CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

21-810

MICROBIOLOGY REVIEW

Product Quality Microbiology Review

19 DECEMBER 2006

NDA: 21-809/AZ (NovoLog Mix 30/70)
21-810/AZ (NovoLog Mix 50/50)

Drug Product Name
Proprietary: see above
Non-proprietary: 30% insulin aspart protamine suspension/70% insulin aspart injection and 50% insulin aspart protamine suspension/50% insulin aspart injection
Drug Product Priority Classification: S

Review Number: 2

Dates of Submission(s) Covered by this Review

Letter	Stamp	Consult Sent	Assigned to Reviewer
8/31/2006	8/31/2006	9/1/2006	9/11/2006

Submission History (for amendments only)

Submission Date(s)	Microbiology Review #	Review Date(s)
6/22/2005	1	3/16/2006

Applicant/Sponsor
Name: Novo Nordisk Inc.
Address: 100 College Park Rd, Princeton, NJ 08540
Representative: Mary Ellen McElligott, Ph.D.
Telephone: 609-987-5831

Name of Reviewer: Bryan S. Riley, Ph.D.

Conclusion: Recommended for Approval

Product Quality Microbiology Data Sheet

A. 1. **TYPE OF SUBMISSION:** Major Amendment in response to NA letter

2. **SUBMISSION PROVIDES FOR:** A sterile parenteral suspension

3. **MANUFACTURING SITE:** Novo Nordisk
Bagsvaerd, Denmark

4. **DOSAGE FORM, ROUTE OF ADMINISTRATION AND STRENGTH/POTENCY:** Sterile Preserved Suspension for s.c. injection in a 3 mL PenFill® cartridge, 100 U/mL

5. **METHOD(S) OF STERILIZATION:** —— b(4)

6. **PHARMACOLOGICAL CATEGORY:** Insulin

B. **SUPPORTING/RELATED DOCUMENTS:** Product Quality Microbiology review of NDAs 21-809 and 21-810 (dated 16 March 2006).

C. **REMARKS:** This submission was made in response to deficiencies conveyed to the applicant in a NA letter (dated 19 April 2006). There were 2 microbiology deficiencies.

filename: N021809R2.doc

Executive Summary

I. Recommendations

A. Recommendation on Approvability – This submission is recommended for approval on the basis of product quality microbiology.

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

II. Summary of Microbiology Assessments

A. Brief Description of the Manufacturing Processes that relate to Product Quality Microbiology – The drug products are b(4)

B. Brief Description of Microbiology Deficiencies – N/A

C. Assessment of Risk Due to Microbiology Deficiencies – N/A

III. Administrative

A. Reviewer's Signature _____
Bryan S. Riley, Ph.D.

B. Endorsement Block _____
James L. McVey
Microbiology Team Leader

C. CC Block
N/A

1 Page(s) Withheld

✓ Trade Secret / Confidential (b4)

_____ Draft Labeling (b4)

_____ Draft Labeling (b5)

_____ Deliberative Process (b5)

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/s/

Bryan Riley
12/21/2006 08:48:23 AM
MICROBIOLOGIST

James McVey
12/21/2006 09:26:12 AM
MICROBIOLOGIST

Product Quality Microbiology Review

16 MARCH 2006

NDA: 21-809 (NovoLog Mix 30/70)
21-810 (NovoLog Mix 50/50)

Drug Product Name
Proprietary: see above
Non-proprietary: 30% insulin aspart protamine suspension/70% insulin aspart injection and 50% insulin aspart protamine suspension/50% insulin aspart injection
Drug Product Priority Classification: S

Review Number: 1

Dates of Submission(s) Covered by this Review

Letter	Stamp	Consult Sent	Assigned to Reviewer
6/22/2005	6/22/2005	6/27/2005	1/23/2006

Submission History (for amendments only): N/A

Applicant/Sponsor
Name: Novo Nordisk, Inc.
Address: 100 College Park Rd, Princeton, NJ 08540
Representative: Mary Ellen McElligott, Ph.D.
Telephone: 609-987-5831

Name of Reviewer: Bryan S. Riley, Ph.D.

Conclusion: Approvable pending resolution of Product Quality Microbiology Deficiencies.

Product Quality Microbiology Data Sheet

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

2. **SUBMISSION PROVIDES FOR:** A sterile parenteral suspension

3. **MANUFACTURING SITE:** Novo Nordisk, Inc.

4. **DOSAGE FORM, ROUTE OF ADMINISTRATION AND STRENGTH/POTENCY:** Sterile Preserved Suspension for s.c. injection in a 3 mL PenFill® cartridge, 100 U/mL

5. **METHOD(S) OF STERILIZATION:** [redacted] b(4)

6. **PHARMACOLOGICAL CATEGORY:** Insulin

B. **SUPPORTING/RELATED DOCUMENTS:** N/A

C. **REMARKS:** These two NDAs cross-reference each other.

filename: N021809R1.doc

Executive Summary

I. Recommendations

A. Recommendation on Approvability – This submission is approvable pending resolution of product quality microbiology deficiencies (please see section H: List of Microbiology Deficiencies" at the end of this review).

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

II. Summary of Microbiology Assessments

A. Brief Description of the Manufacturing Processes that relate to Product Quality Microbiology – The drug product is [redacted] b(4)

B. Brief Description of Microbiology Deficiencies – The media fill acceptance criteria are not clearly defined and the container closure integrity test method is not adequately described.

C. Assessment of Risk Due to Microbiology Deficiencies – The microbiology deficiencies present a moderate risk to sterility assurance. The uncertainty regarding the media fill acceptance criteria make it difficult to judge the usefulness of the media fills as a part of the [redacted] process validation. The ambiguity in the procedure for container closure integrity validation casts doubt on the ability of the container closure to adequately protect the drug product from microbial contamination. b(4)

III. Administrative

A. Reviewer's Signature _____
Bryan S. Riley, Ph.D.

B. Endorsement Block _____
Stephen Langille, Ph.D.

C. CC Block
N/A

7 Page(s) Withheld

✓ Trade Secret / Confidential (b4)

_____ Draft Labeling (b4)

_____ Draft Labeling (b5)

_____ Deliberative Process (b5)

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/s/

Bryan Riley
3/20/2006 10:42:13 AM
MICROBIOLOGIST

Stephen Langille
3/20/2006 01:18:28 PM
MICROBIOLOGIST