approve regulations (21 CFR 314.127) as a reason for FDA to reject filing the proposed application. These regulations outline potential reasons for not approving an ANDA. Ben Venue has the regulatory right to file its ANDA provided that the application contains information to support approval of the proposed buffer system. Ben Venue may also refer to the fact that its proposed formulation is the essentially the same formulation marketed by Novartis for eight years (Ben Venue acknowledges that FDA must make a determination sodium chloride was not withdrawn from the original formulation for safety or efficacy reasons). Should FDA determine during the course of review of the proposed ANDA that there are reasons to withhold approval, it may do so. However, this action is taken only after a thorough review of the information provided in the ANDA to support approval. If, in fact, Novartis now believes that the original formulation is unsafe, it is difficult to explain its rationale for permitting this formulation to be marketed in ampoules for two additional years after the new formulation was approved in multiple-dose vials. Hence, any argument regarding safety of the original formulation is hardly supported by Novartis' own actions.



Novartis also contends that the regulations do not permit a waiver for parenteral formulations that are not identical to the reference-listed drug. In fact, FDA has a long history of waiving in vivo bioequivalence requirements for ANDAs seeking approval of parenteral drug products that differ in preservative, buffer system or substances to adjust pH. Novartis focuses on a single waiver provision as its basis declaring that FDA cannot waive in vivo bioequivalence requirements even though other regulations permit waiving such this requirement. Finally, Novartis refers to a statement from 57 Federal Register 17950 in which FDA stated, "FDA cannot always predict the consequences of minor changes." In fact, FDA has several years of clinical evidence regarding the safety of the proposed product since it was marketed as an approved product for an extended period of time. Novartis appears to utilize this statement by FDA in a context that clearly differs from its intent. FDA was explaining that it cannot always predict the impact of differences between the proposed and approved drug products when there is no evidence regarding the safety of the proposed formulation. In this case, FDA has extensive knowledge regarding the formulation proposed by Ben Venue and the quote by Novartis is misleading in the present situation.

Novartis also contends that the potential difference in pain at the injection site between the old and new formulation will lead to decreased patient compliance and ultimate reduced efficacy. This hypothetical rationale is interesting. Apparently Novartis did not believe that this reduced efficacy was a particular concern while it marketed both formulations for a period of time. Additionally, the now expressed concern of Novartis regarding decreased efficacy due to lower patient compliance with the original formulation did not seem to matter since Novartis did not withdraw its original formulation from the market once the new formulation was approved. It is curious that the concerns regarding efficacy comes to the forefront simultaneous with potential competition in the marketplace. Even by Novartis' own data, the complaints of pain at the injection site were all considered to be mild. Also, Novartis focuses on mild pain at the injection site (please note that the current Novartis formulation had reported mild pain at the injection site, hence pain is not eliminated by the current formulation) as a hypothetical reason for noncompliance with the prescribed dosage regimen. Ben Venue would like to point out that patient compliance is also affected by cost and suggests that the availability of a lower cost generic version provides patients with an opportunity to improve compliance based on the considerable economic considerations for the use of this product.

3. Novartis/Sandoz Worked with FDA to Bring the Improved Formulation to Its Patients



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Ben Venue acknowledges Novartis' efforts to change its product, albeit some six years after its introduction to the market. Ben Venue also recognizes that the differences in reported frequency of mild pain at the injection site do not impact safety or efficacy of the proposed drug product. Both the original and current formulations of Sandostatin are safe and effective.

The position taken by Novartis represents a significant public policy issue. If such minor changes in formulation, which are almost always subject to new patent protection, preclude approval of ANDAs, there may never well be generic availability of parenteral products. It certainly is quite conceivable for innovators to develop formulations that anticipate incremental changes. In this scenario, the innovator will make minor formulation changes that demonstrate slight differences in some aspect of patient use or satisfaction and claim improved safety or efficacy of the 'changed' product. Of course, this 'change' will be subject to patent protection and will forestall the availability of generic products. Even one or two minor changes to a formulation could delay generic approvals for a decade or more in spite of the fact that the changes that do not truly alter the underlying safety or efficacy of the drug product. If, in fact, the innovators make a claim that the old formulation is unsafe, it should be withdrawn at the time that the new formulation is approved and health care providers should be informed of this 'lack of safety or efficacy.'

#### **Withdrawal of Requested Action to Reference Previously Approved Labeling**

The original petition requested three specific actions. Those actions were presented in Part A, page 1 of the petition. Ben Venue Laboratories, Inc. hereby withdraws the request "that an ANDA may reference the discontinued labeling that was previously approved by the FDA". The other requests for action and all other aspects of the petition remain as originally written.



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Ben Venue recognizes that the claims by Novartis are based on economic considerations and not safety or efficacy. If the concerns were the latter, Novartis would have taken steps to remove the old formulation from the market, which it did not do. Rather, the position taken by Novartis represents an ongoing attempt by innovator firms to thwart legitimate generic competition as their products near expiry of market protection. Finally, the regulations clearly permit ANDA applicants to seek approval for products that differ in buffer system. Likewise, FDA may waive in vivo bioequivalence requirements when these differences exist. Therefore, the regulatory interpretations by Novartis are inconsistent with the facts relating to Ben Venue's request for FDA to make a determination that the original Sandostatin formulation was not withdrawn for reasons of safety or efficacy.

Sincerely,

Molly Rapp  
Regulatory Affairs  
Ben Venue Laboratories, Inc.

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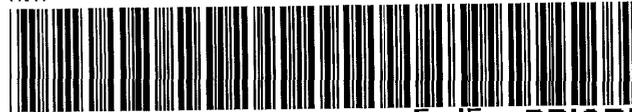
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