

**CENTER FOR DRUG EVALUATION AND
RESEARCH**

APPLICATION NUMBER:

22-028

OTHER ACTION LETTER(s)



DEPARTMENT OF HEALTH & HUMAN SERVICES

Public Health Service

Food and Drug Administration
Rockville, MD 20857

NDA 22-028

12/6/06

Sandoz Inc.
Attention: Beth Brannan
Director, Regulatory Affairs
2555 W. Midway Blvd; P.O. Box 446
Broomfield, CO 80038-0446

Dear Ms. Brannan:

Please refer to your new drug application (NDA) dated February 3, 2006, received February 6, 2006, submitted pursuant to section 505(b)(2) of the Federal Food, Drug, and Cosmetic Act for Cosyntropin Injection, 0.25 mg/mL.

We acknowledge receipt of your submissions dated August 3, and September 7, and 21, 2006.

We completed our review of this application, as amended, and it is **approvable**. Before the application may be approved, however, it will be necessary for you to provide adequate specifications necessary to ensure potency, purity, and sterility of the product.

Information needed to address chemistry deficiencies:

1. As previously communicated to you in the filing letter dated April 17, 2006, a bioassay must be included in either the drug substance or drug product specification, and the potency of your in-house reference standards must be verified by a bioassay using an international reference preparation.

Biological activity is a critical attribute for your product because it is used as a diagnostic agent. In addition, the bioassay is important in assessing the lot-to-lot bioactivity of the product and ensuring product performance after certain manufacturing changes. We find your justification for the lack of a bioassay in your specifications inadequate. A reference to an article on bioassay in the literature is not acceptable in the absence of any bioassay data that is specific to your product.

2. In order to determine an acceptable expiration dating period, a complete characterization study report on the impurities and degradation products must be provided, and adequate controls of impurities and degradation products must be part of the drug substance and drug product specifications. Please include the following in the characterization study report on the impurities and degradation products:

- A summary of the actual and potential impurities and degradation products most likely to arise during the manufacture and storage of the drug substance and drug product; a complete summary of laboratory studies conducted to detect impurities and degradation products in the drug substance and drug product, and cross-references to supporting safety data (nonclinical and/or clinical data with the associated lot or batch numbers) as part of your justification of the proposed limits on impurities and degradation products.
- Regarding the impurity specifications for both the drug substance and drug product, improve the HPLC test method so that the quantitation limit is $\frac{1}{10}$ % or less; add the limit of not more than $\frac{1}{10}$ % for an individual unspecified impurity/degradant, and specify individual impurities/degradants that are found at levels greater than $\frac{1}{10}$ %.
- Regarding your reporting of impurities and degradation products, provide numerical results for all relevant batches of the drug substance and drug product used for clinical, safety, and stability testing, as well as all batches that are representative of the proposed commercial process. Your reporting of all results as "<LOQ" or "< $\frac{1}{10}$ %" is not acceptable because an impurity test method must be a quantitative test and not a limit test.

b(4)

3. In order to establish the sterility of the drug product, the following should be provided:

- Please specify all room locations and filling lines where the drug product will be filled.
- Please identify the room locations for the following equipment: _____
- Specify the maximum period of time from completion of sterile _____ to completion of filling of a batch of the drug product.
- _____
- _____
- _____
- Provide data on the validation of _____ reduction of the _____ used during drug product manufacture.
- Please identify the _____ processing parameters to be used for _____ used in the manufacture of the drug product.
- Submit a list of all _____ to be used for component preparation for the drug product. Any additional or "future" _____ be used in the drug product manufacturing process need to be identified and shown to be equivalent (by data or other suitable rationale). This information should be submitted as an amendment to the pending NDA, prior to its approval, or as a supplement, following its approval.
- Please provide data or detailed rationale for the selection of _____ over other _____ as the worst case for the revalidation of Cycle _____ (Autoclave _____).

b(4)

b(4)

- Confirm if the drug product will be filled within a continuous 24 hour period, or if it will be filled over a two day period. If a two day production filling period is performed, please clarify if different set-up or installation parts are used for Day 2, or if the same parts remain in place for the entire production run of the drug product.
- Please specify if the filled and sealed media fill vials used in the Cosyntropin processing simulations were subjected to external vial washing processes prior to incubation.
- The Media fill acceptance criterion for the number of permitted contaminated units stated in Protocol QV-001.3, are based on a contamination rate (at a 95% confidence level), and no longer reflect current Agency expectations for process simulations. Such a criterion should be reconsidered to be more consistent with the Agency's 2004 Guidance for Industry "Sterility Drug Products Produced by Current Good Manufacturing Practices" (section IX.A.9). As noted in this Guidance, a practical acceptance limit may be based upon the total number of contaminated units in a media fill run, but should not be based on a rate or percent. The presence of an occasional contaminated container may not be the basis for a failed validation, but should initiate an investigation.
- Please submit data on the drug product container closure integrity testing for () and ()

b(4)

If additional information relating to the safety or effectiveness of this drug becomes available, revision of the labeling may be required.

Within 10 days after the date of this letter, you are required to amend this application, notify us of your intent to file an amendment, or follow one of your other options under 21 CFR 314.110. If you do not follow one of these options, we will consider your lack of response a request to withdraw the application under 21 CFR 314.65. Any amendment should respond to all the deficiencies listed. We will not process a partial reply as a major amendment nor will the review clock be reactivated until all deficiencies have been addressed.

Under 21 CFR 314.102(d), you may request a meeting or telephone conference with this division, the Division of Metabolism and Endocrinology Products to discuss what steps need to be taken before the application may be approved.

The drug product may not be legally marketed until you have been notified in writing that the application is approved.

If you have any questions, please call Ms. Jena Weber, Regulatory Project Manager, at 301-796-1306.

Sincerely,

{See appended electronic signature page}

Mary H. Parks, M.D.
Director
Division of Metabolism & Endocrinology Products
Office of Drug Evaluation II
Center for Drug Evaluation and Research

**This is a representation of an electronic record that was signed electronically and
this page is the manifestation of the electronic signature.**

/s/

Mary Parks
12/6/2006 10:20:58 AM