

**CENTER FOR DRUG EVALUATION AND
RESEARCH**

APPLICATION NUMBER:

022472Orig1s000

CHEMISTRY REVIEW(S)

**FDA CDER EES
ESTABLISHMENT EVALUATION REQUEST
DETAIL REPORT**

Application: NDA 22472/000
Start Date: 16-MAR-2009
Priority: 15-JUL-2014

Action Goal:
District Goal: 14-FEB-2014

Applicant: MANNKIND
61 SOUTH PARAMUS RD
PARAMUS, NJ 07652

Brand Name: AFREZZA (INSULIN) INHALATION POWDER
Estab. Name:
Generic Name: INSULIN HUMAN (RDNA ORIG) INH POWDER

Priority: 5S
Org. Code: 510

Product Number; Dosage Form; Ingredient; Strengths
001; POWDER, FOR INHALATION; INSULIN RECOMBINANT HUMAN; 4U
002; POWDER, FOR INHALATION; INSULIN RECOMBINANT HUMAN; 8U

Application Comment:

FDA Contacts:	E. JAO	Prod Qual Reviewer	3017961684
	P. KUMAR	Product Quality PM (HFD-800)	2404023722
	S. TRAN	Team Leader	3017961764

Overall Recommendation:	ACCEPTABLE	on 02-JUL-2014	by T. SHARP	()	3017963208
	PENDING	on 13-NOV-2013	by EES_PROD		
	PENDING	on 24-OCT-2013	by EES_PROD		
	PENDING	on 23-DEC-2011	by EES_PROD		
	WITHHOLD	on 22-AUG-2011	by EES_PROD		
	ACCEPTABLE	on 11-AUG-2010	by EES_PROD		

**FDA CDER EES
ESTABLISHMENT EVALUATION REQUEST
DETAIL REPORT**

Establishment: **CFN:** (b) (4) **FEI:** (b) (4)

DMF No: (b) (4) **AADA:**

Responsibilities: DRUG SUBSTANCE MANUFACTURER
DRUG SUBSTANCE OTHER TESTER

Establishment Comment: DMF (b) (4)
(b) (4) (on 01-APR-2009 by S. TRAN () 3017961764)

Profile: BIOTECHNOLOGY DERIVED API (STERILE & NON-STERILE) **OAI Status:** NONE

<u>Milestone Name</u>	<u>Milestone Date</u>	<u>Request Type</u>	<u>Planned Completion</u>	<u>Decision</u>	<u>Creator</u>
Comment					
OAI Submit To OC					
Request to Extend Re-eval Date To					
Extension Request Comment					
Reason					
SUBMITTED TO OC	01-APR-2009				TRANS
SUBMITTED TO DO	01-APR-2009	Product Specific and GMP Inspection			STOCKM
ASSIGNED INSPECTION TO IB	06-APR-2009	Product Specific and GMP Inspection			JOHNSONE
INSPECTION SCHEDULED	(b) (4)		(b) (4)		IRIVERA
INSPECTION PERFORMED ACCEPTABLE	(b) (4)		(b) (4)		IRIVERA
INSPECTION PERFORMED see hardcopy EIR	(b) (4)		(b) (4)		DOUGLAS.KOVACS
DO RECOMMENDATION	01-JAN-2010			ACCEPTABLE	JOHNSONE
OC RECOMMENDATION	04-JAN-2010			ACCEPTABLE	INYARDA
SUBMITTED TO OC	24-OCT-2013				KUMARP
OC RECOMMENDATION	29-OCT-2013			ACCEPTABLE	WITTORFR

**FDA CDER EES
ESTABLISHMENT EVALUATION REQUEST
DETAIL REPORT**

Establishment: **CFN:** (b) (4) **FEI:** (b) (4)
 (b) (4)

DMF No: (b) (4) **AADA:**

Responsibilities: DRUG SUBSTANCE RELEASE TESTER

Establishment Comment: ADDITIONAL TEST LAB SUBMITTED ON 13-AUG-2009 TO NDA.
 TESTING: BIOIDENTITY (on 13-AUG-2009 by S. TRAN () 3017961764)

Profile: CONTROL TESTING LABORATORY **OAI Status:** NONE

<u>Milestone Name</u>	<u>Milestone Date</u>	<u>Request Type</u>	<u>Planned Completion</u>	<u>Decision</u>	<u>Creator</u>
Comment					
OAI Submit To OC					
Request to Extend Re-eval Date To					
Extension Request Comment					
Reason					

SUBMITTED TO OC	14-AUG-2009				TRANS
SUBMITTED TO DO	17-AUG-2009	10-Day Letter			STOCKM
DO RECOMMENDATION	27-AUG-2009			ACCEPTABLE	JOHNSONE
OC RECOMMENDATION	27-AUG-2009			ACCEPTABLE	STOCKM
SUBMITTED TO OC	24-OCT-2013				KUMARP
OC RECOMMENDATION	29-OCT-2013			ACCEPTABLE	WITTORFR

**FDA CDER EES
ESTABLISHMENT EVALUATION REQUEST
DETAIL REPORT**

Establishment: **CFN:** (b) (4) **FEI:** (b) (4)
 (b) (4)

DMF No: (b) (4) **AADA:**

Responsibilities: DRUG SUBSTANCE MANUFACTURER
 DRUG SUBSTANCE RELEASE TESTER

Establishment Comment: DMF (b) (4)
 (b) (4) (on 01-APR-2009 by S. TRAN () 3017961764)

Profile: BIOTECHNOLOGY DERIVED API (STERILE & NON-STERILE) **OAI Status:** NONE

<u>Milestone Name</u>	<u>Milestone Date</u>	<u>Request Type</u>	<u>Planned Completion</u>	<u>Decision</u>	<u>Creator</u>
Comment					
OAI Submit To OC					
Request to Extend Re-eval Date To					
Extension Request Comment					
Reason					
SUBMITTED TO OC	01-APR-2009				TRANS
SUBMITTED TO DO	01-APR-2009	GMP Inspection			STOCKM
DO RECOMMENDATION	06-APR-2009			ACCEPTABLE	JOHNSONE
COMMENDATION	06-APR-2009			ACCEPTABLE	STOCKM
SUBMITTED TO OC	24-OCT-2013				KUMARP
SUBMITTED TO DO AC 28-JUN-2006 FOR CBI	29-OCT-2013	GMP Inspection			WITTORFR
ASSIGNED INSPECTION TO IB LAST CBI INSPECTION IN 2006	07-NOV-2013	GMP Inspection			MROSE
INSPECTION SCHEDULED	(b) (4)		(b) (4)		BSEEMAN
DO RECOMMENDATION AS PER A. MOZZACHIO, BC. SEE CMS FOR MORE INFO.	03-APR-2014			ACCEPTABLE	PHILPYE
OC RECOMMENDATION	03-APR-2014			ACCEPTABLE	SAFAAIJAZIR

This is a representation of an electronic record that was signed electronically and this page is the manifestation of the electronic signature.

/s/

MARY GRACE LUBAO
07/11/2014

NDA 22-472

Afrezza (insulin, human [rDNA]) Inhalation Powder

MannKind Corporation

Chemistry Review #4

July 2, 2014

Recommendation: Approval

Edwin Jao, Ph.D.

ONDQA/Division III/Branch VIII

for

Division of Metabolism and Endocrine Drug Products

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Chemistry Review Data Sheet

1. NDA 22-472
2. REVIEW #4
3. REVIEW DATE: July 2, 2014
4. REVIEWER: Edwin Jao, Ph.D.
5. Related DOCUMENTS:

<u>Previous Documents</u>	<u>Document Date</u>
Original NDA	16-03-2009
Amendment	11-06-2009
Amendment	22-07-2009
Amendment	14-08-2009
Amendment	11-09-2009
Amendment	29-09-2009
Amendment	12-10-2009
Amendment	30-10-2009
Advice/Information Request	13-11-2009
Amendment	30-11-2009
2 Amendment	04-12-2009
Chemistry Review by Dr. Alan Schroeder	09-12-2009
Chemistry Review by Dr. Alan Schroeder	17-12-2009
Quality/Response To Information Request	19-02-2010
Meeting/Meeting Package	12-05-2010
Resubmission	6-28-2010
Meeting Preliminary Comments	08-06-2010
Amendment	08-27-2010
Amendment	09-15-2010
Amendment	09-23-2010
Amendment	11-4-2010
Amendment	11-15-2010
Amendment	11-24-2010
Resubmission	10-15-2013

6. SUBMISSION(S) BEING REVIEWED:

Submission(s) Reviewed

Resubmission NDA dated October 15, 2013

7. NAME & ADDRESS OF APPLICANT:

Name:	MannKind Corporation
Address:	61 South Paramus Road Paramus, NJ 07652
Representative:	John Bedard. Senior Vice President, Regulatory Affairs
Telephone:	201-983-5143

8. DRUG PRODUCT NAME/CODE/TYPE:

- a) Proprietary Name: Afrezza
- b) Non-Proprietary Name (USAN): insulin, human [rDNA] Inhalation Powder
- c) Code Name/# none provided
- d) Chem. Type/Submission Priority:
 - Chem. Type: 5 (new manufacturer)
 - Submission Priority: S

9. LEGAL BASIS FOR SUBMISSION: 505(b)(1)

10. PHARMACOL. CATEGORY: Anti-diabetic

11. DOSAGE FORM: Inhalation powder (pre-metered DPI)

12. STRENGTH/POTENCY:

20U cartridge (0.70 mg of insulin) provides (b) (4) mg of insulin emitted dose (target)

10U cartridge (0.35 mg of insulin) provides (b) (4) mg of insulin emitted dose (target)

[Note that the target insulin load is 3.0U/mg of the drug formulation.]

13. ROUTE OF ADMINISTRATION: oral inhalation

14. Rx/OTC DISPENSED: Rx OTC

15. SPOTS (SPECIAL PRODUCTS ON-LINE TRACKING SYSTEM):

SPOTS product – (See Dr. Carver’s review)

Not a SPOTS product

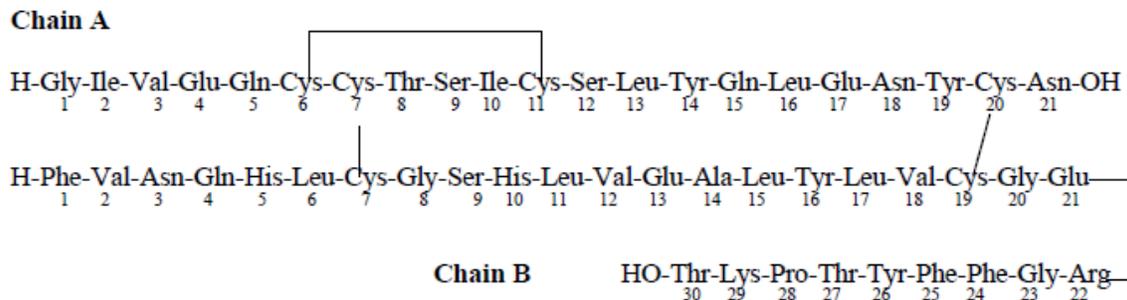
16. CHEMICAL NAME, STRUCTURAL FORMULA, MOLECULAR FORMULA, MOLECULAR WEIGHT:

3.2.S.1.1 Nomenclature (Insulin Human, (b) (4))

Recommended International Nonproprietary Name (rINN):	rec human insulin
Pharmacopoeia name(s) Ph. Eur. USP	insulin, human insulin human, recombinant
Other non-proprietary name(s): US Adopted Name (USAN) British Approved Name (BAN)	insulin human Human Insulin
CAS Registry Number	11061-68-0

Insulin consists of two polypeptide chains, A and B. The A chain has 21 amino acids and the B chain has 30 amino acids. The chains are lined together through the sulfur atoms of cysteine (Cys).

Structural formula of recombinant human insulin:



The molecular formula of Insulin Human is $C_{257}H_{383}N_{65}O_{77}S_6$

The molecular weight of Insulin Human is 5808.

17. RELATED/SUPPORTING DOCUMENTS:

A. DMFs:

[Note that the status of DMF (b)(4) for insulin is included in Dr. Ted Carver's separate review of this NDA]

DMF #	TYP E	HOLDER	ITEM REFERENCED	CODE ¹	STATUS ²	DATE REVIEW COMPLETED	COMMENT S
(b)(4)	III	(b)(4)	(b)(4)	1	Adequate	Edwin Jao 3/18/2014	(b)(4)
	III		1	adequate	Edwin Jao 3/18/2014		
	III		1	adequate	Edwin Jao 3/18/2014		
	III		4				
	III		1		Adequate	Edwin Jao 3/18/2014	

(b) (4)		(b) (4)				(b) (4)
	III		1	Adequate	Edwin Jao 3/18/2014	
	III		1	Adequate	Edwin Jao 3/18/2014	

¹ Action codes for DMF Table:

1 – DMF Reviewed.

Other codes indicate why the DMF was not reviewed, as follows:

2 –Type 1 DMF

3 – Reviewed previously and no revision since last review

4 – Sufficient information in application

5 – Authority to reference not granted

6 – DMF not available

7 – Other (explain under "Comments")

² Adequate, Inadequate, or N/A (There is enough data in the application, therefore the DMF did not need to be reviewed)

B. Other Documents:

DOCUMENT	APPLICATION NUMBER	DESCRIPTION
IND	61729	associated IND for this drug product

18. STATUS:

ONDQA:

CONSULTS/ CMC RELATED REVIEWS	RECOMMENDATION	DATE	REVIEWER
Biometrics	not considered necessary for performance stability data in this application		SAHLROOT, JON T.
EES	acceptable	7/2/2014	
Pharm/Tox	Approve	3/5/2014	Dr. TSAI-TURTON, MIYUN M.
Clinpharm			
LNC	N.A.		
Methods Validation	Not submitted		
EA	Approve	12/18/2009	<i>Dr. Raanan Bloom</i>
Microbiology	Approve	9/22/2009	Dr. Denise A. Miller
BioPharm			
Drug substance			MUTHUKUMAR RAMASWAMY
CDRH			Dr. Melanie Choe

The Chemistry Review for NDA 22-472

This NDA received an “Acceptable” recommendation from the office of compliance on 7/2/2014. The following is the copy of the summary report. There are no any pending issues for this submission, and it is recommended for approval from the CMC perspective.

FDA CDER EES ESTABLISHMENT EVALUATION REQUEST DETAIL REPORT

Application:	NDA 22472/000	Action Goal:	
Stamp Date:	16-MAR-2009	District Goal:	14-FEB-2014
Regulatory:	15-JUL-2014		
Applicant:	MANNKIND 61 SOUTH PARAMUS RD PARAMUS, NJ 07652	Brand Name:	AFREZZA (INSULIN) INHALATION POWDER
		Estab. Name:	
		Generic Name:	INSULIN HUMAN (RDNA ORIG) INH POWDER
Priority:	5S	Product Number; Dosage Form; Ingredient; Strengths	
Org. Code:	510		001; POWDER, FOR INHALATION; INSULIN RECOMBINANT HUMAN; 4U 002; POWDER, FOR INHALATION; INSULIN RECOMBINANT HUMAN; 8U
Application Comment:			
FDA Contacts:	E. JAO P. KUMAR S. TRAN	Prod Qual Reviewer Product Quality PM Team Leader	3017961684 2404023722 3017961764
Overall Recommendation:	ACCEPTABLE PENDING PENDING PENDING WITHHOLD ACCEPTABLE	on 02-JUL-2014 on 13-NOV-2013 on 24-OCT-2013 on 23-DEC-2011 on 22-AUG-2011 on 11-AUG-2010	by T. SHARP by EES_PROD by EES_PROD by EES_PROD by EES_PROD by EES_PROD
			() 3017963208

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/s/

EDWIN JAO
07/02/2014

NDA 22-472

Afrezza (insulin, human [rDNA]) Inhalation Powder

MannKind Corporation

Chemistry Review #3

March 14, 2014

Recommendation: Approval

Edwin Jao, Ph.D.

ONDQA/Division III/Branch VIII

for

Division of Metabolism and Endocrine Drug Products

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A. Reviewer’s Signature	13
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C. CC Block.....	14
Chemistry Assessment	15
I. Review Of Common Technical Document-Quality (Ctd-Q) Module 3.2: Body Of Data.....	15

Chemistry Review Data Sheet

1. NDA 22-472
2. REVIEW #:2
3. REVIEW DATE: December 9, 2010
4. REVIEWER: Edwin Jao, Ph.D.
5. Related DOCUMENTS:

<u>Previous Documents</u>	<u>Document Date</u>
Original NDA	16-03-2009
Amendment	11-06-2009
Amendment	22-07-2009
Amendment	14-08-2009
Amendment	11-09-2009
Amendment	29-09-2009
Amendment	12-10-2009
Amendment	30-10-2009
Advice/Information Request	13-11-2009
Amendment	30-11-2009
2 Amendment	04-12-2009
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Resubmission	6-28-2010
Meeting Preliminary Comments	08-06-2010
Amendment	08-27-2010
Amendment	09-15-2010
Amendment	09-23-2010
Amendment	11-4-2010
Amendment	11-15-2010
Amendment	11-24-2010
Resubmission	10-15-2013

6. SUBMISSION(S) BEING REVIEWED:

Submission(s) Reviewed

Resubmission NDA dated October 15, 2013

7. NAME & ADDRESS OF APPLICANT:

Name:	MannKind Corporation
Address:	61 South Paramus Road Paramus, NJ 07652
Representative:	John Bedard. Senior Vice President, Regulatory Affairs
Telephone:	201-983-5143

8. DRUG PRODUCT NAME/CODE/TYPE:

- a) Proprietary Name: Afrezza
- b) Non-Proprietary Name (USAN): insulin, human [rDNA] Inhalation Powder
- c) Code Name/# none provided
- d) Chem. Type/Submission Priority:
 - Chem. Type: 5 (new manufacturer)
 - Submission Priority: S

9. LEGAL BASIS FOR SUBMISSION: 505(b)(1)

10. PHARMACOL. CATEGORY: Anti-diabetic

11. DOSAGE FORM: Inhalation powder (pre-metered DPI)

12. STRENGTH/POTENCY:

20U cartridge (0.70 mg of insulin) provides (b) (4) mg of insulin emitted dose (target)

10U cartridge (0.35 mg of insulin) provides (b) (4) mg of insulin emitted dose (target)

[Note that the target insulin load is 3.0U/mg of the drug formulation.]

13. ROUTE OF ADMINISTRATION: oral inhalation

14. Rx/OTC DISPENSED: Rx OTC

15. SPOTS (SPECIAL PRODUCTS ON-LINE TRACKING SYSTEM):

SPOTS product – (See Dr. Carver’s review)

Not a SPOTS product

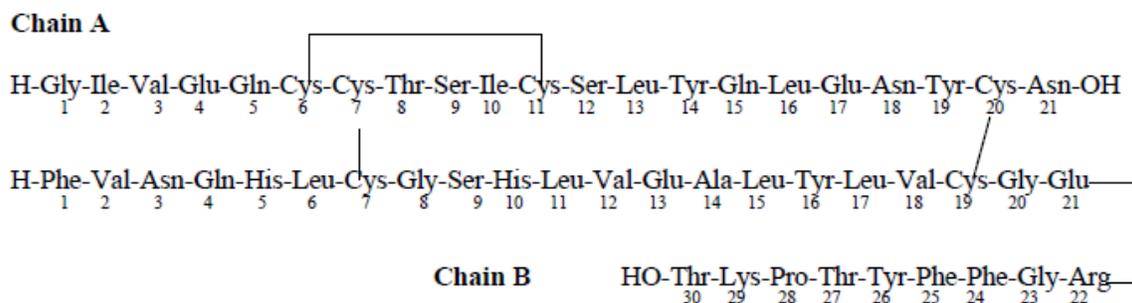
16. CHEMICAL NAME, STRUCTURAL FORMULA, MOLECULAR FORMULA, MOLECULAR WEIGHT:

3.2.S.1.1 Nomenclature (Insulin Human, (b) (4))

Recommended International Nonproprietary Name (rINN):	rec human insulin
Pharmacopoeia name(s) Ph. Eur. USP	insulin, human insulin human, recombinant
Other non-proprietary name(s): US Adopted Name (USAN) British Approved Name (BAN)	insulin human Human Insulin
CAS Registry Number	11061-68-0

Insulin consists of two polypeptide chains, A and B. The A chain has 21 amino acids and the B chain has 30 amino acids. The chains are lined together through the sulfur atoms of cysteine (Cys).

Structural formula of recombinant human insulin:



The molecular formula of Insulin Human is $C_{257}H_{383}N_{65}O_{77}S_6$

The molecular weight of Insulin Human is 5808.

17. RELATED/SUPPORTING DOCUMENTS:

A. DMFs:

[Note that the status of DMF (b)(4) for insulin is included in Dr. Ted Carver's separate review of this NDA]

DMF #	TYP E	HOLDER	ITEM REFERENCED	CODE ¹	STATUS ²	DATE REVIEW COMPLETED	COMMENT S
(b)(4)	III	(b)(4)	(b)(4)	1	Adequate	Edwin Jao 3/18/2014	(b)(4)
	III		1	adequate	Edwin Jao 3/18/2014		
	III		1	adequate	Edwin Jao 3/18/2014		
	III		4				
	III		1	Adequate	Edwin Jao 3/18/2014		

		(b) (4)				(b) (4)
(b) (4)	III		1	Adequate	Edwin Jao 3/18/2014	
	III		1	Adequate	Edwin Jao 3/18/2014	

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1 – DMF Reviewed.

Other codes indicate why the DMF was not reviewed, as follows:

2 –Type 1 DMF

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4 – Sufficient information in application

5 – Authority to reference not granted

6 – DMF not available

7 – Other (explain under "Comments")

² Adequate, Inadequate, or N/A (There is enough data in the application, therefore the DMF did not need to be reviewed)

B. Other Documents:

DOCUMENT	APPLICATION NUMBER	DESCRIPTION
IND	61729	associated IND for this drug product

18. STATUS:

ONDQA:

CONSULTS/ CMC RELATED REVIEWS	RECOMMENDATION	DATE	REVIEWER
Biometrics	not considered necessary for performance stability data in this application		SAHLROOT, JON T.
EES	pending		
Pharm/Tox	Approve	3/5/2014	Dr. TSAI-TURTON, MIYUN M.
Clinpharm			
LNC	N.A.		
Methods Validation	Not submitted		
EA	Approve	12/18/2009	<i>Dr. Raanan Bloom</i>
Microbiology	Approve	9/22/2009	Dr. Denise A. Miller
BioPharm			
Drug substance			MUTHUKUMAR RAMASWAMY
CDRH			Dr. Melanie Choe

Executive Summary Section

The Chemistry Review for NDA 22-472**The Executive Summary**

This is a CMC team review. This review pertains to limited parts of the NDA, i.e., the drug product except for biopharm and microbiology aspects of the submission, which are deferred to the corresponding reviewers. The drug substance is reviewed by Dr. MUTHUKUMAR RAMASWAMY. The device is also currently being separately evaluated by the CDRH reviewer.

This is a resubmission in response to the Complete Response action taken by the Agency on the previous submission. Four CMC related comments were incorporated in the CR letter dated 1/18/2011.

The current review is focused on the response to the four CMC comments and those sections containing new information (e.g., changes or new data). See review1 and 2 for background and more information.

I. Recommendations**A. Recommendation and Conclusion on Approvability**

This conclusion is with reference to the sections of the NDA reviewed in this review only. This application is **recommended for approval**, pending on acceptable recommendation from the Office of Compliance.

B. Recommendation on Phase 4 (Post-Marketing) Commitments, Agreements, and/or Risk Management Steps, if Approvable

NA

II. Summary of Chemistry Assessments**A. Description of the Drug Product(s) and Drug Substance(s)**

The drug substance is human insulin (recombinant). Its manufacturing and controls information are provided in DMF (b) (4). This is separately reviewed by Dr. MUTHUKUMAR RAMASWAMY.

The (b) (4) formulation is manufactured from Insulin Human USP, recombinant, and the following excipients and manufacturing aids: fumaryl diketopiperazine (FDKP), Polysorbate 80 NF, (b) (4). The to-be marketed Technosphere® Insulin Inhalation Powder / Gen2 Inhalation System includes single-use, color coded, pre-metered Cartridges that are manually placed into a re-useable, breath-powered, high resistance dry powder inhaler. The pre-metered cartridges contain either 3.3 mg or 6.7 mg of the same

Executive Summary Section

Technosphere® Insulin Inhalation defined in the original application, providing either 10 U (0.35 mg) or 20 U (0.7 mg) of insulin. The applicant state that the net insulin content of 10 U and 20 U are equivalent to 3 U and 6 U of injection insulin in-vivo. Each single-use Cartridge requires a single inhalation for powder delivery. (b) (4)

The secondary packaging consists of blister cards and foil overwrap, provides environmental protection and pertinent labeling information. The emitted dose targets are as follows: (b) (4)

B. Description of How the Drug Product is Intended to be Used

Users are required to remove a single cartridge from the secondary package and manually place it into the inhaler in the Load Position. Next, users close the inhaler and inhale deeply one time to administer the powder. Upon completion of the inhalation maneuver, users open the device; remove the spent Cartridge for disposal. If an additional Cartridge is required, users insert a new cartridge and repeat the use steps. The inhaler is intended for a 15 day in-use period without cleaning.

C. Basis for Approvability or Not-Approval Recommendation

The followings are the 4 CMC related comments listed in the CR letter (with the original numbering).

4. *Conduct a study of the emitted dose and aerodynamic particle size distribution attributes of the Gen2 10 unit dosage strength cartridges under the following conditions of use: low temperature and low humidity. The purpose of this study is to evaluate whether the performance characteristics of the 10 unit dosage strength cartridges are affected by static on the contact surfaces of the inhaler under these temperature and humidity conditions.*
5. *Conduct a study evaluating the impact of potential issues during shipment, such as settlement or leakage, on the emitted dose and aerodynamic particle size distribution attributes of the Gen2 10 unit dosage strength cartridges.*
6. *Conduct a study of Gen2 inhalers evaluating emitted dose and aerodynamic particle size distribution attributes under misuse scenarios (e.g., dropping, shaking).*
7. *Conduct a study of the insulin adduct impurities and insulin-related degradants in support of the limits on these compounds as proposed in the November 24, 2010 amendment to the NDA. Submit adequate supporting data, including a validated method for monitoring insulin-FDKP adducts on stability.*

In this submission the applicant has provided data to fully address these issues.

1. *Both emitted dose and APSD do not seem to be affected by discharging at environmental extremes.*

Executive Summary Section

2. For the 10 U cartridge the differences between the emitted dose and APSD of the shipped and unshipped samples were insignificant. Similar study was conducted for 20 U cartridges in the previous submission, and the result was satisfactorily.
3. Dropping the inhaler from, or shaking the inhalers in, vertical orientations demonstrated reductions in the 10 U and 20 U emitted dose and fine particle fraction of APSD. For emitted dose, some individual data are below (b) (4) % of the target (b) (4) for 10 U cartridges and (b) (4) for 20 U cartridges). For APSD reduction of the particles collected (b) (4) by as much as (b) (4) % below the lower limit of the acceptance criteria for this group is observed. These observations were conveyed to the clinical team. They considered it is acceptable to address the issues through labeling. From CMC perspective, since the observed out of specification results were not derived from normal use, but rather, from misuse conditions, the potential risk of safety and efficacy implication is relatively low, and can be adequately mitigated through proper labeling.
4. Insulin is known to contain many structurally similar impurities with modifications at various parts of the molecule (see USP monograph for insulin). (b) (4) are not expected to behave significantly from other related substances. (b) (4) Updated stability data indicate that the highest level for (b) (4) among 6 registration batches is below (b) (4) %. Many other identified and unidentified insulin related impurities are not individually controlled, for example, impurity (b) (4). All insulin related substances are controlled as a sum with the acceptance criterion of NMT (b) (4) %, except for individual unknown of NMT (b) (4) % and A-21 desamido insulin of NMT (b) (4) %. The non-clinical reviewer Dr. MIYUN M TSAI-TURTON indicated in his review that based on this 28 day toxicity rat study, insulin impurities and degradation products in the Technosphere Insulin Inhalation Powder were qualified and had 1 to 3 fold safety margins at the proposed acceptance criteria, including total other impurities with (b) (4). Based on this, the applicant's proposal of control insulin related impurity (b) (4) through total impurity is acceptable.

Some changes are made and some new data are provided in this resubmission.

1. Several pilot scaled batches of drug product were manufactured for the new clinical trials conducted per the Agency's request. All these batches met the proposed specification. Among 5,000 devices recovered from the clinical trials it appears that only one device has a defect. Since there are two inhalers packaged in all product configurations, this rate of defect is not expected to have serious safety and efficacy issues and is acceptable. The drug product is considered robust and suitable for commercial use.
2. Among some changes in the manufacturing process, it is worth to mention that the (b) (4). This is considered a significant improvement. In addition to the currently used statistical sampling methodologies that

Executive Summary Section

monitor cartridge fill-weight (weighing selected samples), the applicant added an alternative method- Advanced Mass Verification (AMV) technology which performs non-destructive fill weight verification online for every individual filled cartridge, provides real-time trending of fill weight, and rejects cartridges on-line that do not meet the acceptance criteria is also considered an improvement in quality control.

3. The applicant proposed to revise the drug product specification. Specifically, the acceptance criteria for assay at release from is relaxed from (b) (4) % to (b) (4) % for both strengths. The revision is supported by data. Since the acceptance criteria for assay during shelf life remain the same (b) (4) %, the proposed minor change is not expected to compromise the quality, safety, and efficacy of the drug product. The acceptance criteria for impurities/degradants are also relaxed. The proposed acceptance criteria for A-21 desamido insulin, high molecular weight protein (HMWP), and total other insulin related impurities are supported by stability data. These impurities increased significantly during (b) (4). The pharmtox group concurred with the applicant's safety assessment for the proposed new acceptance criteria, and considered these criteria acceptable.
4. The only major changes in the container/closure system are that the product identifier "3 unit" and "6 unit" are now molded on the corresponding 10 U and 20 U cartridge lids. These 3 units and 6 units refer to the "in-vivo" equivalent to the injection insulin. Whether these equivalents are valid will be discussed at the AC meeting, and eventually decided by the clinical team. Once it is decided that the numbers have to be changed or removed, a CMC amendment will be submitted and evaluated.
5. Thirty six months of stability data from the original 6 registration batches of the drug product are provided. The proposed expiry dating of 24 months stored at (b) (4) C including 10 days in-use period at 25°C is supported by full shelf data and granted.
6. No significant deviations in mechanical functionality and drug product performance in terms of emitted dose and APSD are observed for aged and in-use inhalers. The proposed shelf life of 48 months and in-use period of 15 days, both at (b) (4) oC, for the inhalers are supported by data and granted.

In conclusion, all critical issues are considered resolved satisfactorily. Adequate controls and risk management are in place to provide assurance for the quality and purity of the drug product for its intended use.

The following comments pertinent to labeling and labels should be conveyed to the review team.

The following comments are pertinent to the labeling

1.

(b) (4)

(b) (4) Whether the in-vivo

Executive Summary Section

equivalent numbers are valid and how to designate the strength of this product will be decided by clinical team and DMEPA. Once decided, the pertinent sections of the labeling (e.g., Highlights, section 3, 11, and 16) and all container labels should be revised accordingly.

2. [REDACTED] (b) (4)
3. *Revise the content number 60 counts and 90 counts on the carton labels for the 10 U cartridges such that these two numbers are more prominent and distinguishable from each other.*

The following comments are pertinent to the container labels.

1. [REDACTED] (b) (4) *should be removed from all labels and labeling, since they are not necessary and distractive.*
2. *The net content of in the cartons refers to the number of cartridges. The strength refers to the units of insulin per cartridge.*
3. *Provide a list of inactive ingredients on the carton labels as per 21CFR 201.10(a).*
4. [REDACTED] (b) (4)
5. *Revise the content number 60 counts and 90 counts on the carton labels for the 10 U cartridges such that these two numbers are more prominent and distinguishable from each other.*
6. *Revise the content number “ [REDACTED] (b) (4) and “ [REDACTED] (b) (4) on the 90 counts carton labels such that these two sets of numbers are more prominent and distinguishable from each other.*

III. Administrative

A. Reviewer's Signature

Edwin Jao, Ph.D.

B. Endorsement Block

Prasad Peri, Ph.D.

C. CC Block

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/s/

EDWIN JAO
03/20/2014

PRASAD PERI
03/20/2014
I concur

TO: NDA 22472
THROUGH: Prasad Peri, Ph.D., Branch Chief, Division III, Office New Drug Quality Assessment
FROM: Ramaswamy, Muthukumar, Division III, Office New Drug Quality Assessment
Subject: CMC review for Drug Substance (Insulin Human recombinant, USP) - NDA 22472 Resubmission
DATE: January 14, 2014
CC: Danae Christodoulou, Ph.D.; Edwin Jao, Ph.D. Division III, Office New Drug Quality Assessment

Summary of updated CMC information for drug substance (Section 2.3.S.2):

The NDA resubmission contains updated CMC information on a testing site (name change) and revision to drug substance specification (i.e., commits to performing microbial examination (USP <61>), zinc content (NMT 1.0%, USP<591>) and high molecular weight proteins tests instead of relying on vendor CoA). From CMC reviewer perspective, the proposed are acceptable.

- The microbiology and physicochemical testing of the drug substance will be performed at (b) (4) facility located at (b) (4). This facility has been included in the EER and received acceptable OC recommendation (overall on 13-Nov. 2013).
- Per revised specification, the Applicant will test the drug substance for appearance, identification (FTIR and HPLC), assay (NLT 27.5U/mg), loss on drying (NMT 10.0%, USP<731>), purity (NLT 96.0%), related compounds (A21 Desamido insulin: NMT 2.0%; Total others: NMT 2.0%), *microbial examination (USP <61>), zinc content (NMT 1.0%, USP<591>) and high molecular weight proteins* (NMT 1.0%, USP insulin monograph), which is acceptable. A copy of the revised specification is reproduced below from the NDA (Section 2.3.S.4.1).
- The Applicant plans to accept the test results provided in vendor's CoA for the following attributes: Residual solvents, bacterial endotoxin, identification (peptide mapping), bioidentity, and host cell proteins.
- Based on available stability data, the DMF holder has proposed a shelf life of (b) (4) for the drug substance. The Applicant will accept stability data from DMF holder and will not be performing further stability tests on the drug substance.

Table 1. Specifications Insulin Human Recombinant

Attribute	Method or Source	Acceptance Criteria
Appearance (Visual)	TM5520	White to practically white powder or crystals
Identification (FTIR)	TM5437	Corresponds to standard
Identification (HPLC)	USP Insulin Human Monograph	Major peak of sample corresponds to standard retention time
Insulin Assay (HPLC, Dry Basis)	USP Insulin Human Monograph	NLT 27.5 U/mg
Loss on Drying	USP <731>	NMT 10.0%
Insulin Purity (HPLC)	USP Insulin Human Monograph (Related Compounds Test)	NLT 96.0% (area %)

Attribute	Method or Source	Acceptance Criteria
Related Compounds (HPLC) -A21 Desamido Insulin -Total Others	USP Insulin Human Monograph	A21 Desamido Insulin NMT 2.0% Total Others NMT 2.0%
Residual Solvents (b) (4)	Vendor COA	NMT (b) (4)
Bioidentity	Vendor COA	Meets requirement
Microbial examination	USP <61> (MM50031)	Total bacterial count NMT 300 CFU/g
Bacterial Endotoxins (LAL)	Vendor COA	NMT (b) (4)
Identification (Peptide Mapping)	Vendor COA	Corresponds to Standard
Zinc Content (Dry Basis)	USP <591>	NMT 1.0%
High Molecular Weight Proteins (SEC)	USP Insulin Human Monograph	NMT 1.0%
Host Cell Proteins (EIA)	Vendor COA	NMT (b) (4)

NMT = Not More Than
 NLT = Not Less Than

This is a representation of an electronic record that was signed electronically and this page is the manifestation of the electronic signature.

/s/

MUTHUKUMAR RAMASWAMY
01/14/2014

DANAE D CHRISTODOULOU
01/14/2014

PRASAD PERI
01/15/2014
I concur

MEMORANDUM

DEPARTMENT OF HEALTH AND HUMAN SERVICES
PUBLIC HEALTH SERVICE
FOOD AND DRUG ADMINISTRATION
CENTER FOR DRUG EVALUATION AND RESEARCH

DATE: January 6, 2012
FROM: Edwin Jao, Ph.D., Review Chemist, Branch VIII, ONDQA III/ONDQA
THROUGH: Prasad Peri, Ph.D., Branch Chief, Branch VIII, ONDQA III /ONDQA
SUBJECT: Review of the meeting package submitted on 11/18/2011
TO: NDA 22472 (AFREZZA (insulin human [rDNA] Inhalation Powder) and Inhaler)

NDA 22472 (AFREZZA (insulin human [rDNA] Inhalation Powder) and Inhaler) was issued a complete response letter on 1/8/2011. The applicant submitted a type C meeting package on 11/18/2011 seeking the Agency's feedbacks on questions pertinent to the comments listed in the complete response letter. This review will evaluate the applicant's questions/responses/proposals to the CMC related comments. Any questions/responses/proposals related to Human Factors Usability study (Comments 10, 11, 12, 13, and 16) will be deferred to CDRH. Toxicology study result for (part of the response to comment 7) will be deferred to pharmtox.

The followings are point-by-point listing of the Agency's comments, followed by the response, and evaluation.

Comment 4

Conduct a study of the emitted dose and aerodynamic particle size distribution attributes of the Gen2 10 unit dosage strength cartridges under the following conditions of use: low temperature and low humidity. The purpose of this study is to evaluate whether the performance characteristics of the 10 unit dosage strength cartridges are affected by static on the contact surfaces of the inhaler under these temperature and humidity conditions.

Response

As requested a condition of use study at low temperature and low humidity was conducted with the Gen2 10 U cartridge strength. In this study, Emitted Dose (ED) and Aerodynamic Particle Size Distribution (APSD) were evaluated consistent with the methodology presented in the NDA resubmission, sequence number 0045, 3.2.P.2.4.5.3 Environmental Study (Technosphere □ Insulin Inhalation Powder) for the Gen2 20 U cartridge strength.

As with the 20 U cartridge strength, effects from environmental in-use conditions were not observed in the 10 U cartridge strength testing. The ED target value of (b) (4) and the

APSD target range (b) (4) were unaffected by the low temperature and low humidity condition. The ED and APSD results are provided in Table 1 and Table 2, respectively.

Table 1. ED Test Results (U)

Environment	5°C / 25%RH
Inhaler	ED (U) [10 U cartridge]
1	(b) (4)
2	
3	
4	
5	
6	
AVG	
STD	
MAX	
MIN	
Conducted with six (6) inhalers each tested with three 10 U cartridges	

Table 2. APSD Test Results (U/cartridge)

Condition	5°C, 25%RH ^a			Control ^b	
	AVG	MAX	MIN	AVG	STD
(b) (4)	(b) (4)	(b) (4)	(b) (4)	(b) (4)	(b) (4)
Delivered Dose (U)	(b) (4)	(b) (4)	(b) (4)	(b) (4)	(b) (4)
APSD (U) (3 – MOC)					
^a three inhalers each tested with three 10 U cartridges					
^b six inhalers each tested with three 10 U cartridges					

MannKind believes this study satisfies the Agency’s request. Does the Agency agree?

Evaluation:

Data appears to demonstrate that the delivered dose and APSD of 10 U cartridge strength (worst case scenario) are not adversely affected by the low temperature and low

humidity in-use condition, and are comparable to the test results of 20 U cartridges. The emitted dose and APSD results from both 10 U and 20 U inhalers are comparable to the batch data submitted in the resubmission dated 6/29/2010. This issue is considered adequately addressed.

Comment 5

Conduct a study evaluating the impact of potential issues during shipment, such as settlement or leakage, on the emitted dose and aerodynamic particle size distribution attributes of the Gen2 10 unit dosage strength cartridges.

Response

As requested, a study evaluating the impact of shipping has been conducted with the Gen2 10 U cartridge strength. The study design was consistent with the study conducted with the Gen2 20 U cartridge strength presented in the NDA resubmission, sequence number 0045, 3.2.P.2.4.6.2.1 Suitability for Use (Technosphere Insulin Inhalation Powder). Cartridge emptying and Aerodynamic Particle Size Distribution (APSD) were evaluated consistent with the methodology used for the 20 U cartridge study. As requested, the Emitted Dose (ED) analysis was also conducted. Unshipped samples were used as a control. As with the 20 unit cartridge strength, cartridge emptying, emitted dose, and APSD were unaffected following ISTA ship testing in the 10 unit cartridge strength. The difference between the shipped and unshipped samples was insignificant for all parameters tested. (Table 3, Table 4, and Table 5).

Table 3. Summary of 10 U Cartridge Emptying Results of Shipped and Unshipped Samples

	Shipped	Unshipped
Mean	97.3%	97.9%
Maximum	98.3%	98.5%
Minimum	96.3%	96.7%
%RSD	0.7%	0.6%

Table 4. Summary of 10 U Emitted Dose Results of Shipped and Unshipped Samples

	Shipped (U)	Unshipped (U)
Mean		(b) (4)
Maximum		
Minimum		
%RSD		

Table 5. Summary of 10 U Fine Particle Dose Results of Shipped and Unshipped Samples

	Shipped (U/cartridge)	Unshipped (U/cartridge)
Mean		(b) (4)
Maximum		
Minimum		
%RSD		

MannKind believes this study satisfies the Agency’s request. Does the Agency agree?

Evaluation:

In the resubmission dated 6/29/2010 the applicant reported the ship test results of 20 U filled cartridges. The carton evaluated contained a total of 9 overwraps each containing thirty 20 U filled cartridges, or 270 cartridges total, simulating a one month supply of Technosphere Insulin Inhalation Powder. Simulated shipping conditions were achieved by means of laboratory testing, conducted according to International Safe Transit Association (ISTA) protocol 1A. Protocol 1A represents a stress scenario consisting of fixed displacement vibration & shock testing. Technosphere Insulin taken from the same batch and not shipped was used as control samples.

Data appears to demonstrate that the emptying results, delivered dose and APSD of 10 U cartridge strength are not adversely affected under the simulated shipping conditions, and are comparable to the results of 20 U cartridges. The emitted dose and APSD results from both 10 U and 20 U inhalers are comparable to the batch data submitted in the resubmission dated 6/29/2010. This issue is considered adequately addressed.

Comment 6

Conduct a study of Gen2 inhalers evaluating emitted dose and aerodynamic particle size distribution attributes under misuse scenarios (e.g., dropping, shaking).

Response

A misuse study evaluating Emitted Dose (ED) and Aerodynamic Particle Size Distribution (APSD) was conducted with both the Gen2 10 U and 20 U cartridge strengths. Gen2 inhalers containing cartridges were dropped and shaken to mimic potential mis-use conditions.

All ED testing was conducted after 10 different inhalers each containing either a 10 U or 20 U cartridge were subjected to a single misuse condition once. APSD testing was conducted using the Next Generation Impactor (NGI) and similarly, were performed after

the inhalers were subjected to a single misuse condition once. Three APSD determinations were conducted at each misuse condition. Three separate inhalers each containing a cartridge were utilized for each 10 U NGI determination and two separate inhalers each containing a cartridge were utilized for each 20 U NGI determination.

During the drop testing, Gen2 inhalers loaded with either 10 U or 20 U cartridges were dropped from a horizontal orientation from a height of one meter onto a standard surface and immediately tested for ED and APSD. In addition, after the Gen2 inhalers were dropped and the insulin-filled cartridges removed, ED and APSD evaluations were conducted using empty cartridges. This testing was performed to confirm that any powder escaping from the cartridge did not contribute to the next delivered dose.

During the shake testing, Gen2 inhalers loaded with either 10 U or 20 U cartridges were repeatedly moved two inches in ~ 0.1 seconds along the X, Y, or Z axes (5 cycles in each direction). Horizontal and vertical inhaler orientations were investigated during the testing (Figure 1) using a test apparatus to maintain shake consistency. After shaking, the inhalers with the loaded cartridges were evaluated for ED and APSD.

Figure 1. Shake testing orientations and axes of movement

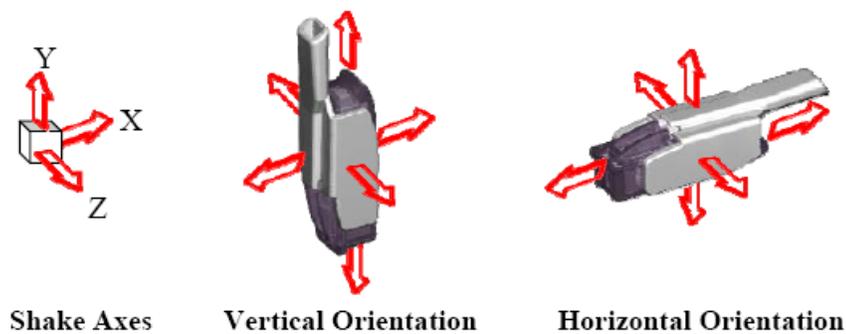


Figure 2. 10 U ED After Gen2 Drop Testing and Shake Testing

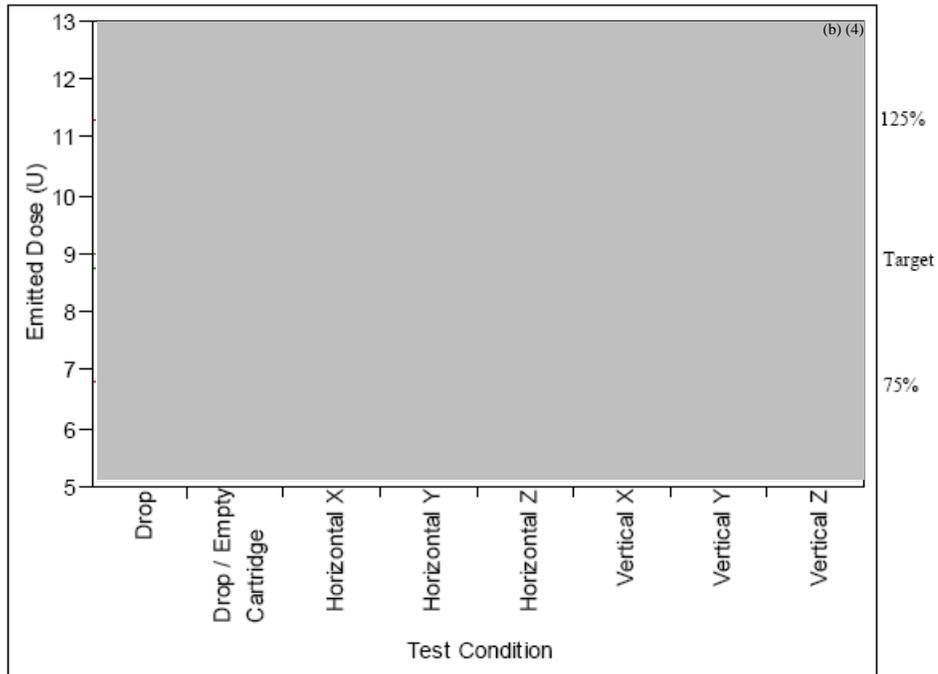


Figure 3. 20 U ED After Gen2 Drop Testing and Shake Testing

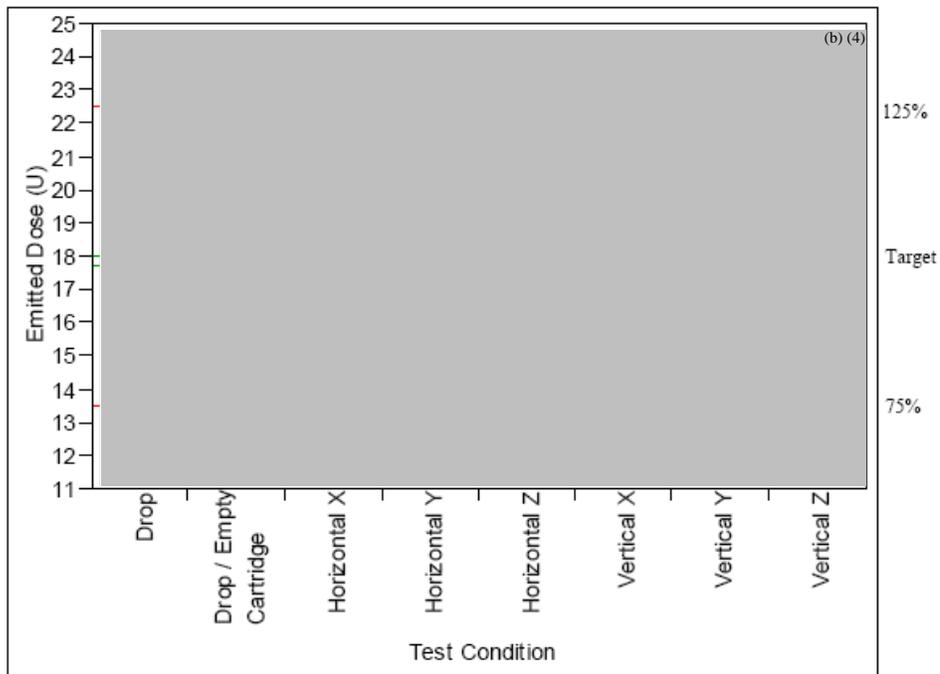
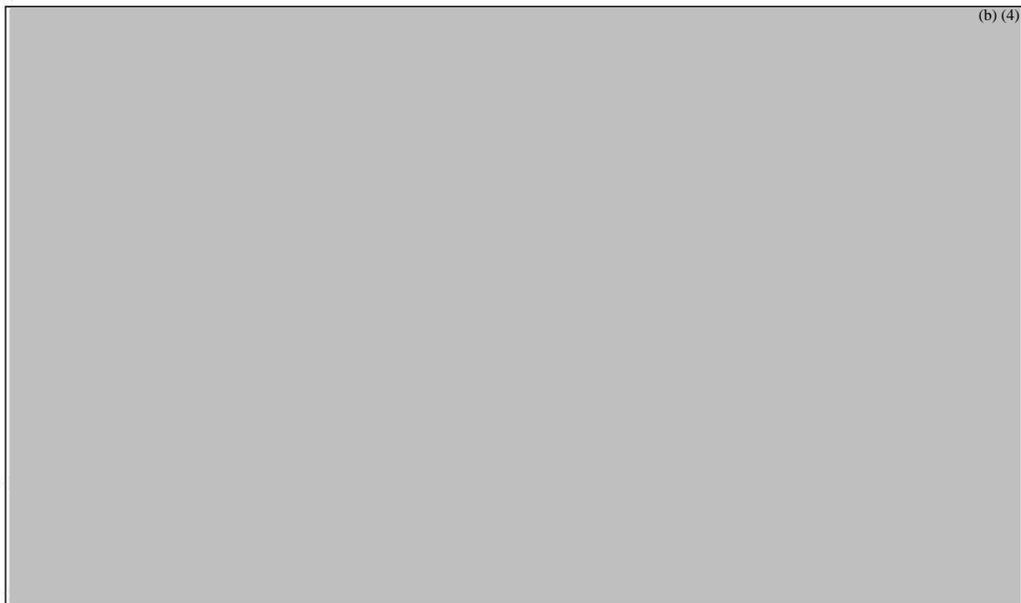


Figure 4. 10 U Mean APSD Performance after Gen2 Drop Testing and Shaking



Figure 5. 20 U Mean APSD Performance after Gen2 Drop Testing and Shaking



In both cartridge strengths, modest reductions in ED and minor effects to APSD were observed after shaking the loaded Gen2 device. As a result, **the instructions for use have been modified to alert users not to shake the Gen2 inhaler prior to use.**

MannKind believes that the study conducted to evaluate the emitted dose and aerodynamic particle size distribution attributes of Gen2 inhalers under misuse conditions (dropping and shaking) satisfies the Agency's request. Does the Agency agree?

The proposed acceptance criteria for emitted dose and APSD are duplicated from the resubmission dated 6/28/2010:

Attribute	Method	Acceptance Criteria
Uniformity of Emitted Dose (HPLC)	TM5557	(b) (4)
Aerodynamic Particle Size Distribution (HPLC)	TM5558	

Evaluation:

1. *Though no numerical values are provided, the graphs indicate that both 10 U and 20 U inhalers failed the proposed acceptance criteria for emitted doses when they are shaken as tested, especially when shaken along x axis at vertical orientation. **In the next resubmission the applicant should report the emitted doses test results in numerical term and discuss the results against the proposed specification.***
2. *Two out of three 10 U inhalers failed the acceptance criteria for APSD ([redacted] (b) (4) [redacted]) after being shaken along x axis at vertical orientation. Majority of 10 U*

*inhalers are below the fine particle dose target of (b) (4) after being shaken, especially at vertical orientation. The mass balances for the APSD testing were well below (b) (4) % of label claim. Compared with the unshaken inhalers (batch data provided in the resubmission dated 6/28/2010), the fine particle dose of APSD data from the shaken inhalers are significantly lower. **Whether this issue can be adequately mitigated through the labeling should be discussed with medical and clinpharm review team.***

- 3. Given that vertical shakings have the greatest adverse impact on the emitted dose, it is recommended to re-conduct dropping test from a vertical orientation.**

Comment 7

Conduct a study of the insulin adduct impurities and insulin-related degradants in support of the limits on these compounds as proposed in the November 24, 2010 amendment to the NDA. Submit adequate supporting data, including a validated method for monitoring insulin-FDKP adducts on stability.

Response

A 28-day subcutaneous toxicity study with a 14-day recovery period (MKC-PC-2010-0042) was conducted in Sprague-Dawley rats to qualify a mixture of insulin-related compounds (impurities and degradation products) in AFREZZA [Technosphere® Insulin Inhalation Powder] that could exceed (b) (4) % during the intended shelf life.

Three batches of Technosphere Insulin Inhalation Powder were filled into Gen2 cartridges (both 10 U and 20 U strengths) packaged in blisters with foil overwrap and placed on stability. Samples have been stored at 5°C for up to 21 months to date. Samples for the “extension” or “end use” study are obtained from the 5°C chamber and then stored at 25°C/60% RH for up to 30 days or at 30°C/65% RH for up to 10 days.

On-going registration stability studies indicate that the acceptance criteria submitted in the November 24, 2010 amendment, sequence number 0053, [3.2.P.5.1 Specification \(Technosphere □ Insulin Inhalation Powder\)](#) will require modification and support modifying the acceptance criteria for A21 from NMT (b) (4) % to NMT (b) (4) %, HMWP from NMT (b) (4) % to NMT (b) (4) %, and Total Others from NMT (b) (4) % to NMT (b) (4) %. A summary of the on-going registration stability data for A21, HMWP, and Total Others is provided.

Table 8. Comparison of proposed product acceptance criteria and qualified doses

Impurity	Mean Achieved Dose (mg/kg/day)	Level Qualified ^a	Acceptance Criterion	Maximum Anticipated Clinical Dose (mg/kg/day) ^{a, b}	Dose Multiple
A21	[REDACTED]	[REDACTED]	[REDACTED]	[REDACTED]	(b) (4)
HMWP					
Total Other Impurities (b) (4)					
^a Based on maximum anticipated clinical dose of 4 U/kg/day or (b) (4) mg/kg/day of insulin. USP defines 1 U = 0.0347 mg ^b Based on acceptance criteria					

Table 9. Comparison of 95% upper confidence limit and proposed product acceptance criteria

Impurity	95% Upper Confidence Limit at 24-month + 20-day	Acceptance Criterion
A21	[REDACTED]	(b) (4)
HMWP	[REDACTED]	
Total Others	[REDACTED]	

The research method used to monitor the insulin-FDKP adducts (b) (4) on stability has been validated. This method (TM5572) has been implemented in the ongoing registration stability study beginning with the 18 month time point. All samples tested to date contained not more than (b) (4) wt% of the insulin-FDKP adduct impurities grouping. The test method and complete validation report will be provided in the resubmission.

MannKind believes that the completed GLP 28-day rat toxicology study supports the acceptance criteria for A21, total others, and HMWP. Does the Agency agree?

Evaluation:

The following comments are excerpted from the pharmtox review by Dr. MIYUN M TSAI-TURTON:

“Pharm/tox Response to Comment 7:

Based on your 28 day toxicity study provided in your briefing document, insulin impurities and degradation products seemed appropriately qualified. The impurities were considered qualified at the following levels: A21 - (b) (4)%; HMWP- (b) (4)%; total other impurities - (b) (4) % and are now considered safe.”

The applicant proposed in the resubmission dated 6/28/2010 the following shelf life for the drug product : 24 months at refrigerated conditions (2 - 8°C or 36 - 46°F); 10 day for

unopened foil pouches and unopened blisters strips at 25°C (77°F); and short term excursions between 15-30°C (59-86°F). Once a blister strip is opened, all cartridges in that strip must be used within 72 hours.

During the second review cycle Dr. Theodore Carver concluded that “based upon the stability data submitted for the Gen2 product, a (b) (4) month shelf life for storage at 2-8°C is granted with an additional 10 days of storage at room temperature permitted before use or disposal of the Afrezza drug product.”

While there is no safety concerns as per pharmtox’s evaluation for the revised acceptance criteria proposed in this meeting package, their appropriateness and supported shelf life are review issues and will be determined when more data and statistical analysis are provided in the next resubmission.

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/s/

EDWIN JAO
01/10/2012

PRASAD PERI
01/10/2012
I concur

NDA 22-472

AFREZZA

(Insulin, human[rDNA]) Inhalation Powder

Mannkind Corporation

Theodore Carver

Division of Pre-Marketing Assessment III, ONDQA

and

Division of Metabolism and Endocrine Drug Products

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Chemistry Review Data Sheet

1. NDA 22-472

2. REVIEW #:2

3. REVIEW DATE: 12/08/2010

4. REVIEWER: Theodore Carver

5. PREVIOUS DOCUMENTS: None

Previous Documents

Document Date

n/a

6. SUBMISSION(S) BEING REVIEWED:

Submission(s) Reviewed

Document Date

Amendment (Resubmission)

6/28/10

Amendment

11/24/10

See Dr. Edwin Jao's review for reviews of additional CMC amendments.

7. NAME & ADDRESS OF APPLICANT:

Name: Mannkind Corporation

Address: 61 South Paramus Road, Paramus, NJ

Representative: N/A

Telephone: (201) 983-5228

Chemistry Review Data Sheet

8. DRUG PRODUCT NAME/CODE/TYPE:

- a) Proprietary Name: AFREZZA
- b) Non-Proprietary Name (USAN): Insulin, human (recombinant)
- c) Code Name/# (ONDC only): n/a
- d) Chem. Type/Submission Priority (ONDQA only): n/a

9. LEGAL BASIS FOR SUBMISSION: 505 b(1)

10. PHARMACOL. CATEGORY: anti-diabetic

11. DOSAGE FORM: Inhalation powder

12. STRENGTH/POTENCY: Insulin, human: 10 units, 20 units

13. ROUTE OF ADMINISTRATION: Inhalation

14. Rx/OTC DISPENSED: Rx OTC15. SPOTS (SPECIAL PRODUCTS ON-LINE TRACKING SYSTEM):

SPOTS product – Form Completed

Not a SPOTS product

16. CHEMICAL NAME, STRUCTURAL FORMULA, MOLECULAR FORMULA, MOLECULAR WEIGHT:

Structural Formula:

Chemistry Review Data Sheet

Chain A

Chain B


Molecular Formula: C₂₅₇H₃₈₃N₆₅O₇₇S₆

Molecular Weight: 5808 g/mol

17. RELATED/SUPPORTING DOCUMENTS:
A. DMFs:

For reviews of DMFs related to the product container/closure, see Dr. Edwin Jao's review.

DMF #	TYPE	HOLDER	ITEM REFERENCED	CODE ¹	STATUS ²	DATE REVIEW COMPLETE	COMMENTS
(b) (4)	II	(b) (4)	(b) (4)	3	Adequate	12/18/09	

¹ Action codes for DMF Table:

1 – DMF Reviewed.

Other codes indicate why the DMF was not reviewed, as follows:

2 – Type 1 DMF

3 – Reviewed previously and no revision since last review

4 – Sufficient information in application

5 – Authority to reference not granted

6 – DMF not available

7 – Other (explain under "Comments")

² Adequate, Inadequate, or N/A (There is enough data in the application, therefore the DMF did not need to be reviewed)

B. Other Documents:

DOCUMENT	APPLICATION NUMBER	DESCRIPTION
IND	61,729	IND under which supporting clinical studies were performed

Chemistry Review Data Sheet

18. STATUS:

ONDC:

CONSULTS/ CMC RELATED REVIEWS	RECOMMENDATION	DATE	REVIEWER
Biometrics	N/A		
EES	Acceptable	8/11/2010	Office of Compliance
Pharm/Tox	Pending		Miyun Tsai-Turton
Biopharm	N/A		
LNC	N/A		
Methods Validation	May be pursued at a later time if application is approved		
OSE	Pending		
EA	Acceptable	12/10/2010	Theodore Carver
Microbiology	Acceptable	9/22/2009	Denise A. Miller

The Chemistry Review for NDA 22-472

The Executive Summary

I. Recommendations

A. Recommendation and Conclusion on Approvability

The CMC recommendation is approval based on the CMC information reviewed. See also Dr. Edwin Jao's CMC review.

B. Recommendation on Phase 4 (Post-Marketing) Commitments, Agreements, and/or Risk Management Steps, if Approvable

None based on the CMC information evaluated in this review. See Dr. Edwin Jao's review for CMC deficiencies.

II. Summary of Chemistry Assessments

A. Description of the Drug Product(s) and Drug Substance(s)

Afrezza® is kit for inhalation of human insulin at mealtimes by diabetic patients, for prandial glycemic control. The kit consists of an inhaler device and plastic cartridges containing a powdered human insulin formulation. The inhaler device includes a mechanism to enable insertion of the cartridges followed by inhalation of the powder through a plastic mouthpiece. The insulin may be delivered in two dosage strengths, 10 USP insulin units (0.35 mg) and 20 USP insulin units (0.7 mg), which, according to the applicant, are equivalent pharmacologically to delivery of approximately 4 and 8 units of injected insulin respectively, depending on efficiency of delivery and absorption in the patient's lungs. The number and strengths of cartridges used by the patient at each meal must be calculated to yield the optimal amount of insulin for prandial glucose control. In this NDA resubmission, the applicant has stated that there are no significant changes to the drug substance, novel excipient, and (b)(4) drug product proposed for use in manufacturing the marketed product; however, the device/cartridge system proposed in the current submission are different from the device/cartridge system that was reviewed in the original NDA. This CMC review concerns only those portions of the submission pertaining to manufacturing of the (b)(4) drug product and its release testing and stability in the new dosage strengths and cartridge container/closure system. For the CMC review concerning the new inhaler device, its components, and performance of the drug product inhaler system, please refer to Dr. Edwin Jao's review.

Drug Substance:

All chemistry, manufacturing and controls information for recombinant human insulin drug substance is contained in Drug Master File (b)(4). This DMF was previously reviewed and found adequate as a source of human insulin drug substance for this NDA. The drug substance consists of (b)(4) human recombinant insulin isolated from a strain of K12 E. coli. The A and B chains of insulin, consisting of 21 and 30 amino acid residues respectively, are linked by 2 disulfide bridges. The A chain also contains one intra-chain disulfide bridge. Stability studies

Executive Summary Section

demonstrated that the human insulin drug substance is stable for at least (b) (4) at (b) (4) °C; a (b) (4) shelf life is granted for the drug substance. A summary of information regarding the recombinant human insulin drug substance may be found in the review of DMF (b) (4)

Drug Product

The drug product, referred to as ‘Gen2’ in the amended NDA, is a white powder filled in plastic cartridges sealed in blister packs, consisting of blister strips with three cartridges each comprising a card of 5 strips separated by perforation (a total of 15 cartridges per card). Each cartridge contains either 3.3 or 6.7 milligrams of a powdered formulation containing 0.35 or 0.69 mg of human insulin, respectively. The cartridges are manufactured specifically for use in the Afrezza inhaler device. The drug product consists of crystalline particles of a novel excipient coated with insulin drug substance, with trace amounts of polysorbate 80 (b) (4)

Table 1 below shows the composition of the two inhaler cartridge dosage strengths. Insulin content corresponds to 0.35 mg of human insulin per 10 USP units and 0.69 mg insulin per 20 USP units.

Table 1: Composition of Each Cartridge Dosage Form

Component	10 U cartridge strength	20 U cartridge strength
	3.3 mg nominal fill	6.7 mg nominal fill
	Quantity per cartridge	Quantity per cartridge
Insulin	10 U	20 U
FDKP	(b) (4)	
Polysorbate 80 ^a	(b) (4)	
(b) (4)	(b) (4)	

The novel excipient FDKP, which constitutes approximately (b) (4)% of the mass of the particles, is (*E*)-3,6-bis[4-(*N*-carboxy-2-propenyl)amidobutyl]-2,5-diketopiperazine, abbreviated as fumaryl diketopiperazine or FDKP. The applicant provided complete manufacturing information for FDKP in an appendix to the chemistry, manufacturing, and controls section. (b) (4)

During development of the particle formulation (termed “Technosphere” particles), FDKP was evaluated in comparison to other compounds for use as the particle-forming excipient. FDKP was found to be the ideal compound for forming the particle matrix because it crystallizes under acidic conditions and the crystals self-assemble to form particles with the appropriate properties. Technosphere[®] and Technosphere[®] Insulin particles are sized appropriately for inhalation, with a typical median particle diameter ~ 2-2.5µm. The particles dissolve readily under physiological conditions at neutral pH. In this NDA

Executive Summary Section

resubmission, the applicant reports no significant changes to the manufacturing and control of the FDKP excipient.

The commercial drug product manufacturing process consists of (b) (4)

(b) (4) For review of additional details regarding the (b) (4) drug product manufacturing and controls, which have not been modified in this submission, see Review #1 of the original NDA. The finished drug product consists of (b) (4) drug product that is filled into a novel inhaler cartridge system manufactured from (b) (4) relative to the original ('Gen1', MedTone) cartridge system. See Dr. Edwin Jao's review of information contained in the resubmission for additional information regarding the drug product container closure system.

Stability studies of the finished drug product revealed (b) (4)

(b) (4) Based upon an evaluation of the cartridge design and the results of stability studies, the stability of the drug in the new Gen2 cartridge system is different from the Gen1 drug product that was previously reviewed, and the stability data submitted for the Gen1 product do not support assignment of a shelf life for the Gen2 product. Therefore, based upon the stability data submitted for the Gen2 product, a (b) (4)-month shelf life for storage at 2-8°C is granted with an additional 10 days of storage at room temperature permitted before use or disposal of the Afrezza drug product.

B. Description of how the drug product is intended to be used

Afrezza is an orally inhaled insulin therapy intended to be used before meals by adult diabetic patients. It is intended to be a replacement for prandial injectable insulin but should also be accompanied by use of an injectable, long-acting form of insulin as part of a regimen for glycemic control. Afrezza is supplied as a reusable inhaler device with disposable cartridges in two dosage strengths. The dosage strengths are 5 or 10 mg of Technosphere-insulin inhalation powder each containing 10U (0.35 mg) or 20 U(0.69 mg) of recombinant human insulin, respectively. The total dose to be administered with each use is a combination of cartridges of each dosage strength based upon the individual diabetic patient's requirements for glycemic control, in consultation with a physician.

C. Basis for Approvability or Not-Approval Recommendation

This application is approvable based on the information provided for the (b) (4) drug product and the stability of the finished drug product. The (b) (4) Technosphere insulin appears to be stable through the recommended shelf life in the new finished product container closure system (Gen2 cartridge) and no other changes were made to the product manufacturing that would affect this portion of the CMC review or change the conclusion of approval from CMC review #1.

Executive Summary Section

III. Administrative**A. Reviewer's Signature**

Theodore Carver, CMC Reviewer, ONDQA/DNDQA III/ Branch VIII

B. Endorsement Block

T. Carver/CMC Reviewer, 12/09/10
P. Prasad/Chief Branch VIII (Acting), 12/09/10

C. CC Block

Suong Tran/Lead Chemist, 12/09/10
Rachel Hartford/RPM, 12/09/10

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/s/

THEODORE E CARVER
12/13/2010

PRASAD PERI
12/13/2010
I concur

NDA 22-472

Afrezza (insulin, human [rDNA]) Inhalation Powder

MannKind Corporation

Chemistry Review #2

December 12, 2010

Recommendation: Approvable

Edwin Jao, Ph.D.

ONDQA/Division III/Branch VIII

for

Division of Metabolism and Endocrine Drug Products

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Chemistry Review Data Sheet

1. NDA 22-472
2. REVIEW #:2
3. REVIEW DATE: December 9, 2010
4. REVIEWER: Edwin Jao, Ph.D.
5. Related DOCUMENTS:

Previous DocumentsDocument Date

Original NDA	16-03-2009
Amendment	11-06-2009
Amendment	22-07-2009
Amendment	14-08-2009
Amendment	11-09-2009
Amendment	29-09-2009
Amendment	12-10-2009
Amendment	30-10-2009
Advice/Information Request	13-11-2009
Amendment	30-11-2009
2 Amendment	04-12-2009
Chemistry Review by Dr. Alan Schroeder	09-12-2009
Chemistry Review by Dr. Alan Schroeder	17-12-2009
Quality/Response To Information Request	19-02-2010
Meeting/Meeting Package	12-05-2010
Resubmission	6-28-2010
Meeting Preliminary Comments	08-06-2010
Amendment	08-27-2010
Amendment	09-15-2010
Amendment	09-23-2010
Amendment	11-4-2010
Amendment	11-15-2010
Amendment	11-24-2010

6. SUBMISSION(S) BEING REVIEWED:

Submission(s) Reviewed

Resubmission NDA dated June 19, 2010

Amendments dated November 15, 2010

Amendments dated November 24, 2010

7. NAME & ADDRESS OF APPLICANT:

Name:	MannKind Corporation
Address:	61 South Paramus Road Paramus, NJ 07652
Representative:	Patricia R. Mayer, Ph.D. Senior Director, CMC Regulatory Affairs
Telephone:	201-983-5228

8. DRUG PRODUCT NAME/CODE/TYPE:

- a) Proprietary Name: Afrezza Inhalation Powder
- b) Non-Proprietary Name (USAN): insulin, human [rDNA]
- c) Code Name/# none provided
- d) Chem. Type/Submission Priority:
 - Chem. Type: 5 (new manufacturer)
 - Submission Priority: S

9. LEGAL BASIS FOR SUBMISSION: 505(b)(1)

10. PHARMACOL. CATEGORY: Anti-diabetic

11. DOSAGE FORM: Inhalation powder (pre-metered DPI)

12. STRENGTH/POTENCY:

20U cartridge provides (b) (4) or 0.7 (b) (4) mg of insulin emitted dose (target)

10U cartridge provides (b) (4) or 0.35 mg of insulin emitted dose (target)

[Note that the target insulin load is 3.0U/mg of the drug formulation.]

13. ROUTE OF ADMINISTRATION: oral inhalation

14. Rx/OTC DISPENSED: Rx OTC

15. SPOTS (SPECIAL PRODUCTS ON-LINE TRACKING SYSTEM):

SPOTS product – (See Dr. Carver's review)

Not a SPOTS product

16. CHEMICAL NAME, STRUCTURAL FORMULA, MOLECULAR FORMULA,
MOLECULAR WEIGHT:

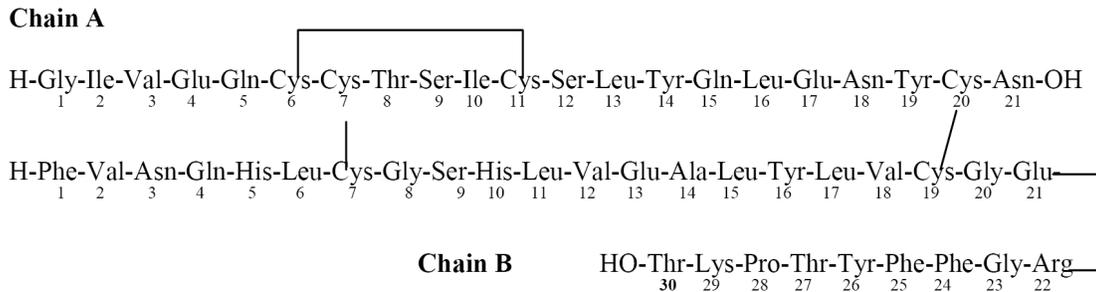
3.2.S.1.1 Nomenclature (Insulin Human, (b) (4))

Recommended International Nonproprietary Name (rINN):	rec human insulin
Pharmacopoeia name(s) Ph. Eur. USP	insulin, human insulin human, recombinant
Other non-proprietary name(s): US Adopted Name (USAN) British Approved Name (BAN)	insulin human Human Insulin
CAS Registry Number	11061-68-0

3.2.S.1.2.1 Structural Formula (Relative Stereochemistry):

Insulin consists of two polypeptide chains, A and B. The A chain has 21- amino acids and the B chain has 30 amino acids. The chains are lined together through the sulfur atoms of cysteine (Cys).

Figure 1: Structural formula of recombinant human insulin



17. RELATED/SUPPORTING DOCUMENTS:

A. DMFs:

[Note that the status of DMF (b) (4) for insulin is included in Dr. Ted Carver's separate review of this NDA]

DMF #	TYP E	HOLDER	ITEM REFERENCED	CODE ¹	STATUS ²	DATE REVIEW COMPLETED	COMMENT S
(b) (4)	III	(b) (4)	(b) (4)	1	Adequate	By Dr. Alan Schroeder on 11/23/2010	(b) (4)
	III			1	adequate	12/1/2010 by Edwin Jao	

(b) (4)	III	(b) (4)	1	adequate	by Dr. Alan Schroeder on 12/8/2010	(b) (4)
	III		4			
	III		1	Adequate	By Dr. Alan Schroeder on 12/1/2010	
	III		1	Adequate	By Dr. Alan Schroeder on 9/29/2010	
	III		1	Adequate	By Dr. Alan Schroeder on 9/29/2010	

¹ Action codes for DMF Table:

1 – DMF Reviewed.

Other codes indicate why the DMF was not reviewed, as follows:

2 –Type 1 DMF

3 – Reviewed previously and no revision since last review

4 – Sufficient information in application

5 – Authority to reference not granted

6 – DMF not available

7 – Other (explain under "Comments")

² Adequate, Inadequate, or N/A (There is enough data in the application, therefore the DMF did not need to be reviewed)

B. Other Documents:

DOCUMENT	APPLICATION NUMBER	DESCRIPTION
IND	61729	associated IND for this drug product

18. STATUS:

[See Dr. Carver's CMC review for this status table]

ONDQA:

CONSULTS/ CMC RELATED REVIEWS	RECOMMENDATION	DATE	REVIEWER
Biometrics	not considered necessary for performance stability data in this application		
EES	Acceptable	8/11/2010	
Pharm/Tox	No new consult is initiated.		
Clinpharm	pending		Dr.Sang Chung
LNC	N.A.		
Methods Validation	Not submitted		
EA	Adequate per Dr. Ted Carver's review	12/18/2009	Dr. Ted Carver
Microbiology	Approve	9/22/2009	Dr. Denise A. Miller
CDRH	pending		Dr. Melanie Choe

Executive Summary Section

The Chemistry Review for NDA 22-472

The Executive Summary

This is a CMC team review. See Dr. Theodore Carver's review for a separate review of the evaluation of (b) (4) TI powder and Dr. Alan Schroeder's reviews of the supporting DMFs.

This review pertains to limited parts of the NDA, i.e., the inhaler device and the drug product performance. Note that the device is also currently being separately evaluated by the CDRH reviewer.

I. Recommendations**A. Recommendation and Conclusion on Approvability**

This conclusion is with reference to the sections of the NDA reviewed in this review only. This application is **Approval with post approval commitments** listed in the attachment A of this review.

B. Recommendation on Phase 4 (Post-Marketing) Commitments, Agreements, and/or Risk Management Steps, if Approvable

No

II. Summary of Chemistry Assessments**A. Description of the Drug Product(s) and Drug Substance(s)**

The drug substance is human insulin (recombinant). Its manufacturing and controls information are provided in DMF (b) (4). This is separately reviewed by Dr. Ted Carver and found adequate.

The (b) (4) formulation is manufactured from Insulin Human USP, recombinant, and the following excipients and manufacturing aids: fumaryl diketopiperazine (FDKP), Polysorbate 80 NF, (b) (4)

(b) (4) The to-be marketed Technosphere® Insulin Inhalation Powder / Gen2 Inhalation System includes single-use, color coded, pre-metered Cartridges that are manually placed into a re-useable, breath-powered, high resistance dry powder inhaler. The cartridges have been redesigned for Gen2 inhalers. The pre-metered powder is provided in 3.3 mg and 6.7 mg fill weights, containing 10 U (insulin unit) and 15 U of the same Technosphere® Insulin Inhalation Powder (same insulin, same excipients) defined in the original application. (b) (4)
(b) (4), the cartridge fill weights have been reduced from 5 mg (15 U) and 10 mg (30 U) to 3.3 mg (10 U) and 6.7 mg (20 U), respectively. Each single-use Cartridge requires a **single inhalation** for powder delivery. (b) (4)

Executive Summary Section

(b) (4) the Medtone inhaler submitted in the original NDA. The secondary packaging consists of blister cards and foil overwrap, provides environmental protection and pertinent labeling information. Users are required to remove a single cartridge from the secondary package and manually place it into the inhaler in the Load Position. Next, users close the inhaler and inhale deeply one time to administer the powder. Upon completion of the inhalation maneuver, users open the device; remove the spent Cartridge for disposal. If an additional Cartridge is required, users insert a new cartridge and repeat the use steps. The inhaler is intended for a 15 day in-use period **without cleaning**. The emitted dose targets are as follows: (b) (4) of formulation for the cartridges containing 10 U of insulin) and (b) (4) of formulation for the cartridges containing 20 U of insulin).

See additional comments in Dr. Theodore Carver's CMC review.

B. Description of How the Drug Product is Intended to be Used

See above and see comments in Dr. Theodore Carver's CMC review.

C. Basis for Approvability or Not-Approval Recommendation

- 1. The applicant conducted environmental study on 20 U strength cartridges (higher strength) only. Ten U strength cartridges represent the worst case scenario of the percentage formulation loss due to possible static on the contact surfaces of inhalers at low temperature and humidity. The applicant should conduct environmental study (3.2.P.2.4.5.3) on 10 U strength cartridges, to demonstrate that emitted dose and aerodynamic particle size distribution are not significantly affected when the 10 U inhalers are operated at low temperature and low humidity (5°C/25% RH) environment. This issue can be addressed post approval from risk management perspective.*
- 2. The applicant conducted shipping study on 20 U strength cartridges (higher strength) only. Since the cartridges have been re-designed from the one used for Medtone, the observations that there is no significant difference in cartridge emptying between 15 U and 30 U for Medtone might not be applicable to that of 10 U and 20 U for Gen2. If there is adverse impact on the cartridge emptying due to settlement or leakage of the formulation during shipment, 10 U strength will be affected more significantly percentage wise. The applicant should conduct a study to demonstrate that emitted dose and APSD profile of 10 U strength Gen2 inhalation systems will not be adversely impacted during shipment. This issue can be addressed post approval from risk management perspective.*
- 3. The applicant should conduct a robustness study on Gen2 inhalers. The study should provide ruggedness "in-use" data with respect to the performance characteristics (emitted dose, APSD) for the inhalers under misuse scenarios (e.g., dropping, shaking, etc.). This issue can be addressed post approval from risk management perspective.*
- 4. The Medtone inhaler submitted in the original NDA has been replaced by a completely newly designed inhaler and new cartridges, i.e., Gen2 inhaler, in the resubmission. Three models of Gen2 inhaler, i.e., Gen2A, Gen2B, and Gen2C, have been developed by the applicant to*

Executive Summary Section

address minor CMC issues and major clinical issues associated with the original Medtone inhalers. (b) (4)

(b) (4). The to be marketed inhalers are Gen2C, which were used in BA/BE, pediatric, and safety and efficacy studies. Most of the CMC data provided in resubmission were collected from Gen2C inhalers. According to the clinical team, the number and scope of the clinical trials using Gen2 inhalers are not adequate to independently evaluate the safety and efficacy of the drug product. While clinical pharmacology team considers that the **PK profiles of Gen2C and Medtone inhalers are comparable based on BA/BE studies**, they do not find the data submitted is adequate to positively correlate to drug product efficacies (NDA status meeting dated 11/9/2010).

5. All new components of container/closure system, i.e., cartridges, inhalers and secondary packaging met the safety requirements listed in the pertinent sections of USP <87>, <88>, and ISO 10993.
6. Due to different fill weight between Gen2 and Medtone inhalers, the emitted dose which contains both inhalable and non-inhalable fractions is not comparable between Gen2 and Medtone inhalers. Specifically, (b) (4)

This may or may not have clinical implications.

7. It is noted that aerodynamic particle size distribution (APSD) data from Medtone inhalers were collected using Anderson Cascade Impactors (ACI) while that from Gen2 inhalers were collected using Next Generation Impactors (NGI). Since the cut-offs of the two impactors are different, the point-by-point comparison of the two impactors for any given particle size can only be conducted using extrapolated data. (b) (4)

8. The applicant also collected APSD data from Medtone and Gen2 inhalers using NGI alone, but using a (b) (4) kPa constant pressure drop. The flow rate at this pressure drop is expected to around (b) (4) LPM, below the normal flow rate of 28.3 LPM for ACI and 60 LPM for NGI (USP<601>). While the applicant's justifications for (b) (4) kPa testing condition is based on clinical data ((b) (4) kPa is the range of pressure drop generated by patients during clinical trials), the in-vitro comparison study results might not be very meaningful since under this test conditions the two impactors might not be adequately discriminating, i.e., not sensitive

Executive Summary Section

enough to display the differences in fine particle dose of the two inhalers. On the other hand, the clinical implications of the testing results conducted at (b) (4) LMP are not very clear, either.

9. Under (b) (4) kPa test condition, the differences in fine particle fractions between Gen2 and Medtone do seem to be minimized. The overall mean of fine particle fraction for Medtone is (b) (4) U, while that for Gen2 is (b) (4) U, a (b) (4) % difference.
10. It is this reviewer's opinion that the observed differences between the Gen2 and Medtone inhalers in drug product in-vitro measurements, e.g., emitted dose and APSD, are not as critical as differences in their PK profiles. Quantifying the differences in in-vitro data and tracking their batch to batch variability are more for quality control purposes than for providing supporting evidence of any clinical implications.
11. Since the device is a high resistance, a pressure drop of (b) (4) kPa is required for a flow rate of (b) (4) LPM. According to the applicant, clinical data shows that the average pressure drop generated by patients is only (b) (4) kPa. Therefore, it seems that the testing range of (b) (4) LPM to (b) (4) LPM (b) (4) kPa) during drug product characterization study is adequate to cover the normal in-use scenarios. The emitted dose does increase with higher flow rate, but not significantly. (b) (4)
- Taking into account that the specification targets for fine particle dose for Medtone inhaler are (b) (4) U with a range of (b) (4) U for 15 U strength and (b) (4) U with a range of (b) (4) U for 30 U strength, and in view of the device specific peak inhalation pressure (PIP) for Gen2 is only (b) (4) kPa (sufficient for the device to function as intended), the observed increase in fine particle fraction with flow rate is acceptable. Since the average pressure drop by patients is around (b) (4) kPa, the clinical relevancy for data generated at (b) (4) kPa (b) (4) LPM) is not clear.
12. While the emitted dose seems to be less sensitive to the inhaler orientations, APSD profile was significantly affected when the inhalers are at 180° cant position (upside down): (b) (4) This requires clear and prominent languages in the labeling.
13. Compared to the specifications for Medtone, the proposed specifications for Gen2 have one more group (b) (4)
- his is considered superior since it will provide better controls in the fine particle region of APSD. For example, (b) (4)

Executive Summary Section

14. *The proposed grouping for APSD is in-line with that for Medtone. The proposed acceptance criteria for all groupings appear to be supported by batch data, and are acceptable.*
15. *The proposed shelf life and in-use period appear to be supported by stability (including stress stability) data for APSD, emitted dose, and foreign particulate. However, the final decision will be contingent on the quality of stability data for other attributes (See review by Dr. Ted Carver).*

III. Administrative**A. Reviewer's Signature****B. Endorsement Block**

Edwin Jao, Ph.D./Date: 12/12/2010

Prasad Peri, Ph.D./

C. CC Block

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/s/

EDWIN JAO
12/13/2010

PRASAD PERI
12/13/2010
I concur

Afrezza® (Insulin, human[rDNA]) inhalation powder)
®Inhaler device (proposed)

NDA 22-472

**Summary of the Basis for the Recommended Action
from Chemistry, Manufacturing, and Controls**

Applicant: Mannkind Corporation.
61 South Paramus Road
Paramus, NJ 07652
USA

Representative: Ms. Eileen Wyka, MS,
Senior Director, CMC Regulatory Affairs
Phone: 201-983-5024

Indication: Treatment of adults with Type 1 and Type 2 diabetes mellitus.

Presentation: Afrezza® is a drug delivery system for inhalation of human insulin at mealtimes by diabetic patients, for prandial glycemic control. In the previous cycle the applicant presented a MedTone Inhalation System. Due to clinical efficacy issues and other human factors issues with the MedTone Inhaler, the applicant developed and submitted a new Gen2 Inhaler system to the Agency's CR letter. The new Gen2 Inhaler is a much simpler device and cartridge utilizing the same formulation that was used in the MedTone® inhaler.

The insulin may be delivered in two dosage strengths, 10 USP units and 20 USP units.

AFREZZA is available as single-use cartridges of:

EER Status: Acceptable 11-Aug-2010

Consults: EA – Categorical exclusion granted under 21 CFR §25.31(c)
Methods Validation – Revalidation by Agency may be requested to get similar results as provided in the applicant.
Pharm/toxicology – Acceptable
CDRH Consult for Device –pending by Melanie Choe.

Original Submission: 16-Mar-2009, resubmission date June 29, 2010

Post-Approval CMC Commitments:

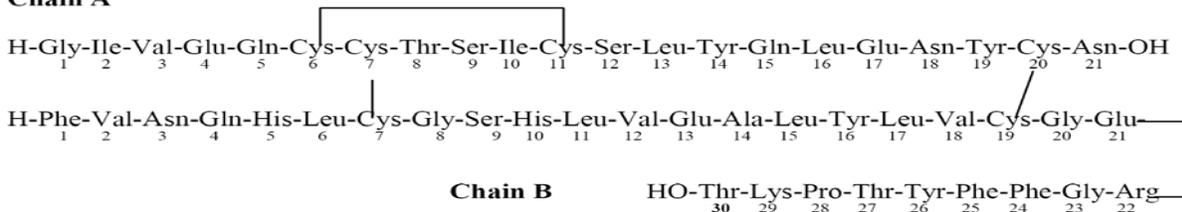
The following missing information is noted during the evaluation of the CMC section of the Afrezza/ (b) (4) drug product. The applicant will be asked to address these issues in a post marketing commitments with a clock of 6 months.

1. Conduct an environmental study (3.2.P.2.4.5.3) on 10 U strength cartridges (worst case scenario), to demonstrate that the emitted dose and aerodynamic particle size distribution are not significantly affected when the 10 U inhalers are operated at low temperature and low humidity (5°C/25% RH) environment.
2. Conduct a study to demonstrate that emitted dose and APSD profile of 10 U strength Gen2 inhalation systems (worst case scenario) will not be adversely impacted during shipment. The results of these characterization studies will need to be evaluated for possible labeling implications.
3. Conduct a robustness study on Gen2 inhalers. The study should provide ruggedness “in-use” data with respect to the performance characteristics (emitted dose, APSD) for the inhalers under misuse scenarios (e.g., dropping, shaking, etc.).

Drug Substance:

The drug substance is (b) (4) human recombinant insulin isolated from a strain of K12 *E. coli*. Insulin is a white to almost white crystalline powder (b) (4) in NDA). The A and B chains of insulin, consisting of 21 and 30 amino acid residues respectively, are linked by 2 disulfide bridges. The A chain also contains one intra-chain disulfide bridge. The molecular weight of insulin is 5808 g/mole and its chemical formula is C₂₅₇H₃₈₃N₆₅O₇₇S₆.

Chain A



All chemistry, manufacturing and controls information for recombinant human insulin is contained in Drug Master File (b) (4). This DMF was reviewed on 12/18/2009 and found adequate by Dr. Ted Carver as a source of human insulin to support this NDA.

The manufacture of the recombinant human insulin is (b) (4)

(b) (4) several international testing sites are listed for the drug substance.

The specifications on the drug substance include Appearance, Identification (IR, HPLC, Peptide Mapping), Solubility, Insulin Assay (HPLC, Dry basis), Loss on Drying, USP-Purity, USP-Related Substances (HPLC), (b) (4) Bioidentity, Microbial Limits, Bacterial

Endotoxins, Zinc Content (Dry basis), High Molecular weight Proteins (SEC), Host Cell Proteins (EIA)

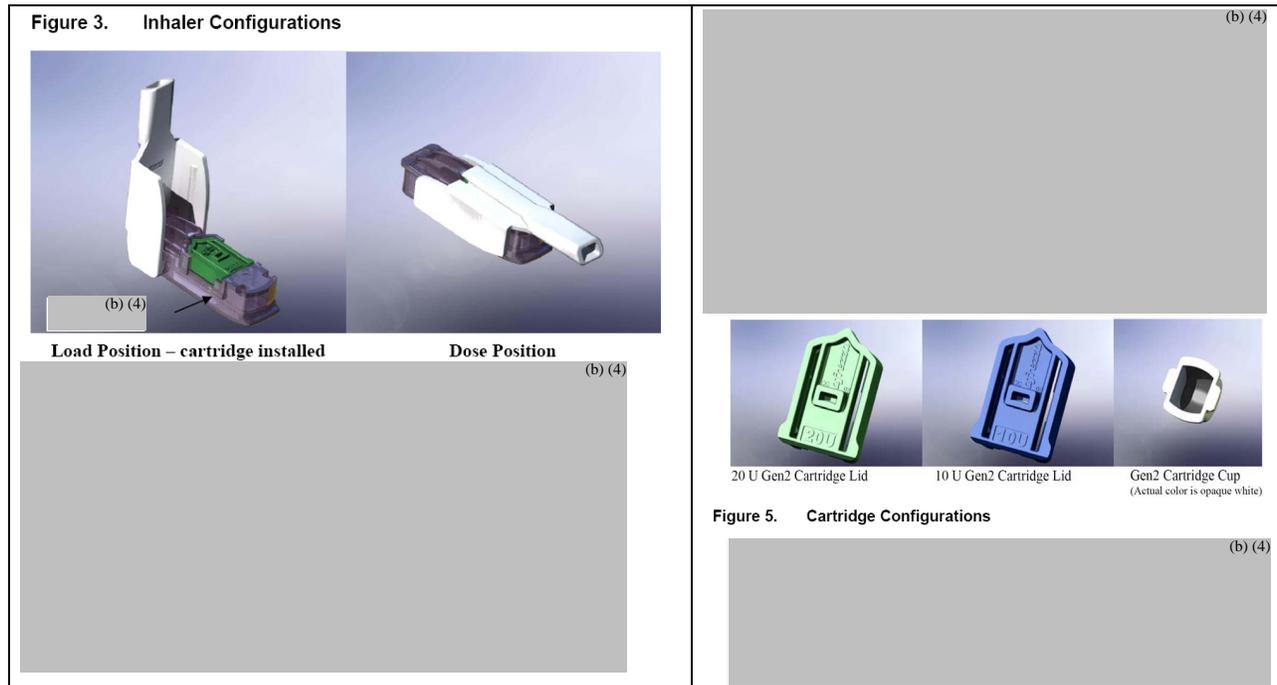
The drug substance is packaged in (b) (4)
(b) (4) Stability and retest period information are all referenced to the Drug Master File.

Stability studies demonstrate that the recombinant human insulin made by (b) (4) (b) (4) is stable for at least (b) (4) at (b) (4) °C; a (b) (4) shelf life is granted for the drug substance. A summary of information regarding the recombinant human insulin drug substance may be found in the review of DMF (b) (4)

Conclusion: The drug substance is satisfactory

Drug Product:

The drug product consists of a combination device ((b) (4) inhaler)/cartridge (Afrezza). A picture of the Afrezza Gen 2 Inhaler device and the cartridges are provided below.



The drug product formulation is a white powder (typical mass median aerodynamic diameter (b)(4)) filled into (b)(4) cartridges (blue and green lids) sealed in blister card and further opaque foil stick packs that are intended to be opened immediately before use in the inhaler device. The cartridges contain either 3.3 or 6.7 milligrams of a powdered formulation containing 0.35 or 0.70 mg of human insulin, respectively. There are 3 components in the drug product: insulin, human; fumaryl diketopiperazine (FDKP); and trace quantities of polysorbate 80. Trace amounts of (b)(4) acetic acid, and water (b)(4)

A novel excipient FDKP, which constitutes approximately (b)(4)% of the mass of the particles, is (*E*)-3,6-bis[4-(*N*-carboxy-2-propenyl)amidobutyl]-2,5-diketopiperazine, abbreviated as fumaryl diketopiperazine or FDKP. This excipient is made by (b)(4) and has been characterized sufficiently from a chemistry standpoint.

The commercial drug product manufacturing process consists of (b)(4)

(b)(4)

The commercial process for manufacturing of the drug product is comparable to the (b)(4) pilot process used for manufacturing of the clinical and primary stability batches, based on the information provided.

The regulatory specifications for the Technosphere Insulin Inhalation powder include Appearance, Identification, Assay, Insulin Related Compounds, High Molecular Weight Proteins, Uniformity of Dosage Units, Uniformity of Emitted Dose, APSD, (b)(4) Foreign Particulates, (b)(4), and Microbial Limits. The proposed target fine particle fraction is about (b)(4)% of the formulation mass of the cartridges ((b)(4) U for 10 U cartridges and U for the 10 U cartridges). All impurities in the drug product were qualified and are deemed acceptable from a safety standpoint in consultation with the pharm-tox reviewers.

The Gen 2® Inhaler and cartridges are manufactured by (b)(4)

It is a high resistance device ((b)(4) (b)(4) LPM) and typical flow rates generated by patients vary from (b)(4) LPM. The applicant has measured the typical pressure drops generated by patients with this device and found the most patients can generate (b)(4) kPa ((b)(4) LPM) through the device. Hence the applicant has claimed that a pressure drop of (b)(4) kPa is a more relevant to the patient population. *In vitro* studies, indicate that with higher flow rates (b)(4)

Three models of Gen2 inhaler, i.e., Gen2A, Gen2B, and Gen2C, have been developed by the applicant to address CMC issues associated with the original Medtone inhalers. While all using the same new cartridges, (b) (4)

The to-be marketed inhalers are Gen2C, which were used in BA/BE, pediatric, and safety and efficacy studies. Most of the CMC data provided in resubmission were collected from Gen2C inhalers.

Summary of the device comparisons

Emitted Dose Comparison between the two devices

Based on the in vitro data provided, the emitted dose targets and results for the Gen2 inhaler are lower compared to the MedTone inhaler. This is due to lower amounts of formulation in the new cartridges. The average emitted dose (76 batches) for 30 U strength MedTone Inhaler was reported as (b) (4) U (range 1 (b) (4)), where as the average emitted dose from 13 batches for the 20 U Gen 2 inhaler was reported as (b) (4) U (range (b) (4)). Similarly the average emitted dose (53 batches) for 15 U strength MedTone Inhalers was reported as (b) (4) U (range (b) (4)), where as the average emitted dose from 13 batches for the 10 U Gen 2 inhaler was reported as (b) (4) U (range (b) (4)).

APSD Comparison between the two devices

The range for fine particle fraction for the Gen 2 inhaler is less compared to that of the MedTone inhaler when tested at (b) (4) kPa ((b) (4) LPM). When tested at (b) (4) kPa ((b) (4) LPM) there is at least (b) (4) % less fine particle fraction for the Gen 2 inhaler system compared to the MedTone inhaler system.

Device	Formulation	Insulin USP Units (mg)	Target Emitted Dose	Target Fine Particle fraction (range) (b) (4)
MedTone (15 U)	5 mg	15 U		
MedTone (30 U)	10 mg	30 U		
Gen 2 ((b) (4) LPM flow rate) 10 U	3.3 mg	10 U (0.35 mg insulin)		
Gen 2 ((b) (4) LPM flow rate) 20 U	6.7 mg	20 U (0.67 mg insulin)		
Gen 2 ((b) (4) LPM flow rate) 10 U	3.3 mg	10 U (0.35 mg insulin)		
Gen 2 ((b) (4) LPM flow rate) 20 U	6.7 mg	20 U (0.67 mg insulin)		

Based on the data presented in the application, it is clear that the emitted doses differ between the devices. Under the stated in vitro quality control tests and patient use scenarios (b) (4) kPa pressure drop ((b) (4) LPM)) the APSD data seem to indicate that the devices are comparable.

Quality control and performance aspects for the device and cartridges are documented in reviews by Dr. Edwin Jao.

Inhaling the correct dose from each cartridge requires that the patient inhale deeply to achieve drug delivery for each cartridge. The total dose to be administered by the patient before each meal is comprised of one or more cartridges of appropriate dosage strengths based upon the individual diabetic patient's requirements for glycemic control, in consultation with a physician. The emitted dose targets are as follows: (b) (4) U (for the cartridges containing 10 U of insulin) and (b) (4) U (for the cartridges containing 20 U of insulin).

Based on the data provided in the application, the shelf life of the insulin cartridges are deemed as (b) (4) months under refrigerated conditions and 10 days at room temperature. Device is stated to be replaced after 15 days of use and its shelf life is determined to be (b) (4) year.

The following additional information is noted as absent during the evaluation of the CMC section of the Afrezza/ (b) (4) drug product. The applicant will be asked to address these issues in a post marketing commitments with a clock of 6 months.

- 1. Conduct an environmental study (3.2.P.2.4.5.3) on 10 U strength cartridges (worst case scenario), to demonstrate that the emitted dose and aerodynamic particle size distribution are not significantly affected when the 10 U inhalers are operated at low temperature and low humidity (5°C/25% RH) environment.*
- 2. Conduct a study to demonstrate that emitted dose and APSD profile of 10 U strength Gen2 inhalation systems (worst case scenario) will not be adversely impacted during shipment. The results of these characterization studies will need to be evaluated for possible labeling implications.*
- 3. Conduct a robustness study on Gen2 inhalers. The study should provide ruggedness "in-use" data with respect to the performance characteristics (emitted dose, APSD) for the inhalers under misuse scenarios (e.g., dropping, shaking, etc.).*

Conclusion: The drug product as presented is acceptable. **If the clinical action is for approval the comments above should be considered post marketing commitments to be completed within one year of approval. If the clinical action is for a Complete Response then the comments above should be sent out in the CR letter for the applicant to address them.**

Additional Items:

All associated Drug Master Files are acceptable or the pertinent information has been adequately provided in the application.

The analytical methods used in the testing procedures (release, stability and in-process) are well known and widely used by the pharmaceutical industry; however the revalidation of the emitted dose and APSD may be requested by Agency labs as necessary because of the unusual nature of the device and methods.

Overall Conclusion: From a CMC perspective, the application is recommended for approval pending adequate labeling. Proposed labeling of the drug product (Afrezza® and (b) (4)® Inhaler) should be evaluated in concert with the clinical division.

If the clinical division plans to take an approval action, then the post marketing commitments should be included in the action letter with a 6 month clock. If the action is going to be a Complete Response, the applicant should be asked to address the three comments listed in the phase 4 commitments section.

This is a representation of an electronic record that was signed electronically and this page is the manifestation of the electronic signature.

/s/

PRASAD PERI
12/13/2010
Approval with PMCs

Afrezza® (Insulin, human[rDNA]) inhalation powder)

NDA 22-472

**Summary of the Basis for the Recommended Action
from Chemistry, Manufacturing, and Controls**

Applicant: Mannkind Corporation.
61 South Paramus Road
Paramus, NJ 07652
USA

Representative: Ms. Eileen Wyka, MS,
Senior Director, CMC Regulatory Affairs
Phone: 201-983-5024

Indication: Treatment of adults with Type 1 and Type 2 diabetes mellitus.

Presentation: Afrezza® is a drug delivery system for inhalation of human insulin at mealtimes by diabetic patients, for prandial glycemic control. The system consists of a MedTone® inhaler device and plastic cartridges containing powdered human insulin formulation. (b) (4)

The insulin may be delivered in two dosage strengths, 15 USP units and 30 USP units.

(b) (4)

EER Status: Recommendation Pending

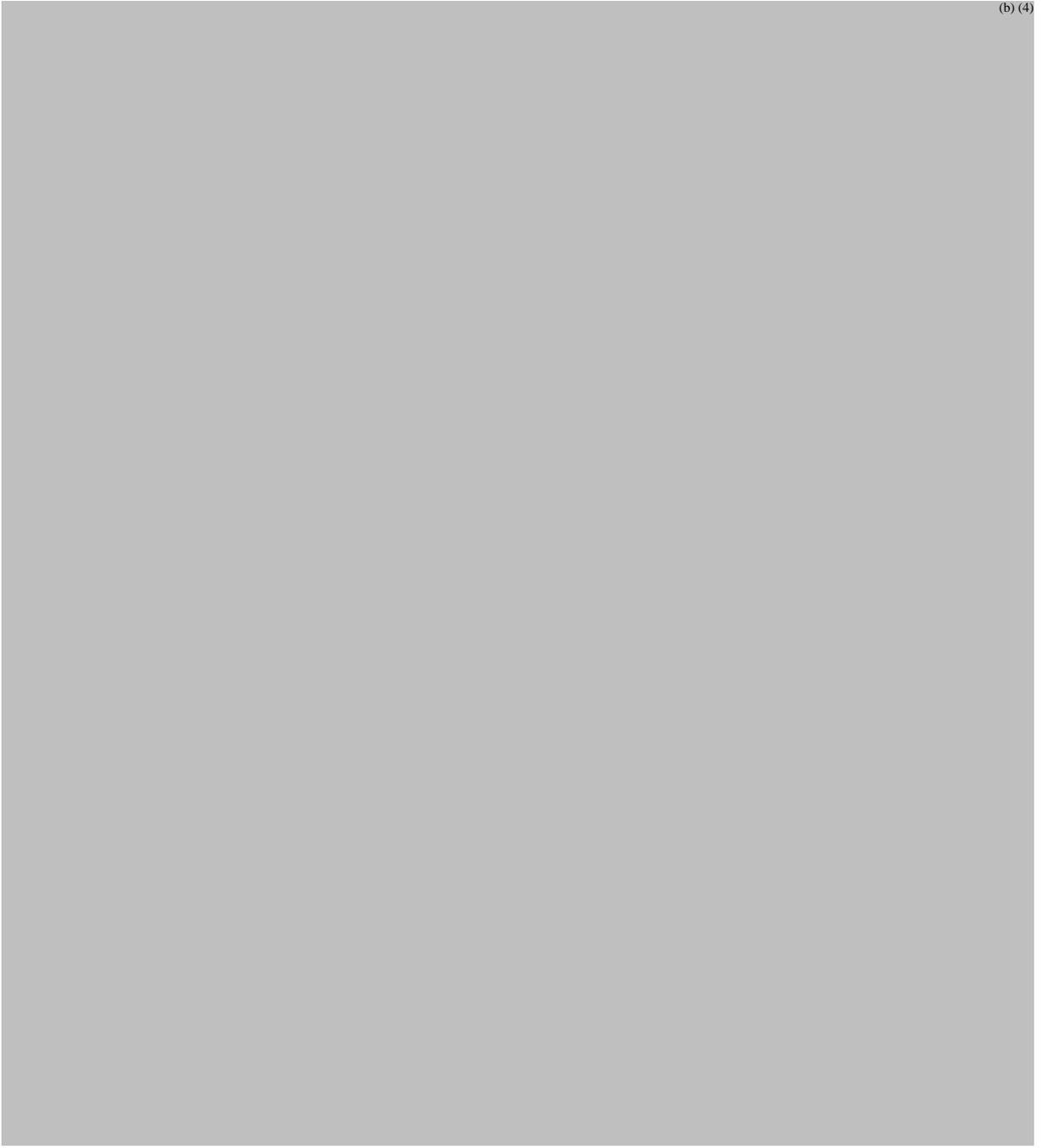
Consults: EA – Categorical exclusion granted under 21 CFR §25.31(c)
Methods Validation – Revalidation by Agency may be requested to get similar results as provided in the applicant.
Pharm/toxicology – Acceptable
CDRH Consult for Device –Acceptable in review dated 12/14/09 by Melanie Choe.

Original Submission: 16-Mar-2009

Post-Approval CMC Commitments:

The applicant has made the following post-approval agreements:

- 1.
- 2.
- 3.
- 4.
- 5.
- 6.
- 7.
- 8.



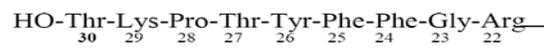
Drug Substance:

The drug substance is (b) (4) human recombinant insulin isolated from a strain of K12 *E. coli*. Insulin is a white to almost white crystalline powder (b) (4) (b) (4) in NDA). The A and B chains of insulin, consisting of 21 and 30 amino acid residues respectively, are linked by 2 disulfide bridges. The A chain also contains one intra-chain disulfide bridge. The molecular weight of insulin is 5508 g/mole and its chemical formula is C₂₅₇H₃₈₃N₆₅O₇₇S₆.

Chain A



Chain B



All chemistry, manufacturing and controls information for recombinant human insulin is contained in Drug Master File (b)(4). This DMF was reviewed on 12/18/2009 and found adequate by Dr. Ted Carver as a source of human insulin to support this NDA.

The manufacture of the recombinant human insulin is (b)(4).
Several international testing sites are listed for drug substance.

The specifications on the drug substance include Appearance, Identification (IR, HPLC, Peptide Mapping), Solubility, Insulin Assay (HPLC, Dry basis), Loss on Drying, USP-Purity, USP-Related Substances (HPLC), (b)(4) Biotidentity, Microbial Limits, Bacterial Endotoxins, Zinc Content (Dry basis), High Molecular weight Proteins (SEC), Host Cell Proteins (EIA)

The drug substance is packaged in (b)(4).
Stability and retest period information are all referenced to the Drug Master File.

Stability studies demonstrate that the recombinant human insulin made by (b)(4) (b)(4) is stable for at least (b)(4) months at (b)(4)°C; a (b)(4) month shelf life is granted for the drug substance. A summary of information regarding the recombinant human insulin drug substance may be found in the review of DMF (b)(4).

Conclusion: The drug substance is satisfactory

Drug Product:

The drug product consists of a combination device/cartridge. A picture of the MedTone Inhaler device and the cartridges are provided below.



The drug product formulation is a white powder (typical mass median aerodynamic diameter (b) (4) (b) (4)) filled in (b) (4) plastic cartridges sealed in opaque foil stick packs that are intended to be opened immediately before use in the inhaler device. The cartridges contain either 5 or 10 milligrams of a powdered formulation containing (b) (4) mg of human insulin, respectively. There are 3 components in the drug product: insulin, human; fumaryl diketopiperazine (FDKP); and trace quantities of polysorbate 80. Trace amounts of (b) (4) acetic acid, and water (b) (4) (b) (4).

A novel excipient FDKP, which constitutes approximately (b) (4) % of the mass of the particles, is (*E*)-3,6-bis[4-(*N*-carboxy-2-propenyl)amidobutyl]-2,5-diketopiperazine, abbreviated as fumaryl diketopiperazine or FDKP. This excipient is made by (b) (4) and has been characterized sufficiently from a chemistry standpoint.

The commercial drug product manufacturing process consists of (b) (4)

(b) (4) The commercial process for manufacturing of the drug product is comparable to the (b) (4) pilot process used for manufacturing of the clinical and primary stability batches, based on the information provided.

The regulatory specifications for the Technosphere Insulin Inhalation powder include Appearance, Identification, Assay, Insulin Related Compounds, High Molecular Weight Proteins, Uniformity of Dosage Units, Uniformity of Emitted Dose, APSD, (b) (4), Foreign Particulates, (b) (4), and Microbial Limits. The proposed target fine particle fraction is about (b) (4) % of the formulation mass of the cartridges ((b) (4) for 15 U cartridges and (b) (4) for the 10 U cartridges). All impurities in the drug product were qualified and are deemed acceptable from a safety standpoint in consultation with the pharm-tox reviewers.

The MedTone® Inhaler and cartridges are manufactured by (b) (4)

The MedTone device underwent improvements during development and Model C was used in phase 3 studies and Model D inhaler with the Model D cartridge is proposed from marketing. Changes were made in the Model C inhaler to produce the Model D inhaler; these changes include improvements to address problems encountered with use of the Model C inhalers. Quality control and performance aspects for the device and cartridges are documented in reviews by Dr. Alan Schroeder.

(b) (4)
The total dose to be administered by the patient before each meal is comprised of one or more cartridges of appropriate dosage strengths based upon the individual diabetic patient's requirements for glycemic control, in consultation with a physician. The emitted dose targets are as follows: (b) (4) U (for the cartridges containing 15 U of insulin) and (b) (4) U (for the cartridges containing 30 U of insulin).

Based on the data provided in the application, the shelf life of the insulin cartridges are deemed as (b) (4) under refrigerated conditions and (b) (4) at room temperature. The shelf life of the MedTone inhaler device is (b) (4) including a (b) (4) use life when stored at (b) (4).

Conclusion: The drug product is acceptable pending an acceptable status from the Office of Compliance for all establishments.

Additional Items:

All associated Drug Master Files are acceptable or the pertinent information has been adequately provided in the application.

The analytical methods used in the testing procedures (release, stability and in-process) are well known and widely used by the pharmaceutical industry; however the revalidation of the emitted dose and APSD may be requested by Agency labs as necessary because of the unusual nature of the device and methods.

An overall acceptable compliance status has not been provided (until the writing of this review) by the Office of Compliance for all sites.

Overall Conclusion:

From a CMC perspective, the application is recommended for approval. **Note that the facility inspection is still outstanding and that the CMC recommendation does not incorporate any potential facility inspection issues.**

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/

PRASAD PERI

01/06/2010

Approval pending Acceptable EES from office of compliance.



NDA 22-472

Afrezza (insulin, human [rDNA]) Inhalation Powder

MannKind Corporation

**Addendum to
Chemistry Review #1**

December 17, 2009

Recommendation: Approval (see Executive Summary)

Alan C. Schroeder, Ph.D.

**ONDQA/Division I/Branch II
for**

Division of Metabolism and Endocrine Drug Products

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I. Review Of Common Technical Document-Quality (Ctd-Q) Module 3.2: Body Of Data	Error! Bookmark no



Chemistry Review Data Sheet

1. NDA 22-472
2. REVIEW #: ADDENDUM TO REVIEW #1
3. REVIEW DATE: December 17, 2009
4. REVIEWER: Alan C. Schroeder, Ph.D.

5. PREVIOUS DOCUMENTS (in Review #1):

Previous Documents

Original NDA dated March 16, 2009
Amendment dated June 11, 2009
Amendment dated July 22, 2009
Amendment dated August 14, 2009
Amendment dated September 11, 2009
Amendment dated September 29, 2009
Amendment dated October 12, 2009
Amendment dated October 30, 2009
Amendment dated November 30, 2009
2 Amendments dated December 4, 2009

6. SUBMISSION(S) BEING REVIEWED (in Addendum to Review #1):

Submission(s) Reviewed

Amendment dated December 11, 2009
Amendment dated December 14, 2009



CHEMISTRY REVIEW



Chemistry Review Data Sheet

7. NAME & ADDRESS OF APPLICANT:

Name: MannKind Corporation
Address: 61 South Paramus Road
Paramus, NJ 07652
Representative: Eileen Wyka, MS
Senior Director, CMC Regulatory Affairs
Telephone: 201-983-5024

8. DRUG PRODUCT NAME/CODE/TYPE:

- a) Proprietary Name: Afrezza Inhalation Powder
- b) Non-Proprietary Name (USAN): insulin, human [rDNA]
- c) Code Name/# none provided
- d) Chem. Type/Submission Priority:
 - Chem. Type: 5 (new manufacturer)
 - Submission Priority: S

9. LEGAL BASIS FOR SUBMISSION: 505(b)(1)

10. PHARMACOL. CATEGORY:

Anti-diabetic

11. DOSAGE FORM: inhalation powder (pre-metered DPI)

12. STRENGTH/POTENCY:

30U cartridge provides (b)(4) emitted dose (target)
15U cartridge provides (b)(4) emitted dose (target)
[Note that the target insulin load is 3.0U/mg of the drug formulation.]

13. ROUTE OF ADMINISTRATION: oral inhalation

14. Rx/OTC DISPENSED: ___x___ Rx ___ OTC



CHEMISTRY REVIEW



Chemistry Review Data Sheet

15. SPOTS (SPECIAL PRODUCTS ON-LINE TRACKING SYSTEM):

SPOTS product – (See Dr. Carver's review)

Not a SPOTS product

16. CHEMICAL NAME, STRUCTURAL FORMULA, MOLECULAR FORMULA, MOLECULAR WEIGHT:

3.2.S.1.1 Nomenclature (Insulin Human, (b) (4))

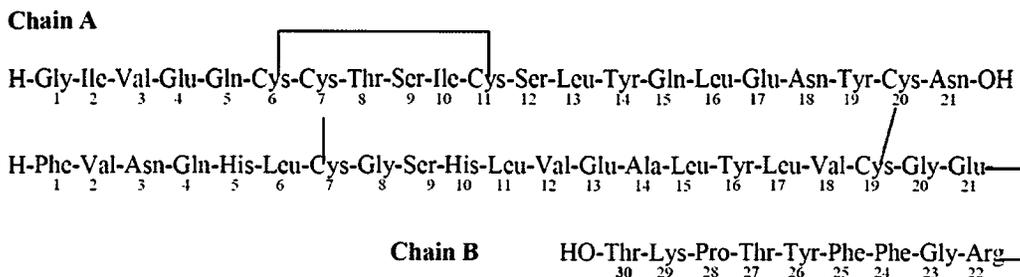
Recommended International Nonproprietary Name (rINN):	rec human insulin
Pharmacopoeia name(s) Ph. Eur. USP	insulin, human insulin human, recombinant
Other non-proprietary name(s): US Adopted Name (USAN) British Approved Name (BAN)	insulin human Human Insulin
CAS Registry Number	11061-68-0

Chemistry Review Data Sheet

3.2.S.1.2.1 Structural Formula (Relative Stereochemistry):

Insulin consists of two polypeptide chains, A and B. The A chain has 21- amino acids and the B chain has 30 amino acids. The chains are lined together through the sulfur atoms of cysteine (Cys).

Figure 1: Structural formula of recombinant human insulin



17. RELATED/SUPPORTING DOCUMENTS:

A. DMFs:

[Note that the status of DMF (b) (4) for insulin is included in Dr. Ted Carver's separate review of this NDA]

DMF #	TYPE	HOLDER	ITEM REFERENCED	CODE ¹	STATUS ²	DATE REVIEW COMPLETED	COMMENTS
(b) (4)	III	(b) (4)	(b) (4)	1	Adequate	6/05/2009 A. Schroeder	(b) (4)
	III			1	Adequate	6/09/2009 A. Schroeder	
	III			3	Adequate	3/23/2006 C. Bertha found this (b) (4) to be adequate for (b) (4)	



CHEMISTRY REVIEW



Chemistry Review Data Sheet

						there is no new technical information about this (b) (4) in this DMF subsequent to Dr. Bertha's review.	(b) (4)
(b) (4)	III	(b) (4)		(b) (4)	4		
	III				1	Adequate	6/22/2009 A.Schroeder
	III				1	Adequate	6/24/2009 A. Schroeder

¹ Action codes for DMF Table:

1 – DMF Reviewed.

Other codes indicate why the DMF was not reviewed, as follows:

2 – Type 1 DMF

3 – Reviewed previously and no revision since last review

4 – Sufficient information in application

5 – Authority to reference not granted

6 – DMF not available

7 – Other (explain under "Comments")

² Adequate, Inadequate, or N/A (There is enough data in the application, therefore the DMF did not need to be reviewed)

B. Other Documents:

DOCUMENT	APPLICATION NUMBER	DESCRIPTION
IND	61729	associated IND for this drug product



CHEMISTRY REVIEW



Chemistry Review Data Sheet

18. STATUS: This table is updated here.

[See Dr. Carver's CMC review for this status table]

ONDQA:

CONSULTS/ CMC RELATED REVIEWS	RECOMMENDATION	DATE	REVIEWER
Biometrics	not considered necessary for performance stability data in this application		
EES	pending		
Pharm/Tox	The pharm/tox supervisor, Dr. Karen Davis Bruno, will address in her memo the safety evaluation of extractables, leachables and foreign particulates. She has not indicated any safety problem with the levels of these impurities.		
Biopharm	N.A.		
LNC	N.A.		
Methods Validation	pending		
EA	Adequate per Dr. Ted Carver's review		Dr. Ted Carver
Microbiology	Approve	9/22/2009	Dr. Denise A. Miller
CDRH	Adequate	12/14/2009	Dr. Melanie Choe
Radiopharmaceutical	N.A.		

The Chemistry Review for NDA 22-472

The Executive Summary

This is a team review. See Dr. Theodore Carver's review for a separate review of the rest of the CMC material in this NDA. This summary has been updated since Review #1.

This review pertains to limited parts of the NDA (i.e., the inhaler device and the drug product performance) which were reviewed in this review.

I. Recommendations

A. Recommendation and Conclusion on Approvability

This conclusion is with reference to the limited parts of the NDA reviewed in this review only. See Dr. Theodore Carver's review for a recommendation on approvability for the remainder of the NDA. This application is recommended for APPROVAL from a CMC perspective (NOTE: the facilities inspection is still outstanding, and this CMC recommendation does not incorporate any potential facility inspection issues.).

B. Recommendation on Phase 4 (Post-Marketing) Commitments, Agreements, and/or Risk Management Steps, if Approvable

The applicant has made the following post-approval agreements (this list has been updated:



Executive Summary Section

(b) (4)

The applicant has made the following stability commitments (in the original NDA):

- Continuation of on-going stability protocols, which includes the first 3 production batches from the validated process.
- Minimum of 5% of the batches manufactured per year for the first three years (not to exceed 10 additional batches of each marketed strength product) will be placed in the post approval stability program.
- For year four and beyond, representative samples from one batch of each marketed strength product will be included in the program for each year.
- Results from on-going and future studies will be periodically submitted to the application in the NDA annual report.
- If any significant manufacturing changes occur that require re-validation of the process then the stability program will revert back to the protocol provided for the first three production batches incorporating the manufacturing changes.

Executive Summary Section

- MannKind commits to withdraw from the market any batch found to fall outside the approved specifications for the drug product. If the deviation does not affect the safety and efficacy of the drug product, the deviation will be promptly discussed with the reviewing division of the FDA to determine if commercial distribution may be continued. The change or deterioration in the distributed drug product will be reported as required under 21 CFR 314.81(b)(1)(ii).”

II. Summary of Chemistry Assessments**A. Description of the Drug Product(s) and Drug Substance(s)**

The drug substance is human insulin (recombinant). Its manufacturing and controls information are provided in DMF (b)(4). This is separately reviewed by Dr. Ted Carver.

The drug product is manufactured from Insulin Human USP, recombinant, and the following excipients and manufacturing aids: fumaryl diketopiperazine (FDKP), Polysorbate 80 NF, (b)(4)

“The Technosphere® Insulin Inhalation Powder / MedTone® Inhaler system includes single-use, pre-metered cartridges that are manually inserted into a re-useable, breath-powered, high resistance dry powder inhaler. The pre-metered powder is provided in 5 mg and 10 mg fill weights [of formulated drug, containing 15U and 30U, of insulin, respectively]...The secondary packaging around the plastic cartridge and its drug content provides environmental protection and pertinent labeling information.

(b)(4)

[Redacted text block]

See additional comments in Dr. Theodore Carver’s CMC review.

Executive Summary Section

B. Description of How the Drug Product is Intended to be Used

See above and see comments in Dr. Theodore Carver's CMC review.

C. Basis for Approvability or Not-Approval Recommendation

This review pertains to limited parts of the NDA (i.e., the inhaler device and the drug product performance) which were reviewed in this review. Note that the device was also separately evaluated by the CDRH reviewer, Dr. Melanie Choe.

The particle size distribution data from analysis of the emitted dose of the drug product, show some decrease in particle size (Mass Mean Aerodynamic Diameter) with increasing airflow rate through the device (b) (4)

(b) (4). Information from clinical study MKC-TI-129 suggests that some diabetes patients could only generate air flow rates below 20 liters per minute, although mean values in these study appear to be in the mid 20's for LPM. Therefore the particle size distribution (which may determine regions of lung deposition) varies with patient air flow rates, especially at lower airflow rates. This information has been shared with the clinical reviewers for their consideration.

Over 10,000 model C inhalers were given to patients in phase 2 and phase 3 studies. The applicant has stated that no serious adverse events associated with device failure and/or malfunction were reported. The applicant also claims to be unaware of any adverse events resulting from device failure. The main complaints about the product in the clinical studies were for (b) (4) and these defects are said to have been rectified through design modifications.

The Model C inhaler (with the Model C cartridge) was used in phase 3 studies, and the Model D inhaler (with the Model D cartridge) is proposed for marketing. Changes were made in the Model C inhaler to produce the Model D inhaler; these changes include improvements to address problems encountered with use of the Model C inhalers. It is claimed that the improvements in Model D did not alter the air flow path through the device relative to Model C, and the functionality of the device was not changed. Both drug product strengths (15U and 30U) demonstrated very similar *in vitro* performances in emitted dose and aerodynamic particle size distribution for the Model C and Model D inhalers.

Overall, the stability data (for drug product stored at (b) (4)) show that the aerodynamic particle size distribution and the delivered dose uniformity are not trending parameters.

See the separate CDRH review of the MedTone Inhaler device by Dr. Melanie Choe (consult review is dated 12/14/2009). Her comments (Section 3 of the Summary) will be



CHEMISTRY REVIEW



Executive Summary Section

forwarded to the applicant. Based on the data provided (see the CDRH consult review and the CMC review), the shelf life of the device will be (b) (4), including (b) (4) of use life, when stored at (b) (4). The device should be brought to room temperature prior to use.

See additional Executive Summary comments in Dr. Theodore Carver's CMC review.

III. Administrative

A. Reviewer's Signature

B. Endorsement Block

Alan C. Schroeder, Ph.D./12-17-2009
Prasad Peri, Ph.D./
Rachel Hartford/

C. CC Block

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

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/s/

ALAN C SCHROEDER
12/18/2009

PRASAD PERI
12/18/2009
I concur

NDA 22-472

AFREZZA

(Insulin, human[rDNA]) Inhalation Powder

Mannkind Corporation

Theodore Carver

Division of Pre-Marketing Assessment I, ONDQA

and

Division of Metabolism and Endocrine Drug Products

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Chemistry Review Data Sheet

1. NDA 22-472
2. REVIEW #:1
3. REVIEW DATE: 12/04/2009
4. REVIEWER: Theodore Carver
5. PREVIOUS DOCUMENTS: None

Previous Documents

Document Date

n/a

6. SUBMISSION(S) BEING REVIEWED:

Submission(s) Reviewed

Document Date

Original submission	03-16-2009
Amendment (seq. 04; response to filing comments)	06-11-2009
Amendment (seq. 07; Response to 74-day letter)	07-22-2009
Amendment (seq. 09; stability update)	08-14-2009
Amendment (seq. 10)	08-14-2009
Amendment (seq. 13; stability update)	09-11-2009
Amendment (seq. 17)	09-29-2009
Amendment (seq. 20)	10-12-2009
Amendment (seq. 22)*	10-30-2009
Amendment (seq. 25)	11-30-2009
Amendment (seq. 29)*	12-4-2009
Amendment (seq. 31)	12-11-2009
Amendment (seq. 32)*	12-14-2009

*These CMC amendments were reviewed entirely by Dr. Alan Schroeder.

Chemistry Review Data Sheet

7. NAME & ADDRESS OF APPLICANT:

Name: Mannkind Corporation
Address:
Representative:
Telephone: (847) 582-3504

8. DRUG PRODUCT NAME/CODE/TYPE:

- a) Proprietary Name: AFRESA
- b) Non-Proprietary Name (USAN): Insulin, human
- c) Code Name/# (ONDC only): n/a
- d) Chem. Type/Submission Priority (ONDC only): n/a

9. LEGAL BASIS FOR SUBMISSION: Not applicable

10. PHARMACOL. CATEGORY: anti-diabetic

11. DOSAGE FORM: Inhalation powder

12. STRENGTH/POTENCY: Insulin, human: 15 units, 30 units

13. ROUTE OF ADMINISTRATION: Inhalation

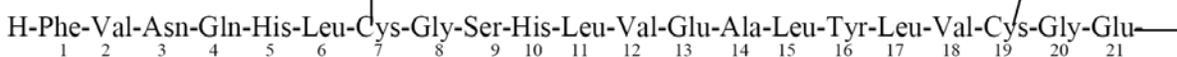
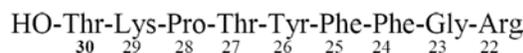
14. Rx/OTC DISPENSED: Rx OTC15. SPOTS (SPECIAL PRODUCTS ON-LINE TRACKING SYSTEM):

SPOTS product – Form Completed

Not a SPOTS product

Chemistry Review Data Sheet

16. CHEMICAL NAME, STRUCTURAL FORMULA, MOLECULAR FORMULA, MOLECULAR WEIGHT:

Structural Formula:**Chain A****Chain B**

Molecular Formula: C₂₅₇H₃₈₃N₆₅O₇₇S₆

Molecular Weight: 5808 g/mol

17. RELATED/SUPPORTING DOCUMENTS:

A. DMFs:

For DMFs related to the product container/closure, see Dr. Alan Schroeder's review of NDA 22-472.

DMF #	TYPE	HOLDER	ITEM REFERENCED	CODE ¹	STATUS ²	DATE REVIEW COMPLETE	COMMENTS
(b) (4)	II		(b) (4)	1	Adequate	12/10/09	

¹ Action codes for DMF Table:

1 – DMF Reviewed.

Other codes indicate why the DMF was not reviewed, as follows:

2 – Type 1 DMF

3 – Reviewed previously and no revision since last review

4 – Sufficient information in application

5 – Authority to reference not granted

6 – DMF not available

7 – Other (explain under "Comments")

Chemistry Review Data Sheet

² Adequate, Inadequate, or N/A (There is enough data in the application, therefore the DMF did not need to be reviewed)

B. Other Documents:

DOCUMENT	APPLICATION NUMBER	DESCRIPTION
IND	61,729	IND under which supporting clinical studies were performed

18. STATUS:

ONDC:

CONSULTS/ CMC RELATED REVIEWS	RECOMMENDATION	DATE	REVIEWER
Biometrics	N/A		
EES	Pending		Office of Compliance
Pharm/Tox	Acceptable	12/8/09	Miyun Tsai-Turton
Biopharm	N/A		
LNC	N/A		
Methods Validation			
OSE			
EA	Acceptable		Theodore Carver
Microbiology	Acceptable	9/22/09	Denise A. Miller
Device/CDRH	Acceptable	12/17/09	Melanie Choi

The Chemistry Review for NDA 22-472

The Executive Summary

I. Recommendations

A. Recommendation and Conclusion on Approvability

The CMC recommendation is approval. A final recommendation from the office of compliance is pending, and the CMC recommendation does not incorporate any potential facility inspection issues.

B. Recommendation on Phase 4 (Post-Marketing) Commitments, Agreements, and/or Risk Management Steps, if Approvable

As part of their post-marketing stability commitment, the applicant has agreed to complete the ongoing 36-month long-term stability studies for 3 commercial lots of the drug product; in addition, the applicant agrees to add a minimum of 5% of lots manufactured per year to the stability program for the first 4 years and a minimum of 1 lot each year thereafter. See Dr. Alan Schroeder's review for CMC postmarketing commitments to be included in the action letter.

II. Summary of Chemistry Assessments

A. Description of the Drug Product(s) and Drug Substance(s)

Afrezza® is a drug delivery system for inhalation of human insulin at mealtimes by diabetic patients, for prandial glycemic control. The system consists of an inhaler device and plastic cartridges containing a powdered human insulin formulation. (b) (4)

(b) (4) The insulin may be delivered in two dosage strengths, 15 USP units and 30 USP units, which, according to the applicant, are equivalent pharmacologically to delivery of approximately 4 and 8 units of injected insulin respectively, depending on efficiency of delivery and absorption in the patient's lungs. (b) (4)

(b) (4) and the number and strengths of cartridges used by the patient at each meal must be calculated to yield the optimal amount of insulin for prandial glucose control.

Drug Substance:

All chemistry, manufacturing and controls information for recombinant human insulin drug substance is contained in Drug Master File (b) (4). This DMF was reviewed and found adequate as a source of human insulin drug substance for this NDA. The drug substance consists of (b) (4) human recombinant insulin isolated from a strain of K12 E. coli. The A and B chains of insulin, consisting of 21 and 30 amino acid residues respectively, are linked by 2 disulfide bridges. The A chain also contains one intra-chain disulfide bridge. Stability studies demonstrated that the human insulin drug substance is stable for at least (b) (4) months at (b) (4) C; a

Executive Summary Section

(b) (4)-month shelf life is granted for the drug substance. A summary of information regarding the recombinant human insulin drug substance may be found in the review of DMF (b) (4)

Drug Product

The drug product is a white powder filled in (b) (4) plastic cartridges sealed in opaque foil stick packs that are intended to be opened immediately before use in the inhaler device. The cartridges contain either 5 or 10 milligrams of a powdered formulation containing (b) (4) mg of human insulin, respectively. The cartridges are manufactured specifically for use in the Afrezza inhaler device, (b) (4)

(b) (4) For additional details regarding the operation of the inhaler, its components, and its use with the cartridges, please refer to Dr. Alan Schroeder’s review.

The drug product consists of crystalline particles of a novel excipient coated with insulin drug substance, with trace amounts of polysorbate 80 (b) (4)

(b) (4) Table 1 below shows the composition of the two inhaler cartridge dosage strengths. Insulin content corresponds to (b) (4) mg of human insulin per 15 USP units and (b) (4) mg insulin per 30 USP units.

Table 1: Composition of Each Cartridge Dosage Form

Component	15U (5mg) dose strength	30U (10 mg) dose strength
	Quantity per cartridge	Quantity per cartridge
Insulin	15 U	30 U
FDKP	(b) (4)	
Polysorbate 80 ^a	(b) (4)	
(b) (4)	(b) (4)	
(b) (4)		

The novel excipient FDKP, which constitutes approximately (b) (4) % of the mass of the particles, is (*E*)-3,6-bis[4-(*N*-carboxy-2-propenyl)amidobutyl]-2,5-diketopiperazine, abbreviated as fumaryl diketopiperazine or FDKP. The applicant provided complete manufacturing information for FDKP in an appendix to the chemistry, manufacturing, and controls section. (b) (4)

(b) (4)

(b) (4) uring development of the particle formulation (termed “Technosphere ” particles), FDKP was evaluated in comparison to other compounds for use as the particle-forming excipient. FDKP was found to be the ideal compound for forming the particle matrix because it crystallizes under acidic conditions and the crystals self-assemble to form particles with the appropriate properties. Technosphere[®] and Technosphere[®] Insulin particles are sized appropriately for inhalation, with a typical median particle diameter ~ 2-2.5µm. The particles dissolve readily under physiological conditions at neutral pH.

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The excipient for marketed lots of the drug product is manufactured at (b) (4). Lots of excipient used in batches of drug product for pivotal clinical studies and primary stability studies were manufactured by a different manufacturer, (b) (4). There are no significant differences in the quality and composition of excipient manufactured at each site, based on evaluation of their respective manufacturing process and impurities profiles, from information provided by the applicant. The only significant change to the FDKP manufacturing process was (b) (4). Appropriate bridging stability studies of the drug product were initiated by the applicant for lots of drug product containing FDKP manufactured at the (b) (4) site to demonstrate comparability to the FDKP (b) (4) manufacturing process. Bridging drug product stability studies were also performed for two different models of inhaler device and cartridge: the version primarily used for clinical trials is termed "Model C" and the intended marketed version is termed "Model D". A discussion of the comparability of these models may be found in Dr. Alan Schroeder's review. A pivotal bioequivalence study was conducted to bridge the Model C and Model D devices, and the review conducted by CDRH concluded that the applicant provided adequate validation to demonstrate the comparability of the two models.

The commercial drug product manufacturing process consists of (b) (4)

(b) (4) commercial process for manufacturing of the drug product is comparable to the (b) (4) pilot process used for manufacturing of the clinical and primary stability batches, based on the information provided.

The impurities present in the drug product consist of typical insulin -related substances found in USP human insulin as well as insulin-FDKP adduct impurities. The applicant has characterized these impurities as (b) (4)

(b) (4) The proposed thresholds for the insulin-related impurities and high molecular weight proteins were deemed to be too broad based upon the levels of these impurities reported in clinical lots of drug product. The applicant agreed to lower the acceptance criteria for these impurities to acceptable levels. Impurities from the FDKP excipient that are carried over into the drug product are reduced relative to their levels in the excipient substance and are found at consistently low levels across batches of the drug product. Based upon a lack of evidence for

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any degradation of FDKP in all batches of drug product on stability, FDKP-related impurities were not included in the commercial drug product specification.

Stability studies of the drug product were conducted for a total of 12 batches of drug product manufactured at (b) (4) % of the intended commercial scale and filled in the to-be-marketed presentation, plastic cartridges in unit-of-use foil stick packs. 6 of the primary batches (3 of each dosage strength) were manufactured at the (b) (4) sites, respectively, to bridge the two manufacturing sites. These 12 primary batches were manufacturing using FDKP excipient substance manufactured at (b) (4) and filled in the Model C cartridges used in clinical trials. For bridging purposes, an additional 6 batches of drug product (3 batches of each dose strength) containing FDKP manufactured at (b) (4) (the commercial supplier of FDKP) and filled in the Model D cartridge (the commercial cartridge) were placed on stability. The results of these stability studies revealed (b) (4)

(b) (4) Based upon the clinical batch data and the results of stability studies, a (b) (4) shelf life for storage at 2-8°C is granted with an additional (b) (4) of storage at room temperature permitted before use or disposal of the Afrezza drug product.

B. Description of how the drug product is intended to be used

Afrezza is an orally inhaled insulin therapy intended to be used before meals by adult diabetic patients. It is intended to be a replacement for prandial injectable insulin but should be accompanied by use of an injectable, long-acting form of insulin, as part of a regimen for glycemic control. Afrezza is supplied as a reusable inhaler device with disposable cartridges in two dosage strengths. The dosage strengths are 5 or 10 mg of Technosphere-insulin inhalation powder, each containing 15U ((b) (4) mg) or 30 U ((b) (4) mg) of recombinant human insulin, respectively. (b) (4)

(b) (4) The total dose to be administered by the patient before each meal is comprised of one or more cartridges of appropriate dosage strengths based upon the individual diabetic patient's requirements for glycemic control, in consultation with a physician.

C. Basis for Approvability or Not-Approval Recommendation

See the introductory section of Review #2 of DMF (b) (4) for comments regarding the basis for finding the source of insulin drug substance to be adequate.

For the Technosphere® insulin drug product, which consists of crystalline particles of fumaryl diketopiperazine coated with insulin, the manufacturing process was suitably described and critical process steps and intermediates were appropriately controlled during manufacture of the drug product. As part of formulation and manufacturing development, appropriate studies were conducted to establish optimal conditions for excipient particle formation, insulin deposition, and (b) (4) of the insulin-coated particles. A suitably controlled manufacturing process was established for the excipient fumaryl diketopiperazine, and the impurities generated in the manufacture of the excipient are adequately controlled by its specification. The final drug product specification and stability data provided by the applicant provide assurance that the

Executive Summary Section

quality of the drug product will be maintained throughout its shelf life and during the period of use by diabetic patients.

The applicant has satisfactorily addressed all issues and deficiencies raised during the CMC review of the drug substance and drug product, and the CMC recommendation is approval. For discussion of the basis for approvability based on the device and container closure aspects of the drug product, see Dr. Alan Schroeder's review. A final recommendation from the Office of Compliance is pending, and the CMC recommendation does not incorporate any potential facility inspection issues.

III. Administrative**A. Reviewer's Signature**

Theodore Carver, CMC Reviewer, ONDQA/PMA Division I

B. Endorsement Block

T. Carver/CMC Reviewer, 12/08/09
P. Prasad/Acting Team Leader, 12/08/09

C. CC Block

Suong Tran/Lead Chemist, 12/08/09
Rachel Hartford/RPM, 12/08/09

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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/

THEODORE E CARVER

12/18/2009

Approved by CMC. Facilities inspections are still pending.

PRASAD PERI

12/18/2009

I concur

NDA 22-472

Afrezza (insulin, human [rDNA]) Inhalation Powder

MannKind Corporation

Chemistry Review #1

December 9, 2009

Recommendation: Approvable

Alan C. Schroeder, Ph.D.

**ONDQA/Division I/Branch II
for**

Division of Metabolism and Endocrine Drug Products

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Chemistry Review Data Sheet

1. NDA 22-472
2. REVIEW #: 1
3. REVIEW DATE: December 9, 2009
4. REVIEWER: Alan C. Schroeder, Ph.D.

5. PREVIOUS DOCUMENTS:

Previous Documents

Document Date

N.A.

6. SUBMISSION(S) BEING REVIEWED:

Submission(s) Reviewed

Original NDA dated March 16, 2009
Amendment dated June 11, 2009
Amendment dated July 22, 2009
Amendment dated August 14, 2009
Amendment dated September 11, 2009
Amendment dated September 29, 2009
Amendment dated October 12, 2009
Amendment dated October 30, 2009
Amendment dated November 30, 2009
2 Amendments dated December 4, 2009

Chemistry Review Data Sheet

7. NAME & ADDRESS OF APPLICANT:

Name: MannKind Corporation
Address: 61 South Paramus Road
Paramus, NJ 07652
Representative: Eileen Wyka, MS
Senior Director, CMC Regulatory Affairs
Telephone: 201-983-5024

8. DRUG PRODUCT NAME/CODE/TYPE:

- a) Proprietary Name: Afrezza Inhalation Powder
- b) Non-Proprietary Name (USAN): insulin, human [rDNA]
- c) Code Name/# none provided
- d) Chem. Type/Submission Priority:
 - Chem. Type: 5 (new manufacturer)
 - Submission Priority: S

9. LEGAL BASIS FOR SUBMISSION: 505(b)(1)

10. PHARMACOL. CATEGORY:

Anti-diabetic

11. DOSAGE FORM: inhalation powder (pre-metered DPI)

12. STRENGTH/POTENCY:

30U cartridge provides (b)(4) emitted dose (target)
15U cartridge provides (b)(4) emitted dose (target)
[Note that the target insulin load is 3.0U/mg of the drug formulation.]

13. ROUTE OF ADMINISTRATION: oral inhalation

14. Rx/OTC DISPENSED: Rx OTC

Chemistry Review Data Sheet

15. [SPOTS \(SPECIAL PRODUCTS ON-LINE TRACKING SYSTEM\):](#) SPOTS product – (See Dr. Carver's review) Not a SPOTS product

16. CHEMICAL NAME, STRUCTURAL FORMULA, MOLECULAR FORMULA, MOLECULAR WEIGHT:

3.2.S.1.1 Nomenclature (Insulin Human, (b) (4))

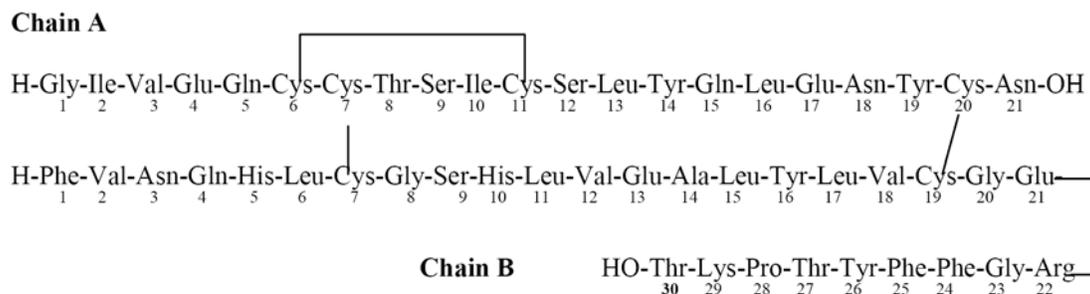
Recommended International Nonproprietary Name (rINN):	rec human insulin
Pharmacopoeia name(s) Ph. Eur. USP	insulin, human insulin human, recombinant
Other non-proprietary name(s): US Adopted Name (USAN) British Approved Name (BAN)	insulin human Human Insulin
CAS Registry Number	11061-68-0

Chemistry Review Data Sheet

3.2.S.1.2.1 Structural Formula (Relative Stereochemistry):

Insulin consists of two polypeptide chains, A and B. The A chain has 21- amino acids and the B chain has 30 amino acids. The chains are lined together through the sulfur atoms of cysteine (Cys).

Figure 1: Structural formula of recombinant human insulin



17. RELATED/SUPPORTING DOCUMENTS:

A. DMFs:

[Note that the status of DMF (b)(4) for insulin is included in Dr. Ted Carver's separate review of this NDA]

DMF #	TYPE	HOLDER	ITEM REFERENCED	CODE ¹	STATUS ²	DATE REVIEW COMPLETED	COMMENTS
(b)(4)	III	(b)(4)	(b)(4)	1	Adequate	6/05/2009 A. Schroeder	(b)(4)
	III			1	Adequate	6/09/2009 A. Schroeder	
	III			3	Adequate	3/23/2006 C. Bertha found this (b)(4) to be adequate (b)(4)	

Chemistry Review Data Sheet

						there is no new technical information about this ^{(b) (4)} in this DMF subsequent to Dr. Bertha's review.	
^{(b) (4)}	III		^{(b) (4)}	4			
	III			1	Adequate	6/22/2009 A.Schroeder	
	III			1	Adequate	6/24/2009 A. Schroeder	

¹ Action codes for DMF Table:

1 – DMF Reviewed.

Other codes indicate why the DMF was not reviewed, as follows:

2 –Type 1 DMF

3 – Reviewed previously and no revision since last review

4 – Sufficient information in application

5 – Authority to reference not granted

6 – DMF not available

7 – Other (explain under "Comments")

² Adequate, Inadequate, or N/A (There is enough data in the application, therefore the DMF did not need to be reviewed)

B. Other Documents:

DOCUMENT	APPLICATION NUMBER	DESCRIPTION
IND	61729	associated IND for this drug product

Chemistry Review Data Sheet

18. STATUS:

[See Dr. Carver's CMC review for this status table]

ONDC:

CONSULTS/ CMC RELATED REVIEWS	RECOMMENDATION	DATE	REVIEWER
Biometrics	not considered necessary for performance stability data in this application		
EES	pending		
Pharm/Tox	informal consult is pending (consult by e-mail) – see information in this review. This pertains to safety evaluation of extractables, leachables and foreign particulates.		
Biopharm	N.A.		
LNC	N.A.		
Methods Validation	pending		
EA	Adequate per Dr. Ted Carver's review		Dr. Ted Carver
Microbiology	Approve	9/22/2009	Dr. Denise A. Miller
CDRH	pending		Dr. Melanie Choe
Radiopharmaceutical	N.A.		

The Chemistry Review for NDA 22-472

The Executive Summary

This is a team review. See Dr. Theodore Carver's review for a separate review of the rest of the CMC material in this NDA.

This review pertains to limited parts of the NDA (i.e., the inhaler device and the drug product performance) which were reviewed in this review. Note that the device is currently being separately evaluated by the CDRH reviewer.

I. Recommendations

A. Recommendation and Conclusion on Approvability

This conclusion is with reference to the sections of the NDA reviewed in this review only. This application is APPROVABLE pending satisfactory responses to the additional comments near the end of this review, and pending a satisfactory CDRH consult review of the inhaler device, satisfactory facilities status from the Office of Compliance (EES), and satisfactory safety review of extractables, leachables and foreign particulates from the pharmacology/ toxicology reviewer. The CDRH consult review will assess (in collaboration with this ONDQA reviewer) the proposed shelf life and the proposed in use life of the device.

B. Recommendation on Phase 4 (Post-Marketing) Commitments, Agreements, and/or Risk Management Steps, if Approvable

The applicant has made the following post-approval agreements:



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(b) (4)

The standard stability commitment is provided, plus the following stability commitments:

- “Continuation of on-going stability protocols, which includes the first 3 production batches from the validated process.
- Minimum of 5% of the batches manufactured per year for the first three years (not to exceed 10 additional batches of each marketed strength product) will be placed in the post approval stability program.
- For year four and beyond, representative samples from one batch of each marketed strength product will be included in the program for each year.
- Results from on-going and future studies will be periodically submitted to the application in the NDA annual report.
- If any significant manufacturing changes occur that require re-validation of the process then the stability program will revert back to the protocol provided for the first three production batches incorporating the manufacturing changes.”

II. Summary of Chemistry Assessments

A. Description of the Drug Product(s) and Drug Substance(s)

The drug substance is human insulin (recombinant). Its manufacturing and controls information are provided in DMF (b) (4). This is separately reviewed by Dr. Ted Carver.

The drug product is manufactured from Insulin Human USP, recombinant, and the following excipients and manufacturing aids: fumaryl diketopiperazine (FDKP), Polysorbate 80 NF, (b) (4)

“The Technosphere® Insulin Inhalation Powder / MedTone® Inhaler system includes single-use, pre-metered

Executive Summary Section

cartridges that are manually inserted into a re-useable, breath-powered, high resistance dry powder inhaler. The pre-metered powder is provided in 5 mg and 10 mg fill weights [of formulated drug, containing 15U and 30U, of insulin, respectively]... The secondary packaging around the plastic cartridge and its drug content provides environmental protection and pertinent labeling information.



See additional comments in Dr. Theodore Carver's CMC review.

B. Description of How the Drug Product is Intended to be Used

See above and see comments in Dr. Theodore Carver's CMC review.

C. Basis for Approvability or Not-Approval Recommendation

This review pertains to limited parts of the NDA (i.e., the inhaler device and the drug product performance) which were reviewed in this review. Note that the device is currently being separately evaluated by the CDRH reviewer.

The particle size distribution data from analysis of the emitted dose of the drug product, show some decrease in particle size (Mass Mean Aerodynamic Diameter) with increasing airflow rate through the device (

Information from clinical study MKC-TI-129 suggests that some diabetes patients could only generate air flow rates below 20 liters per minute, although mean values in these study appear to be in the mid 20's for LPM. Therefore the particle size distribution (which may determine regions of

Executive Summary Section

lung deposition) varies with patient air flow rates, especially at lower airflow rates. This information has been shared with the clinical reviewers for their consideration.

Over 10,000 model C inhalers were given to patients in phase 2 and phase 3 studies. The applicant has stated that no serious adverse events associated with device failure and/or malfunction were reported. The applicant also claims to be unaware of any adverse events resulting from device failure. The main complaints about the product in the clinical studies were for [REDACTED] (b) (4) and these defects are said to have been rectified through design modifications.

The Model C inhaler (with the Model C cartridge) was used in phase III studies, and the Model D inhaler (with the Model D cartridge) is proposed for marketing. It is claimed that the improvements in Model D did not alter the air flow path through the device relative to Model C, and the functionality of the device was not changed. Model D has a somewhat higher mean emitted dose in this study than does Model C, and this applies to both the 30 U and 15 U cartridges. This mean difference in emitted dose (i.e., greater emitted dose for Model D than for Model C) is (b) (4) % for the 15U cartridges, and (b) (4) % for the 30U cartridges. The aerodynamic particle size distributions (APSD) are similar (especially for fine particles) between Model C and Model D in the data which were provided for a small sampling of C and D inhalers, although not identical. Some of the APSD differences may only be due to variability of the test. The data provided in the original NDA do support the similarity of the performance of the Model C and Model D inhalers.

Overall, the stability data (for drug product stored a [REDACTED] (b) (4) C) show that the aerodynamic particle size distribution and the delivered dose uniformity are not trending parameters.

See additional Executive Summary comments in Dr. Theodore Carver's CMC review.

III. Administrative

A. Reviewer's Signature

B. Endorsement Block

Alan C. Schroeder, Ph.D./Date: 12/9/2009
Prasad Peri, Ph.D./
Rachel Hartford/

C. CC Block

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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/

ALAN C SCHROEDER
12/09/2009

PRASAD PERI
12/09/2009

Initial Quality Assessment

Division of Metabolism and Endocrinology Products

NDA: 22-472

Applicant: MannKind Corp.

Stamp Date: 16-MAR-2009

PDUFA Date: 16-JAN-2010

Proposed Proprietary Name: Afresa

Established Name: Insulin Human [rDNA origin]

Dosage form and strength: Dry powder for inhalation, 15 or 30 filled units/
cartridge

Route of Administration: Oral inhalation

Indications: Treatment of Type 1 and Type 2 diabetes mellitus

PAL: Su (Suong) Tran, Branch II/DPA I/ONDQA

ONDQA Fileability: Yes

Filing date: 15-MAY-2009

Comments for 74-Day Letter: Yes, on the last page.

Initial Quality Assessment

CONSULTS/ CMC RELATED REVIEWS	COMMENT
Biopharm	<i>May not be applicable. This is an inhalation product, and all the dosage strengths were used in Phase 3 studies.</i>
CDRH	Review of the mechanical aspects of the inhalation device (e.g., design, mechanism, usage, specification, robustness)
EA	Categorical exclusion request will be assessed by Primary Reviewer.
EES	EER was sent to Office of Compliance on 01-APR-2009.
OSE	<i>Labeling consult request will be sent as part of DMEP's request.</i>
Methods Validation	<i>Validation may be requested of FDA labs after test methods are finalized.</i>
Microbiology	Review of microbial limits.
Pharm/Tox	Review of limits on (b) (4) polysorbate 80, impurities, extractables, and particulates.

Summary:

This is an electronic NDA, filed as a 505(b)(1) application. The associated IND is IND 61729.

- The drug substance is human insulin and is produced by recombinant DNA (rDNA) technology in the non-pathogenic laboratory of *Escherichia coli* K12.
- The drug product, “Technosphere® Insulin”, is a (b) (4) powder with 3 units of insulin per milligram of formulation. It consists of insulin adsorbed onto a carrier excipient called Technosphere® particles. The Technosphere particles are crystallized FDKP (fumaryl diketopiperazine, a novel excipient), which self-assembles into spherical particles. The product formulation contains (b) (4)
- The drug product and delivery system consists of the drug product powder in a plastic, unit-dose (pre-metered), single-use cartridge and a dedicated re-useable (one-year use) inhalation device (inhaler). Each single-use cartridge contains 15 filled units of insulin (5 mg formulation, with 3 units/mg) or 30 filled units of insulin (10 mg formulation with 3 units/mg). (b) (4)

Initial Quality Assessment

- At the 14-JUL-2008 pre-NDA meeting, the sponsor informed FDA that the clinical studies were conducted with the Model C inhaler (with dedicated drug-filled cartridges) and the commercial product will have a new Model D inhaler (with dedicated drug-filled cartridges). FDA required that a pivotal bioequivalence study be conducted to bridge the two devices, in addition to comparative CMC information.
- The proposed labeling states that the dosage strengths are “4 units” and “8 units”. This reviewer requested an explanation for the difference between these labeled strengths and the metered amounts of 15 units and 30 units per cartridge. On 07-APR-2009 the applicant explained that the labeled “4 units” and “8 units” are based on the in vivo correlated amounts of absorbed insulin after a subcutaneous injection, for example, the 15-unit cartridge provides similar exposure as the 4-unit subcutaneous injection. This issue was conveyed to OSE and the Clinical team for their assessment. From the CMC perspective, the dosage strength should be the metered amount of the drug substance per unit dose, so it should be “15 units” or “30 units” per cartridge.
- The applicant proposes (b) (4) to be the established name, which is not acceptable because it is not a USAN name. This issue was conveyed to OSE and the Clinical team for their assessment. From the CMC perspective, the established name should be “insulin human [rDNA]”.

The following table is from the applicant’s proposed labeling:



(b) (4)

CRITICAL ISSUES

Has all information requested during the IND phases, and at the pre-NDA meetings been included?

Yes. The NDA includes some information as requested by FDA during the IND development. There is no item-by-item response to FDA's comments, which makes it difficult to assess in the limited time allotted for this filing memo/IQA whether the applicant has provided a satisfactory response to each question.

The primary reviewer will assess the information in the NDA and decide whether issues previously raised have been satisfactorily addressed.

ONDQA review team:

It is recommended that the CMC information of the NDA be reviewed by two chemists: one chemist will evaluate all information on the drug substance insulin, the novel excipient FDKP (fumaryl diketopiperazine), and most of the information on the drug product except for that on the product-specific performance of the inhalation device and cartridge system, which will be reviewed by another chemist with experience with inhalation drugs.

Consults and CMC-related reviews:

- The Microbiology Team will review the microbial limits proposed for the drug product.
- The Center for Devices and Radiological Health (CDRH) will review mechanical aspects of the inhalation device (e.g., design, mechanism, usage, specification, robustness). The product-specific performance of the device will be reviewed by the ONDQA chemists.

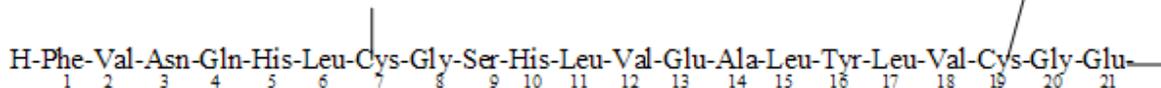
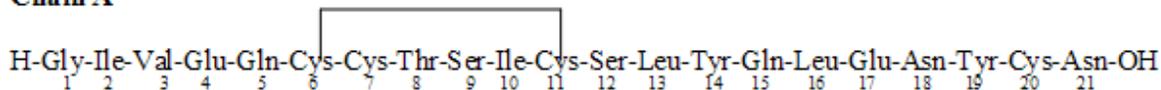
Critical issues: To be discussed in the following sections.

Initial Quality Assessment

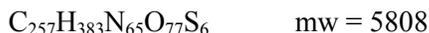
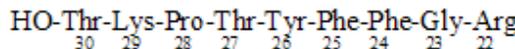
Drug substance:

The drug substance is human insulin and is produced by recombinant DNA (rDNA) technology in the non-pathogenic laboratory strain of *Escherichia coli* K12. Insulin consists of two Cysteine-linked polypeptide chains, A with 21 amino acids and B with 30 amino acids.

Chain A



Chain B



Reference is made to DMF (b) (4) (holder: (b) (4)) for all CMC information on the drug substance. The NDA includes the drug substance specification (copied on page 28 of this review), which complies with the USP monograph for insulin. MannKind, the drug product manufacturer (same as applicant), will perform confirmatory testing of the drug substance for appearance, identity by IR and HPLC, assay, purity, related compounds, and loss on drying.

Critical Issues:

No specific comment regarding the CMC information on the drug substance can be discussed in this review because the information is in a DMF. The following general issues will be evaluated by the primary reviewer in the review of DMF (b) (4)

- **History and characteristics of the recombinant cell line.** The reviewer will document the source of (b) (4). The reviewer will also confirm that the same cell line was used throughout the IND development and for the commercial product, or document any difference.
- **Characterization and stability testing of the master and working cell banks (MCB and WCB, respectively) and the end-of-production (EOP) cells.** The reviewer will document the generation of the cell bank system (master cells and working cells) and will evaluate the characterization of these cell banks and the end-of-production (EOP) cells. The cell bank characterization will include information on adventitious agents. The reviewer will confirm that

Initial Quality Assessment

there is a stability test program in place for the cell banks, and that the EOP cells are shown to retain the required characteristics of the cell line (viability, phenotype, DNA sequence, etc.)

- **Manufacture of the drug substance.** The reviewer will document all steps in the manufacture of insulin and will evaluate the critical process controls and validation data (b) (4))
- **Comparability of the drug substance used in the clinical studies, stability studies, and commercial drug product.** The reviewer will confirm that there is no change to the manufacturing process of the drug substance used in the Phase 3 clinical studies, primary stability studies, and commercial drug product. If there are differences, the reviewer will document them, evaluate comparability data (refer to ICH Q5E), and confirm that the differences in manufacturing should have no impact on the quality (pertinent to safety and effectiveness) of the commercial product.
- **Characterization of the drug substance.** The reviewer will confirm that the proposed structure of the drug substance is adequately supported by analytical data. The characterization results will determine what attributes should be added to the specifications. An evaluation of the product-related substances will be necessary to document molecular variants that have full biological activity comparable to insulin. In addition, the reviewer will evaluate the characterization of process-related and product-related impurities and assess the capability of the purification process to remove/reduce them. As per ICH Q6B, acceptance criteria or limits for impurities should be based on data from nonclinical, clinical, and stability batches. The reviewer will determine whether each limit is adequately justified. In particular, the biologically active product-related substances, if any, should have individual limits
- **Specification of the drug substance.** A copy of the proposed drug substance specification is on page 28 of this review. It complies with the USP monograph for insulin. MannKind, the drug product manufacturer (same as applicant), will perform confirmatory testing of the drug substance for appearance, identity by IR and HPLC, assay, purity, related compounds, and loss on drying. Based on the characterization and stability results, the reviewer will determine whether the proposed specification is adequate for quality control of the drug substance. Additional tests, beyond those in the USP monograph, may be required in the specification if necessary to ensure the safety and effectiveness of the final drug product. See the previous comments on impurities. Reference standards used in the analytical methods will also be evaluated.

Initial Quality Assessment

- **Container closure and shelf life of the drug substance.** The reviewer will evaluate the safety and compatibility of the container closure system used to store the drug substance. Based on all available stability data and with no extrapolation to extend the dating period beyond the long term data, the reviewer will determine a shelf life (i.e., not a retest period) for the protein drug substance.

Initial Quality Assessment

Drug product:

[Redacted] (b) (4)

Route of administration	Oral inhalation
Dosage form	Powder
Package type	[Redacted] (b) (4)
Potency	15 or 30 filled units of insulin per cartridge, 3 units/ mg formulation

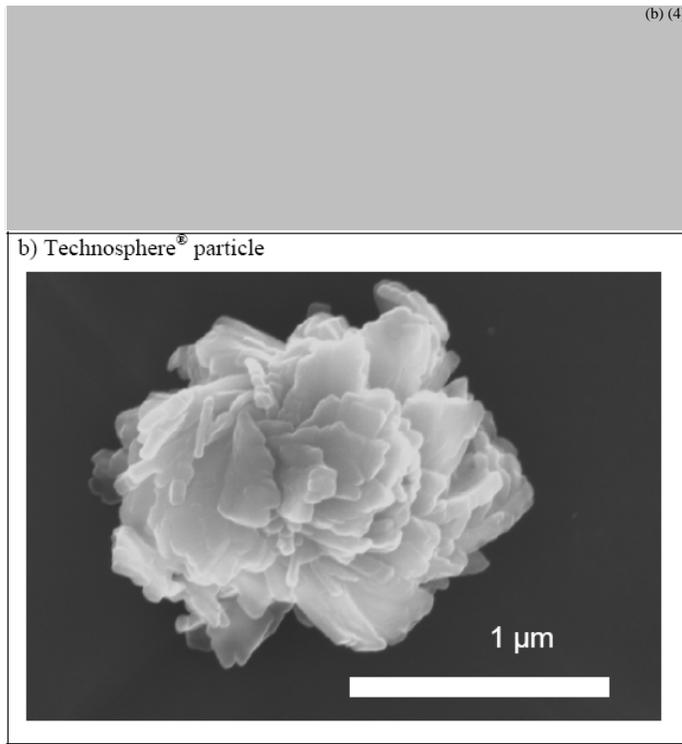
The drug product and delivery system consists of the drug product as a powder in a plastic, unit-dose cartridge and a dedicated one-year-use plastic inhalation device (inhaler). Each single-use cartridge contains 15 filled units of insulin (5 mg formulation with 3 units/mg) or 30 filled units of insulin (10 mg formulation with 3 units/mg).

[Redacted] (b) (4)

The drug product, “Technosphere® Insulin”, consists of insulin adsorbed onto a carrier excipient called Technosphere® particles. The Technosphere particles are crystallized FDKP (fumaryl diketopiperazine, a novel excipient), which self-assembles into spherical particles. The particles are highly porous [Redacted] (b) (4) % porosity), [Redacted] (b) (4) have a median diameter of approximately 2.5 µm, and 90% of the particles are smaller than 5 µm. The Technosphere particles have low solubility in acid (FDKP crystallizes under acidic conditions). They readily dissolved at neutral (physiological conditions) or basic pH.

Initial Quality Assessment

Figure 6. Morphology of FDKP crystal and Technosphere® particle



Quantitative Composition of Technosphere® Insulin Powder

Component	Grade	Quantity (per mg of formulation)	Function
Insulin Human Recombinant	USP	3.0 U ^a	Drug Substance
Fumaryl Diketopiperazine (FDKP)	In-house	(b) (4)	Raw material to form carrier particle
Polysorbate 80	NF		(b) (4)
(b) (4)			
(b) (4)			

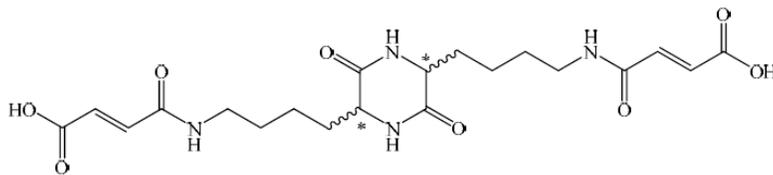
Initial Quality Assessment

Critical Issues:

- **Composition.** The quantitative and qualitative composition statement (copied above) is incomplete because it does not include the amount of each component and total fill weight on a per-unit basis. The applicant should provide the complete quantitative composition (i.e., amount of each component that is in the final drug product and total fill weight) of the drug product per cartridge for each dosage strength. In addition, the content of polysorbate 80 present in the product should be indicated as supported by batch analysis data.
- **Dosage strength.** The drug product is labeled by potency units, not by mass. There are two issues concerning this labeling.
 - [This issue is also discussed earlier in this review.] This reviewer requested an explanation for the difference between these labeled strengths and the pre-metered amounts of 5 units and 30 units per cartridge. On 07-APR-2009 the applicant explained that the labeled “4 units” and “8 units” are based on the correlated amounts of absorbed insulin after a subcutaneous injection, for example, the 15-unit cartridge provides similar exposure as the 4-unit subcutaneous injection. This issue was conveyed to OSE and the Clinical team for their assessment. From the CMC perspective, the dosage strength should be the pre-metered amount of the drug substance per unit dose, in this case, it should be 15 units or 30 units per cartridge.
 - [This issue is also discussed later in this review.] Insulin assay is determined by reverse-phase chromatography (RP-HPLC) which quantifies the protein mass, not the biological activity (potency). The applicant calculates the potency of the product by using the specific activity of the USP reference standard. This calculated potency may not reflect the actual biological activity of the product. The applicant should provide data to show the correlation between the potency calculated from HPLC results and the actual potency of the product.

Initial Quality Assessment

- Novel excipient **FDKP (fumaryl diketopiperazine)**.



Chemical name(s) (E)-3,6-bis[4-(N-carboxy-2-propenyl)amidobutyl]-2,5-diketopiperazine

3,6-bis[N-fumaryl-N-(n-butyl)amino]2,5-diketopiperazine

The NDA includes CMC information on this novel excipient in the 3.2.A Appendices section.

The primary reviewer will review the information with the same level of details as that on a drug substance. The applicant claims that FDKP-impurities (b) (4)

(b) (4)

(b) (4) were qualified in toxicology studies (supposed to be in Section 2.6.6.9 of NDA). This information was conveyed to the PharmTox team for their assessment. The primary reviewer will confirm that the remaining impurities (such as (b) (4) are

(b) (4) and do not require qualification. (b) (4)

(b) (4)

(b) (4)

(b) (4)

During the IND development, the manufacturer of FDKP was changed from (b) (4)

in (b) (4) to (b) (4) in (b) (4). The (b) (4) FDKP will be used in the commercial drug product. The NDA includes stability data on FDKP from both manufacturers. Six drug product batches were manufactured with the (b) (4) FDKP and placed on stability. The batch numbers are: PPT2008.27, PPT2008.28, PPT2008.29, PPT2008.30, PPT2008.31, and PPT2008.32.

Batches PPT2008.27 and PPT2008.28 were used in toxicology studies.

Taking into account the material's properties and comparability of all available data for FDKP produced by different manufacturers and the resulting drug product batches, the reviewer will determine whether the proposed quality controls and manufacturing process will be adequate to produce an acceptable excipient for use in the commercial Technosphere particles.

Initial Quality Assessment

Manufacturing process of the drug product

The process consists of [REDACTED] (b) (4)
[REDACTED]. The flow diagram is copied
on pages 29-30 of this review.

Critical Issues:

- [REDACTED] (b) (4)

Initial Quality Assessment

From: Ferguson, Shirnette D
Sent: Wednesday, March 25, 2009 3:48 PM
To: Tran, Suong T
Cc: Stock, Marisa
Subject: RE: question about novel excipients and inhalation devices
[This is true, novel excipients and inhalation devices are not entered into EES.](#)

[Shirnette](#)

From: Tran, Suong T
Sent: Wednesday, March 25, 2009 1:41 PM
To: CDER EESQUESTIONS
Subject: question about novel excipients and inhalation devices

Hello!

I'd like to confirm that manufacturers and testers of a novel excipient or of an inhalation device are NOT entered into an EER. This was the case in the past. Please confirm that this is still true!

Thank you for your help!

[Su](#)

Su (Suong) Tran, PhD
Pharmaceutical Assessment Lead
(Division of Metabolism and Endocrinology Products)
Pre-Marketing I/ ONDQA
301.796.1764

Initial Quality Assessment

DRUG SUBSTANCE SPECIFICATION

Table 3. Specifications of Insulin Human Recombinant

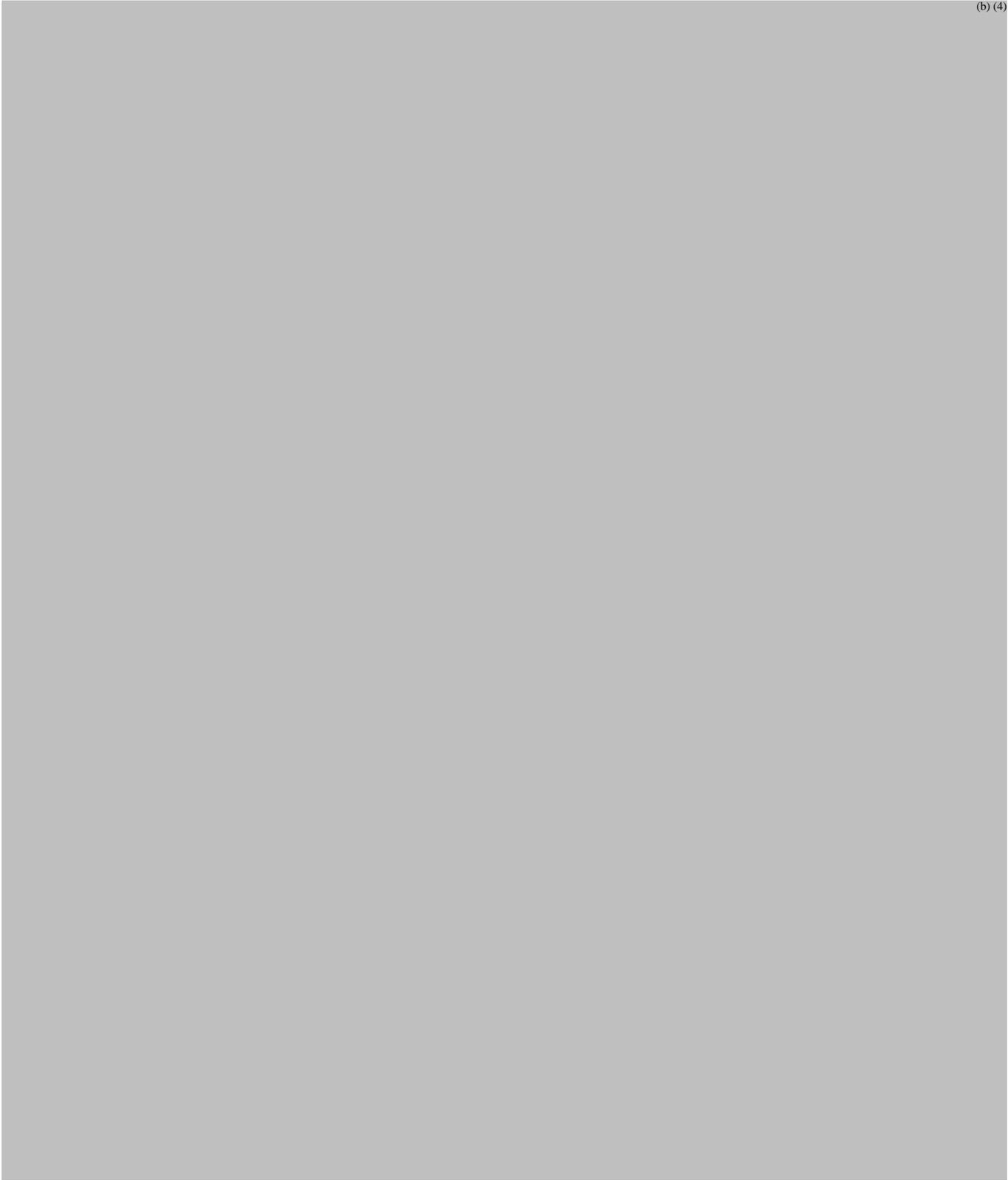
Attribute	Method or Source	Acceptance Criteria
Appearance (Visual)	TM5520	White to practically white powder or crystals
Identification (IR)	TM5437	Corresponds to standard
USP – Identification (HPLC)	USP Insulin Human Monograph	Major peak of sample corresponds to standard retention time
USP – Insulin Assay (HPLC, Dry Basis)	USP Insulin Human Monograph	NLT 27.5 U/mg
USP – Loss on Drying	USP Insulin Human Monograph	NMT 10.0%
USP- Insulin Purity (HPLC)	USP Related Compounds Test	NLT 96.0% (area %)
USP – Related Compounds (HPLC) -A21 Desamido Insulin -Total Others (b) (4)	USP Insulin Human Monograph	A21 Desamido Insulin NMT 2.0% Total Others NMT 2.0%
(b) (4)	Vendor COA	NMT (b) (4)

Attribute	Method or Source	Acceptance Criteria
USP – Bioidentity	Vendor COA	Conform to requirement
USP – Microbial Limits/ Viable Counts	Vendor COA	NMT (b) (4) CFU/g
USP – Bacterial Endotoxins (LAL)	Vendor COA	NMT (b) (4) EU/mg
USP – Identification (Peptide Mapping)	Vendor COA	Corresponds to Standard
USP – Zinc Content (Dry Basis)	Vendor COA	NMT (b) (4) %
USP – High Molecular Weight Proteins (SEC)	Vendor COA	NMT (b) (4) %
USP – Host Cell Proteins (EIA)	Vendor COA	NMT (b) (4) ppm
NMT = Not More Than NLT = Not Less Than		

Initial Quality Assessment

2.3.P.3.3.2 Process Flow Schematic

(b) (4)



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Initial Quality Assessment

DRUG PRODUCT SPECIFICATION

Table 8. Technosphere® Insulin Inhalation Powder Specifications

Attribute	Method	Acceptance Criteria									
Appearance	TM5518	(b) (4)									
Insulin Identification	TM5508	Sample retention time corresponds to USP standard (± 3%)									
Insulin Assay (HPLC)	TM5508	(b) (4)									
Insulin related Compounds (HPLC)	TM5508	<table border="0"> <tr> <td>A-21 desamido insulin:</td> <td>NMT</td> <td rowspan="4">(b) (4)</td> </tr> <tr> <td>Insulin Adducts Group:</td> <td>NMT</td> </tr> <tr> <td>Individual Unspecified Impurity:</td> <td>NMT</td> </tr> <tr> <td>Total Others:</td> <td>NMT</td> </tr> </table>	A-21 desamido insulin:	NMT	(b) (4)	Insulin Adducts Group:	NMT	Individual Unspecified Impurity:	NMT	Total Others:	NMT
A-21 desamido insulin:	NMT	(b) (4)									
Insulin Adducts Group:	NMT										
Individual Unspecified Impurity:	NMT										
Total Others:	NMT										
High Molecular Weight Proteins (SEC)	TM5504	NMT (b) (4)									

Initial Quality Assessment

Attribute	Method	Acceptance Criteria
Uniformity of Dosage Units (Content Uniformity)	TM5515	(b) (4)
Uniformity of Emitted Dose	TM5514	(b) (4)

Initial Quality Assessment

Attribute	Method	Acceptance Criteria
Aerodynamic Particle Size Distribution (HPLC)	TM5516	(b) (4)
Foreign Particulate	TM5471	NMT (b) (4)
		(b) (4)
		(b) (4)
Microbial Limits ^a	USP <61> USP <62>	Total Aerobic Microbial Count NMT (b) (4) CFU/g Total Yeast and Mold Count NMT (b) (4) CFU/g Specified Microorganisms: <ul style="list-style-type: none"> • Absence of <i>S. aureus</i> per gram • Absence of <i>P. aeruginosa</i> per gram • Absence of Bile-tolerant gram negative bacteria per gram
^a The microbial limit method uses a weight adjusted sample of (b) (4)		

Initial Quality Assessment

CHEMISTRY NDA FILEABILITY CHECKLIST

IS THE CMC SECTION OF APPLICATION FILEABLE? Yes

The following parameters are necessary in order to initiate a full review, i.e., complete enough to review but may have deficiencies.

	Content Parameter	Yes	No	Comment
1	Is the section legible, organized, indexed, and paginated adequately?	x		
2	Are ALL of the manufacturing and testing sites (including contract sites) identified with full street addresses (and CFNs, if applicable)?	x		All facilities are listed.
3	Is a statement provided to indicate whether each manufacturing or testing site is ready for inspection or, if not, when it will be ready?		x	Request for this statement will be part of the 74-day letter.
4	Is a statement on the Environmental Impact provided as required in 21 CFR 314.50(d)(1)(iii)?	x		Exclusion request per 21 CFR 25.31 is included.
5	Is information on the Drug Substance provided as required in 21 CFR 314.50(d)(1)(i)?	x		
6	Is information on the Drug Product provided as required in 21 CFR 314.50(d)(1)(ii)?	x		
7	If applicable, has all information requested during the IND phases and at the pre-NDA meetings been included?	x		
8	Have draft container labels and package insert been provided?	x		
9	Have all DMF References been identified?	x		
10	Is information on the investigational formulations included?	x		
11	Is information on the methods validation included?	x		
12	If applicable, is documentation on the sterilization process validation included?			(b) (4)

74-Day Letter – Draft Comments to the Applicant:

(on next page)

Initial Quality Assessment

74-Day Letter – Draft Comments to the Applicant:

1. The established name should be “insulin human [rDNA]” instead of your proposed (b) (4).
2. The labeled dosage strength should be the pre-metered dose of the drug substance: “15 units” or “30 units” per cartridge.
3. Provide the complete quantitative composition of the drug product per cartridge for each dosage strength (i.e., amount of each component present in the final drug product and total fill weight). Include the quantitative ranges for (b) (4) present in the product.
4. The only testing of the Technosphere particle is the in-process test (b) (4).
(b) (4) justify the lack of a more complete specification (with additional attributes such as specific surface area, porosity, shape, morphology) for the Technosphere particles, (b) (4).
5. Justify the lack of testing for (b) (4) in the drug product specification.
6. Revise the drug product specification to include the FDKP-related impurities that are present in the drug product.
7. You state that “3.0 U insulin human is equivalent to (b) (4) mg insulin human on a dried basis.” Provide data to show this equivalence and to show the correlation between the potency calculated from HPLC results and the actual potency of the product.
8. (b) (4)
9. Submit additional stability data for Batches PPT2008.31 and PPT2008.32 (formulated with the commercial (b) (4) FDKP and packaged in the commercial Model D cartridges), and Batches PPT2008.27, PPT2008.28, PPT2008.29, and PPT2008.30 (formulated with the commercial (b) (4) FDKP but packaged in the non-commercial Model C cartridges). The additional data should be received by FDA prior to Month 5 of the review cycle in order to be included in the determination of the expiration dating periods (long term and in-use) for your product.
10. (b) (4)
11. Confirm that the manufacturing and testing facilities listed in the NDA Form 356h are all the facilities involved in the manufacture and testing of the commercial drug substance and drug product, and indicate whether each facility is ready for inspection or, if not, when it will be ready.

**This is a representation of an electronic record that was signed electronically and
this page is the manifestation of the electronic signature.**

/s/

Suong Tran
5/4/2009 03:32:30 PM
CHEMIST

as we discussed

Ali Al-Hakim
5/4/2009 03:37:36 PM
CHEMIST