CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

50-793

MICROBIOLOGY REVIEW

Product Quality Microbiology Review
Review for HFD-510

29 August 2005

NDA: 21-858

Drug Product Name
Proprietary: Boniva™
Non-proprietary: Ibandronate sodium.
Drug Product Priority Classification: S

Review Number: 1

Dates of Submission(s) Covered by this Review

Letter	Stamp	Consult Sent	Assigned to Reviewer
06 DEC 2004	07 DEC 2004	07 FEB 2005	14 FEB 2005
13 JULY 2005	15 July 2005	N/A	N/A
19 August 2005	22 August 2005	N/A	N/A

Submission History (for amendments only)

Submission Date(s)	Microbiology Review #	Review Date(s)
N/A	N/A	N/A

Applicant/Sponsor
Name: Hoffmann-La Roche, Inc.
Address: 340 Kingsland St.
Nutley, NJ. 07110
Representative: Barbara Kowal Wilson
Telephone: 973-562-5608

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

Conclusion: Recommended for Approval.

Product Quality Microbiology Data Sheet

A. 1. **TYPE OF SUBMISSION:** Original NDA.

2. **SUBMISSION PROVIDES FOR:** A new drug product.

3. **MANUFACTURING SITE:**
Prefilled syringes (in bulk) Manufacturer:
[redacted]

Secondary packaging, stability and release testing:
Roche Diagnostics GmbH
Mannheim, GM.

Finished Dosage Packager:
Hoffman-LaRoche Inc.
Nutley, NJ.

4. **DOSAGE FORM, ROUTE OF ADMINISTRATION AND STRENGTH/POTENCY:**
- Solution in prefilled glass syringe.
- Intravenous injection.
- 3 mg/3mL [redacted]

5. **METHOD(S) OF STERILIZATION:** [redacted]

6. **PHARMACOLOGICAL CATEGORY:** Indicated for treatment of postmenopausal osteoporosis.

B. **SUPPORTING/RELATED DOCUMENTS:**

C. **REMARKS:**
The submission is electronic.

A phone call was placed on 22 June 2005 by this reviewer to Ms. Barbara Kowal Wilson, CMC representative for the applicant for the purpose of addressing the following questions/comments.

- The environmental microbiological monitoring program is described in a narrative found in module 3.2.P.3.3, however no discussion of the methods or alert/action limits is provided. Please provide this information.
- It is stated that the [redacted] will be used for sterility testing according to USP/Ph. Eur. (module 3.2.P.5, page 69), however there are no data provided regarding the validation of this test method with the subject drug product (bacteriostasis/fungistasis testing). Please provide these data.

An amendment response (#006) to these questions was forwarded to The Agency on 13 July 2005 by the applicant. Summaries of the applicant response are incorporated into relevant sections of this review.

On 13 July 2005 an additional phone call was made by this reviewer to Ms. Kowal Wilson for the purpose of asking the following questions. Ms. Kowal Wilson's responses are provided in *italics*.

- It is stated in section 3.2.P.3.1 of the submission that secondary packaging, stability and release testing are performed at [redacted] Since secondary packaging includes the addition of the [redacted], will release testing be performed on units that contain the [redacted]
  The applicant representative will contact European colleagues to determine the answer to this question.
- Meeting minutes from a 16 September 2004 meeting between The Agency and the applicant state in item #14 that container closure integrity studies "need to be performed using the final to-be-marketed container closure system with the [redacted] in place". Stability study container closure integrity data presented in the original submission and the 17 June 2005 amendment represent units containing the syringe barrel, tip cap and [redacted] only, without the [redacted]
  The applicant representative stated that they have committed to performing the stability studies in the manner suggested by The Agency on the validation batches of product. These data have not been forwarded to The Agency as of yet, but will be. Also, the applicant representative pledged to forward to this reviewer copies of historical communication between the applicant and The Agency regarding the issue of stability testing on units with and without the [redacted]

An amendment response (#009) to the 13 July 2005 questions was forwarded to The Agency on 19 August 2005 by the applicant. The applicant provided the following information in this amendment:

- Regarding the question of whether release sterility testing will be performed on units that contain the [redacted], the applicant states "batch release testing is routinely performed upon receipt of the bulk pre-filled syringes from [redacted] not in place) since batch release is required prior to packaging operations, in accord with cGMPs. Therefore, it is not planned to routinely conduct batch release testing on pre-filled syringes with [redacted] in place."
- Three commercial scale process validation batches [redacted] 3 mg/mL presentations were manufactured in April of 2005 at [redacted]. Data were submitted in amendment 009 from the initial sterility and container closure integrity testing of units with the [redacted] in place. All samples tested met the USP/EP standards for sterility. The applicant plans to conduct further testing at [redacted] time points and annually thereafter.

Reviewer comments regarding this amendment are incorporated into sections E (stability considerations) and F2 (release sterility testing) of this review.

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Executive Summary

I. Recommendations

A. Recommendation on Approvability – NDA 21-858 is recommended for approval from the standpoint of product quality microbiology.

B. Recommendations on Phase 4 Commitments and/or Agreements, if Approvable – NA.

II. Summary of Microbiology Assessments

A. Brief Description of the Manufacturing Processes that relate to Product Quality Microbiology – The drug product is [redacted] prior to being filled in a [redacted] environment into previously sterilized syringes followed by [redacted]

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
Bryan Riley, Ph.D.

C. CC Block
In DFS

10 Page(s) Withheld

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_____ Draft Labeling

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Withheld Track Number: Microbiology- 4

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/s/

John Metcalfe
9/7/2005 03:31:48 PM
MICROBIOLOGIST

Bryan Riley
9/8/2005 08:05:15 AM
MICROBIOLOGIST