CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

75-290

CHEMISTRY REVIEW(S)

Chemistry Closed

1. CHEMISTRY REVIEW NO. 4

2. ANDA # 75-290

3. NAME AND ADDRESS OF APPLICANT

Bedford Laboratories
A Division of Ben Venue Laboratories, Inc.
Bedford, OH 44146

4. LEGAL BASIS FOR SUBMISSION

505(j)(1) & 21 CFR 314.94.

5. SUPPLEMENT(s)

N/A

6. PROPRIETARY NAME

N/A

7. NONPROPRIETARY NAME

Pamidronate Disodium for Injection

8. SUPPLEMENT(s) PROVIDE(s) FOR:

N/A

9. AMENDMENTS AND OTHER DATES:

Original	12/23/97
New Correspondence	2/13/98
New Correspondence	4/14/98
Amendment	3/12/99
Amendment	7/14/99 (microbiology information)
Amendment	11/16/99
*Amendment	12/5/00
Telecon	1/8/01 (requesting revised COA and updated stability data)
*Amendment	1/18/01

*(subject of this review)

10. PHARMACOLOGICAL CATEGORY

Suppressant for severe hypercalcemia

11. Rx or OTC

Rx

12. RELATED IND/NDA/DMF(s)

13. DOSAGE FORM

Lyophilized
(White to off White Cake)

14. POTENCY

30 mg/vial
90 mg/vial

The original submission included a 60-mg/vial. The 60 mg/vial has been withdrawn (December 5, 2000 amendment, page 2).

Satisfactory

15. CHEMICAL NAME AND STRUCTURE

See review #1.

16. RECORDS AND REPORTS

N/A

17. COMMENTS

Additional request per FDA's comments of May 24, 2000 and the applicant's response:

1. **The original submission included a 60 mg/vial presentation. Please formally withdraw it.**

   Response: The 60 mg/vial is withdrawn. (December 5, 2000 amendment)

2. **Please provide any additional stability data that are available.**

   Response: Data are provided in Attachment V. (December 5, 2000 amendment)

   Response: Data are provided in Attachment IV. (January 18, 2001 amendment)

3. **We will schedule Methods Validation for this ANDA after the testing issues are resolved. Your amendment should provide a copy of the current drug substance and drug product methods and current specifications for the drug substance and drug**

product in a separate section. This information will be used for the Methods Validation study.

Response: Refer to Attachment VIII.
(December 5, 2000 amendment)

Reviewer's Comment: The information referenced above is in Attachment VII of the December 5, 2000 amendment.

4. **You will need to resubmit your request for in vivo biowaiver with supporting information due to your reformulation of the drug product.**

Response: Refer to Attachment VI for request for waiver of *in vivo* studies.
(December 5, 2000 amendment)

18. CONCLUSIONS AND RECOMMENDATIONS

Chemistry issues are closed.

Pending:

A. Review of Bio Waiver request per the December 5, 2000 amendment.
B. Satisfactory MV report.
C. Acceptable updated EER.

19. REVIEWER:
Shirley S. Brown

DATE COMPLETED:
Jan. 31, 2001
December 13, 2000 (review of 12/15/00 amendment)

January 30, 2001 (review of 1/18/01 amendment)

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Chem Rev 4

1/31/01

MAY 24 2000

38. Chemistry Comments to be Provided to the Applicant

ANDA: 75-290 APPLICANT: Bedford Laboratories Inc.

DRUG PRODUCT: Pamidronate Disodium for Injection: 30 mg/vial and 90 mg/vial.

The deficiencies presented below represent MINOR deficiencies.

A. Deficiencies:

1. for the drug substance remains deficient. The DMF Holder has been notified. Please confirm a response.

2. The Loss on Drying specification for should be tightened per available data.

3. The batch records state that protection is not required (3/12/99 amendment, pages 162 and 247). The Composition Statement (11/16/99 amendment page 004A) lists Please clarify.

4. Your proposal to adjust the to compensate for

y.

5. Please revise the proposed pH specification for the drug product to include a range of no greater than 1 pH unit. This applies to both release and stability.

6. The specification for release should be tightened.

7. The proposed release specifications for the drug product should be revised to of the theoretical content (i.e., for the 30 mg vial, ppm for the 90 mg vial) to be consistent with the assay limits.

8. Update Certificates of Analyses for lots 0985-35-108464 for the 30 mg/vial and Lot 0987-36-108466 for the 90 mg/vial including all the revised specifications should be provided.

9. The proposed stability assay specification should be tightened as previously requested to '

10. A dissolution or constitution time specification (e.g. seconds) for the should be added for release and stability.

B. In addition to responding to the deficiencies presented above:

1. The original submission included a 60 mg/vial presentation. Please formally withdraw it.

2. Please provide any additional stability data that are available.

3. We will schedule Methods Validation for this ANDA after the testing issues are resolved. Your amendment should provide a copy of the current drug substance and drug product methods and current specifications for the drug substance and drug product in a separate section. This information will be used for the Methods Validation study.

4. You will need to resubmit your request for in vivo biowaiver with supporting information due to your reformulation of the drug product.

Sincerely yours,

/s/ Rashmikant M. Patel, Ph.D.
Director
Division of Chemistry I
Office of Generic Drugs
Center for Drug Evaluation and Research

AUG 19 1999

38. Chemistry Comments to be Provided to the Applicant

ANDA: 75-290 APPLICANT: Bedford Laboratories Inc.

DRUG PRODUCT: Pamidronate Disodium for Injection: 30 mg/vial, 60 mg/vial and 90 mg/vial.

The deficiencies presented below represent FACSIMILE deficiencies.

A. Deficiencies:

1. An additional formulation for the drug product was proposed. The proposed formulation uses and to form the active ingredient, Pamidronate Disodium. Two formulations are not permitted in the same ANDA. Additionally, Chemistry, Manufacturing and Control information (e.g. DMF reference) for the was not provided. This formulation and related documentation and data should be withdrawn and filed as a separate ANDA.

2. In-process after filtration assay limits are of label claim. If the results do not meet this specification, you propose that the to 100.0% of label. Batches failing in-process assay limits should be rejected. should not be adjusted to compensate for in-process failure.

3. The reason for not including testing for in the specifications for the drug product release and stability should be justified.

4. A test for has been included for release. This test is appropriate but it is not adequate as a second identification test. A second identification test for the organic portion of the molecule should be added.

5. You were asked to tighten the assay specification for stability to of label claim. The specification was not tightened. Please justify as this change appears appropriate.

6. You were asked to add a test and specification for dissolution of the to your release and stability testing. This test was not added. Please justify as this test appears appropriate.

7. Please clarify your limits for and . Is this ug/g of the powder or ug/mL of the constituted solution?

B. In addition to responding to the deficiencies presented above, please note and acknowledge the following comments in your response:

1. is under review in another FDA unit. Deficiencies, if any, will need to be resolved.

2. Your response must also reply to the labeling deficiencies.

3. Your recently submitted sterility assurance information is pending review.

4. We will schedule Methods Validation for this ANDA after the testing issues are resolved. Your amendment should provide a copy of the current drug substance and drug product methods and current specifications for the drug substance and drug product. This information will be used for the Methods Validation study.

5. Please provide any additional stability data that is available.

Sincerely yours,

/s/ Rashmikant M. Patel, Ph.D.
Director
Division of Chemistry I
Office of Generic Drugs
Center for Drug Evaluation and Research

JUL 14 1998

38. Chemistry Comments to be Provided to the Applicant

ANDA: 75-290 APPLICANT: Bedford Laboratories Inc.

DRUG PRODUCT: Pamidronate Disodium for Injection: 30 mg/vial, 60 mg/vial and 90 mg/vial.

The deficiencies presented below represent MAJOR deficiencies.

A. Deficiencies:

1. Please include in your Component and Composition page, and provide a representative Certificate of Analysis.

2. As Pamidronate Disodium is supposed to be the specification for Water should be lowered from "Not More Than to "Not More Than .

3. The Certificates of Conformation for the 10 cc, 15 cc, and 20 cc flint glass vials say that these vials meet the USP's light transmission test for amber vials. Please clarify this statement, since there is no evidence in the application that your vials are colored amber.

4. Please provide Certificates of Analysis that demonstrate that the 10 cc, 15 cc, and 20 cc flint glass vials pass the USP's test for Powdered Glass and Arsenic, and, if the glass is amber, Light Transmission.

5. Please explain how the 2 sets of in-process Fill Adjustment Limits are used to adjust the Fill of Solution to 100% of label claim.

6. Please add tests and specifications for the analysis of in the drug products, both as a release test and as a stability test.

7. Please tighten the assay specification of the drug products to s of label claim for both release and stability.

8. The sample preparation for the 30 mg/vial product for release assay testing appears to be different from the way the 60 mg/vial and 90 mg/vial products are handled. The 30 mg/vial product should be handled generally in the same manner as the 60 mg/vial and 90 mg/vial products are handled. The weight of 5

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7/14/98

B. In addition to responding to the deficiencies presented above, please note and acknowledge the following comments in your response:

1. A satisfactory compliance evaluation for the firms referenced in the ANDA is required prior to approval. We have requested an evaluation from the Office of Compliance.

2. Your response should also reply to all labeling deficiencies.

3. Your sterility assurance information is pending review.

4. The regulatory methods for the drug substance and drug product shall be validated by an FDA Field laboratory at the appropriate time. A satisfactory validation is required to support the ANDA.

Sincerely yours,

Rashmikant M. Patel, Ph.D.
Director
Division of Chemistry I
Office of Generic Drugs
Center for Drug Evaluation and Research