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*APPLICATION NUMBER:*

**21-817**

**MICROBIOLOGY REVIEW**

# Product Quality Microbiology Review

## Review for HFD-510

08 Feb 2005

**NDA:** 21-817

**Drug Product Name**

**Proprietary:** Aclasta®  
**Non-proprietary:** Zoledronic Acid  
**Drug Product Classification:** 3

**Review Number:** 1

**Subject of this Review**

**Submission Date:** September 21, 2004  
**Receipt Date:** September 22, 2004  
**Consult Date:** November 29, 2004  
**Date Assigned for Review:** December 1, 2004

**Submission History (for amendments only)**

**Date(s) of Previous Submission(s):** Not applicable.  
**Date(s) of Previous Micro Review(s):** Not applicable.

**Applicant/Sponsor**

**Name:** Novartis Pharmaceuticals Corp.  
**Address:** One Health Plaza  
East Hanover, NJ 07936-1080  
**Representative:** Joan Materna  
**Telephone:** 862-778-3379

**Name of Reviewer:** John W. Metcalfe, Ph.D.

**Conclusion:** Recommended for Approval.

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## Product Quality Microbiology Data Sheet

- A.
1. **TYPE OF SUBMISSION:** Original NDA.
  2. **SUBMISSION PROVIDES FOR:** New drug product.
  3. **MANUFACTURING SITE:**  
Novartis Pharma Stein AG  
Schaffhauserstrasse  
4332-Stein  
Switzerland
  4. **DOSE FORM, ROUTE OF ADMINISTRATION AND STRENGTH/POTENCY:**
    - 100 mL solution in clear plastic \_\_\_\_\_ vials.
    - Intravenous Infusion.
    - 5 mg/100 mL.
  5. **METHOD(S) OF STERILIZATION:** \_\_\_\_\_
  6. **PHARMACOLOGICAL CATEGORY:** Treatment of Paget's disease of bone.
- B. **SUPPORTING/RELATED DOCUMENTS:** None

C. **REMARKS:**

The subject NDA was submitted electronically.

A phone call was placed by this reviewer on January 4, 2005 to Ms. Joan Materna (applicant representative) to pose the following questions/comments.



A written response was forwarded by Ms. Materna to this reviewer by FAX on January 7, 2004. Following are the responses provided:

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A phone call was placed on January 26, 2005 by this reviewer to Ms. Materna to ask the following question regarding the stability protocol.

Regarding the post approval stability protocol for the annual batches, are sterility and bacterial endotoxin testing planned? There is no mention of these tests in the annual batch stability protocol provided in section 3.2.P.8.2 of the submission.

Ms. Materna stated that

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An additional phone call was placed on January 26, 2005 by this reviewer to Ms. Materna informing her that the Product Microbiology team would not support approval of the application with an annual stability protocol which lacks sterility and endotoxin testing. Reference was made to the FDA stability guidance which states that annual stability testing of parenteral drugs should include both sterility and bacterial endotoxin testing. This information was left as a voice mail message for Ms. Materna since she was not in the office at the time of the call. On January 28, 2005, Ms. Materna phoned this reviewer to discuss the rationale for requiring microbiological testing to be performed as part of the annual stability protocol. She will discuss the issue with her colleagues in Switzerland next week, and inform this reviewer of the applicant's response.

On February 7, 2005, this reviewer received a facsimile which provided a written response to the concerns described above regarding the annual stability protocol. Following is a summary taken from the cover page of the 11 page fax:

"Novartis agrees to revise the Aclasta Stability Protocol for Annual Batches to include sterility and BET testing at the initial time point and at expiry. An updated stability protocol for annual batches reflecting this change is provided as separate attachment (document 3769387\_P82\_M\_840\_2)".

Further, the written response contained copies of both the revised Post-Approval Stability Protocol and Stability Commitment and the Drug Product Stability Protocol for Annual Batches. The applicant will amend the subject NDA to include these revised documents.

**Satisfactory**

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On Original**

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**Executive Summary****I. Recommendations**

- A. Recommendation on Approvability** – NDA 21-817 is recommended for approval from the standpoint of drug product microbiological quality.
- B. Recommendations on Phase 4 Commitments and/or Agreements, if Approvable** – Not Applicable.

**II. Summary of Microbiology Assessments**

- A. Brief Description of the Manufacturing Processes that relate to Product Quality Microbiology -**



- B. Brief Description of Microbiology Deficiencies** – There are no microbiology deficiencies.
- C. Assessment of Risk Due to Microbiology Deficiencies** – Not applicable.

**III. Administrative**

- A. Reviewer's Signature** \_\_\_\_\_  
John W. Metcalfe, Ph.D.
- B. Endorsement Block**  
David Hussong, Ph.D.
- C. CC Block**  
In DFS

8 Page(s) Withheld

X § 552(b)(4) Trade Secret / Confidential

       § 552(b)(4) Draft Labeling

       § 552(b)(5) Deliberative Process

Withheld Track Number: Microbiology-  /

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/s/  
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John Metcalfe  
2/14/05 10:01:37 AM  
MICROBIOLOGIST

David Hussong  
2/17/05 01:52:45 PM  
MICROBIOLOGIST