

**CENTER FOR DRUG EVALUATION AND
RESEARCH**

APPLICATION NUMBER:

022472Orig1s000

MICROBIOLOGY / VIROLOGY REVIEW(S)

Product Quality Microbiology Review

05 February 2014

NDA: 022-472/N000

Drug Product Name

Proprietary: Afrezza (Proposed)

Non-proprietary: insulin human [rDNA origin]

Review Number: 2

Dates of Submission(s) Covered by this Review

Submit	Received	Review Request	Assigned to Reviewer
13 October 2013	15 October 2013	15 October 2013	17 October 2013

Submission History (for 2nd Reviews or higher)

Submit Date(s)	Microbiology Review #	Review Date(s)
16 March 2009	1	22 September 2009
29 June 2010	NA	NA

Applicant/Sponsor

Name: Mannkind Corporation

Address: 61 South Paramus Roads
Paramus NJ 07652

Representative: John Bedard
Sr. Vice President, Regulatory Affairs

Telephone: (210) 983-5143

Name of Reviewer: Denise A. Miller

Conclusion: Recommended for approval

Product Quality Microbiology Data Sheet

- A.**
- 1. TYPE OF SUBMISSION:** Resubmission
 - 2. SUBMISSION PROVIDES FOR:** Manufacture of (b) (4) inhalant.
 - 3. MANUFACTURING SITE:**
MannKind Corporation
One Casper Street
Danbury CT 06810
 - 4. DOSAGE FORM, ROUTE OF ADMINISTRATION AND STRENGTH/POTENCY:**
 - Dosage Form: Powder for Inhalation
 - Route of Administration: Oral Inhalation
 - Strength/Potency: 3 or 6 units/cartridge
 - 5. METHOD(S) OF STERILIZATION:** (b) (4)
 - 6. PHARMACOLOGICAL CATEGORY:** Glycemic control in adults with Type I and Type II diabetes mellitus.
- B. SUPPORTING/RELATED DOCUMENTS:** N/A
- C. REMARKS:**
This is a second resubmission. The original submission was recommended for approval from a quality microbiology perspective. The first resubmission was not reviewed by quality microbiology.

This drug product includes an inhaler device.

filename: N022472N000R2.doc

Executive Summary

I. Recommendations

- A. Recommendation on Approvability** - Recommended for approval from a quality microbiology perspective.
- 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** – This drug product is a (b) (4) powder packaged in cartridges for use in a specifically designed inhaler (Gen2 inhaler).
- B. Brief Description of Microbiology Deficiencies** – None identified.
- C. Assessment of Risk Due to Microbiology Deficiencies** – NA
- D. Contains Potential Precedent Decision(s)**- Yes No

III. Administrative

- A. Reviewer's Signature** _____
Denise A. Miller
Microbiologist, OPS/NDMS
- B. Endorsement Block** _____
Bryan S. Riley, Ph.D.
Senior Microbiologist, OPS/NDMS
- C. CC Block**
N/A

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/s/

DENISE A MILLER
02/10/2014

BRYAN S RILEY
02/10/2014
I concur.

Product Quality Microbiology Review

18 September 2009

NDA: 22-472/N000

Drug Product Name

Proprietary: AFRESA® Inhalation Powder

Non-proprietary: Insulin Monomer Human Inhalation Powder

Review Number: 1

Dates of Submission(s) Covered by this Review

Letter	Stamp	Review Request	Assigned to Reviewer
16-MAR-2009	16-MAR-2009	23-MAR-2009	26-MAR-2009
22-JUL-2009 (BC)	22-JUL-2009	NA	NA

Submission History (for amendments only) – NA

Applicant/Sponsor

Name: MannKind Corporation

Address: 64 South Paramus Rd.
Paramus, N.J. 07652

Representative: Peter C. Richardson

Telephone: (201) 983-5064

Name of Reviewer: Denise A. Miller

Conclusion: Approve

Product Quality Microbiology Data Sheet

- A.**
- 1. TYPE OF SUBMISSION:** Original submission
 - 2. SUBMISSION PROVIDES FOR:** New drug
 - 3. MANUFACTURING SITE:**
MannKind Corporation
One Casper Street
Danbury, CT 06810
 - 4. DOSAGE FORM, ROUTE OF ADMINISTRATION AND STRENGTH/POTENCY:**
 - Powder in premeasured single-use cartridges
 - Inhalation with provided inhalation device
 - 15 units and 30 units/cartridge
 - 5. METHOD(S) OF STERILIZATION:** (b) (4)
 - 6. PHARMACOLOGICAL CATEGORY:** Insulin (hormone)
- B. SUPPORTING/RELATED DOCUMENTS:** NA
- C. REMARKS:**
- 1) Submission was in e-CTD format.
 - 2) A BC amendment dated 22-JUL-2009 was submitted in response to an information request for method suitability data to support the microbial limit testing.
 - 3) An e-mail communication was received from the sponsor on 16-SEP-2009 in response to second information request dated 09-SEPT-2009.

filename: 022472N000R1.doc

Executive Summary

I. Recommendations

- A. Recommendation on Approvability** – Recommend to approve from a quality microbiology standpoint.
- 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** – (b) (4) powder for inhalation.
- B. Brief Description of Microbiology Deficiencies** - None
- C. Assessment of Risk Due to Microbiology Deficiencies** - NA

III. Administrative

- A. Reviewer's Signature** _____
Denise A. Miller, Microbiologist
- B. Endorsement Block** _____
Bryan S. Riley, Ph. D.
- C. CC Block**
N/A

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Application Type/Number	Submission Type/Number	Submitter Name	Product Name
NDA-22472	ORIG-1	MANKIND CORP	INSULIN HUMAN (RDNA ORIG)INH POWDER

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/s/

DENISE A MILLER
09/22/2009

BRYAN S RILEY
09/22/2009
I concur.

PRODUCT QUALITY MICROBIOLOGY FILING CHECKLIST

NDA Number: 22-472

Applicant: MannKind

Letter Date: 16-MAR-2009

Drug Name: AFRESA

NDA Type: Standard

Stamp Date: 16-MAR-2009

The following are necessary to initiate a review of the NDA application:

	Content Parameter	Yes	No	Comments
1	Is the product quality microbiology information described in the NDA and organized in a manner to allow substantive review to begin? Is it legible, indexed, and/or paginated adequately?	√		Submission is in e-CTD format.
2	Has the applicant submitted an overall description of the manufacturing processes and microbiological controls used in the manufacture of the drug product?	√		Product is (b) (4) inhalant packaged in single dose cartridges
3	Has the applicant submitted protocols and results of validation studies concerning microbiological control processes used in the manufacture of the drug product?		√	No description of the filling environment
4	Are any study reports or published articles in a foreign language? If yes, has the translated version been included in the submission for review?		√	
5	Has the applicant submitted preservative effectiveness studies (if applicable) and container-closure integrity studies?	√		PE is NA CC is based on chemical stability
6	Has the applicant submitted microbiological specifications for the drug product and a description of the test methods?	√		Microbial limit per USP<61> and USP<62>
7	Has the applicant submitted the results of analytical method verification studies?		√	Will need suitability of <61> and <62>
8	Has the applicant submitted all special/critical studies/data requested during pre-submission meetings and/or discussions?	NA		
9	Is this NDA fileable? If not, then describe why.	√		

Additional Comments:

USP <61> and USP <62> are performed by a contract testing lab. The suitability of these methods with this product was not included in the submission.

Reviewing Microbiologist

Date

Microbiology Secondary Reviewer/Team Leader

Date

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/s/

Denise Miller
4/14/2009 11:26:21 AM
MICROBIOLOGIST

Bryan Riley
4/14/2009 03:26:49 PM
MICROBIOLOGIST
I concur.