CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

022472Orig1s000

ADMINISTRATIVE and CORRESPONDENCE DOCUMENTS

EXCLUSIVITY SUMMARY

NDA # 022472 HFD # 510

Trade Name Afrezza

Generic Name (insulin human) Inhalation Powder

Applicant Name MannKind Corporation

Approval Date, If Known June 27, 2014

PART I IS AN EXCLUSIVITY DETERMINATION NEEDED?

1. An exclusivity determination will be made for all original applications, and all efficacy supplements. Complete PARTS II and III of this Exclusivity Summary only if you answer "yes" to one or more of the following questions about the submission.

a) Is it a 505(b)(1), 505(b)(2) or efficacy supplement?

YES ☒ NO ☐

If yes, what type? Specify 505(b)(1), 505(b)(2), SE1, SE2, SE3,SE4, SE5, SE6, SE7, SE8

505(b)(1)

c) Did it require the review of clinical data other than to support a safety claim or change in labeling related to safety? (If it required review only of bioavailability or bioequivalence data, answer "no.")

YES ☒ NO ☐

If your answer is "no" because you believe the study is a bioavailability study and, therefore, not eligible for exclusivity, EXPLAIN why it is a bioavailability study, including your reasons for disagreeing with any arguments made by the applicant that the study was not simply a bioavailability study.

NA

If it is a supplement requiring the review of clinical data but it is not an effectiveness supplement, describe the change or claim that is supported by the clinical data:

NA

d) Did the applicant request exclusivity?

YES ☒ NO ☐

If the answer to (d) is "yes," how many years of exclusivity did the applicant request?

3 years

e) Has pediatric exclusivity been granted for this Active Moiety?

YES ☐ NO ☒

If the answer to the above question in YES, is this approval a result of the studies submitted in response to the Pediatric Written Request?

IF YOU HAVE ANSWERED "NO" TO ALL OF THE ABOVE QUESTIONS, GO DIRECTLY TO THE SIGNATURE BLOCKS AT THE END OF THIS DOCUMENT.

2. Is this drug product or indication a DESI upgrade?

YES ☐ NO ☒

IF THE ANSWER TO QUESTION 2 IS "YES," GO DIRECTLY TO THE SIGNATURE BLOCKS ON PAGE 8 (even if a study was required for the upgrade).

PART II FIVE-YEAR EXCLUSIVITY FOR NEW CHEMICAL ENTITIES
(Answer either #1 or #2 as appropriate)

1. Single active ingredient product.

Has FDA previously approved under section 505 of the Act any drug product containing the same active moiety as the drug under consideration? Answer "yes" if the active moiety (including other esterified forms, salts, complexes, chelates or clathrates) has been previously approved, but this particular form of the active moiety, e.g., this particular ester or salt (including salts with hydrogen or coordination bonding) or other non-covalent derivative (such as a complex, chelate, or clathrate) has not been approved. Answer "no" if the compound requires metabolic conversion (other than deesterification of an esterified form of the drug) to produce an already approved active moiety.

YES ☒ NO ☐

If "yes," identify the approved drug product(s) containing the active moiety, and, if known, the NDA #(s).

NDA# 021868 EXUBERA (insulin human [rDNA origin]) Inhalation

NDA# 018780 Humulin R Insulin [Human Injection (rDNA Origin)]

NDA# 019938 Novolin R (Regular, Human Insulin [rDNA origin] USP)

2. Combination product.

If the product contains more than one active moiety(as defined in Part II, #1), has FDA previously approved an application under section 505 containing any one of the active moieties in the drug product? If, for example, the combination contains one never-before-approved active moiety and one previously approved active moiety, answer "yes." (An active moiety that is marketed under an OTC monograph, but that was never approved under an NDA, is considered not previously approved.)

YES ☐ NO ☐

If "yes," identify the approved drug product(s) containing the active moiety, and, if known, the NDA #(s).

NDA#

NDA#

NDA#

IF THE ANSWER TO QUESTION 1 OR 2 UNDER PART II IS "NO," GO DIRECTLY TO THE SIGNATURE BLOCKS ON PAGE 8. (Caution: The questions in part II of the summary should only be answered "NO" for original approvals of new molecular entities.)
IF "YES," GO TO PART III.

PART III THREE-YEAR EXCLUSIVITY FOR NDAs AND SUPPLEMENTS

To qualify for three years of exclusivity, an application or supplement must contain "reports of new clinical investigations (other than bioavailability studies) essential to the approval of the application and conducted or sponsored by the applicant." This section should be completed only if the answer to PART II, Question 1 or 2 was "yes."

1. Does the application contain reports of clinical investigations? (The Agency interprets "clinical investigations" to mean investigations conducted on humans other than bioavailability studies.) If

the application contains clinical investigations only by virtue of a right of reference to clinical investigations in another application, answer "yes," then skip to question 3(a). If the answer to 3(a) is "yes" for any investigation referred to in another application, do not complete remainder of summary for that investigation.

YES ☒ NO ☐

IF "NO," GO DIRECTLY TO THE SIGNATURE BLOCKS ON PAGE 8.

2. A clinical investigation is "essential to the approval" if the Agency could not have approved the application or supplement without relying on that investigation. Thus, the investigation is not essential to the approval if 1) no clinical investigation is necessary to support the supplement or application in light of previously approved applications (i.e., information other than clinical trials, such as bioavailability data, would be sufficient to provide a basis for approval as an ANDA or 505(b)(2) application because of what is already known about a previously approved product), or 2) there are published reports of studies (other than those conducted or sponsored by the applicant) or other publicly available data that independently would have been sufficient to support approval of the application, without reference to the clinical investigation submitted in the application.

(a) In light of previously approved applications, is a clinical investigation (either conducted by the applicant or available from some other source, including the published literature) necessary to support approval of the application or supplement?

YES ☒ NO ☐

If "no," state the basis for your conclusion that a clinical trial is not necessary for approval AND GO DIRECTLY TO SIGNATURE BLOCK ON PAGE 8:

NA

(b) Did the applicant submit a list of published studies relevant to the safety and effectiveness of this drug product and a statement that the publicly available data would not independently support approval of the application?

YES ☐ NO ☒

(1) If the answer to 2(b) is "yes," do you personally know of any reason to disagree with the applicant's conclusion? If not applicable, answer NO.

YES ☐ NO ☐

If yes, explain:

NA

(2) If the answer to 2(b) is "no," are you aware of published studies not conducted or sponsored by the applicant or other publicly available data that could independently

demonstrate the safety and effectiveness of this drug product?

YES ☐ NO ☒

If yes, explain:

NA

(c) If the answers to (b)(1) and (b)(2) were both "no," identify the clinical investigations submitted in the application that are essential to the approval:

NA

Studies comparing two products with the same ingredient(s) are considered to be bioavailability studies for the purpose of this section.

3. In addition to being essential, investigations must be "new" to support exclusivity. The agency interprets "new clinical investigation" to mean an investigation that 1) has not been relied on by the agency to demonstrate the effectiveness of a previously approved drug for any indication and 2) does not duplicate the results of another investigation that was relied on by the agency to demonstrate the effectiveness of a previously approved drug product, i.e., does not redemonstrate something the agency considers to have been demonstrated in an already approved application.

a) For each investigation identified as "essential to the approval," has the investigation been relied on by the agency to demonstrate the effectiveness of a previously approved drug product? (If the investigation was relied on only to support the safety of a previously approved drug, answer "no.")

Investigation #1 YES ☐ NO ☒

Investigation #2 YES ☐ NO ☒

If you have answered "yes" for one or more investigations, identify each such investigation and the NDA in which each was relied upon:

NA

b) For each investigation identified as "essential to the approval", does the investigation duplicate the results of another investigation that was relied on by the agency to support the effectiveness of a previously approved drug product?

Investigation #1 YES ☐ NO ☒

Investigation #2 YES ☐ NO ☒

If you have answered "yes" for one or more investigation, identify the NDA in which a similar investigation was relied on:

NA

c) If the answers to 3(a) and 3(b) are no, identify each "new" investigation in the application or supplement that is essential to the approval (i.e., the investigations listed in #2(c), less any that are not "new"):

MKC-TI-171: A Phase 3, Multicenter, Open-label, Randomized, Forced-titration Clinical Trial Evaluating the Efficacy and Safety of Technosphere® Insulin Inhalation Powder in Combination with a Basal Insulin Versus Insulin Aspart in Combination with a Basal Insulin in Subjects with Type 1 Diabetes Mellitus Over a 24-week Treatment Period

MKC-TI-175: A Phase 3, Multicenter, Double-blind, Placebo-controlled, Randomized, Clinical Trial Evaluating the Efficacy and Safety of Prandial Technosphere® Insulin Inhalation Powder Versus Technosphere® Inhalation Powder (Placebo) in Insulin Naïve Subjects With Type 2 Diabetes Mellitus Poorly Controlled With Oral Antidiabetic Agents Over a 24-week Treatment Period

4. To be eligible for exclusivity, a new investigation that is essential to approval must also have been conducted or sponsored by the applicant. An investigation was "conducted or sponsored by" the applicant if, before or during the conduct of the investigation, 1) the applicant was the sponsor of the IND named in the form FDA 1571 filed with the Agency, or 2) the applicant (or its predecessor in interest) provided substantial support for the study. Ordinarily, substantial support will mean providing 50 percent or more of the cost of the study.

a) For each investigation identified in response to question 3(c): if the investigation was carried out under an IND, was the applicant identified on the FDA 1571 as the sponsor?

Investigation #1: MKC-TI-171 !

IND # 061729 YES ☒ ! NO ☐

! Explain:

Investigation #2: MKC-TI-175 !

IND # 061729 YES ☒ ! NO ☐
! Explain:

(b) For each investigation not carried out under an IND or for which the applicant was not identified as the sponsor, did the applicant certify that it or the applicant's predecessor in interest provided substantial support for the study?

Investigation #1 !
!
YES ☐ ! NO ☐
Explain: ! Explain:

Investigation #2 !
!
YES ☐ ! NO ☐
Explain: ! Explain:

(c) Notwithstanding an answer of "yes" to (a) or (b), are there other reasons to believe that the applicant should not be credited with having "conducted or sponsored" the study? (Purchased studies may not be used as the basis for exclusivity. However, if all rights to the drug are purchased (not just studies on the drug), the applicant may be considered to have sponsored or conducted the studies sponsored or conducted by its predecessor in interest.)

YES ☐ NO ☒

If yes, explain:

NA

==========

Name of person completing form: Richard Whitehead, M.S.
Title: Regulatory Health Project Manger
Date: June 23, 2014

Name of Office/Division Director signing form: Jean-Marc Guettier, M.D.
Title: Director

Form OGD-011347; Revised 05/10/2004; formatted 2/15/05; removed hidden data 8/22/12;

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

/s/

RICHARD E WHITEHEAD
06/30/2014

ERIC C COLMAN
06/30/2014
on behalf of Jean Marc Guettier

ACTION PACKAGE CHECKLIST

APPLICATION INFORMATION[1]		
NDA # 022472	NDA Supplement # NA	If NDA, Efficacy Supplement Type: NA *(an action package is not required for SE8 or SE9 supplements)*
Proprietary Name: Afrezza Established/Proper Name: (insulin human [rDNA origin]) Inhalation Powder and Inhaler Dosage Form: 3 units per cartridge; 6 units per cartridge		Applicant: MannKind Corporation
RPM: Richard Whitehead, M.S.		Division: Division of Metabolism and Endocrinology Products
NDA Application Type: ☒ 505(b)(1) ☐ 505(b)(2)	**For ALL 505(b)(2) applications, two months prior to EVERY action:** • **Review the information in the 505(b)(2) Assessment and submit the draft[2] to CDER OND IO for clearance.** • **Check Orange Book for newly listed patents and/or exclusivity (including pediatric exclusivity)** ☐ No changes ☐ New patent/exclusivity *(notify CDER OND IO)* Date of check: ***Note: If pediatric exclusivity has been granted or the pediatric information in the labeling of the listed drug changed, determine whether pediatric information needs to be added to or deleted from the labeling of this drug.***	

❖ Actions	
• Proposed action • User Fee Goal Date is July 15, 2014	☒ AP ☐ TA ☐ CR
• Previous actions *(specify type and date for each action taken)*	CR: March 12, 2010; CR: January 18, 2011
❖ If accelerated approval or approval based on efficacy studies in animals, were promotional materials received? Note: Promotional materials to be used within 120 days after approval must have been submitted (for exceptions, see http://www fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/ucm069965.pdf). If not submitted, explain _____	☐ Received
❖ Application Characteristics [3]	

[1] The **Application Information** Section is (only) a checklist. The **Contents of Action Package** Section (beginning on page 2) lists the documents to be included in the Action Package.
[2] For resubmissions, 505(b)(2) applications must be cleared before the action, but it is not necessary to resubmit the draft 505(b)(2) Assessment to CDER OND IO unless the Assessment has been substantively revised (e.g., new listed drug, patent certification revised).
[3] Answer all questions in all sections in relation to the pending application, i.e., if the pending application is an NDA or BLA supplement, then the questions should be answered in relation to that supplement, not in relation to the original NDA or BLA. For example, if the application is a pending BLA supplement, then a new *RMS-BLA Product Information Sheet for TBP* must be completed.

Review priority: ☒ Standard ☐ Priority
Chemical classification (new NDAs only): inhaled insulin
(confirm chemical classification at time of approval)

☐ Fast Track
☐ Rolling Review
☐ Orphan drug designation
☐ Breakthrough Therapy designation

☐ Rx-to-OTC full switch
☐ Rx-to-OTC partial switch
☐ Direct-to-OTC

NDAs: Subpart H
☐ Accelerated approval (21 CFR 314.510)
☐ Restricted distribution (21 CFR 314.520)
Subpart I
☐ Approval based on animal studies

BLAs: Subpart E
☐ Accelerated approval (21 CFR 601.41)
☐ Restricted distribution (21 CFR 601.42)
Subpart H
☐ Approval based on animal studies

☐ Submitted in response to a PMR
☐ Submitted in response to a PMC
☐ Submitted in response to a Pediatric Written Request

REMS: ☐ MedGuide
☒ Communication Plan
☐ ETASU
☐ MedGuide w/o REMS
☐ REMS not required

Comments:

❖ BLAs only: Ensure *RMS-BLA Product Information Sheet for TBP* and *RMS-BLA Facility Information Sheet for TBP* have been completed and forwarded to OPI/OBI/DRM (Vicky Carter)	☐ Yes, dates
❖ BLAs only: Is the product subject to official FDA lot release per 21 CFR 610.2 *(approvals only)*	☐ Yes ☐ No
❖ Public communications *(approvals only)*	
• Office of Executive Programs (OEP) liaison has been notified of action	☒ Yes ☐ No
• Indicate what types (if any) of information were issued	☐ None ☒ FDA Press Release ☐ FDA Talk Paper ☐ CDER Q&As ☐ Other
❖ Exclusivity	
• Is approval of this application blocked by any type of exclusivity (orphan, 5-year NCE, 3-year, pediatric exclusivity)? • If so, specify the type	☒ No ☐ Yes
❖ Patent Information (NDAs only)	
• Patent Information: Verify that form FDA-3542a was submitted for patents that claim the drug for which approval is sought.	☒ Verified ☐ Not applicable because drug is an old antibiotic.

CONTENTS OF ACTION PACKAGE

Officer/Employee List

❖ List of officers/employees who participated in the decision to approve this application and consented to be identified on this list *(approvals only)*	☒ Included
Documentation of consent/non-consent by officers/employees	☒ Included

Action Letters	
❖ Copies of all action letters *(including approval letter with final labeling)*	Actions and dates: CR: March 12, 2010 CR: January 18, 2011 AP: June 27, 2014
Labeling	
❖ Package Insert *(write submission/communication date at upper right of first page of PI)*	
• Most recent draft labeling *(if it is division-proposed labeling, it should be in track-changes format)*	☐ Included Note: final Package Insert included with Action letter
• Original applicant-proposed labeling	☐ Included
❖ Medication Guide/Patient Package Insert/Instructions for Use/Device Labeling *(write submission/communication date at upper right of first page of each piece)*	☒ Medication Guide ☐ Patient Package Insert ☒ Instructions for Use ☐ Device Labeling ☐ None
• Most-recent draft labeling *(if it is division-proposed labeling, it should be in track-changes format)*	☐ Included Note: final Medication Guide and Instructions for Use included with Action letter
• Original applicant-proposed labeling	☐ Included
❖ Labels (**full color** carton and immediate-container labels) *(write submission/communication date on upper right of first page of each submission)*	
• Most-recent draft labeling	☐ Included Note: final carton and immediate-container labels included with Action letter
❖ Proprietary Name • Acceptability/non-acceptability letter(s) *(indicate date(s))* • Review(s) *(indicate date(s)*	6-30-09; 12-16-09; 9-14-10; 12-13-10; 1-14-14 6-30-09; 12-08-09; 12-13-10; 1-13-14
❖ Labeling reviews *(indicate dates of reviews)*	RPM: 6-26-14 DMEPA: 12-28-09; 12-14-10; 1-30-14; 6-26-14 DMPP/PLT (DRISK): 1-22-10; 1-05-11; 6-13-14; 6-19-14; 6-24-14 OPDP: 6-10-14; 6-20-14 SEALD: ☒ None CSS: ☒ None Other: DMPP: 6-25-14
Administrative / Regulatory Documents	
❖ RPM Filing Review[4]/Memo of Filing Meeting *(indicate date of each review)* ❖ All NDA 505(b)(2) Actions: Date each action cleared by 505(b)(2) Clearance Committee	5-22-09 ☒ Not a (b)(2)
❖ NDAs only: Exclusivity Summary *(signed by Division Director)*	☒ Included

[4] Filing reviews for scientific disciplines are NOT required to be included in the action package.

❖ Application Integrity Policy (AIP) Status and Related Documents http://www fda.gov/ICECI/EnforcementActions/ApplicationIntegrityPolicy/default.htm	
• Applicant is on the AIP	☐ Yes ☒ No
• This application is on the AIP ○ If yes, Center Director's Exception for Review memo *(indicate date)* ○ If yes, OC clearance for approval *(indicate date of clearance communication)*	☐ Yes ☒ No ☐ Not an AP action
❖ Pediatrics *(approvals only)* • Date reviewed by PeRC 11-04-09 If PeRC review not necessary, explain:	
❖ Outgoing communications: letters, emails, and faxes considered important to include in the action package by the reviewing office/division (e.g., clinical SPA letters, RTF letter, etc.) *(do not include previous action letters, as these are located elsewhere in package)*	NDA Ack: 3-24-09 Filing comm: 5-21-09 Class 2 resub Ack: 7-19-10; 10-28-13 Rev Ext- Maj Amend: 4-04-14 IR: 5-05-09; 7-21-09; 7-21-09; 8-21-09; 9-14-09; 9-16-09; 9-24-09; 10-09-09; 10-13-09; 10-20-09; 10-26-09; 10-26-09; 10-29-09; 10-30-09; 11-02-09; 11-02-09; 11-02-09; 11-03-09; 11-03-09; 11-03-09; 11-04-09; 11-06-09; 11-10-09; 11-12-09; 11-18-09; 11-20-09; 11-20-09; 11-22-09; 12-03-09; 12-07-09; 12-07-09; 12-11-09; 12-15-09; 12-18-09; 12-18-09; 12-29-09; 12-29-09; 12-31-09; 1-06-10; 1-13-10; 1-14-10; 1-19-10; 1-19-10; 1-20-10; 2-01-10; 2-15-10; 7-13-10; 7-19-10; 7-19-10; 9-10-10; 9-26-10; 11-02-10; 11-09-10; 12-01-10; 12-07-10; 9-13-11; 1-05-12; 1-12-12; 11-20-12; 10-28-13; 1-17-14; 1-17-14; 1-27-14; 2-13-14; 2-13-14; 3-03-14; 4-04-14; 4-17-14; 5-30-14; 6-02-14
❖ Internal documents: memoranda, telecons, emails, and other documents considered important to include in the action package by the reviewing office/division (e.g., Regulatory Briefing minutes, Medical Policy Council meeting minutes)	NA
❖ Minutes of Meetings	
• If not the first review cycle, any end-of-review meeting *(indicate date of mtg)*	6-09-10; 4-15-11
• Pre-NDA/BLA meeting *(indicate date of mtg)*	7-14-08
• EOP2 meeting *(indicate date of mtg)*	10-12-04
• Mid-cycle Communication *(indicate date of mtg)*	☒ N/A
• Late-cycle Meeting *(indicate date of mtg)*	☒ N/A
• Other milestone meetings (e.g., EOP2a, CMC pilots) *(indicate dates of mtgs)*	Type C: 2-28-12; 7-23-12; 11-02-12; 1-09-13; 3-05-13

❖ Advisory Committee Meeting(s)	
• Date of Meeting	April 1, 2014
Decisional and Summary Memos	
❖ Office Director Decisional Memo *(indicate date for each review)*	☒ None
Division Director Summary Review *(indicate date for each review)*	3-12-10; 1-18-11; 6-27-14
Cross-Discipline Team Leader Review *(indicate date for each review)*	3-12-10; 1-04-11; 6-27-14
PMR/PMC Development Templates *(indicate total number)*	6-27-14
Clinical	
❖ Clinical Reviews	
• Clinical Team Leader Review(s) *(indicate date for each review)*	☒ No separate review
• Clinical review(s) *(indicate date for each review)*	12-24-09; 12-10-10
• Social scientist review(s) (if OTC drug) *(indicate date for each review)*	☒ None
❖ Financial Disclosure reviews(s) or location/date if addressed in another review OR If no financial disclosure information was required, check here ☐ and include a review/memo explaining why not *(indicate date of review/memo)*	6-27-14 CDTL Memo, Page 30
❖ Clinical reviews from immunology and other clinical areas/divisions/Centers *(indicate date of each review)*	DPARP: 5-20-09; 12-28-09; 12-14-10; 6-26-14 CDRH: 12-17-09; 12-21-10; 5-24-11; 1-24-12; 1-24-12; 7-02-14 QT: 12-23-09 DOP2: 1-22-14 DEPI: 2-28-14; 3-28-14
❖ Controlled Substance Staff review(s) and Scheduling Recommendation *(indicate date of each review)*	☒ N/A
❖ Risk Management • REMS Documents and REMS Supporting Document *(indicate date(s) of submission(s))* • REMS Memo(s) and letter(s) *(indicate date(s))* • Risk management review(s) and recommendations (including those by OSE and CSS) *(indicate date of each review and indicate location/date if incorporated into another review)*	6-27-14 3-16-10; 10-24-11 11-23-09; 12-09-09; 3-25-14; 6-24-14
❖ OSI Clinical Inspection Review Summary(ies) *(include copies of OSI letters to investigators)*	11-30-09; 12-29-09; 12-29-09; 1-07-10; 2-26-10; 2-24-10; 8-18-10; 12-09-10; 1-03-13; 4-16-14
Clinical Microbiology ☒ None	
❖ Clinical Microbiology Team Leader Review(s) *(indicate date for each review)*	☒ No separate review
Clinical Microbiology Review(s) *(indicate date for each review)*	☒ None
Biostatistics ☐ None	
❖ Statistical Division Director Review(s) *(indicate date for each review)*	☒ No separate review
Statistical Team Leader Review(s) *(indicate date for each review)*	12-12-10
Statistical Review(s) *(indicate date for each review)*	9-28-09; 12-09-09; 12-18-09; 3-18-14; 4-15-14;

Clinical Pharmacology ☐ None	
❖ Clinical Pharmacology Division Director Review(s) *(indicate date for each review)*	☒ No separate review
Clinical Pharmacology Team Leader Review(s) *(indicate date for each review)*	☒ No separate review
Clinical Pharmacology review(s) *(indicate date for each review)*	5-08-09; 12-18-09; 1-12-10; 12-13-10; 5-19-14
❖ OSI Clinical Pharmacology Inspection Review Summary *(include copies of OSI letters)*	1-05-10; 12-27-10
Nonclinical ☐ None	
❖ Pharmacology/Toxicology Discipline Reviews	
• ADP/T Review(s) *(indicate date for each review)*	☒ No separate review
• Supervisory Review(s) *(indicate date for each review)*	12-18-09
• Pharm/tox review(s), including referenced IND reviews *(indicate date for each review)*	5-18-09; 12-08-09; 1-05-12; 1-13-14; 3-04-14
❖ Review(s) by other disciplines/divisions/Centers requested by P/T reviewer *(indicate date for each review)*	☒ None
❖ Statistical review(s) of carcinogenicity studies *(indicate date for each review)*	☐ No carc
❖ ECAC/CAC report/memo of meeting	☒ None 10-01-09 Included in P/T review, page
❖ OSI Nonclinical Inspection Review Summary *(include copies of OSI letters)*	☒ None requested
Product Quality ☐ None	
❖ Product Quality Discipline Reviews	
• ONDQA/OBP Division Director Review(s) *(indicate date for each review)*	☒ No separate review
• Branch Chief/Team Leader Review(s) *(indicate date for each review)*	1-06-10; 12-13-10
• Product quality review(s) including ONDQA biopharmaceutics reviews *(indicate date for each review)*	5-04-09; 12-09-09; 12-18-09; 12-13-10; 12-13-10; 1-10-12; 1-15-14; 3-20-14
❖ Microbiology Reviews ☐ NDAs: Microbiology reviews (sterility & pyrogenicity) (OPS/NDMS) *(indicate date of each review)* ☐ BLAs: Sterility assurance, microbiology, facilities reviews (OMPQ/MAPCB/BMT) *(indicate date of each review)*	4-14-09; 9-22-09; 2-10-14
❖ Reviews by other disciplines/divisions/Centers requested by CMC/quality reviewer *(indicate date of each review)*	☒ None
❖ Environmental Assessment (check one) (original and supplemental applications)	
☒ Categorical Exclusion *(indicate review date)(all original applications and all efficacy supplements that could increase the patient population)*	See page 102 of CMC review dated 3-20-14
☐ Review & FONSI *(indicate date of review)*	
☐ Review & Environmental Impact Statement *(indicate date of each review)*	

❖ Facilities Review/Inspection	
☒ NDAs: Facilities inspections (include EER printout or EER Summary Report only; do NOT include EER Detailed Report; date completed must be within **2 years** of action date) *(only original NDAs and supplements that include a new facility or a change that affects the manufacturing sites[5])*	Date completed: 8-11-10; 7-02-14 ☒ Acceptable ☐ Withhold recommendation ☐ Not applicable
☐ BLAs: TB-EER (date of most recent TB-EER must be within **30 days** of action date) *(original and supplemental BLAs)*	Date completed: ☐ Acceptable ☐ Withhold recommendation
❖ NDAs: Methods Validation *(check box only, do not include documents)*	☐ Completed ☐ Requested ☐ Not yet requested ☐ Not needed (per review)

[5] i.e., a new facility or a change in the facility, or a change in the manufacturing process in a way that impacts the Quality Management Systems of the facility.

Day of Approval Activities	
❖ For all 505(b)(2) applications: • Check Orange Book for newly listed patents and/or exclusivity (including pediatric exclusivity)	☐ No changes ☐ New patent/exclusivity *(Notify CDER OND IO)*
• Finalize 505(b)(2) assessment	☐ Done
❖ Send a courtesy copy of approval letter and all attachments to applicant by fax or secure email	☒ Done
❖ If an FDA communication will issue, notify Press Office of approval action after confirming that applicant received courtesy copy of approval letter	☒ Done
❖ Ensure that proprietary name, if any, and established name are listed in the *Application Product Names* section of DARRTS, and that the proprietary name is identified as the "preferred" name	☒ Done
❖ Ensure Pediatric Record is accurate	☐ Done
❖ Send approval email within one business day to CDER-APPROVALS	☒ Done

---

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

/s/

RICHARD E WHITEHEAD
07/02/2014

From: Bedard, John
To: Whitehead, Richard
Subject: Re: NDA22472 Afrezza: Nonclinical Information Request
Date: Monday, June 02, 2014 1:03:54 PM

Received and we will get right on your request.
John

From: Whitehead, Richard [mailto:Richard.Whitehead@fda.hhs.gov]
Sent: Monday, June 02, 2014 12:50 PM
To: Bedard, John
Subject: NDA22472 Afrezza: Nonclinical Information Request

John,

We are reviewing the nonclinical sections 8 &13 and do not understand how you calculate the exposure multiples relative to the animal NOAELs in your proposed labeling. Please provide your calculations for the exposure multiples in these sections by 8AM Thursday, June 5, 2014. Let me know if you have any questions and please confirm receipt of this request.

Regards,
Rich

Richard Whitehead, MS; Regulatory Project Manager; FDA/CDER/OND/ODEII/ Division of Metabolism and Endocrinology Products;
(t) 301.796.4945; (f) 301.796.9712; richard.whitehead@fda.hhs.gov

---

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

/s/

RICHARD E WHITEHEAD
06/02/2014

From: Whitehead, Richard
To: "Bedard, John"
Subject: NDA22472 Afrezza: Post Marketing Document
Date: Friday, May 30, 2014 8:49:38 PM
Attachments: NDA 22472 (Afrezza) PMRs and PMCs .docx

John,

I am forwarding a copy of the PMR/PMC list for NDA 22472 Afrezza for your review. Please return the milestone dates back to us by next Friday at the latest, preferably sooner. Let me know if you have any questions.

Regards,
Rich

Richard Whitehead, MS; Regulatory Project Manager; FDA/CDER/OND/ODEII/ Division of Metabolism and Endocrinology Products;
(t) 301.796.4945; (f) 301.796.9712; richard.whitehead@fda.hhs.gov

PMR/PMC list for NDA 22472
AFREZZA (insulin human) Inhalation Powder

While review of your application continues, we are sending you a draft list of PMRs/PMCs based on the data and internal analyses available to date. These brief study/trial summaries are intended to describe the main objective and study/trial characteristics of interest.

Please submit by email a copy of the PMR and PMC studies/trials to us with milestone dates, which include **Final Protocol Submission**, **Study Completion** and **Final Report Submission**.

- Note that milestone dates only need month and year
- For milestone calculation purposes only, assume that an approval occurs on the PDUFA date.
- Note that the "Final Protocol Submission" date is the date by which you have submitted a complete protocol that has already received full concurrence by FDA.
- For PMCs, include a statement that you agree to conduct these studies/trials.

<u>Postmarketing Requirements</u>

1. [redacted] (b) (4)

   Final Protocol Submission:
   Study Completion:
   Final Report Submission:

2. [redacted] (b) (4)

   Final Protocol Submission:
   Study Completion:
   Final Report Submission:

3. Conduct a 5-year, [redacted] (b) (4) trial in patients with type-2 diabetes to assess the serious potential risk of pulmonary malignancy with AFREZZA use. The primary objective of the trial should be [redacted] (b) (4)

(b) (4) Secondary endpoints should include mortality due to pulmonary malignancy and all-cause mortality. Randomization to AFREZZA or (b) (4) should be 1 to 1. The patient population should be enriched with respect to lung cancer risk (i.e., predicted incidence of no less than 200/100,000 patient-year). The potential for detection bias should be adequately addressed in the trial design. Subjects who discontinue randomized intervention due to lack of efficacy or tolerability should continue to be followed for the outcomes of interest. Glucose control and glycemic rescue should be per standard of care. The trial must also include an assessment of cardiovascular risk based on prospectively defined, collected and independently adjudicated major adverse cardiovascular events or MACE (i.e., cardiovascular death, non-fatal myocardial infarction, and non-fatal stroke). Also include as part of the trial a substudy ((b) (4) also with 1 to 1 randomization to either AFREZZA or (b) (4)) to evaluate the long-term effect of AFREZZA on pulmonary function. Patients in the substudy should have pulmonary function tests at baseline and every 6 months until end of treatment, (b) (4)

Final Protocol Submission:
Trial Completion:
Final Report Submission:

4. Conduct a dose-ranging PK-PD euglycemic glucose-clamp trial to characterize the dose-response of AFREZZA relative to subcutaneous insulin in patients with type 1 diabetes. Select at least three to four doses for each route of insulin administration to ensure both the linear and curvilinear portions of the dose-response curves (b) (4)

   Final Protocol Submission:
   Trial Completion:
   Final Report Submission:

5. A PK-PD eugylcemic glucose-clamp trial to characterize within-subject variability for AFREZZA pharmacokinetic (PK) and pharmacodynamic (PD) parameters

   Final Protocol Submission:
   Trial Completion:
   Final Report Submission:

Postmarketing Commitments

6. Modify removable mouthpiece cover to address potential risk of aspiration

   Completion date:

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

/s/

RICHARD E WHITEHEAD
05/30/2014

From: Whitehead, Richard
To: "Bedard, John"
Subject: NDA22472 Afrezza: Information Request
Date: Thursday, April 17, 2014 12:52:57 PM

John,

Your current device includes a removable mouth piece cover. We note the issue of aspiration was raised at the Advisory Committee meeting and we do believe this is a real concern in the post-market setting. Propose a plan to address this potential risk, considerations may include tethering of the mouth piece cover.

Please provide your response by April 24, 2014 and confirm receipt of this email.

Regards,
Rich

Richard Whitehead, MS; Regulatory Project Manager; FDA/CDER/OND/ODEII/ Division of Metabolism and Endocrinology Products;
(t) 301.796.4945; (f) 301.796.9712; richard.whitehead@fda.hhs.gov

---

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

/s/

RICHARD E WHITEHEAD
04/17/2014

DEPARTMENT OF HEALTH AND HUMAN SERVICES

Food and Drug Administration
Silver Spring MD 20993

NDA 022472

REVIEW EXTENSION – MAJOR AMENDMENT

MannKind Corporation
Attention: John Bedard
Sr. Vice President, Regulatory Affairs
61 South Paramus Road
Paramus, NJ 07652

Dear Mr. Bedard:

Please refer to your New Drug Application (NDA) dated October 13, 2013, received October 15, 2013, submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act (FDCA) for Afrezza (insulin human [rDNA origin]) Inhalation Powder.

On February 10, and 28, 2014, we received your February 8, and 28, 2014, major amendment to this application in response to our January 17, 2014 Request for Information. Therefore, we are extending the goal date by three months to provide time for a full review of the submission. The extended user fee goal date is **Tuesday, July 15, 2014**.

If you have any questions, call Richard Whitehead, M.S., Regulatory Project Manager, at (301) 796-4945.

Sincerely,

{See appended electronic signature page}

Jean-Marc Guettier, M.D.
Director
Division of Metabolism and Endocrinology Products
Office of Drug Evaluation II
Center for Drug Evaluation and Research

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

/s/

JEAN-MARC P GUETTIER
04/04/2014

From: Whitehead, Richard
To: "Bedard, John"
Subject: RE: Response to 13 Feb Info Requests
Date: Monday, March 03, 2014 12:03:01 PM

John,

We are not able to open the dataset (using SAS 9.3) from T1D trial (q4data.sas7bdat) submitted to Agency on February 24, 2014 in response to the clinical pharmacology information request dated February 13, 2014. Please resubmit this dataset and in addition to the avgwkbmi variable, also include BMI and average weekly dose as separate variables.

Regards,
Rich

Richard Whitehead, MS; Regulatory Project Manager; FDA/CDER/OND/ODEII/ Division of Metabolism and Endocrinology Products;
(t) 301.796.4945; (f) 301.796.9712; richard.whitehead@fda.hhs.gov

---

From: Bedard, John [mailto:jbedard@mannkindcorp.com]
Sent: Monday, February 24, 2014 4:51 PM
To: Whitehead, Richard
Subject: Response to 13 Feb Info Requests

Rich,

This is a desk copy of our response to the two Info Requests we received on 13 Feb. 2014. The formal submission is being transmitted at this time through ESG.

If you have questions, feel free to contact me: (b) (6).

Best regards,

John

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

/s/

RICHARD E WHITEHEAD
03/03/2014

From: Whitehead, Richard
To: Bedard, John
Subject: NDA22472 Afrezza: clinical Information Request
Date: Thursday, February 13, 2014 4:33:55 PM
Attachments: Clinical info request MannKind Feb 13.doc

John,

I am forwarding a list of Clarification Questions for Phase 3 Studies (below and attached as a word Document) for Afrezza, NDA 22472. Please provide your responses to these questions **no later than Monday, February 24, 2014**. Send your responses to me via email and submit to your application. Let me know if you have any questions and please confirm receipt of this email request.

Clarification Questions for Phase 3 Studies

1. We are aware that in the phase 3 studies, subjects who reached a dose of at least 30 U per meal and who no longer saw a decrease of least 10 mg/dL (0.5 mmol/L) in the corresponding median 90-minute postprandial glucose (PPG) level, despite 3 subsequent 10 U dose increases (above 30 U), were required to stop mealtime dose increases and to consult the investigator. Please clarify to how many patients this situation applied in each trial.
2. In study 175, twelve (6.8%) subjects of the TI Gen2 group required rescue therapy. It is unclear why so many patients in the TI treatment group would require rescue therapy given that TI is a titratable product. Please provide further information about these patients or any other available data that might explain this finding.
3. Our analyses of the data from study 171 suggest that females in the insulin aspart group had the greatest reduction compared to insulin aspart treated males, TI treated females, and TI treated males. Please provide any data to explain this finding, i.e. were females more compliant than males in the trial? Alternatively, provide any data to support that this is a chance finding.
4. We have noted the following The mean aspart dose was 24 units at Week 1 in the aspart arm (24units*2.5 = 60 Afrezza equivalent units) and yet the Week 1 Afrezza dose in the Afrezza arm was 34 aspart units (i.e., 85 Afrezza units). It would expected that the Afrezza and aspart doses would have been more similar at Week 1 (rather than 40% higher) since they should have been equal at baseline if randomization worked. Please explain this finding.

Evaluation of overall basal and prandial insulin titration

In study 171, based on the percentage of patients in each arm who reached HbA1c<7% we assume that both groups were inadequately titrated; the TI Gen2 titration algorithm allowed for an increase of 10 U per week, which theoretically would allow for an increase of 120 U over the 12 week prandial insulin titration period. Why the average daily dose only increased by 30 U over the 24 week randomized study period (i.e. mean dose going from 85 U to 115 U) is unclear; further, in the comparator (aspart) arm, there was no increase in mean prandial (aspart) dose from randomization to week 12, i.e. it appears that virtually no titration occurred.

Therefore, we are trying to determine whether insulin titration, which was supposed to happen in both study arms, up to study Week 12 occurred as planned. We have the following requests

5. Provide graphs of the mean (SE) change in prandial insulin dose from baseline (set baseline at zero) across trial visits from randomization to end of treatment (EOT) for the Afrezza and Aspart arms (in a single graph). Provide a graph with actual units administered and one graph with "aspart equivalent units" for the Afrezza arms using your proposed protocol-specified conversion factor.
6. Provide a graph of the mean (SE) change in basal insulin dose from baseline (set baseline at zero) across trial visits from randomization to EOT for the Afrezza and Aspart arms (in a single graph).
7. Please provide the mean (SE), median (IQR), total daily prandial doses used to establish baseline dose for the aspart arm and used for the purpose of converting baseline injectable insulin dose to baseline inhaled insulin dose in the Gen2 and MedTone arms.
8. Please complete the following shell table (adapted from Table 28 in the study CSR).

Table 1 Average Daily Dose of Prandial Insulin Since Randomization by Time Periods (Safety Population)

	Category/Statistics	TI Gen2	TI MedTone	Insulin aspart
Overall	Mean (SD)			
	Median			
	Range			
Baseline	Mean (SD)			
	Median			
	Range			
Week 1	Mean (SD)			
	Median			
	Range			
Week 4	Mean (SD)			
	Median			
	Range			
Week 8	Mean (SD)			
	Median			
	Range			
Week 12	Mean (SD)			
	Median			
	Range			
Week 24	Mean (SD)			
	Median			
	Range			

Table 1. Average Daily Dose of Basal Insulin Since Randomization by Time Periods (Safety Population)

	Category/Statistics	TI Gen2	TI MedTone	Insulin aspart
Overall	Mean (SD)			
	Median			
	Range			
Baseline	Mean (SD)			
	Median			
	Range			
Week 1	Mean (SD)			
	Median			
	Range			
Week 4	Mean (SD)			
	Median			
	Range			
Week 8	Mean (SD)			
	Median			
	Range			
Week 12	Mean (SD)			
	Median			
	Range			
Week 24	Mean (SD)			
	Median			
	Range			

Evaluation for Differential Titration Between the Treatment Arms

9. With regards to adherence to the protocol-specified titration targets provide the following
   - The proportion of randomized patients achieving "protocol-specified" **basal insulin** titration goals by 12 weeks in the Afrezza and Aspart arms. Clearly state how you have defined achievement of basal titration goal to generate your response and how you have handled missing data for this time point.
   - The proportion of randomized patients achieving "protocol-specified" **prandial insulin** titration goals by 12 weeks in the Afrezza and Aspart arms. Clearly state how you have defined achievement of prandial-related (pre or post) insulin titration goals to generate your response and how you have handled missing data for this time point.
10. With regards to the adherence report generated to assess the investigator and titration committee s performance
    a. The report does not distinguish adherence by arm. Was adherence similar or different between arms for basal insulin and for prandial insulin? Provide these data.
    b. Were investigator discretionary reasons for non-adherence captured and organized for reporting (e.g., safety concern, lack of adequate data to make a decision)? If yes please provide these data.
11. Fill in the following shell tables

Table 2 Proportion of subjects with at least (x) adjustment(s) in prandial insulin dose (for at least one of the three meals*) between randomization time and end-of-treatment time.

		Any Adjustment		**Dose Increase**		**Dose Decrease**	
ARM (Number Random-ized)		**Afrezza Gen-2 (N)**	**Comparator (N)**	**Afrezza Gen-2 (N)**	**Comparator (N)**	**Afrezza-Gen-2 (N)**	**Comparator (N)**
INSULIN TYPE		**Afrezza**	**Aspart**	**Afrezza**	**Aspart**	**Afrezza**	**Aspart**
	NUMBER OF ADJUST-MENTS						
	0	n (%)					
	2						
	4						
	8						

	10						
	12						
	14						
	16						
	≥20						

* Example a change in breakfast and lunch and dinner dose at a single visit would count as one dose adjustment. A change in a single meal for one visit would also count as one dose adjustment.

Table 3: Proportion of subjects with at least (x) adjustment(s) in daily basal insulin dose between randomization and end-of-treatment.

	Any Adjustment		**Dose Increase**		**Dose Decrease**	
ARM (Number Randomized)	**Afrezza Gen-2 (N)**	**Comparator (N)**	**Afrezza Gen-2 (N)**	**Comparator (N)**	**Afrezza Gen-2 (N)**	**Comparator (N)**
INSULIN TYPE	NPH or DETEMIR or Glargine	NPH or DETEMIR or Glargine	NPH or DETEMR or Glargine	NPH or DETEMIR or Glargine	NPH or DETEMIR or Glargine	NPH or DETEMIR or Glargine
0	n (%)					
2						
4						
6						
8						
10						
12						
14						
>20						

Table 4: Proportion of subjects with an at least (x%) increase above baseline in total daily basal insulin dose between randomization and end-of-treatment.

Dose Increase

ARM(Number Randomized)		**Afrezza Gen-2 (N)**	**Comparator (N)**
INSULIN TYPE		Any Allowed	Any Allowed
	% increase above baseline		
	0%	n (%)	
	10%		
	20%		
	30%		
	40%		
	50%		
	60%		
	100%		
	>100%		

Table 5: Proportion of subjects with an at least x% increase above baseline in total daily prandial insulin dose between randomization and end of treatment.

Dose Increase

ARM (Number Randomized)		**Afrezza Gen-2(N)**	**Comparator (N)**
INSULIN TYPE		Afrezza	Aspart
	% increase above baseline		
	0%	n (%)	
	10%		
	20%		
	30%		
	40%		
	50%		
	60%		
	100%		
	>100%		

12. Provide a scatter plot for the number of Afrezza, Aspart and basal insulin dose adjustments made in the Afrezza and Aspart arms respectively. Provide the following descriptive statistics total number of dose adjustments made, mean number of dose adjustments made (SE), median number of dose adjustments made (and interquartile range), range of dose adjustments made.

Regards,
Rich

Richard Whitehead MS; Regulatory Project Manager; FDA/CDER/OND/ODEII/ Division of Metabolism and Endocrinology Products;
(t) 301.796.4945; (f) 301.796.9712; richard.whitehead@fda.hhs.gov

Clarification Questions for Phase 3 Studies

1. We are aware that in the phase 3 studies, subjects who reached a dose of at least 30 U per meal and who no longer saw a decrease of least 10 mg/dL (0.5 mmol/L) in the corresponding median 90-minute postprandial glucose (PPG) level, despite 3 subsequent 10 U dose increases (above 30 U), were required to stop mealtime dose increases and to consult the investigator. Please clarify to how many patients this situation applied in each trial.

2. In study 175, twelve (6.8%) subjects of the TI Gen2 group required rescue therapy. It is unclear why so many patients in the TI treatment group would require rescue therapy given that TI is a titratable product. Please provide further information about these patients or any other available data that might explain this finding.

3. Our analyses of the data from study 171 suggest that females in the insulin aspart group had the greatest reduction compared to insulin aspart treated males, TI treated females, and TI treated males. Please provide any data to explain this finding, i.e. were females more compliant than males in the trial? Alternatively, provide any data to support that this is a chance finding.

4. We have noted the following: The mean aspart dose was 24 units at Week 1 in the aspart arm (24units*2.5 = 60 Afrezza equivalent units) and yet the Week 1 Afrezza dose in the Afrezza arm was 34 aspart units (i.e., 85 Afrezza units). It would expected that the Afrezza and aspart doses would have been more similar at Week 1 (rather than 40% higher) since they should have been equal at baseline if randomization worked. Please explain this finding.

Evaluation of overall basal and prandial insulin titration

In study 171, based on the percentage of patients in each arm who reached HbA1c<7% we assume that both groups were inadequately titrated; the TI Gen2 titration algorithm allowed for an increase of 10 U per week, which theoretically would allow for an increase of 120 U over the 12 week prandial insulin titration period. Why the average daily dose only increased by 30 U over the 24 week randomized study period (i.e. mean dose going from 85 U to 115 U) is unclear; further, in the comparator (aspart) arm, there was no increase in mean prandial (aspart) dose from randomization to week 12, i.e. it appears that virtually no titration occurred.

Therefore, we are trying to determine whether insulin titration, which was supposed to happen in both study arms, up to study Week 12 occurred as planned. We have the following requests:

5. Provide graphs of the mean (SE) change in prandial insulin dose from baseline (set baseline at zero) across trial visits from randomization to end of treatment (EOT) for the Afrezza and Aspart arms (in a single graph). Provide a graph with actual units administered and one graph with "aspart equivalent units" for the Afrezza arms using your proposed protocol-specified conversion factor.

6. Provide a graph of the mean (SE) change in basal insulin dose from baseline (set baseline at zero) across trial visits from randomization to EOT for the Afrezza and Aspart arms (in a single graph).

7. Please provide the mean (SE), median (IQR), total daily prandial doses used to establish baseline dose for the aspart arm and used for the purpose of converting baseline injectable insulin dose to baseline inhaled insulin dose in the Gen2 and MedTone arms.

8. Please complete the following shell table (adapted from Table 28 in the study CSR).

Table 1. Average Daily Dose of Prandial Insulin Since Randomization by Time Periods (Safety Population)

	Category/Statistics	TI Gen2	TI MedTone	Insulin aspart
Overall	Mean (SD)			
	Median			
	Range			
Baseline	Mean (SD)			
	Median			
	Range			
Week 1	Mean (SD)			
	Median			
	Range			
Week 4	Mean (SD)			
	Median			
	Range			
Week 8	Mean (SD)			
	Median			
	Range			
Week 12	Mean (SD)			
	Median			
	Range			
Week 24	Mean (SD)			
	Median			
	Range			

Table 1. Average Daily Dose of Basal Insulin Since Randomization by Time Periods (Safety Population)

	Category/Statistics	TI Gen2	TI MedTone	Insulin aspart
Overall	Mean (SD)			
	Median			
	Range			
Baseline	Mean (SD)			
	Median			
	Range			
Week 1	Mean (SD)			
	Median			
	Range			
Week 4	Mean (SD)			
	Median			
	Range			

Week 8	Mean (SD)			
	Median			
	Range			
Week 12	Mean (SD)			
	Median			
	Range			
Week 24	Mean (SD)			
	Median			
	Range			

Evaluation for Differential Titration Between the Treatment Arms

9. With regards to adherence to the protocol-specified titration targets provide the following

    - The proportion of randomized patients achieving "protocol-specified" **basal insulin** titration goals by 12 weeks in the Afrezza and Aspart arms. Clearly state how you have defined achievement of basal titration goal to generate your response and how you have handled missing data for this time point.

    - The proportion of randomized patients achieving "protocol-specified" **prandial insulin** titration goals by 12 weeks in the Afrezza and Aspart arms. Clearly state how you have defined achievement of prandial-related (pre or post) insulin titration goals to generate your response and how you have handled missing data for this time point.

10. With regards to the adherence report generated to assess the investigator and titration committee's performance

    a. The report does not distinguish adherence by arm. Was adherence similar or different between arms for basal insulin and for prandial insulin? Provide these data.

    b. Were investigator discretionary reasons for non-adherence captured and organized for reporting (e.g., safety concern, lack of adequate data to make a decision)? If yes please provide these data.

11. Fill in the following shell tables:

<u>Table 2:</u> Proportion of subjects with at least (x) adjustment(s) in prandial insulin dose (for at least one of the three meals*) between randomization time and end-of-treatment time.

		Any Adjustment		**Dose Increase**		**Dose Decrease**	
ARM (Number Random-ized)		**Afrezza Gen-2 (N)**	**Compara tor (N)**	**Afrezza Gen-2 (N)**	**Compar ator (N)**	**Afrezza-Gen-2 (N)**	**Comparato r (N)**
INSULIN TYPE		**Afrezza**	**Aspart**	**Afrezza**	**Aspart**	**Afrezza**	**Aspart**
	NUMBER OF ADJUST-MENTS						
	0	n (%)					
	2						
	4						
	8						
	10						
	12						
	14						
	16						
	≥20						

* Example: a change in breakfast and lunch and dinner dose at a single visit would count as one dose adjustment. A change in a single meal for one visit would also count as one dose adjustment.

<u>Table 3:</u> Proportion of subjects with at least (x) adjustment(s) in daily basal insulin dose between randomization and end-of-treatment.

	Any Adjustment		**Dose Increase**		**Dose Decrease**	
ARM (Number Randomized)	**Afrezza Gen-2 (N)**	**Comparator (N)**	**Afrezza Gen-2 (N)**	**Comparator (N)**	**Afrezza Gen-2 (N)**	**Comparator (N)**
INSULIN TYPE	NPH or DETEMIR or Glargine	NPH or DETEMIR or Glargine	NPH or DETEMR or Glargine	NPH or DETEMIR or Glargine	NPH or DETEMIR or Glargine	NPH or DETEMIR or Glargine
0	n (%)					
2						
4						
6						
8						
10						
12						
14						
>20						

<u>Table 4:</u> Proportion of subjects with an at least (x%) increase above baseline in total daily basal insulin dose between randomization and end-of-treatment.

Dose Increase

ARM(Number Randomized)		**Afrezza Gen-2 (N)**	**Comparator (N)**
INSULIN TYPE		Any Allowed	Any Allowed
	% increase above baseline		
	0%	n (%)	
	10%		
	20%		
	30%		
	40%		
	50%		
	60%		
	100%		
	>100%		

<u>Table 5:</u> Proportion of subjects with an at least x% increase above baseline in total daily prandial insulin dose between randomization and end of treatment.

Dose Increase

ARM (Number Randomized)		**Afrezza Gen-2(N)**	**Comparator (N)**
INSULIN TYPE		Afrezza	Aspart
	% increase above baseline		
	0%	n (%)	
	10%		
	20%		
	30%		
	40%		
	50%		

	60%		
	100%		
	>100%		

12. Provide a scatter plot for the number of Afrezza, Aspart and basal insulin dose adjustments made in the Afrezza and Aspart arms respectively. Provide the following descriptive statistics: total number of dose adjustments made, mean number of dose adjustments made (SE), median number of dose adjustments made (and interquartile range), range of dose adjustments made.

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

/s/

RICHARD E WHITEHEAD
02/13/2014

From: Whitehead, Richard
To: "Bedard, John"
Subject: NDA22472 Afrezza: Information Request
Date: Thursday, February 13, 2014 7:12:21 PM
Attachments: IR to sponsor_rev3.doc

John,

I am forwarding an Information Request (below and attached as a Word Document) for Afrezza, NDA 22472. Please provide your responses to these questions **no later than Monday, February 24, 2014**. Send your responses to me via email and submit to your application. Let me know if you have any questions and please confirm receipt of this email request.

Information Request for MannKind

We are evaluating the dosing regimen you proposed in your prescribing information, and have the following requests for clarification and/or further information.

1. The dosing regimen proposed in the prescribing information (Afrezza cartridge strengths defined as 3 Units and 6 Units respectively) is different than the dosing regimen tested in the Phase 3 trials (cartridge strengths defined as equivalent to 4 IU and 8 IU of rapid acting insulin respectively). We are not aware of any data in your submission to support this new proposed dosing regimen. Please provide your rationale for this change.

2. Based on the data available from PK/PD studies, we are unable to verify the adequacy of the recommended dosing conversion proposed to go from subcutaneous insulin to Gen-2 delivered Afrezza insulin. Data from study MKC-T1-176, the only dose-ranging data available with the new device, suggest a non-proportional increase in $GIRAUC_{0-240}$ with increasing doses of Afrezza. Dosing conversions based on $GIRAUC_{0-240}$ comparison between Afrezza (Gen2) and subcutaneous insulin (i.e., regular human insulin) are listed in table below. Only one dose of subcutaneously delivered insulin was evaluated in this study and it is not possible to directly evaluate whether the non-proportional increase in GIRAUC observed for Afrezza would have also been observed for subcutaneous insulin.

Route	Dose (IU)	AUCGIR 0-240	Based on AUCGIR inhalation dose is equal to sc dose (IU) of	Assumed equal sc doses in the label
SC	15	1596		
Afrezza	10	760	7.14	3
Afrezza	30	1342	12.61	7-9
Afrezza	60	1929	18.13	16-18
Afrezza	80	2188	20.56	

To understand whether the dose conversion algorithm tested in Phase 3 trials was

adequate and to assess whether the observed non-proportional PD response observed for Afrezza had an effect on dosing titration and/or efficacy, we want to further look at the doses/dosing titrations at the individual patient level in these trials. Therefore, please provide us the following graphs and any other information you might consider useful in understanding the dosing/dosing titration issue.

3. **<u>From Phase 3 Trial in T2DM (MKC-TI-175)</u>**

   a. For each meal, (i.e., breakfast, lunch, and dinner), provide a simple line plot of total meal time Afrezza dose (y-axis) as a function of time in weeks (x-axis) from Baseline to Week 12, representing individual level data (i.e., show dose data points for each individual and connect them with a line).

   b. For each meal, (i.e., breakfast, lunch, and dinner), provide a simple line plot of total meal time Afrezza dose (y—axis) as a function of time in weeks (x-axis) from Baseline to Week 24, representing individual level data.

   c. Provide an analysis of responders (proportion of subjects with an HbA1c above 7% at baseline who had an HbA1c target of <7% at trial end) by subgroup for the following subgroups: patients for whom at least one meal time Afrezza dose (i.e., not the total meal time dose) was ≥ 60 units vs. patients for whom all of the meal time Afrezza doses were <60 units. For these patient subgroups, also provide the percentage of patients who required supplemental doses and the average units of supplemental doses.

      If graphs 3(a) and 3(b) are not informative consider supplementing them with graphs adjusting for BMI and/or dosing requirements (≥ 60 units vs. < 60 units).

4. **<u>From Phase 3 Trial in T1DM (MKC-TI-171)</u>**

   d. For each meal, (i.e., breakfast, lunch, and dinner), provide a simple line plot of total meal time Gen-2 Afrezza dose (y—axis) as a function of time in weeks (x-axis), and total meal time comparator dose (y—axis) as a function of time in weeks (x-axis), from Week -4 to Week 12, representing individual level data. Provide similar comparison between Afrezza (Medtone) and subcutaneous insulin.

   e. For each meal, (i.e., breakfast, lunch, and dinner), provide a line plot of total meal time Gen-2 Afrezza dose (y—axis) as a function of time in weeks (x-axis), and total meal time comparator dose (y—axis) as a function of time in weeks (x-axis), from Week -4 to Week 24, representing individual level data.

   f. Create plots similar to point (d) comparing the doses for Afrezza (Gen2) and subcutaneous insulin separately for the following patient subgroups based on baseline pre-conversion prandial insulin requirements (i.e., for the subgroups based on dosing regimen tested in the Phase 3 trial): up to 4 units, >4 up to 8 units, >8 up to 12 units, >12- up to 16 units, >16- up to 20 units, and >20 up to 24 units. Again, plot the prandial and basal insulin doses separately.

   g. Provide an analysis of responders (proportion of subjects with an HbA1c above 7% at baseline who had an HbA1c target of <7% at trial end) by subgroup for the following subgroups: patients for whom at least one meal time Afrezza (Gen2) dose (i.e., not the total meal time dose) was ≥ 60 units vs. patients for whom all of the meal time Afrezza (Gen2) doses were <60 units. For these patient subgroups, also provide the

percentage of patients who required supplemental doses and the average units of supplemental doses.

Again, if graphs 4(d) and 4(e) are not informative, consider supplementing them with graphs adjusting for BMI and/or dosing requirements (≥ 60 units vs. < 60 units).

Please submit all the datasets and codes used to generate the graphs above.

Regards,
Rich

Richard Whitehead, MS; Regulatory Project Manager; FDA/CDER/OND/ODEII/ Division of Metabolism and Endocrinology Products;
(t) 301.796.4945; (f) 301.796.9712; richard.whitehead@fda.hhs.gov

Information Request for MannKind

We are evaluating the dosing regimen you proposed in your prescribing information, and have the following requests for clarification and/or further information.

1. The dosing regimen proposed in the prescribing information (Afrezza cartridge strengths defined as 3 Units and 6 Units respectively) is different than the dosing regimen tested in the Phase 3 trials (cartridge strengths defined as equivalent to 4 IU and 8 IU of rapid acting insulin respectively). We are not aware of any data in your submission to support this new proposed dosing regimen. Please provide your rationale for this change.

2. Based on the data available from PK/PD studies, we are unable to verify the adequacy of the recommended dosing conversion proposed to go from subcutaneous insulin to Gen-2 delivered Afrezza insulin. Data from study MKC-T1-176, the only dose-ranging data available with the new device, suggest a non-proportional increase in $GIRAUC_{0-240}$ with increasing doses of Afrezza. Dosing conversions based on $GIRAUC_{0-240}$ comparison between Afrezza (Gen2) and subcutaneous insulin (i.e., regular human insulin) are listed in table below. Only one dose of subcutaneously delivered insulin was evaluated in this study and it is not possible to directly evaluate whether the non-proportional increase in GIRAUC observed for Afrezza would have also been observed for subcutaneous insulin.

Route	Dose (IU)	AUCGIR 0-240	Based on AUCGIR inhalation dose is equal to sc dose (IU) of	Assumed equal sc doses in the label
SC	15	1596		
Afrezza	10	760	7.14	3
Afrezza	30	1342	12.61	7-9
Afrezza	60	1929	18.13	16-18
Afrezza	80	2188	20.56	

To understand whether the dose conversion algorithm tested in Phase 3 trials was adequate and to assess whether the observed non-proportional PD response observed for Afrezza had an effect on dosing titration and/or efficacy, we want to further look at the doses/dosing titrations at the individual patient level in these trials. Therefore, please provide us the following graphs and any other information you might consider useful in understanding the dosing/dosing titration issue.

3. **From Phase 3 Trial in T2DM (MKC-TI-175)**

   a. For each meal, (i.e., breakfast, lunch, and dinner), provide a simple line plot of total meal time Afrezza dose (y-axis) as a function of time in weeks (x-axis) from Baseline to Week 12, representing individual level data (i.e., show dose data points for each individual and connect them with a line).

   b. For each meal, (i.e., breakfast, lunch, and dinner), provide a simple line plot of total meal time Afrezza dose (y—axis) as a function of time in weeks (x-axis) from Baseline to Week 24, representing individual level data.

   c. Provide an analysis of responders (proportion of subjects with an HbA1c above 7% at baseline who had an HbA1c target of <7% at trial end) by subgroup for the following subgroups: patients for whom at least one meal time Afrezza dose (i.e., not the total meal time dose) was ≥ 60 units vs. patients for whom all of the meal time Afrezza doses were <60 units. For these patient subgroups, also provide the percentage of patients who required supplemental doses and the average units of supplemental doses.

      If graphs 3(a) and 3(b) are not informative consider supplementing them with graphs adjusting for BMI and/or dosing requirements (≥ 60 units vs. < 60 units).

4. **From Phase 3 Trial in T1DM (MKC-TI-171)**

   d. For each meal, (i.e., breakfast, lunch, and dinner), provide a simple line plot of total meal time Gen-2 Afrezza dose (y—axis) as a function of time in weeks (x-axis), and total meal time comparator dose (y—axis) as a function of time in weeks (x-axis), from Week -4 to Week 12, representing individual level data. Provide similar comparison between Afrezza (Medtone) and subcutaneous insulin.

   e. For each meal, (i.e., breakfast, lunch, and dinner), provide a line plot of total meal time Gen-2 Afrezza dose (y—axis) as a function of time in weeks (x-axis), and total meal time comparator dose (y—axis) as a function of time in weeks (x-axis), from Week -4 to Week 24, representing individual level data.

   f. Create plots similar to point (d) comparing the doses for Afrezza (Gen2) and subcutaneous insulin separately for the following patient subgroups based on baseline pre-conversion prandial insulin requirements (i.e., for the subgroups based on dosing regimen tested in the Phase 3 trial): up to 4 units, >4 up to 8 units, >8 up to 12 units, >12- up to 16 units, >16- up to 20 units, and >20 up to 24 units. Again, plot the prandial and basal insulin doses separately.

   g. Provide an analysis of responders (proportion of subjects with an HbA1c above 7% at baseline who had an HbA1c target of <7% at trial end) by subgroup for the following subgroups: patients for whom at least one meal time Afrezza (Gen2) dose (i.e., not the total meal time dose) was ≥ 60 units vs. patients for whom all of the meal time Afrezza

(Gen2) doses were <60 units. For these patient subgroups, also provide the percentage of patients who required supplemental doses and the average units of supplemental doses.

Again, if graphs 4(d) and 4(e) are not informative, consider supplementing them with graphs adjusting for BMI and/or dosing requirements (≥ 60 units vs. < 60 units).

Please submit all the datasets and codes used to generate the graphs above.

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

/s/

RICHARD E WHITEHEAD
02/13/2014

From: Whitehead, Richard
To: Bedard, John
Subject: Afrezza NDA22472: Information Request
Date: Monday, January 27, 2014 12:28:22 PM

John:

Please see below for an information request from the review team in reference to NDA22427 Afrezza. Provide your responses directly to me via email as soon as possible (no later than COB March 1) and submit officially to your application. Let me know if there are any questions and please confirm receipt of this Information Request.

> Figure 3 in the Study 171 CSR shows box plots of the average daily dose of prandial insulin since randomization by time periods. Please submit a similar figure showing box plots of the average daily dose of basal insulin.

Regards,
Rich

Richard Whitehead, MS; Regulatory Project Manager; FDA/CDER/OND/ODEII/ Division of Metabolism and Endocrinology Products;
(t) 301.796.4945; (f) 301.796.9712; richard.whitehead@fda.hhs.gov

---

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

/s/

RICHARD E WHITEHEAD
01/27/2014

From: Whitehead, Richard
To: "Bedard, John"
Subject: Afrezza NDA22472: Information Request
Date: Friday, January 17, 2014 9:07:14 AM

John:

Please see below for an information request from the review team in reference to NDA22427 Afrezza. Provide your responses directly to me via email as soon as possible **no later than February 8th** and submit officially to your application. Let me know if there are any questions and please confirm receipt of this Information Request.

Overview of Clinical Safety Data

Please update the table below, that you submitted previously, with the 2013 data Cutoff July 31, 2013.

Overview of Clinical Safety Data for TI		
Controlled safety/ efficacy trials	T1DM	2 Trials: 009 and 101
	T2DM	6 Trials: 005, 0008, 102, 014, 026, and 103
Controlled long-term safety trial	Combined T1DM and T2DM	030 – 2 year pulmonary safety trial
Uncontrolled long-term safety data	T2DM	010 – 4 years
Follow-up observational study	Combined T1DM and T2DM	126 – 2 months
Clinical Pharmacology	Healthy volunteers, T1DM and T2DM	25 studies: 0001, 0001A, 0001B, 0001C, 0002, 0002A, 0003, 0003A, 03B, 03B2, 0004, 0004A, 0006, 0007, 00011, 025, 110, 113, 114, 116, 122, 123, 129, 138, 104
Special Safety Clinical Pharmacology studies		131 (QT study), 017 (renal impairment), 111 (hepatic impairment), 016 (smokers), 015 (COPD), 112 (URI), 027 (asthma)
Terminated (asthma)	Combined T1DM and T2DM	105
Ongoing Trials	T1DM	117
	T2DM	118

Total TI Development Program

Please replace the "XX"s with data.

The total TI development program has exposed 2647 subjects to TI using the MedTone inhaler and 370 using the Gen2 inhaler (total 3017) in phase 2/3 clinical studies. Overall, XX subjects were exposed to TI Inhalation Powder for 0 to 3 months, XX for >3 to 6 months, XX for >6 to 12 months, and XX for >12 months.

ISS Table 20 and 22

In Table 20 of the ISS, the range of BMI for the comparator group listed is 0.3 – 41 kg/m2. Furthermore, in Table 20 of the ISS, you provide a lower range of -0.4 for the duration of diabetes for the comparator group. Please check the numbers you provide for the lower end of the range for accuracy. Additionally, Table 22 may have some inaccuracies as well, as the lower range for duration of diabetes in the MedTone group is a negative number.

Statistics

For studies MKC-TI-171 and MKC-TI-175: Provide analyses on the primary endpoint involving imputation under the null hypothesis using an appropriate multiple imputation method that includes baseline HbA1c, and the stratification variables as factors. For study

MKC-TI_171 the imputation under the non-inferiority null would involve adding 0.4% to the imputed values in the TI-Gen2 group."

Regards,
Rich

Richard Whitehead, MS; Regulatory Project Manager; FDA/CDER/OND/ODEII/ Division of Metabolism and Endocrinology Products;
(t) 301.796.4945; (f) 301.796.9712; richard.whitehead@fda.hhs.gov

---

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

/s/

RICHARD E WHITEHEAD
01/17/2014

From: Whitehead, Richard
To: "Bedard, John"
Subject: Afrezza NDA22472: Information Request
Date: Friday, January 17, 2014 8:48:19 AM
Attachments: NDA22472 Afrezza Lung NeoplasmTables.pdf

John:

Please see below for an information requests from the review team in reference to NDA22427 Afrezza. Provide your responses directly to me via email as soon as possible (no later than the date indicated) and submit officially to your application. Let me know if there are any questions and please confirm receipt of this Information Request.

In the Complete Response Letter from 18 Jan 2011 we requested that in your resubmission you "Submit updated analyses of lung cancer cases in the Afrezza program. These analyses should include adjustments for patient-year exposure and should compare the rates of lung cancer among Afrezza-treated patients to the background rates among smokers and non-smokers."

Since the 2011 Complete Response you report two spontaneous post-trial cases of lung cancer in patients exposed to Afrezza (ID358 and ID618, squamous cell cancer) in addition to the two previously reported cases (ID3316, bronchogenic carcinoma and ID 2909 neuroendocrine/small cell ca). Furthermore, we have identified 19 additional cases concerning for possible lung malignancies in the TI inhalation powder studies, (15 in TI treated, 4 in comparator) with AE preferred term (PT) of lung neoplasm/pleural/lung nodules/lung mass or squamous cell carcinoma, site unspecified in the submission (see attached Tables).

We note that case report forms (CRF) are not available for review in the majority of the cases and narratives, and when provided contain insufficient information to evaluate whether these cases represent a respiratory tract cancer versus another diagnosis and perform an adequate causality assessment. Many of these cases were identified in the previous review cycles and follow-up data on all these cases should have been obtained.

We request that you provide the CRFs and detailed narratives for the following 19 subjects:

- Treated with TI: IDs 8472, 0108, 1906, 157, 323, 399, 3953 , 154, 403, 1751, 261, 406, 3316, 2973, 814;
- Comparator: IDs 1764, 2221, 3543 and 1200

In addition, for patients ID358, ID618 (spontaneous reports) provide the case report forms while on study.

Detailed case narratives should contain description of pertinent medical history, any

comorbid illnesses, smoking history, date of study treatment initiation and termination, date of pulmonary AE diagnosis, AE treatment and AE outcome information. Include all pertinent radiographic and pathology reports. If early termination from study, provide the reason for study termination.

We ask that you provide the requested information **no later than COB February 8**.

We appreciate the limitations you have outlined with regards to interpretation of spontaneously reported data. However some of the limitations related to interpretation of spontaneous adverse event reporting in the post-marketing setting can be circumvented when dealing with data arising from patients who participated in clinical trials. Namely, the number of patients exposed and not exposed are known and querying previous participants (exposed and non-exposed) for the outcomes of interest is a possibility. We would like to better understand the efforts made to address the safety concerns of lung CA raised at the pre-NDA meeting and of rare respiratory tract cancers raised in a communication dated (07/07/2011).

Clarify the attempts made to obtain follow-up data on previously exposed patients for respiratory tract cancers.

Are we correct in our assumption that you followed a passive approach (i.e., relying on spontaneous submission of AE reports)?

If not already done, we request that you attempt to pro-actively obtain information regarding incidence of lung cancer on all patients enrolled in clinical trials of both type 1 and type 2 diabetes of 3 months duration or greater. Vital statistics information and information important for a causality assessment (see above) should be provided for these patients.

Please provide the results of these queries **no later than COB March 1**.

Regards,
Rich

Richard Whitehead, MS; Regulatory Project Manager; FDA/CDER/OND/ODEII/ Division of Metabolism and Endocrinology Products;
(t) 301.796.4945; (f) 301.796.9712; richard.whitehead@fda.hhs.gov

NDA22472 Afrezza

Subjects with Neoplasm AEs - DM type 2 subjects in controlled phase 2/3 studies

ID	Age/Sex	AE onset	AE PT	Outcome Recovered/Resolved	AE lead to withdraw	Treatment emergent
TI						
MKC-TI-005/8472	72YOF	2005-01-27	Pleural neoplasm	No/No	No	Yes
MKC-TI-030/0108	54yof	2008-01-08	Lung neoplasm	Yes/Yes	No	Yes
MKC-TI-102/1906	55yof	2008-02-19	Lung neoplasm	No/No	No	Yes
MKC-TI-102-2909	61yom	2008-02-22	Neuroendocrine tumor	No/No	No	No
PDC-INS-0008/157	57yom	2004-06-02	Lung neoplasm	Yes/Yes	No	Yes
PDC-INS-0008-323	54yom	2004-08-27	Lung neoplasm	No/No	No	Yes
PDC-INS-0008/399	37yom	2004-10-18	Lung neoplasm	Unknown	No	Yes
TP						
MKC-TI-175/3953	48yom	2012-11-24	Squamous cell ca (site ??)	Yes/Yes	Yes	Yes
PDC-INS-0008-154	49yom	2004-06-04	Lung neoplasm	No/No	No	Yes
PDC-INS-0008-403	62yom	2004-10-25	Lung neoplasm	No/No	No	Yes
Comparator						
MKC-TI-030/1764	58yom	2008-06-20	Lung neoplasm	No/No	No	Yes
MKC-TI-102/2221	73yof	2008-04-15	Lung neoplasm	No/No	No	Yes
MKC-TI-030/3543	70yom	2007-09-04	Lung neoplasm	No/No	No	Yes

Subjects with Neoplasm AEs - DM type 1 subjects in controlled phase 2/3 studies

ID	Age/Sex	AE onset	AE PT	Outcome Recovered/Resolved	AE lead to withdraw	Treatment emergent
TI						
MKC-TI-009-1751	22yom	2008-03-12	Pulmonary mass	No/No	No	Yes
MKC-TI-030/0814	46yom	2007-11-29	Squamous cell ca (site??)	Yes/Yes	No	Yes
Comparator						
MKC-TI-009-1200	43yom	2007-10-05	Lung neoplasm	No/No	No	Yes

Adverse Events Narratives: Neoplasm

ID/Study	Demographic	Study Treatment	Narrative	CRF
Site 112 no. 1751 MKC-TI-009 study (is not listed in the Tabular Listing of All Clinical Studies)	22 yom, Caucasian DM1 Non smoker	TI inhalation powder and Lantus 377 days in treatment	Enlarging lung mass (per chest x rays at beginning & end of study) Not resolved Relationship to TI: possible No action taken with study drug (completed study)	Not available
Site 006, no. 403 Study MKC-TI-010	63yom, Caucasian, Non-smoker	1 (??) day in treatment TI inhalation powder Start 10/25/04, Visit 2 form dated 11/8/04 states investigational drug dispensed at the visit ?? terminated from study 12/13/04	3 mm pulmonary nodule RLL, lung neoplasm, unrelated, permanently discontinued CT: benign calcified granuloma. Withdrawn from study	Treatment discontinued on 12/13/04. To Sponsor: please clarify the length of treatment received.
Site 022, no. 261 MKC-TI-010	53yom, Caucasian, TI inhalation powder Smoker, 17 years, quit 19.8 years, 17 pack-years	340 days in treatment	Lung neoplasm, RLL nodule, enlarged mediastinal LN No action was taken concerning study drug Action specified: to repeat CT in 3 months	Not available
Site 23, no. 406	57yof, Caucasian Non smoker	TI inhalation powder 1241 days in treatment	6.7 mm nodule in LLL No action taken with study drug. Patient out of study.	Not available
Site 407, no. 3316 study MKC-TI-102	66yom, Caucasian Past history, 27 years smoking history, 54 pack-years Quit 20.4 years	TI inhalation powder 627 days in treatment	Bronchogenic carcinoma, ongoing, possible relationship, permanently discontinued	
Site 80, ID 0108	54yof Caucasian, DM2 Non-smoker	677 days in treatment TI inhalation powder	2 cm nodular infiltrated inferior R lobe, never biopsied Outcome resolved in follow-up scan No action taken	
Site 80, subject 2973	55yom, Caucasian, TI inhalation powder No smoking	114 days in treatment	4 mm nodule LLL CT (1/18/07) to follow up Ct advised Subject withdrew consent (cough,	

			inconvenience with product)	
Site 067, ID2909 Study MKC-TU-102	62yom, Caucasian DM2 Smoking history: 20/day x 41 years	137 days to onset of symptoms TI inhalation and Lantus	Neck lymphadenopathy elevated CEA, CT mediastinal, and hilar nodes Biopsy LN - oat cell, small cell and neuroendocrine type Rx carbo/etoposide, Study treatment discontinued, Worsening tumor, stopped chemo, palliative care	
CONTROL				
Site 196, subject 3543	70yom, Caucasian No smoker	Control "usual anti-diabetic treatment" 242 days in treatment	4.5mm soft tissue nodule mid RL Referral to primary care physician	
Site 69, no. 1764	58yom, Caucasian DM 2	Control "usual anti-diabetic treatment" 612 days in treatment	LUL nodule	

Spontaneous Reports after Study Ending

PDC-IN0008/358	59yom Smoking history: not provided	TI inhalation Duration of rx: 3 year, 6 months	Squamous cell lung ca (stage III) 2.5 year after discontinuation Possibly related to TI	No case report form
MKC-TI-030/618	73yof DM2 Smoking history: not provided.	TI inhalation powder Duration of rx: 1 year, 11 months (4/06 - 3/08)	Stage II squamous cell, 3.5 year after discontinued participation	No case report form

---

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

/s/

RICHARD E WHITEHEAD
01/17/2014

DEPARTMENT OF HEALTH AND HUMAN SERVICES

Food and Drug Administration Silver Spring MD 20993

NDA 022472

PROPRIETARY NAME REQUEST CONDITIONALLY ACCEPTABLE

MannKind Corporation
61 South Paramus Road
Paramus, NJ, 07652

Attention: John Bedard
Sr. Vice President, Regulatory Affairs

Dear Mr. Bedard:

Please refer to your New Drug Application (NDA) dated October 13, 2013, received October 15, 2013, submitted under section 505(b)(1) of the Federal Food, Drug, and Cosmetic Act for Insulin Human [rDNA origin] Inhalation Powder, 3 units and 6 units per cartridge.

We also refer to your correspondence, submitted and received October 17, 2013, requesting review of your proposed proprietary name, Afrezza. We have completed our review of the proposed proprietary name and have concluded that it is acceptable.

If **any** of the proposed product characteristics as stated in your October 17, 2013, submission are altered prior to approval of the marketing application, the proprietary name should be resubmitted for review.

If you have any questions regarding the contents of this letter or any other aspects of the proprietary name review process, contact Margarita Tossa, Safety Regulatory Project Manager in the Office of Surveillance and Epidemiology, at (301) 796-4053. For any other information regarding this application, contact the Office of New Drugs (OND) Regulatory Project Manager Richard Whitehead at (301) 796-4945.

Sincerely,

{See appended electronic signature page}

Kellie A. Taylor, Pharm.D., MPH
Deputy Director
Office of Medication Error Prevention and Risk Management
Office of Surveillance and Epidemiology
Center for Drug Evaluation and Research

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

/s/

TODD D BRIDGES on behalf of KELLIE A TAYLOR
01/14/2014

DEPARTMENT OF HEALTH AND HUMAN SERVICES

Food and Drug Administration
Silver Spring MD 20993

NDA 022472

ACKNOWLEDGE –
CLASS 2 RESPONSE

MannKind Corporation
Attention: John Bedard
Sr. Vice President, Regulatory Affairs
61 South Paramus Road
Paramus, NJ 07652

Dear Mr. Bedard:

We acknowledge receipt on October 15, 2013, of your October 13, 2013, resubmission of your new drug application submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act for Afrezza (insulin human [rDNA origin]) 3 units per cartridge and 6 units per cartridge inhalation powder and inhaler.

We consider this a complete, class 2 response to our January 18, 2011, action letter. Therefore, the user fee goal date is **Tuesday, April 15, 2014**.

If you have any questions, call me at (301) 796-4945.

Sincerely,

{See appended electronic signature page}

Richard Whitehead, M.S.
Regulatory Project Manager
Division of Metabolism and Endocrinology Products
Office of Drug Evaluation II
Center for Drug Evaluation and Research

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

/s/

RICHARD E WHITEHEAD
10/28/2013

DEPARTMENT OF HEALTH AND HUMAN SERVICES

Food and Drug Administration
Silver Spring MD 20993

NDA 022472

GENERAL ADVICE

MannKind Corporation
Attention: John Bedard
Sr. Vice President, Regulatory Affairs
61 South Paramus Road
Paramus, NJ 07652

Dear Mr. Bedard:

Please refer to your New Drug Application (NDA) submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act for Afrezza (insulin human [rDNA origin] Inhalation Powder) and Inhaler.

We also refer to your December 19, 2012, submission, received on December 20, 2012, containing your Type B meeting request with your proposed questions. We granted Type C Written Responses in our letter dated January 9, 2013. We also refer to your February 1, 2013, Type C Meeting Background Package, received February 1, 2013, which include the previously proposed questions and two additional questions. In our March 5, 2013, Meeting Request - Written Response, we provided responses to the proposed questions from December 19, 2012. This advice letter provides a response to the two remaining questions from your February 1, 2013 submission.

We have reviewed the referenced material and have the following comments:

Background Package Question 3:
Does the Agency agree with MannKind's pooling approach to bridging safety from the MedTone studies in the Original NDA to the Gen2 studies to be provided in the 2013 Resubmission?

FDA Response: we agree with your approach

Background Package Question 6:
Does the FDA agree that this approach for reporting hypoglycemia data in the 2013 Resubmission Safety Update is adequate?

FDA Response: your approach is acceptable

If you have any questions, call Richard Whitehead, Regulatory Project Manager, at (301) 796-4945.

Sincerely,

{See appended electronic signature page}

Mary H. Parks, M.D.
Director
Division of Metabolism and Endocrinology Products
Office of Drug Evaluation II
Center for Drug Evaluation and Research

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

/s/

MARY H PARKS
03/20/2013

DEPARTMENT OF HEALTH AND HUMAN SERVICES

Food and Drug Administration
Silver Spring MD 20993

NDA 022472

MEETING REQUEST - WRITTEN RESPONSES

MannKind Corporation
Attention: John Bedard
Sr. Vice President, Regulatory Affairs
61 South Paramus Road
Paramus, NJ 07652

Dear Mr. Bedard:

Please refer to your New Drug Application (NDA) submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act for Afrezza (insulin human [rDNA origin] Inhalation Powder) and Inhaler.

We also refer to your submission dated December 20, 2012, containing a Type C meeting request. The purpose of the requested meeting was to discuss NDA resubmission content and format, review the plan the Integrated Summaries of Safety and Efficacy updates, and discuss the timing of the resubmission.

Further reference is made to our Meeting Granted letter dated January 9, 2013, wherein we stated that written responses to your questions would be provided in lieu of a meeting.

The enclosed document constitutes our written responses to the questions contained in your February 1, 2013 background package.

If you have any questions, call Richard Whitehead, Regulatory Project Manager at (301) 796-4945.

Sincerely,

{See appended electronic signature page}

Mary H. Parks, M.D.
Director
Division of Metabolism and Endocrinology Products
Office of Drug Evaluation II
Center for Drug Evaluation and Research

Enclosure:
Written Responses

WRITTEN RESPONSES

Meeting Type:	Type C
Meeting Category:	Guidance
Application Number:	NDA 022472
Product Name:	Afrezza (insulin human [rDNA origin] Inhalation Powder) and Inhaler
Indication:	treatment of diabetes mellitus
Applicant Name:	MannKind Corporation
Regulatory Pathway:	505(b)(1)

1.0 BACKGROUND

Afrezza (insulin human [rDNA origin]) Inhalation Powder and Inhaler contains ultra-rapid acting, recombinant human insulin. The proposed indication for this product is for the treatment of adults with type 1 or type 2 diabetes mellitus for the control of hyperglycemia. The inhalation powder is administered via oral inhalation and it is administered at the beginning of a meal.

The IND (061729) for this product was submitted on December 22, 2000. The NDA (022472) was submitted on March 16, 2009 and received a Complete Response letter on March 12, 2010. NDA 022472 was resubmitted as a Class 2 resubmission on June 29, 2010, and received another Complete Response letter on January 18, 2011. The proprietary name Afrezza was conditionally accepted for this product on December 13, 2010.

On February 11, 2011, MannKind submitted an End-of Review meeting request to discuss the Complete Response, to gain clarity on the proposed clinical studies and to discuss the regulatory path for a resubmission. The Division granted the meeting and it was held May 4, 2011. Topics discussed included head-to-head comparisons of pulmonary safety, insulin glargine twice daily injections, special safety assessments, patient use and device robustness, immunogenicity, and others.

On October 7, 2011, MannKind submitted a Type C meeting to discuss issues from the January 18, 2011 Complete Response, including clinical site selection/inspection results, review Quality comments, and toxicological evaluation of insulin related impurities. The Division granted a Written Response and this was provided on February 28, 2012. Topics discussed in the Written Response include clinical pharmacology, Product Quality, Device, human factors, labeling, and others.

On July 20, 2012, MannKind submitted a Type C meeting request covering issues of product quality, device, human factors, and labeling. The Division granted a Written Response and this was provided on November 2, 2012. Topics discussed in the Written Response include labeling and summative human factors usability validation protocol.

On December 19, 2012, MannKind submitted a Type B Pre-submission meeting to facilitate the NDA resubmission, to review content and format of the Integrated Summaries of Safety and

Efficacy updates and to discuss timing or resubmission. The Division granted a Written Response on January 9, 2013 and this is the written response.

2. QUESTIONS AND RESPONSES

The sponsor's questions from the background package (submitted on October 19, 2012) are repeated below in plain font, followed by FDA's responses in **bold font**.

2.1. Clinical

Question 1- *Integrated Summary of Efficacy:* Does the FDA agree with this approach for ISE data analysis?

FDA Response to Question 1: Yes, we agree with your plan for the ISE as described on page 7 of the briefing document, Section 9.1 and in Appendix 1.

Question 2- *Integrated Summary of Safety:* Does FDA agree with the presentation of the updated safety data as shown in the sample table shells?

FDA Response to Question 2: Yes, we agree. On page 30 of Appendix 2 you describe your planned categories for reasons for discontinuation. For the categories of Subject Withdrew Consent, Investigator Decision, and Other please hyper-link data from tables to verbatim descriptions of the reasons for discontinuation.

Question 3-*Integrated Summary of Safety:* Does the FDA agree with this approach for summaries of medical history, concomitant medications, vital signs and clinical laboratory data?

FDA Response to Question 3: Yes, your approach is acceptable provided that there are no clinically meaningful differences in clinical laboratory data and vital signs results between the newly completed Phase 3 studies and the studies previously submitted.

Question 4- *Pulmonary safety data*: Does the FDA agree that this approach for reporting pulmonary safety data in the ISS update is acceptable?

FDA Response to Question 4: Yes, your approach is acceptable.

Question 5- *Adverse events:* Does FDA agree that this approach is acceptable for the difference tables when incorporating new safety data?

FDA Response to Question 5: Yes, this approach is acceptable.

Question 6- *Cardiac events:* Does FDA agree that the approach for analyzing cardiac events is acceptable?

FDA Response to Question 6: Your approach is acceptable.

Question 7-*cardiac events*: Does FDA have any advice regarding this new analysis of cardiac events?

FDA Response to Question 7: Please clarify how you identified the Preferred Terms to be included in the new analyses.

2.2. Regulatory

Question 8- *Endocrine and Metabolic Division Advisory Committee:* Does FDA anticipate referring the review of AFREZZA to an EMDAC?

FDA Response to Question 8: This decision will be made after filing.

Additional comment: Please see attached document listing requested information to be included with your re-submission.

The Office of Scientific Investigations (OSI) requests that the following items be provided to facilitate development of clinical investigator and sponsor/monitor/CRO inspection assignments, and the background packages that are sent with those assignments to the FDA field investigators who conduct the inspections (Item I and II).

The dataset that is requested, as per Item III below, is for use in a clinical site selection model that is being piloted in CDER. Electronic submission of site level datasets will facilitate the timely selection of appropriate clinical sites for FDA inspection as part of the application and/or supplement review process.

This request also provides instructions for where OSI requested items should be placed within an eCTD submission (Attachment 2, Technical Instructions: Submitting Bioresearch Monitoring (BIMO) Clinical Data in eCTD Format).

I. Request for general study related information and specific Clinical Investigator information (if items are provided elsewhere in submission, describe location or provide link to requested information).

1. Please include the following information in a tabular format in the original NDA for each of the completed Phase 3 clinical trials:
   a. Site number
   b. Principal investigator
   c. Site Location: Address (e.g. Street, City, State, Country) and contact information (i.e., phone, fax, email)
   d. Current Location of Principal Investigator (if no longer at Site): Address (e.g. Street, City, State, Country) and contact information (i.e., phone, fax, email)

2. Please include the following information in a tabular format by site in the original NDA for each of the completed Phase 3 clinical trials:
   a. Number of subjects screened for each site by site
   b. Number of subjects randomized for each site by site, if appropriate
   c. Number of subjects treated who prematurely discontinued for each site by site

3. Please include the following information in a tabular format in the NDA for each of the completed Phase 3 clinical trials:
   a. Location of Trial Master File [actual physical site(s) where documents are maintained and would be available for inspection]
   b. Name, address and contact information of all CROs used in the conduct of the clinical trials
   c. The location (actual physical site where documents are maintained and would be available for inspection) for all source data generated by the CROs with respect to their roles and responsibilities in conduct of respective studies
   d. The location (actual physical site where documents are maintained and would be available for inspection) of sponsor/monitor files (e.g. monitoring master files, drug accountability files, SAE files, etc.)

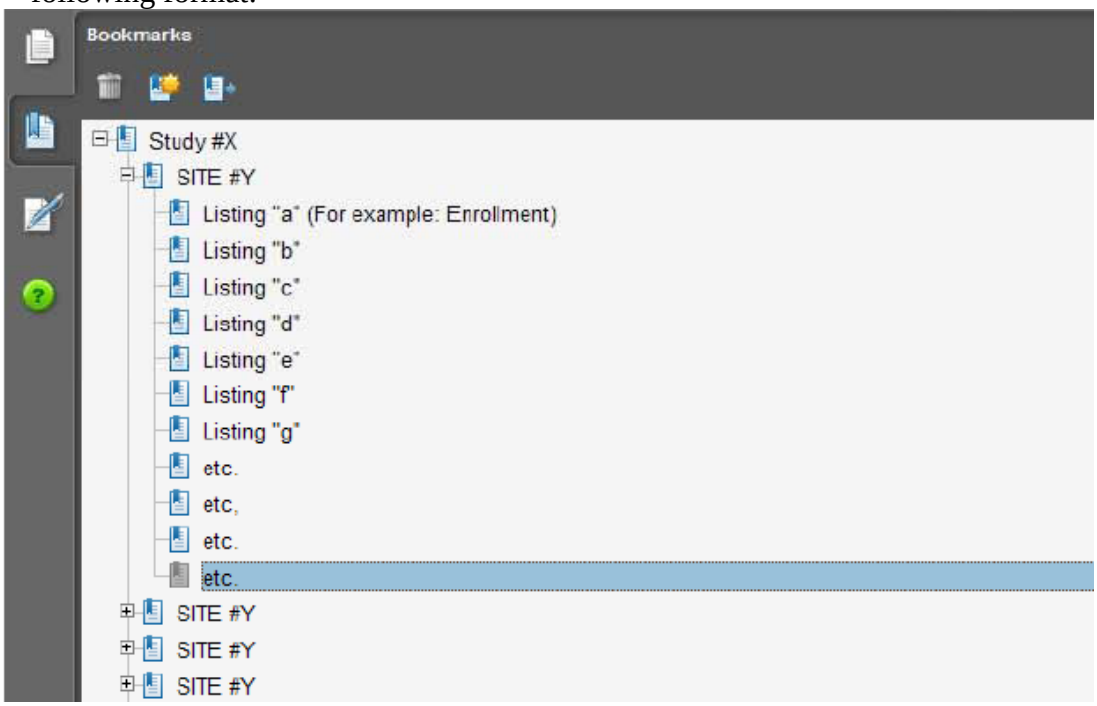
4. For each pivotal trial provide a sample annotated Case Report Form (if items are provided elsewhere in submission, please describe location or provide a link to requested information).

5. For each pivotal trial provide original protocol and all amendments (if items are provided elsewhere in submission, please describe location or provide a link to requested information).

II. Request for Subject Level Data Listings by Site

1. For each pivotal trial: Site-specific individual subject data ("line") listings. For each site provide line listings for:
   a. Listing for each subject/number screened and reason for subjects who did not meet eligibility requirements
   b. Subject listing for treatment assignment (randomization)
   c. Subject listing of drop-outs and subjects that discontinued with date and reason
   d. Evaluable subjects/ non-evaluable subjects and reason not evaluable
   e. By subject listing of eligibility determination (i.e., inclusion and exclusion criteria)
   f. By subject listing, of AEs, SAEs, deaths and dates
   g. By subject listing of protocol violations and/or deviations reported in the NDA, description of the deviation/violation
   h. By subject listing of the primary and secondary endpoint efficacy parameters or events. For derived or calculated endpoints, provide the raw data listings used to generate the derived/calculated endpoint.
   i. By subject listing of concomitant medications (as appropriate to the pivotal clinical trials)
   j. By subject listing, of laboratory tests performed for safety monitoring

2. We request that one PDF file be created for each pivotal Phase 3 study using the following format:



III. Request for Site Level Dataset:

OSI is piloting a risk based model for site selection. Electronic submission of site level datasets will facilitate the timely selection of appropriate clinical sites for FDA inspection as part of the application and/or supplement review process. Please refer to Attachment 1, "Summary Level Clinical Site Data for Data Integrity Review and Inspection Planning in NDA and BLA Submissions" for further information. We request that you provide a dataset, as outlined, which includes requested data for each pivotal study submitted in your application.

Attachment 1

1 Summary Level Clinical Site Data for Data Integrity Review and Inspection Planning in NDA and BLA Submissions

1.1 Introduction

The purpose of this pilot for electronic submission of a single new clinical site dataset is to facilitate the timely selection of appropriate clinical sites for FDA inspection as part of the application and/or supplement review process in support of the evaluation of data integrity.

1.2 Description of the Summary level clinical site dataset

The summary level clinical site data are intended (1) to clearly identify individual clinical investigator sites within an application or supplement, (2) to specifically reference the studies to which those clinical sites are associated, and (3) to present the characteristics and outcomes of the study at the site level.

For each study used to support efficacy, data should be submitted by clinical site and treatment arm for the population used in the primary analysis to support efficacy. As a result, a single clinical site may contain multiple records depending on the number of studies and treatment arms supported by that clinical site.

The site-level efficacy results will be used to support site selection to facilitate the evaluation of the application. To this end, for each study used to support efficacy, the summary level clinical site dataset submission should include site-specific efficacy results by treatment arm and the submission of site-specific effect sizes.

The following paragraphs provide additional details on the format and structure of the efficacy related data elements.

Site-Specific Efficacy Results

For each study and investigator site, the variables associated with efficacy and their variable names are:

- Treatment Efficacy Result (TRTEFFR) – the efficacy result for each primary endpoint, by treatment arm (see below for a description of endpoint types and a discussion on how to report this result)
- Treatment Efficacy Result Standard Deviation (TRTEFFS) – the standard deviation of the efficacy result (treatEffR) for each primary endpoint, by treatment arm
- Site-specific Efficacy Effect Size (SITEEFFE) – the effect size should be the same representation as reported for the primary efficacy analysis
- Site-specific Efficacy Effect Size Standard Deviation (SITEEFFS) – the standard deviation of the site-specific efficacy effect size (SITEEFFE)

- Endpoint (endpoint) – a plain text label that describes the primary endpoint as described in the Define file data dictionary included with each application.
- Treatment Arm (ARM) – a plain text label for the treatment arm that is used in the Clinical Study Report.

In addition, for studies whose primary endpoint is a time-to-event endpoint, include the following data element:

- Censored Observations (CENSOR) –the number of censored observations for the given site and treatment.

If a study does not contain a time-to-event endpoint, record this data element as a missing value.

To accommodate the variety of endpoint types that can be used in analyses please reference the below endpoint type definitions when tabulating the site-specific efficacy result variable by treatment arm, "TRTEFFR."

- Discrete Endpoints – endpoints consisting of efficacy observations that can take on a discrete number of values (e.g., binary, categorical). Summarize discrete endpoints by an event frequency (i.e., number of events), proportion of events, or similar method at the site for the given treatment.
- Continuous Endpoints – endpoints consisting of efficacy observations that can take on an infinite number of values. Summarize continuous endpoints by the mean of the observations at the site for the given treatment.
- Time-to-Event Endpoints – endpoints where the time to occurrence of an event is the primary efficacy measurement. Summarize time-to-event endpoints by two data elements: the number of events that occurred (TRTEFFR) and the number of censored observations (CENSOR).
- Other – if the primary efficacy endpoint cannot be summarized in terms of the previous guidelines, a single or multiple values with precisely defined variable interpretations should be submitted as part of the dataset.

In all cases, the endpoint description provided in the "endpoint" plain text label should be expressed clearly to interpret the value provided in the (TRTEFFR) variable.

The site efficacy effect size (SITEEFFE) should be summarized in terms of the primary efficacy analysis (e.g., difference of means, odds ratio) and should be defined identically for all records in the dataset regardless of treatment.

The Define file for the dataset is presented in Exhibit 1: *Table 1 Clinical Site Data Elements Summary Listing (DE)*. A sample data submission for the variables identified in Exhibit 1 is provided in Exhibit 2. The summary level clinical site data can be submitted in SAS transport file format (*.xpt).

Exhibit 1: Table 1 Clinical Site Data Elements Summary Listing (DE)

Variable Index	Variable Name	Variable Label	Type	Controlled Terms or Format	Notes or Description	Sample Value
1	STUDY	Study Number	Char	String	Study or trial identification number.	ABC-123
2	STUDYTL	Study Title	Char	String	Title of the study as listed in the clinical study report (limit 200 characters)	Double blind, randomized placebo controlled clinical study on the influence of drug X on indication Y
3	DOMAIN	Domain Abbreviation	Char	String	Two-character identification for the domain most relevant to the observation. The Domain abbreviation is also used as a prefix for the variables to ensure uniqueness when datasets are merged.	DE
4	SPONNO	Sponsor Number	Num	Integer	Total number of sponsors throughout the study. If there was a change in the sponsor while the study was ongoing, enter an integer indicating the total number of sponsors. If there was no change in the sponsor while the study was ongoing, enter “1”.	1
5	SPONNAME	Sponsor Name	Char	String	Full name of the sponsor organization conducting the study at the time of study completion, as defined in 21 CFR 312.3(a).	DrugCo, Inc.
6	IND	IND Number	Num	6 digit identifier	Investigational New Drug (IND) application number. If study not performed under IND, enter -1.	010010
7	UNDERIND	Under IND	Char	String	Value should equal "Y" if study at the site was conducted under an IND and "N" if study was not conducted under an IND (i.e., 21 CFR 312.120 studies).	Y
8	NDA	NDA Number	Num	6 digit identifier	FDA new drug application (NDA) number, if available/applicable. If not applicable, enter -1.	021212
9	BLA	BLA Number	Num	6 digit identifier	FDA identification number for biologics license application, if available/applicable. If not applicable, enter -1.	123456
10	SUPPNUM	Supplement Number	Num	Integer	Serial number for supplemental application, if applicable. If not applicable, enter -1.	4
11	SITEID	Site ID	Char	String	Investigator site identification number assigned by the sponsor.	50
12	ARM	Treatment Arm	Char	String	Plain text label for the treatment arm as referenced in the clinical study report (limit 200 characters).	Active (e.g., 25mg), Comparator drug product name (e.g., Drug x), or Placebo
13	ENROLL	Number of Subjects Enrolled	Num	Integer	Total number of subjects enrolled at a given site by treatment arm.	20
14	SCREEN	Number of Subjects Screened	Num	Integer	Total number of subjects screened at a given site.	100

Variable Index	Variable Name	Variable Label	Type	Controlled Terms or Format	Notes or Description	Sample Value
15	DISCONT	Number of Subject Discontinuations	Num	Integer	Number of subjects discontinuing from the study after being enrolled at a site by treatment arm as defined in the clinical study report.	5
16	ENDPOINT	Endpoint	Char	String	Plain text label used to describe the primary endpoint as described in the Define file included with each application (limit 200 characters).	Average increase in blood pressure
17	ENDPTYPE	Endpoint Type	Char	String	Variable type of the primary endpoint (i.e., continuous, discrete, time to event, or other).	Continuous
18	TRTEFFR	Treatment Efficacy Result	Num	Floating Point	Efficacy result for each primary endpoint by treatment arm at a given site.	0, 0.25, 1, 100
19	TRTEFFS	Treatment Efficacy Result Standard Deviation	Num	Floating Point	Standard deviation of the efficacy result (TRTEFFR) for each primary endpoint by treatment arm at a given site.	0.065
20	SITEEFFE	Site-Specific Efficacy Effect Size	Num	Floating Point	Site effect size with the same representation as reported for the primary efficacy analysis.	0, 0.25, 1, 100
21	SITEEFFS	Site-Specific Efficacy Effect Size Standard Deviation	Num	Floating Point	Standard deviation of the site-specific efficacy effect size (SITEEFFE).	0.065
22	CENSOR	Censored Observations	Num	Integer	Number of censored observations at a given site by treatment arm. If not applicable, enter -1.	5
23	NSAE	Number of Non-Serious Adverse Events	Num	Integer	Total number of non-serious adverse events at a given site by treatment arm. This value should include multiple events per subject and all event types (i.e., not limited to only those that are deemed related to study drug or treatment emergent events).	10
24	SAE	Number of Serious Adverse Events	Num	Integer	Total number of serious adverse events excluding deaths at a given site by treatment arm. This value should include multiple events per subject.	5
25	DEATH	Number of Deaths	Num	Integer	Total number of deaths at a given site by treatment arm.	1
26	PROTVIOL	Number of Protocol Violations	Num	Integer	Number of protocol violations at a given site by treatment arm as defined in the clinical study report. This value should include multiple violations per subject and all violation type (i.e., not limited to only significant deviations).	20
27	FINLMAX	Maximum Financial Disclosure Amount	Num	Floating Point	Maximum financial disclosure amount ($USD) by any single investigator by site. Under the applicable regulations (21 CFR Parts 54, 312, 314, 320, 330, 601, 807, 812, 814, and 860). If unable to obtain the information required to the corresponding statements, enter -1.	20000.00
28	FINLDISC	Financial Disclosure Amount	Num	Floating Point	Total financial disclosure amount ($USD) by site calculated as the sum of disclosures for the principal investigator and all sub-investigators to include all required parities. Under the applicable regulations (21 CFR Parts 54, 312, 314, 320, 330, 601, 807, 812, 814, and 860). If unable to obtain the information required to the corresponding statements, enter -1.	25000.00

Variable Index	Variable Name	Variable Label	Type	Controlled Terms or Format	Notes or Description	Sample Value
29	LASTNAME	Investigator Last Name	Char	String	Last name of the investigator as it appears on the FDA 1572.	Doe
30	FRSTNAME	Investigator First Name	Char	String	First name of the investigator as it appears on the FDA 1572.	John
31	MINITIAL	Investigator Middle Initial	Char	String	Middle initial of the investigator, if any, as it appears on the FDA 1572.	M
32	PHONE	Investigator Phone Number	Char	String	Phone number of the primary investigator. Include country code for non-US numbers.	44-555-555-5555
33	FAX	Investigator Fax Number	Char	String	Fax number of the primary investigator. Include country code for non-US numbers.	44-555-555-5555
34	EMAIL	Investigator Email Address	Char	String	Email address of the primary investigator.	john.doe@mail.com
35	COUNTRY	Country	Char	ISO 3166-1-alpha-2	2 letter ISO 3166 country code in which the site is located.	US
36	STATE	State	Char	String	Unabbreviated state or province in which the site is located. If not applicable, enter NA.	Maryland
37	CITY	City	Char	String	Unabbreviated city, county, or village in which the site is located.	Silver Spring
38	POSTAL	Postal Code	Char	String	Postal code in which site is located. If not applicable, enter NA.	20850
39	STREET	Street Address	Char	String	Street address and office number at which the site is located.	1 Main St, Suite 100

The following is a fictional example of a data set for a placebo-controlled trial. Four international sites enrolled a total of 205 subjects who were randomized in a 1:1 ratio to active or placebo. The primary endpoint was the percent of responders. The site-specific efficacy effect size (SITEEFFE) is the difference between the active and the placebo treatment efficacy result. Note that since there were two treatment arms, each site contains 2 rows in the following example data set and a total of 8 rows for the entire data set.

Exhibit 2: Example for Clinical Site Data Elements Summary Listing (Table 1)

STUDY	STUDYTL	DOMAIN	SPONNO	SPONNAME	IND	UNDERIND	NDA	BLA	SUPPNUM	SITEID	ARM	ENROLL	SCREEN	DISCONT
ABC-123	Double blind…	DE	1	DrugCo, Inc.	000001	Y	200001	-1	0	001	Active	26	61	3
ABC-123	Double blind…	DE	1	DrugCo, Inc.	000001	Y	200001	-1	0	001	Placebo	25	61	4
ABC-123	Double blind…	DE	1	DrugCo, Inc.	000001	Y	200001	-1	0	002	Active	23	54	2
ABC-123	Double blind…	DE	1	DrugCo, Inc.	000001	Y	200001	-1	0	002	Placebo	25	54	4
ABC-123	Double blind…	DE	1	DrugCo, Inc.	000001	Y	200001	-1	0	003	Active	27	62	3
ABC-123	Double blind…	DE	1	DrugCo, Inc.	000001	Y	200001	-1	0	003	Placebo	26	62	5
ABC-123	Double blind…	DE	1	DrugCo, Inc.	000001	Y	200001	-1	0	004	Active	26	60	2
ABC-123	Double blind…	DE	1	DrugCo, Inc.	000001	Y	200001	-1	0	004	Placebo	27	60	1

ENDPOINT	ENDTYPE	TRTEFFR	TRTEFFS	SITEEFFE	SITEEFFS	CENSOR	NSAE	SAE	DEATH	PROTVIOL	FINLMAX	FINLDISC	LASTNAME	FRSTNAME
Percent Responders	Binary	0.48	0.0096	0.34	0.0198	-1	0	2	0	1	-1	-1	Doe	John
Percent Responders	Binary	0.14	0.0049	0.34	0.0198	-1	2	2	0	1	-1	-1	Doe	John
Percent Responders	Binary	0.48	0.0108	0.33	0.0204	-1	3	2	1	0	45000.00	45000.00	Washington	George
Percent Responders	Binary	0.14	0.0049	0.33	0.0204	-1	0	2	0	3	20000.00	45000.00	Washington	George
Percent Responders	Binary	0.54	0.0092	0.35	0.0210	-1	2	2	0	1	15000.00	25000.00	Jefferson	Thomas
Percent Responders	Binary	0.19	0.0059	0.35	0.0210	-1	3	6	0	0	22000.00	25000.00	Jefferson	Thomas
Percent Responders	Binary	0.46	0.0095	0.34	0.0161	-1	4	1	0	0	0.00	0.00	Lincoln	Abraham
Percent Responders	Binary	0.12	0.0038	0.34	0.0161	-1	1	2	0	1	0.00	0.00	Lincoln	Abraham

MINITIAL	PHONE	FAX	EMAIL	COUNTRY	STATE	CITY	POSTAL	STREET
M	555-123-4567	555-123-4560	John@mail.com	RU	Moscow	Moscow	103009	Kremlin Road 1
M	555-123-4567	555-123-4560	John@mail.com	RU	Moscow	Moscow	103009	Kremlin Road 1
	020-3456-7891	020-3456-7890	george@mail.com	GB	Westminster	London	SW1A 2	10 Downing St
	020-3456-7891	020-3456-7890	george@mail.com	GB	Westminster	London	SW1A 2	10 Downing St
	01-89-12-34-56	01-89-12-34-51	tom@mail.com	FR	N/A	Paris	75002	1, Rue Road
	01-89-12-34-56	01-89-12-34-51	tom@mail.com	FR	N/A	Paris	75002	1, Rue Road
	555-987-6543	555-987-6540	abe@mail.com	US	Maryland	Rockville	20852	1 Rockville Pk.
	555-987-6543	555-987-6540	abe@mail.com	US	Maryland	Rockville	20852	1 Rockville Pk.

Attachment 2

Technical Instructions: Submitting Bioresearch Monitoring (BIMO) Clinical Data in eCTD Format

A. Data submitted for OSI review belongs in Module 5 of the eCTD. For items I and II in the chart below, the files should be linked into the Study Tagging File (STF) for each study. Leaf titles for this data should be named "BIMO [list study ID, followed by brief description of file being submitted]." In addition, a BIMO STF should be constructed and placed in Module 5.3.5.4, Other Study reports and related information. The study ID for this STF should be "bimo." Files for items I, II and III below should be linked into this BIMO STF, using file tags indicated below. The item III site-level dataset filename should be "clinsite.xpt."

DSI Pre-NDA Request Item[1]	STF File Tag	Used For	Allowable File Formats
I	data-listing-dataset	Data listings, by study	.pdf
I	annotated-crf	Sample annotated case report form, by study	.pdf
II	data-listing-dataset	Data listings, by study (Line listings, by site)	.pdf
III	data-listing-dataset	Site-level datasets, across studies	.xpt
III	data-listing-data-definition	Define file	.pdf

B. In addition, within the directory structure, the item III site-level dataset should be placed in the M5 folder as follows:

C. It is recommended, but not required, that a Reviewer's Guide in PDF format be included. If this Guide is included, it should be included in the BIMO STF. The leaf title should be "BIMO Reviewer Guide." The guide should contain a description of the BIMO elements being submitted with hyperlinks to those elements in Module 5.

[1] Please see the OSI Pre-NDA Request document for a full description of requested data files

References:

eCTD Backbone Specification for Study Tagging Files v. 2.6.1
(http://www.fda.gov/downloads/Drugs/DevelopmentApprovalProcess/FormsSubmissionRequirements/ElectronicSubmissions/UCM163560.pdf)

FDA eCTD web page
(http://www.fda.gov/Drugs/DevelopmentApprovalProcess/FormsSubmissionRequirements/ElectronicSubmissions/ucm153574.htm)

For general help with eCTD submissions: ESUB@fda.hhs.gov

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

/s/

MARY H PARKS
03/05/2013

DEPARTMENT OF HEALTH AND HUMAN SERVICES

Food and Drug Administration
Silver Spring MD 20993

NDA 022472

MEETING REQUEST GRANTED
WRITTEN RESPONSES ONLY

MannKind Corporation
Attention: John Bedard
Senior Vice President, Regulatory Affairs
61 South Paramus Road
Paramus, NJ 07652

Dear Mr. Bedard:

Please refer to your New Drug Application (NDA) submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act for Afrezza (insulin human [rDNA origin]) Inhalation Powder and Inhaler.

We also refer to your correspondence dated December 19, 2012, requesting a meeting to discuss your planned resubmission of this NDA. Based on the statement of purpose, objectives, and proposed agenda, we consider the meeting a Type C meeting.

We have determined that written responses to your questions would be the most appropriate means for responding to the meeting request. Therefore, a meeting will not be scheduled. Our goal date for providing our written responses is **March 5, 2013**.

Submit background information (three paper copies or one electronic copy to the application and 20 paper desk copies to the RPM) as soon as possible but no later than 1 month prior to our goal date for sending written responses (as stated above) for our review and response. If the materials presented in the background package are inadequate to answer the questions or if we do not receive the package by **February 5, 2013**, we may cancel the agreement to provide written responses. If we cancel the agreement to provide written responses, a new meeting request will be required.

Submit 20 desk copies to the following address:

Mehreen Hai
Food and Drug Administration
Center for Drug Evaluation and Research
White Oak Building 22, Room: 3391
10903 New Hampshire Avenue
Silver Spring, Maryland
Use zip code **20903** *if shipping via United States Postal Service (USPS).*
Use zip code **20993** *if sending via any carrier other than USPS (e.g., UPS, DHL, FedEx).*

If you have any questions, please call me at (301) 796-5073.

Sincerely,

{See appended electronic signature page}

Mehreen Hai, Ph.D.
Regulatory Project Manager
Division of Metabolism & Endocrinology Products
Office of Drug Evaluation II
Center for Drug Evaluation and Research

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

/s/

MEHREEN HAI
01/09/2013

Hartford, Rachel

From: Parks, Mary H
Sent: Saturday, September 08, 2012 9:12 PM
To: Hartford, Rachel
Subject: FW: Letter

fyi

-----Original Message-----
From: Mann, Al [mailto:al.mann@MANNKINDCORP.COM]
Sent: Saturday, September 08, 2012 8:46 PM
To: Parks, Mary H
Subject: Letter

I sincerely appreciated your exceptionally prompt response to my August 28 letter regarding the (b) (4). Of course I did remember that we had discussed almost the same questions among others during the meeting in May of last year. Somehow I never received the minutes of that meeting. I have now obtained and have read those minutes.

Clearly my recent letter was unnecessary. I apologize for troubling you.

Sincerely, Alfred Mann

Hartford, Rachel

From: Parks, Mary H
Sent: Thursday, August 30, 2012 11:52 AM
To: Al Mann
Cc: Hartford, Rachel; Parks, Mary H
Subject: RE: Letter from Alfred E. Mann

Dear Mr. Mann and Ms. McAdams,

Thank you for your letter. I have forwarded this to Ms. Rachel Hartford, regulatory project manager for (b) (4) Afrezza (b) (4) There is a regulatory process through which questions related to (b) (4) applications are to be submitted to the FDA. (b) (4)

(b) (4)

Regards,

Mary H. Parks, M.D.
Director
Division of Metabolism and Endocrinology Products
Center for Drug Evaluation and Research
U.S. Food and Drug Administration
301-796-2290
301-796-9712 (fax)

-----Original Message-----
From: Mary Ellen McAdams [mailto:mary.mcadams@aemf.org] On Behalf Of Al Mann
Sent: Tuesday, August 28, 2012 7:30 PM
To: Parks, Mary H
Subject: Letter from Alfred E. Mann
Importance: High

<<Parks, Dr. Mary- 8-28-12.doc>>
Please see the attached letter from Mr. Mann

Hartford, Rachel

From: Hartford, Rachel
Sent: Thursday, August 30, 2012 12:07 PM
To: 'Jeff Goldberg'
Cc: Al Mann
Subject: (b) (4)

Attachments: Parks, Dr. Mary- 8-28-12.doc

Hi Jeff,

Hope you had an enjoyable summer. Just wanted to touch base with you, the (b) (4) regulatory contact, concerning the attached letter from Mr. Mann.

As always, feel free to contact me; I am delighted to help you navigate the regulatory process for requesting feedback.

Thanks,

Rachel

Parks, Dr. Mary- 8-28-12.doc (...

Rachel E. Hartford
Regulatory Project Manager
Division of Metabolism and Endocrinology Products
Center for Drug Evaluation and Research
Food and Drug Administration
rachel.hartford@fda.hhs.gov
301-796-0331 (phone)
301-796-9712 (fax)

7 Page(s) has been Withheld in Full as b4 (CCI/TS) immediately following this page

---

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

/s/

RACHEL E HARTFORD
11/20/2012

For Internal Use Only

Meeting Cancellation Form

(Use this form to cancel a meeting that was granted and scheduled after which time the sponsor or FDA has subsequently cancelled.)

Please remember to update the Meeting Status field in DARRTS for this cancellation.

Complete the information below and check form into DARRTS.

Application Type	☐ P-IND ☐ IND ☐ NDA/sNDA ☐BLA/sBLA
Application Number	NDA 22472
DATE Meeting Cancelled (per communication with requester)	November 2, 2012 (letter sent with written response)
Scheduled Meeting Date	
Reason for Cancellation	Letter sent with written responses in lieu of meeting
Project Manager	Mehreen Hai

v8-23-10

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

/s/

MEHREEN HAI
11/02/2012

DEPARTMENT OF HEALTH AND HUMAN SERVICES

Food and Drug Administration
Silver Spring, MD 20993

NDA 022472

MEETING REQUEST -
Written Responses

MannKind Corporation
Attention: Eileen Wyka
Sr. Director, CMC, Regulatory Affairs
61 South Paramus Road
Paramus, NJ 07652

Dear Ms. Wyka:

Please refer to your New Drug Application (NDA) submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act for Afrezza (insulin human [rDNA origin]) Inhalation Powder and Inhaler.

We also refer to our communication dated July 23, 2012, notifying you that we would provide a written response to the questions in your July 20, 2012 meeting request within 90 days after receiving your background materials. The background materials were received on August 17, 2012.

Our responses to your questions are enclosed. If you have additional questions, you must submit a new meeting request.

If you have any questions, please call me at (301) 796-5073.

Sincerely,

{See appended electronic signature page}

Mehreen Hai, Ph.D.
Regulatory Project Manager
Division of Metabolism & Endocrinology Products
Office of Drug Evaluation II
Center for Drug Evaluation and Research

Enclosure:
Written Responses

Your background and questions are repeated below followed by our responses in **bold** text.

LABELING

Based on input from physicians and patients, as well as Agency comments, MannKind proposes to label AFREZZA prominently with the approximate injected insulin dose on the labeling components and in the prescribing information leaflets for physicians and patients, i.e., "each cartridge approximates (X) units of injected insulin". This labeling will be integrated with the text and format previously accepted or recommended by the Agency (Meeting Request - Written Responses dated 28 February 2012).

Question 1: As previously agreed, Cartridges will be labeled with proprietary name (Afrezza), cartridge strength and lot number. Due to space constraints on the cartridge, the cartridge strength will be depicted numerically only (as '4' or '8') and will not contained "U" or "units" after the number. Does the Agency agree with the proposed cartridge labeling?

FDA Response: Your proposal appears acceptable; however, due to the size and color (same as the cartridge) of the numbers, your human factors validation results should demonstrate that the color differentiation and association with the strengths (i.e. blue for '4' and green for '8') will be sufficient to prevent medication errors involving strength confusion from occurring. Color blind patients may not be able to distinguish between blue and green. Thus, we recommend that you include blue/green color blind participants or simulate blue/green color blindness. Additionally, patients may not be able to read the numbers on the cartridges and may rely on their memory to choose the cartridges in cases where they have loose cartridges in their glucose bag (i.e. Dose 3 scenario in your proposed study, pages 7 and 18 of the Appendix 5, Summative Human Factors =Validation Test Plan).

Question 2: The Cartridge Blister Pack will display cartridge strength (as '4 units' or '8 units'), the statement "each cartridge approximates 4 or 8 units of injected insulin" and cartridge content (as 0.35 mg or 0.7 mg insulin). Does the Agency agree with the proposed Cartridge Blister Pack labeling?

FDA Response: Your approach to use the dosage strengths of "4 units" and "8 units" appears reasonable. The detailed information on the Cartridge Blister Pack label will be reviewed as part of our review of the NDA resubmission, and we have no further comments at this time. Acceptability of your proposal is a review issue.

We have a concern regarding the design of the blister packs containing the cartridges. Currently, the design of the blister pack, i.e. (b) (4)

(b) (4)

Therefore, we recommend, if feasible, that each cartridge be packaged in individual wells that can be torn off separately, so that each cartridge is in the blister packaging until ready for use. In addition, each blister should be labeled with the product name, strength, lot number, expiration date, and manufacturer.

Question 3: The Cartridge Foil Wrap and the Cartridge and Gen2 Inhaler Carton will incorporate all the same modifications as listed above for the Cartridge Blister Pack. Does the Agency agree with the proposed Cartridge Foil Wrap and Cartridge and Gen2 Inhaler Carton labeling?

FDA Response: See our response to Question 2.

Question 4: The IFU has been modified taking into account the Agency's recommendations provided in Meeting Request - Written Responses dated 28February 2012 and the Advice to Request for Comment: Summative Human Factors Usability Validation Study Protocol dated 03May2012. In addition, throughout the IFU, the cartridge strengths have been updated as proposed above, i.e., in terms of injected insulin. The final version will be used in the Human Factors study. Does the Agency agree with the modified Instructions for Use?

FDA Response: Yes, we agree.

Question 5: MannKind understands that the Summative Human Factors Usability Validation study must be performed with the labeling representative of the final commercial labeling. Does the Agency agree that the revised labeling approach to label AFREZZA prominently with the approximate injected insulin dose is acceptable for use in the Human Factors study?

FDA Response: See our response to Question 2.

SUMMATIVE HUMAN FACTORS USABILITY VALIDATION PROTOCOL

Question 6: Does the Agency agree that the revised Human Factors protocol addresses all of their requests?

FDA Response: We note that you have incorporated the majority of our previous recommendations into the Human Factors protocol. However, we have the following additional recommendations:

i. **Add healthcare providers (HCPs) (i.e. primarily nurses) as a separate group and incorporate Insulin Only or Insulin + OAA participants into one group.**

(b) (4)

ii. **Increase the size of each group to at least 15 participants for each trained and untrained arm (refer to the table below). Data suggest that enrolling as few as 8 participants per arm (e.g., 8 OAA participants in trained arm vs. 8 in untrained arm or 8 previous insulin users in trained arm vs. 8 in untrained arm) may result in roughly 30% to 45% of the problems that patients may experience with the proposed device going undetected[2].**

	Insulin Only or Insulin + OAA	**HCPs**	**OAA Only**	**Total**
Trained by CDE	**15**	**15**	**15**	**45**
Untrained	**15**	**15**	**15**	**45**
Total	**30**	**30**	**30**	**90**

iii. **For the untrained group we recommend that you provide the Afrezza kit. However, do not specifically instruct participants to read the IFU prior to attempting to use the product. This approach will simulate the actual use scenario regarding what users will do when training is not provided.**

iv. **Knowledge Probes: We recommend that when the moderator asks the questions that the moderator does not remind the participants to refer to the IFU if they are not sure of the answer. This approach will simulate the actual use scenario regarding what users will do when they need to remember any information for the product.**

Question 7: Does the Agency agree the [Human Factors] study design is acceptable and that the study can be conducted as proposed?

FDA Response: Provided you incorporate the recommendations in our response to Question 6, the study may proceed.

[2] Faulkner, Laura. Beyond the five-user assumption: Benefits of increased sample sizes in usability testing. (2003). Behavior Research Methods, Instruments and Computers. 35 (3): 379-383.

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

/s/

MEHREEN HAI
11/02/2012

DEPARTMENT OF HEALTH AND HUMAN SERVICES

Food and Drug Administration
Silver Spring MD 20993

NDA 022472

MEETING REQUEST -
Granting Written Response

MannKind Corporation
Attention: Eileen Wyka
Sr. Director, CMC, Regulatory Affairs
61 South Paramus Road
Paramus, NJ 07652

Dear Ms. Wyka:

Please refer to your New Drug Application (NDA) submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act for Afrezza (insulin human [rDNA origin]) Inhalation Powder and Inhaler.

We also refer to your correspondence dated and received July 20, 2012, requesting a Type C meeting to discuss labeling and a Human Factors protocol. Based on the statement of purpose, objectives, and proposed agenda, we consider the meeting a type C meeting.

We believe that the questions you have posed can be answered adequately in writing and that providing a written response will prove the best use of resources and assist you in your drug development plan. If we determine it is too early in the drug development process to answer certain questions, those questions should be resubmitted at a later date.

We will provide our answers to your questions within 90 days after receiving your additional background packages. However, if we do not receive your background packages within three months, we will consider your request to be withdrawn. Submit background information (three paper copies or one electronic copy to the application and 20 desk copies to me).

Regulatory Address:

Food and Drug Administration, CDER, Central Document Room
Attention: Division of Metabolism and Endocrinology Products
5901-B Ammendale Road
Beltsville, MD 20705-1266

Submit the 20 desk copies to the following address:

Rachel Hartford
Food and Drug Administration

Center for Drug Evaluation and Research
White Oak Building 22, Room: 3118
10903 New Hampshire Avenue
Silver Spring, Maryland 20903

If you have any questions, call me at (301) 796-0331.

Sincerely,

{See appended electronic signature page}

Rachel Hartford
Regulatory Project Manager
Division of Metabolism & Endocrinology Products
Office of Drug Evaluation II
Center for Drug Evaluation and Research

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

/s/

RACHEL E HARTFORD
07/23/2012

DEPARTMENT OF HEALTH AND HUMAN SERVICES

Food and Drug Administration
Silver Spring MD 20993

NDA 022472 **MEETING MINUTES**

Mannkind Corporation
Attention: Donna Donigi Gale
Senior Director, Regulatory Affairs
61 South Paramus Road
Paramus, NJ 07652

Dear Ms. Gale:

Please refer to your New Drug Application (NDA) submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act for Afrezza (insulin human [rDNA origin]) Inhalation Powder and Inhaler.

We also refer to the End of Review meeting between representatives of your firm and the FDA on June 9, 2010.

A copy of the official minutes of the meeting is attached for your information. Please notify us of any significant differences in understanding regarding the meeting outcomes.

If you have any questions, call me at (301) 796-0331.

Sincerely,

{See appended electronic signature page}

Rachel Hartford
Regulatory Project Manager
Division of Metabolism and Endocrinology Products
Office of Drug Evaluation II
Center for Drug Evaluation and Research

Enclosure:
Memorandum of Meeting Minutes

FOOD AND DRUG ADMINISTRATION
CENTER FOR DRUG EVALUATION AND RESEARCH

MEMORANDUM OF MEETING MINUTES

Meeting Type:	**B**
Meeting Category:	End-of-Review
Meeting Date and Time:	June 9, 2010
Meeting Location:	WO 22
Application Number:	022472
Product Name:	Afrezza (insulin human [rDNA origin]) Inhalation Powder and Inhaler
Indication:	**Treatment of Type 1 and Type 2 Diabetes Mellitus**
Sponsor/Applicant Name:	MannKind Corporation
Meeting Chair:	Mary H. Parks, M.D.
Meeting Recorder:	Rachel Hartford

FDA ATTENDEES(alphabetic)

Theodore Carver, Ph.D.	Chemist, Office of New Drug Quality Assessment (ONDQA)
Melanie Choe, Ph.D.	Biomedical Engineer, Center for Devices and Radiological Health (CDRH), Office of Device Evaluation (ODE), Division of Anesthesiology, General Hospital, Infection Control, and Dental Devices (DAGID), Anesthesiology & Respiratory Devices Branch (ARDB)
Sang Chung, Ph.D.	Pharmacologist, Division of Clinical Pharmacology II
Karen Davis Bruno, Ph.D.	Supervisory Pharmacologist, Division of Metabolism and Endocrinology Products (DMEP)
Eric Duffy, Ph.D.	Director, Division of New Drug Quality Assessment III, ONDQA
Amy Egan, M.D.	Deputy Director (Safety), DMEP

Rachel Hartford	Regulatory Project Manager, DMEP
Hylton Joffe, M.D., M.Sc.	Diabetes Team I Leader, DMEP
Banu Karimi-Shah, M.D.	Medical Officer, Division of Pulmonary, Allergy, and Rheumatology Products (DPARP)
Cynthia Liu, Ph.D.	Statistician, Division of Biometrics II
Mary H. Parks, M.D.	Director, DMEP
Laura Pincock, R.Ph., Pharm D.	Acting Team Leader, Drug Safety Evaluator, Office of Surveillance and Epidemiology, Division of Medication Error and Prevention (DMEPA)
Prasad Peri, Ph.D.	Supervisory Chemist, ONDQA
Todd Sahlroot, Ph.D.	Statistics Team Leader, Division of Biometrics II
Sally Seymour, M.D.	Deputy Division Director (Safety), DPARP
Alan Schroeder, Ph.D.	Chemist, ONDQA
Lester Schultheis, M.D.	Director, CDRH/ODE/DAGID/ARDB
Miyun Tsai-Turton, Ph.D.	Pharmacologist, DMEP
Lisa Yanoff, M.D.	Medical Officer, DMEP

SPONSOR ATTENDEES

Nik Amin, M.D.	Medical Director, Pulmonary
Robert Baughman, Ph.D.	Vice President, Experimental Pharmacology
Anders H. Boss, M.D.	Senior Vice President, Chief Medical Officer
Donna Donigi Gale, M.S.	Director, Worldwide Regulatory Affairs
Joseph Kocinsky, Ph.D.	Senior Vice President, Pharmaceutical Technology Development
Mark Marino, M.D.	Vice President, Early Clinical Development

Patricia R. Mayer, Ph.D.	Vice President, Worldwide Regulatory Affairs
Jim Nezamis, M.S.	Director, Biometrics
Richard Petrucci, M.D.	Vice President, Diabetes – Medical Affairs
Peter Richardson, M.D.	Corporate Vice President, Chief Scientific Officer
Chad Smutney, M.E.	Senior Director, Device Design
David Townson, Ph.D.	Vice President, Development
Eileen Wyka, M.S.	Senior Director, CMC Regulatory Affairs
John Bedard, Ph.D.	Bedard and Associates, Regulatory Consultant

(b) (4)

[redacted]

1.0 BACKGROUND

MannKind submitted the Afrezza NDA 022472 on March 16, 2009. FDA issued a Complete Response letter on March 12, 2010, that contained clinical, clinical pharmacology, labeling, and device deficiencies. MannKind requested an End-of-Review meeting on March 26, 2010, to discuss their approach for resolving these deficiencies.

2. DISCUSSION

Preliminary responses to the questions enclosed in the May 12, 2010, meeting package were sent to you via email on June 8, 2010. Your questions appear below followed by our responses in **bold**. A summary of the discussion at the meeting is shown in *italics*. Post-meeting comments are shown in underlined regular font. For questions where no additional discussion is indicated, neither MannKind nor FDA raised any additional issues pertaining to the questions.

REGULATORY

MannKind will prepare a resubmission as a response to the Complete Response Letter, which will include information that addresses all deficiencies in:

- Clinical
  - o New clinical data available from study MKC-TI-117
  - o Additional analyses of clinical data previously submitted in NDA 22-472
- Clinical Pharmacology
  - o New data to support bioequivalence (study MKC-TI-142) of the new Gen2 Inhalation System with the MedTone Inhalation System in accordance with prior FDA guidance
- CMC and Device
  - o New data from clinical use of the Gen2 inhaler generated according to previous FDA advice (study MKC-TI-158 and MKC-TI-159)
  - o A Usability Validation Study on the Gen2 Inhalation System as part of the overall Human Factors Evaluation
  - o CMC data to support the Gen2 inhalation system
- Updated Labeling
- Updated REMS
- Safety update
- Updated Pediatric Plan

Question A: Does the Agency agree that the proposed contents for resubmission address all deficiencies contained in the Complete Response Letter?

FDA Response: No. Please see our responses to your other questions. The deficiencies were directed towards the MedTone product submitted in the NDA, not to the Gen2 inhaler device. As explained below, additional controlled, clinical data will be needed to support the Gen2 inhaler device, which differs substantially in design from the MedTone device.

It is our assumption that the resubmission is a Class 2 resubmission with a PDUFA goal review time of 6 months.

Question B: Does the Agency concur?

FDA Response: Not necessarily. It is possible that the Gen2 inhaler product might need to be submitted as a separate NDA and that a Complete Response submission to the MedTone NDA may not be a possible regulatory pathway for the Gen2 device.

Post Meeting Comment: The User Fee Staff determined that the Gen2 inhaler could be included in the Complete Response.

CLINICAL

In the Complete Response Letter, the Agency raised a question regarding the clinical utility of Afrezza and suggested that MannKind document how the currently available clinical data support the clinical utility of Afrezza in the marketplace. MannKind intends to provide new clinical data and new analyses of previously submitted data.

Question C: Does the Agency agree that MannKind's presented approach of new data from MKC-TI-117 and new analyses of data presented in the original NDA is adequate and complete for a successful resubmission to address the clinical utility of AFREZZA with the Gen2 inhaler?

FDA Response: New analyses of data presented in the original NDA are not adequate to address the clinical utility of Afrezza, because these data were already taken into consideration during the review of the original NDA. New data from study MKC-TI-117 may be adequate to support the MedTone device but this will be a review issue. Given your intention to proceed with the Gen2 inhaler, there will be further clinical requirements for resubmission. For example, clinical evidence of pulmonary safety and evidence of adequate glycemic effect (based on HbA1c) will be required with the new device. The extent of clinical data needed can be discussed at the End-of-Review meeting.

Discussion: FDA stated that the MedTone and Gen2 devices differ substantially and that FDA's general approach for locally-acting pulmonary products is to require clinical efficacy and safety data if a device undergoes substantial modification. We also informed MannKind that bridging the local pulmonary safety from one device to another was new territory for FDA, and not a pathway that has been defined with those devices used to treat pulmonary diseases. As a path forward, FDA recommended that MannKind submit the detailed in vitro comparability data for MedTone and Gen2 to FDA for review before we make a determination regarding the extent of clinical trial data needed for the Gen2 system (MannKind was to await our recommendations as to the format and approach for submitting these in vitro data).

Post Meeting Comment: MannKind did not wait to submit the in vitro data for FDA review as discussed above and instead submitted a Complete Response about three weeks after the End-of-

Review meeting. This Complete Response sought approval of the Gen2 system without clinical efficacy and safety data.

BIOEQUIVALENCE

MannKind completed a new bioequivalence (BE) study, MKC-TI-142, with the following specifics: 1) the new study compared the Gen2 and MedTone® Model C devices; 2) the protocol followed the Agency's analysis recommendations (Advice Letter, dated 13Nov2009); and, 3) utilized the ECLIA method which completely incorporated the DSI inspector's recommendations. In addition, the serum samples are being analyzed by RIA.

Question D: Does the Agency reaffirm the proposed BE approach to demonstrate that the MedTone Model C inhaler and the Gen2 inhaler are bioequivalent? And, if bioequivalence is demonstrated, does the Agency agree that the clinical data generated with MedTone Model C supplemented with the Gen2 Inhalation System data would serve as the basis for approving AFREZZA with the Gen2 inhaler?

FDA Response: The proposed BE approach is acceptable. However, the BE assessment should be based on the pharmacokinetic parameters generated from a reliable bioanalytical study. Regarding the basis for approving Gen2 inhaler, in addition to the BE study see the responses to Questions C and F.

In the Complete Response Letter, the Agency provided a comprehensive list of tables for the safety update. We would like to discuss this list, present and agree on the scope of the safety update.

Question E: Is the Agency in agreement with MannKind's proposal for the Safety Update?

FDA Response: Your proposal for the safety update will need to be updated to reflect the additional clinical data that will be needed for the Gen2 device.

CMC/DEVICE

The Agency had a number of questions/comments regarding the originally planned commercial device MedTone Model D and also the recommendation that a Human Factors evaluation should be performed following the FDA Guidance on Medical Device Use- Safety and Human Factors. MannKind designed a Usability Validation study based upon the above referenced guidance and our evaluation indicates that the CMC documentation for Gen2 will address all the comments and recommendation in your Complete Response Letter.

In the resubmission, MannKind will include a revised Module 3, including complete CMC documentation for the Gen2 Inhalation System, which incorporates a Human Factors evaluation. The protocol for the summative usability test was submitted to IND 61,729 as SN 0351, 05Feb2010.

Question F: Based on the information provided in the Briefing Document does the Agency agree that this information will sufficiently address the design and use of the new Gen2 Inhalation System?

FDA Response: The CMC information provided in the briefing package is not complete in order for us to evaluate your proposal. We remind you to provide in the NDA the complete information on the drug product system using the Gen2 inhaler, including the sections Description and Composition, Pharmaceutical development, Manufacture, Control of Drug Product, Container Closure System (including Letters Of Authorizations to Drug Master Files), Stability, etc.

The following comments are relevant to your Gen2 device proposal:

Regarding the information provided in your IND 061729 amendment dated 28-AUG-2009:

1. Submit complete stability data for the Gen2 inhaler as recommended for new drug products in the International Conference on Harmonisation (ICH) Q1A(R2) Stability Testing of New Drug Substances and Products (http://www.fda.gov/downloads/RegulatoryInformation/Guidances/ucm128204.pdf) and Q1E Evaluation of Stability Data (http://www.fda.gov/downloads/RegulatoryInformation/Guidances/ucm128122.pdf) guidelines, including 12 months of long-term data and 6 months accelerated data. Provide data for a minimum of 3 batches for each dosage strength and formulation to support the proposed expiration dating in this product, which contains new components and materials as compared to the MedTone inhaler. Bracketing and matrixing designs may be used for stability studies where appropriately justified, as per ICH Q1D Bracketing and Matrixing Designs for Stability Testing of New Drug Substances and Products (http://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/ucm073379.pdf).

2) As you have proposed, provide stability data to support the proposed in-use period of the device. Note that these data should be sufficient for statistical evaluation of the drug product stability for periods that exceed the recommended use period (by a factor of 2) and should include data collected under accelerated conditions as appropriate.

3.) Provide comparative in vitro performance data comparing the MedTone inhaler with the Gen2 inhaler. This includes aerodynamic particle size distribution (APSD) as well as delivered dose uniformity (DDU). The data should be from sufficient samples as to be fully representative of performances of the two devices (including the to-be-marketed devices).

4.) Provide full drug product CMC data for the Gen2 inhaler, including but not limited to: drug product performance data; CMC information for the container closure system; extractables and leachables data for the inhaler device and for the cartridge; and letters of authorization to all drug master files for the device, its components, and its materials of construction.

5.) Provide a tabular point-by-point comparison listing all differences in the proposed marketed presentation of the Gen2 inhaler as compared to the MedTone inhaler, including all device and cartridge components, the Technosphere insulin drug product, and the insulin drug substance used. Please note that changes you have proposed to the Gen2 inhaler product in IND 061729 have not been fully addressed in the briefing information package. These changes will affect the amount of supporting CMC information required.

In addition:
6) In the 12-JAN-2010 amendment to IND 061729, you proposed (b) (4) **described in the briefing information package you provided on 10-MAY-2010 for NDA 022472.** (b) (4) **. Be advised that significant changes to the composition, manufacturing, in-process controls, and specifications for the Technosphere® particles and the Technosphere Insulin® bulk powder, relative to the drug product information submitted in NDA 022472, will require additional supporting CMC data, for example stability studies (see ICH Q5C Quality of Biotechnological Products: Stability Testing of Biotechnological/Biological Products (http://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/ucm073466.pdf), ICH Q5E Comparability of Biotechnological/Biological Products Subject to Changes in Their Manufacturing Process (http://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/ucm073476.pdf), and Q1A(R2)), and may require additional nonclinical and/or clinical studies.**

7.) In the 27-JAN-2010 amendment to IND 061729, you proposed to add a new insulin source to the IND, referencing DMF 16482. To qualify the new supplier of insulin drug substance for use in the same drug product, you will be required to demonstrate similarity between the drug substances from the different sources and the resulting drug products. An assessment of similarity between two protein products (i.e. drug substance and drug product) depends upon their full characterization, comparative physicochemical and biological studies, and preclinical studies (which may include bridging toxicology studies), Pharmacokinetic/Pharmacodynamic, and/or clinical data (which may include immunogenicity studies), as appropriate. This assessment also includes assessment of product-related substances and impurities, as well as process-related impurities (see ICH Q6B Specifications: Test Procedures and Acceptance Criteria for Biotechnological/Biological Products (http://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/ucm073488.pdf). The USP insulin reference standard should be used as the reference standard in the analyses, as appropriate. The use of a different host cell and/or expression construct for each insulin drug substance as well as different manufacturing processes may result in protein impurity differences, which may have clinical consequences with regards to immunogenicity, particularly since insulin is a drug for chronic administration. We note that the holder of DMF 16482 is MannKind Corporation. Therefore, submit the assessment of similarity to your IND 061729 and future NDA submissions.

Comments from the Center for Devices and Radiological Health (CDRH) regarding the proposed Human Factors study plan and device verification and validation are as follows:

1. **We note that you have conducted a Human Factors study with 15 users to date and provided a brief descriptive summary of the results in section 11.7. However, without fully understanding the scope of the test plan and results, or agreement on the proposed test plan, we cannot comment on the adequacy of the study conducted to date.**

   While you have provided a Final Test Plan for Summative Usability Test of Gen2 Delivery System, additional Human Factors information is necessary to evaluate the safety and effectiveness of the device in the hands of representative users. Specifically, the submission does not indicate how you have systematically evaluated use-related risks and how you propose to validate user-performance on the highest-priority task pertinent to your device. To complete our review, we will need this information to assess the safety and effectiveness of your device in the hands of representative users. Address the following issues:

   a. **Submit a detailed description of the intended user population, use environment, user interfaces, and anticipated user interaction with the proposed device in the test plan.**

   b. **Submit a revised test plan that includes an evaluation of use-related hazards and relative risks associated with the use of the device that has been conducted as part of your Human Factors study. Provide this evaluation in the context of overall risk management of the device and mitigation strategies intended to reduce the risks associated with your device.**

   c. **You stated that Gen2 is a prescription device intended for use with or without prior instructions. For example, some users may receive training by a diabetes nurse educator and/or a physician, while others may receive no training. It does not appear that all representative users are captured in your study plan. You have only included "untrained" individuals as a "worst case' scenario in your proposed study plan. Although this kind of information can be useful early in the process of product development, we expect your study of the final device to include users with varying levels of training, unless you specify a training program that all users will receive. Your Human Factors study is expected to evaluate at least 15 typical users from each representative user group.**

      We acknowledge that realistic time periods for "training decay" are difficult to build into a testing approach. However, a period of time is expected to elapse between training and testing. Incorporate a likely time interval into your study and justify the length of the interval. Also, provide information regarding training regime that will be provided when the device is on the market.

d. **The relative priority of the tasks you selected for testing is unclear. We expect the tasks selected to be those tasks that are the most difficult for users to perform. You stated in the test plan that participants will perform all tasks supported by the delivery system and no tasks would be excluded from the usability study. Based on this approach, you concluded that there was no need to rank the tasks based on their risks-related priority. However, the purpose of prioritizing the tasks is three-fold: (1) to develop conditions/use scenarios for which inadequate performance would occur, (2) to evaluate user performance on the tasks that could lead to use-related problems, and (3) to evaluate the effectiveness of the mitigation strategies developed to minimize use errors and patient harm. Indicate where in the final test plan you have addressed these concerns or revise your test plan to include the above information.**

e. **In the introduction section of the study plan (page 3), you indicated that testing will focus on high-risk use scenarios and use errors identified during prior analyses. However, the final test plan did not provide a description of the high-risk use scenarios. Provide detailed description of high-risks use scenarios, and include this information in the revised test plan.**

f. **The high priority use-related risk associated with users selecting cartridge(s) of correct dosage was not included in the directed tasks list or the instructions for use. It is also unclear how this user task will be evaluated. Provide clarification, and include this information in the revised test plan.**

g. **Direct your Human Factors analysis toward assessment of task failures. The analysis should determine the nature of failures based on objective and subjective data. Also separate and submit the results of the validation study into separate tables for each distinct user groups. These tables should include objective data based on user performing specific tasks, and subjective data based on user questionnaire for assessment of device performance.**

    i. **Pertaining to objective data, the table should show a list of prioritized use related tasks that have the highest potential occurrence of hazards, the results of user performance (i.e. pass or fail), risk evaluation for the failures in terms of clinical impact, root cause, mitigation, and how those mitigations have been re-evaluated or validated. Additionally, note that study results should be recorded as a success or failure to complete a critical task. If failures are identified, discuss how those failures are to be evaluated in terms of root cause analysis, clinical impact, and mitigation strategies. If the mitigation strategies involve modifications to user interface, please discuss how your strategies are reevaluated or validated for safety and effectiveness. The study report should describe how the design is reasonably safe and will meet user's needs based on a discussion of results of the usability testing and evaluations.**

Furthermore, provide a summary of the results in a tabular format that identifies the types of users. The following information is needed for each user: number of errors per task, error rate per task, types of error for related tasks, risk evaluation of the clinical impact of each type of error, root cause, mitigation strategy, and how mitigation strategy will be evaluated and validated. Address this concern and provide a revised test plan for review.

ii. **Include in your subjective data, descriptions by test participants of difficulties encountered and their suggestions regarding device user interface characteristics, particularly the logic of device operation. Collection of subjective assessment of device use can identify problems encountered by test participants as "concerns" or "close calls", but did not manifest themselves as errors during use and/or did not affect measures of objective performance. Rating scales (e.g., Likert scales) that assess overall "ease of use" may be considered supportive information, but are not represent all of the subjective data necessary for an adequate Human Factors test. Include a detailed discussion of how you plan to incorporate user suggestions.**

h. **It appears that you intend to market Gen2 version 2C. However, your risk assessment was based on "GEN2 V1.5". Clarify the model used in the risk assessment and how it correlates to the version that you intend to market. Also clarify the version intended for use in the Human Factors study. We recommend that you use the final version that will be marketed in your study.**

i. **Provide a complete response to each of the deficiencies above and include any supporting documents as appendices. Also refer to FDA's Guidance on Medical Device Use-Safety: Incorporating Human Factors Engineering into Risk Management available at: http://www.fda.gov/downloads/MedicalDevices/DeviceRegulationandGuidance/GuidanceDocuments/ucm094461.pdf for further information.**

2. **During the initial review of the Gen2 inhaler under IND 061729, we provided nine additional device-related comments in an Advice/Information Request letter dated November 13, 2009. These comments should also be addressed in clarifying the Gen2 inhaler system in your future submission.**

3. **You have provided a new set of verification testing of the Gen2 inhaler system in Table 14. Provide a discussion of how these set of tests will address the verification and validation of the Gen2 inhaler system, and provide a complete test report for all tests conducted. A complete test report consists of a purpose, introduction, test setup, methods, pass/fail criteria, results, and conclusion is needed. In addition, provide a scientifically valid rationale for the pass/fail criteria selected for each test.**

Discussion: MannKind expressed interest in meeting with the Center for Devices and Radiological Health (CDRH) to discuss the Human Factors study.

Post Meeting Comment: MannKind subsequently submitted the Complete Response without meeting with CDRH.

The Agency outlined a number of deficiencies associated with the Afrezza labeling. All of these deficiencies have been addressed and solutions are incorporated into the Gen2 Inhalation System label.

Question G: Based on the proposed labeling described in the Briefing Document, does the Agency agree that all labeling concerns have been addressed?

FDA Response: No, we do not agree that our labeling concerns are addressed. We are awaiting the results of the Human Factors and Useability studies which will inform our evaluation of the device design and labeling. We also have identified the following concerns.
-The proposal to state that " (b) (4) **requires further evaluation to determine the acceptability of this statement.**
-The cartridges should include the full proprietary name 'Afrezza' (b) (4)

Also, we request full color mock-ups of the cartridges with blister strips, overwrap and carton labeling.

Discussion: FDA also requested that MannKind submit a useability study for the new device and cartridges that it plans to market. This study should include evaluation of human factors. FDA also requested evidence that patients are able to understand the product strength and calculate their specific dose of Afrezza.

ADDITIONAL COMMENTS:

1. **Due to the change in product characteristics (cartridge strengths to 10 units and 20 units), the proprietary name Afrezza will need to be resubmitted and evaluated by FDA for acceptability.**

2. **It is unusual for a device to have a 15-day recommended in-use period. A more typical in-use period is one month. Clarify the basis for the 15-day period.**

3.0 ISSUES REQUIRING FURTHER DISCUSSION

No issues remained open at the end of the meeting requiring further discussion at a later date.

4.0 ATTACHMENTS AND HANDOUTS

MannKind slides

4 Page(s) has been Withheld in Full as b4 (CCI/TS) immediately following this page

---

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

/s/

RACHEL E HARTFORD
07/02/2012

For Internal Use Only

Meeting Cancellation Form

(Use this form to cancel a meeting that was granted and scheduled after which time the sponsor or FDA has subsequently cancelled.)

Please remember to update the Meeting Status field in DARRTS for this cancellation.

Complete the information below and check form into DARRTS.

Application Type	☐ P-IND ☐ IND ☒ NDA/sNDA ☐BLA/sBLA
Application Number	022472
DATE Meeting Cancelled (per communication with requester)	N/A
Scheduled Meeting Date	N/A
Reason for Cancellation	Written Responses Granted – Preliminary Comments Issued 28Feb12
Project Manager	Rachel Hartford

v8-23-10

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

/s/

RACHEL E HARTFORD
02/28/2012

DEPARTMENT OF HEALTH AND HUMAN SERVICES

Food and Drug Administration
Silver Spring, MD 20993

NDA 022472

MEETING REQUEST - Written Responses

MannKind Corporation
Attention: Eileen Wyka
Sr. Director, CMC, World-Wide Regulatory Affairs
61 South Paramus Road
Paramus, NJ 07652

Dear Ms. Wyka:

Please refer to your New Drug Application (NDA) submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act for Afrezza (insulin human [rDNA origin]) Inhalation Powder and Inhaler.

We also refer to our October 13, 2011, communication notifying you that we would provide a written response to the questions in your October 7, 2011 meeting request within 90 days after receiving your background materials. The background materials were received on November 28, 2011.

Our responses to your questions are enclosed. If you have additional questions, you must submit a new meeting request.

If you have any questions, call me at (301) 796-0331.

Sincerely,

{See appended electronic signature page}

Rachel Hartford
Regulatory Project Manager
Division of Metabolism and Endocrinology Products
Office of Drug Evaluation II
Center for Drug Evaluation and Research

Enclosure

The comment numbers below are aligned with the corresponding comments in our Complete Response letter.

CLINICAL PHARMACOLOGY

Comment 3: MannKind requests an update on the status of the clinical site and analytical inspection results for clinical pharmacology study MKC-TI-142.

FDA Response: This study compared the pharmacokinetics of Afrezza administered by the Gen2C inhaler vs. the MedTone Model C inhaler. A decision on whether to inspect the clinical site and analytical results will be made at the time of NDA resubmission. The inspection may not be needed if your clinical evaluation of the Gen2C inhaler is adequately supported by your new Phase 3 trials.

Product Quality

Comment 4: MannKind assumes that our actions are satisfactory, however if the Agency does not agree we would appreciate feedback.

FDA Response: This issue is considered adequately addressed.

Comment 5: MannKind assumes that our actions are satisfactory, however if the Agency does not agree we would appreciate feedback.

FDA Response: This issue is considered adequately addressed.

Comment 6: 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?

FDA Response: Although no numerical values are provided, the graphs indicate that both 10 unit and 20 unit inhalers failed the proposed acceptance criteria for emitted dose when they are shaken as tested, especially when shaken along the x-axis at vertical orientation. In the resubmission, report the numerical test results for emitted dose test and discuss the results against the proposed specification.

Two out of three 10 unit inhalers failed the acceptance criteria for APSD (group 2, cup 3 to 5) after being shaken along the x-axis at vertical orientation. A majority of the 10 unit inhalers were below the fine particle dose target of (b) (4) units after being shaken, especially at vertical orientation. The mass balances for the aerodynamic particle size distribution (APSD) testing were well below (b) (4) % of the label claim. Compared with the unshaken inhalers (batch data provided in the resubmission dated June 28, 2010), the fine particle dose of APSD data from the shaken inhalers are significantly lower.
Given that vertical shakings have the greatest adverse impact on the emitted dose, we recommend that you re-conduct the dropping test from a vertical orientation.

Drop and vibration testing demonstrated that the proposed device can deliver an emitted dose well below the (b)(4)% limit under simulated use conditions. The test conditions are representative of the type of conditions which the device may encounter. For example, the device may be carried in a purse or in a backpack during walking. You acknowledged the test results and updated the labeling to inform the user not to shake the device prior to use. However, there is a risk that the patient may have to use a device that was inadvertently dropped or shaken. Clarify what impact this could have on the clinical efficacy and safety of Afrezza, how such conditions should be handled, and how you propose to mitigate potential safety concerns that may arise in such settings.

Comment 7: 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?

FDA Response: 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.

For the 28-day rat toxicity study report, the (b)(4) Study Report in Appendix 2 was incomplete; there were only 37 out of 813 pages submitted in your briefing document for review. We also do not agree that there was a 10-fold safety margin at the proposed acceptance criteria, using the mid-dose as your No Observed Adverse Effect Level (NOAEL). The NOAEL of this study should be based on the dose for which there was no observable toxicity, which would be the low-dose used in this study.

Although there are no safety concerns for the revised acceptance criteria based on the 28-day non-clinical toxicity study, the appropriateness of these acceptance criteria and the supported shelf-life will be review issues determined when more data and statistical analysis are provided in your resubmission.

DEVICE

Comment 8: MannKind assumes that our actions are satisfactory, however if the Agency does not agree we would appreciate feedback.

FDA Response: You have met USP standards and provide adequate labeling.

Comment 9: MannKind assumes that our actions are satisfactory, however if the Agency does not agree we would appreciate feedback.

FDA Response: The drop in insulin deposition in the mouthpiece increased the variability in the total emitted dose per each device use. Clarify what impact this could have on the clinical efficacy and safety of Afrezza and how you propose to mitigate potential safety concerns that may arise as a result of this variability.

In your submission dated November 11, 2011, 3.2.P.8.4.1 Mouthpiece Retention Testing (Gen2 Inhaler), you provided test data for eight 20 Unit cartridges only. Provide complete mouthpiece retention testing for the 10 Unit inhaler.

HUMAN FACTORS

FDA Comment: We disagree with your general methodology to test for possible dosing errors resulting from confusion between the labeled drug content of the cartridges (10 units or 20 units) and the deliverable insulin dose (equivalent to ~4 or 8 units of subcutaneous insulin) when identifying the correct cartridge(s) and when performing a dose conversion. Modify the protocol to address the risk of dosing error, as this is a critical use variable for this product. Product labeling including Instructions For Use (IFU) and extent of training to be provided during the validation study should be representative of actual use. Please see specific concerns in comments 10-13 below.

In addition, address the following deficiencies identified in our review of the revised protocol.

1. **You state that participants will be assigned to receive one of two doses (10 units and 30 units).**
   a. **Also include a 20-unit dose in this study because it has a different cartridge color.**
   b. **Clarify how your study design addresses situations where participants use an insulin sliding scale (variable dosing).**
   c. **In your proposed study, once the participants have been prescribed to either 10 Units or 20 Units, it is assumed that those participants have a fixed dose. For this scenario, clarify if both types of cartridges would be present so that the patients would identify the correct one, or if they will only be given the cartridge according to the prescribed dose.**
   d. **Provide a copy of the prescription that the patient will read prior to selecting the cartridge(s).**
   e. **Discuss how in the study the simulated prescribed doses of 10 units and 30 units reflects the actual dose patients will receive if Afrezza is approved, and how these prescribed doses relate to the subcutaneous insulin amount.**

2. **You state that 6 of the 30 participants will be color-blind or have a color-blind-induced condition. We understand that diabetic patients have conditions such as retinopathy and neuropathy, and that these conditions can progressively worsen over time. Therefore, each condition represents unique user profiles that can impact safe and effective use of the product. As a result, the study participants should consist of at least 15 diabetic patients with retinopathy and at least 15 diabetic patients with neuropathy.**

3. **The composition of the participant group is not completely representative of the proposed patient population. The participants should encompass a greater number**

of insulin users and fewer patients that are simply on oral anti-diabetic medications, as the intended population will include those already on injected insulin. Ensure that each subgroup of users contains at least 15 participants.

Comment 10: In the Summative Human Factors Usability Validation study, MannKind proposes to evaluate subjects for possible confusion between the labeled drug content of the cartridges and the approximate subcutaneous insulin dose by evaluating representative user's ability to select the correct cartridges for their dose. Does the agency agree?

FDA Response: We agree that the user's ability to select the correct cartridges for their dose should be demonstrated during the final Human Factors/usability validation study. The selection of the correct cartridge has to be demonstrated such that the intended users can understand the differences between the insulin contained in the cartridges and the corresponding subcutaneous insulin dose, so that they can then correctly select the cartridge(s) for the prescribed dose. As stated in the proposed protocol, the prescribed doses are presented in increments of 10 units and 20 units of insulin, which match with the amount of insulin that is contained in the 10 unit and 20 unit cartridges but not the corresponding subcutaneous insulin dose (4 units and 8 units). In addition, the prescribed dose may be different than the 10 unit and 20 unit insulin cartridges or the subcutaneous insulin units. There may be times when patients or caregivers will have to convert from subcutaneous to inhaled insulin and may be required to calculate the dosage conversion, especially in the event of inhaler malfunction. This information should also be readily available to healthcare providers in the event that a patient is admitted to an inpatient care setting and would not be managed with inhaled insulin. Therefore, revise the protocol to clearly address the potential risk of user confusion between the labeled drug content of the cartridges and the approximate subcutaneous insulin dose.

Does the agency agree with MannKind's approach for evaluating alternative labeling (prominently depicting the deliverable insulin dose of 4 and 8 units) to facilitate the safe and effective use of Afrezza by providing clear, meaningful prescribing information to physicians, pharmacists, diabetes educators and patients?

FDA Response: Regarding the proposed approach for evaluating alternative labeling, the product labeling should contain necessary information for intended users to use the product safely and effectively. As you stated, input solicited from opinion leaders and patient advocates indicated some concerns that the current labeling may lead to confusion for healthcare providers. It is also possible that the labeling may lead to confusion for the patient user group. Address these concerns by conducting further evaluation on the labeling, and then finalize the labeling prior to conducting your final Human Factors/usability validation study. Also validate the product labeling to demonstrate that the patient users will be able to successfully understand and follow the labeling and to support a conclusion that the product labeling supports safe and effective use of your system. All final labeling (e.g., packaging, inserts) should be included in your final Human Factors/usability validation testing. Any errors, problems or hesitations that were observed should be evaluated along with the participants' subjective feedback regarding the labeling and any wording that they found confusing, misleading or incomplete.

Comment 11: The Summative Human Factors Usability Validation study will not evaluate a patient's ability to perform a dose conversion as this is best performed under the supervision of a health care professional. Does the Agency agree?

FDA Response: While the dose conversion is performed under the supervision of a healthcare professional, we still have concerns about potential patient confusion between the insulin contained in the cartridges and the corresponding subcutaneous insulin dose. Furthermore, it is possible that not all home users will have the benefit of the prescribing physician providing specific dosing instructions. These patients would be at home, and be using the device for the first time with potential access to both the Afrezza inhalation device, and other subcutaneous insulin delivery devices. We are most concerned with patients who are switching from subcutaneous insulin to the Afrezza inhalation delivery device, and those that have variable insulin dosing/sliding scale. Patients should also be able to convert back to injected insulin dosing regimens in the event of device failure or breakage or, as needed, in the setting of illness. Therefore, it is necessary to demonstrate in the final Human Factors/usability validation study that patients understand the difference in the insulin contained in the cartridges and the approximate subcutaneous insulin dose, to be able to perform a conversion, and to be able to select the correct cartridge(s) for the prescribed dose.

Comment 12: The Summative Human Factors Usability Validation study will incorporate patient orientation including reference to the IFU. Does the agency agree?

FDA Response: Please note that we consider the orientation sessions as part of product training. See our response to Question 13 for product training.

If you claim that your IFU is effective, your final validation study and your root cause assessment should show results that do not implicate the IFU as the cause for use errors or failures identified in the study.

Comment 13: In the Summative Human Factors Usability Validation study, MannKind will incorporate product orientation and instruction in a manner consistent with all other insulin delivery devices. Does the Agency agree?

FDA Response: We recommend that the training ("orientation') that will be provided to the test participants be representative of the training that patients will receive in actual use. In addition, you stated that you expect dose conversion to be performed under the supervision of a healthcare professional. Revise the protocol to include this step in the patient orientation session.

We also recommend the inclusion of a group of at least 15 participants who will not be trained (oriented) by Certified Diabetes Educators. In a non-ideal environment, not all patients who are prescribed Afrezza will receive adequate prior training before handling the device, and your product does not have a proposed registry program to ensure this training does, in fact, occur. This tested group can have access to all training tools and instructions for use included in your commercial product packaging.

LABELING

Comment 14: MannKind assumes that our actions are satisfactory, however if the Agency does not agree we would appreciate feedback.

FDA Response: Your proposal is acceptable.

Comment 15: MannKind assumes that our actions are satisfactory, however if the Agency does not agree we would appreciate feedback.

FDA Response: Your proposal is acceptable.

Comment 16: Based on formative testing, Mannkind has revised the cartridge blister pack labeling and will include this labeling in the Summative Human Factors Usability Validation study. Does the agency agree?

FDA Response: We agree. It is also noted that the demonstration kit cartridges are well-differentiated from the actual starter kit cartridges via red coloring. Ensure that the final version of your demonstration kit cartridges contain the statement "Does Not Contain Actual Drug".

Comment 17: MannKind assumes that our actions are satisfactory, however if the Agency does not agree we would appreciate feedback.

FDA Response: Your proposal is acceptable.

Comment 18: MannKind assumes that our actions are satisfactory, however if the Agency does not agree we would appreciate feedback.

FDA Response: Your proposal is acceptable.

Comment 19: MannKind assumes that our actions are satisfactory, however if the Agency does not agree we would appreciate feedback.

FDA Response: Your proposal is acceptable. However, we recommend bolding the text of the statement "Cartridge must be at room temperature for 10 minutes before use".

Comment 20: MannKind assumes that our actions are satisfactory, however if the Agency does not agree we would appreciate feedback.

FDA Response: While this has been incorporated, we recommend increasing the prominence of this statement.

Comment 21: MannKind assumes that our actions are satisfactory, however if the Agency does not agree we would appreciate feedback.

FDA Response: Your proposal is acceptable.

Comments 22, 23, 24: Based on formative testing, MannKind intends to use an improved IFU pamphlet, a purple Mouthpiece Cover and a device etched with the statement "Replace After 15 Days Use" in the Summative Human Factors Usability Validation Study. MannKind does not intend to mark the Mouthpiece Cover with "top" and the Mouthpiece with "this side up". Does the Agency agree?

FDA Response: While we agree with the above approach, we also recommend foil-wrapping each inhaler separately, so that with the aid of the included calendar, a user will know which inhaler is the currently in-use inhaler. If this suggestion is implemented, update the Instructions for Use and Human Factors Testing protocol accordingly.

Comment 25: MannKind assumes that our actions are satisfactory, however if the Agency does not agree we would appreciate feedback.

FDA Response: While our initial comments were incorporated into the design, we also recommend the following:

1. **Reduce the size of the graphic, as it currently is more prominent than the proprietary name.**
2. **Increase the size of the established name to at least half that of the proprietary name.**
3. **Revise the inhaler "calendar" to more closely resemble an actual calendar, as it is an easier format for users to recognize.**

Comment 26: MannKind assumes that our actions are satisfactory, however if the Agency does not agree we would appreciate feedback.

FDA Response: Your proposal is acceptable.

Comment 27: MannKind is uncertain how Comment 22, which pertains to the label of the mouthpiece, applies to the Cartridge and Gen2 Inhaler Carton Labeling section and requests clarification.

FDA Response: Comment 22 refers to an update on the design of the inhaler, and we request that any depiction of the device on any carton and container labeling be an accurate depiction of the device.

Comment 28: MannKind assumes that our actions are satisfactory, however if the Agency does not agree we would appreciate feedback.

FDA Response: (b) (4) **we again recommend what was stated in Comment 28 of the Complete Response.**

Comment 29: MannKind assumes that our actions are satisfactory, however if the Agency does not agree we would appreciate feedback.

FDA Response: Your proposal is acceptable.

ADDITIONAL COMMENTS

These comments pertain to your Instructions for Use:

a. **When referring to [redacted] (b) (4), preface the word insulin with 'injected'.**

b. **Spell out the word "units" wherever it may occur, as the letter U is an error-prone abbreviation which has been confused with the letter 0, and the first place this abbreviation appears is in the components section of the IFU, therefore, a patient who has not been trained could misread this section to state that the blue cartridges are 100 units (misreading 10U) and 200 units (misreading 20U).**

c. **In your formative human factors testing, patients frequently were unable to discern the top from the bottom of the inhaler. While the statement "Replace after 15 days use" has been added to the top of the inhaler, we also recommend the addition of a section in the "know your inhaler" section of the IFU to reinforce to the user that this is the top of the inhaler.**

d. [redacted] (b) (4)

e. **Bold the text for the statement "[redacted] (b) (4) must be used within 3 days" on page 7, as this is a critical step in the use of Afrezza, and could lead to inadequate dosing and treatment.**

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

/s/

RACHEL E HARTFORD
02/28/2012

Hartford, Rachel

From: Hartford, Rachel
Sent: Wednesday, January 11, 2012 10:21 AM
To: 'Wyka, Eileen'
Subject: Information Request

Hello Eileen,

Please respond initially via email and follow-up with a formal submission. Compile a list of reasons and/or situations where Afrezza users would need to temporarily convert back to injectable insulin.

Thanks

Rachel E. Hartford
Regulatory Project Manager
Division of Metabolism and Endocrinology Products
Center for Drug Evaluation and Research
Food and Drug Administration
rachel.hartford@fda.hhs.gov
301-796-0331 (phone)
301-796-9712 (fax)

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

/s/

RACHEL E HARTFORD
01/12/2012

Hartford, Rachel

From: Hartford, Rachel
Sent: Thursday, January 05, 2012 1:15 PM
To: 'Wyka, Eileen'
Subject: Afrezza NDA 022472 - Written Response Granted

Hello Eileen,

Please submit four physical samples of all the labels, labeling, and device (10U and 20U). The image resolution of these items in both the electronic and paper briefing packages is very poor. Please also submit higher resolution images.

Thanks,

Rachel

Rachel E. Hartford
Regulatory Project Manager
Division of Metabolism and Endocrinology Products
Center for Drug Evaluation and Research
Food and Drug Administration
rachel.hartford@fda.hhs.gov
301-796-0331 (phone)
301-796-9712 (fax)

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

/s/

RACHEL E HARTFORD
01/05/2012

DEPARTMENT OF HEALTH AND HUMAN SERVICES

Food and Drug Administration
Silver Spring MD 20993

NDA 022472

MEETING REQUEST -
Granting Written Response

MannKind Corporation
Attention: Eileen Wyka
Sr. Director, CMC, World-Wide Regulatory Affairs
61 South Paramus Road
Paramus, NJ 07652

Dear Ms. Wyka:

Please refer to your New Drug Application (NDA) submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act for Afrezza (insulin human [rDNA origin]) Inhalation Powder and Inhaler.

We also refer to your correspondence dated and received October 7, 2011, requesting a type C meeting. Based on the statement of purpose, objectives, and proposed agenda, we consider the meeting a type C meeting.

We believe that the questions you have posed can be answered adequately in writing and that providing a written response will assist you in your drug development plan. If we determine it is too early in the drug development process to answer certain questions, those questions should be resubmitted at a later date.

We will provide our answers to your questions within 90 days after receiving your background packages. However, if we do not receive your background packages within three months, we will consider your request to be withdrawn. Submit background information (three paper copies or one electronic copy to the application to the regulatory address below and 20 desk copies to me at the RPM address that follows.

Regulatory Address:

Food and Drug Administration, CDER, Central Document Room
Attention: Division of Metabolism and Endocrinology Products
5901-B Ammendale Road
Beltsville, MD 20705-1266

Submit the 20 desk copies to the following RPM address:

Rachel Hartford
Food and Drug Administration
Center for Drug Evaluation and Research
White Oak Building 22, Room: 3118
10903 New Hampshire Avenue
Silver Spring, Maryland 20993

If you have any questions, call me at (301) 796-0331.

Sincerely,

{See appended electronic signature page}

Rachel Hartford
Regulatory Health Project Manager
Division of Metabolism and Endocrinology Products
Office of Drug Evaluation II
Center for Drug Evaluation and Research

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

/s/

RACHEL E HARTFORD
10/13/2011

3 Page(s) have been Withheld in Full as B4 (CCI/TS) immediately following this page

DEPARTMENT OF HEALTH AND HUMAN SERVICES

Food and Drug Administration
Silver Spring MD 20993

NDA 022472

MEETING MINUTES

MannKind Corporation
Attention: Patricia R. Mayer, Ph.D.
Vice President, WWRA & Clinical Compliance
61 South Paramus Road
Paramus, NJ 07652

Dear Dr. Mayer:

Please refer to your New Drug Application (NDA) submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act (FDCA) for Afrezza (insulin human [rDNA origin]) Inhalation Powder and Inhaler.

We also refer to the End-of-Review Meeting between representatives of your firm and the FDA on May 4, 2011.

A copy of the official minutes of the meeting is attached for your information. Please notify us of any significant differences in understanding regarding the meeting outcomes.

If you have any questions, call me at (301) 796-0331.

Sincerely,

{See appended electronic signature page}

Rachel Hartford
Regulatory Project Manager
Division of Metabolism and Endocrinology Products
Office of Drug Evaluation II
Center for Drug Evaluation and Research

ENCLOSURE:
Meeting Minutes

FOOD AND DRUG ADMINISTRATION
CENTER FOR DRUG EVALUATION AND RESEARCH

MEMORANDUM OF MEETING MINUTES

Meeting Type:	B
Meeting Category:	End-of-Review
Meeting Date and Time:	May 4, 2011
Meeting Location:	10903 New Hampshire Avenue White Oak Building 22, Conference Room: 1313 Silver Spring, Maryland 20903
Application Number:	022472
Product Name:	Afrezza (insulin human [rDNA origin]) Inhalation Powder and Inhaler
Sponsor/Applicant Name:	MannKind Corporation
Meeting Chair:	Mary H. Parks, M.D.
Meeting Recorder:	Rachel Hartford

FDA ATTENDEES (alphabetic)

John Bishai, Ph.D.	Safety Project Manager, Division of Metabolism and Endocrinology Products (DMEP)
Karen Davis Bruno, Ph.D.	Supervisory Pharmacologist, DMEP
Sugato De, Ph.D.	Anesthesiology and Respiratory Devices/ Division of Anesthesia, General Hospital, and Infection Control and Dental Devices/ Office of Device Evaluation/ Center for Devices and Radiological Health
Amy Egan, M.D.	Deputy Director (Safety), DMEP
Enid Galliers	Chief, Project Management Staff, DMEP
Rachel Hartford	Regulatory Project Manager, DMEP

Hylton Joffe, M.D., M.M.Sc.	Diabetes Team I Leader, DMEP
Banu Karimi-Shah, M.D.	Medical Officer, Division of Pulmonary, Allergy, and Rheumatology Products (DPARP)
Yelena Maslov, Pharm.D.	Safety Evaluator, Division of Medication Error Prevention and Analysis (DMEPA), Office of Surveillance and Epidemiology (OSE)
Zachary Oleszczuk, Pharm.D.	Team Leader, DMEPA, OSE
Mary H. Parks, M.D.	Director, DMEP
Todd Sahlroot, Ph.D.	Statistics Team Leader, Division of Biometrics II
Sally Seymour, M.D.	Deputy Division Director (Safety), DPARP
Miyun Tsai-Turton, Ph.D., M.S.	Pharmacologist, DMEP
Lisa Yanoff, M.D.	Medical Officer, DMEP

SPONSOR ATTENDEES

Nik Amin, M.D.	Medical Director, Pulmonary
Anders H. Boss, M.D.	Senior Vice President, Chief Medical Officer
Hakan Edstrom, MBA	President, Chief Operating Officer
Patricia R. Mayer, Ph.D.	Vice President, Worldwide Regulatory Affairs
Jim Nezamis, M.S.	Director, Biometrics
Richard Petrucci, M.D.	Vice President, Diabetes – Medical Affairs
Sandy Suh, PharmD.	Director, Worldwide Regulatory Affairs
David Townson, Ph.D.	Senior Vice President, Development
Joseph Kocinsky	Vice President, Pharmaceutical Technology Development
Donna Donigi Gale	Senior Director, Worldwide Regulatory Affairs

1.0 BACKGROUND

MannKind submitted the Afrezza NDA 022472 on March 16, 2009, seeking FDA approval of the MedTone inhalation system. FDA issued a Complete Response letter on March 12, 2010, containing clinical, clinical pharmacology, labeling, and device deficiencies. On March 26, 2010, MannKind requested an End-of-Review (EOR) meeting to discuss their approach for resolving these deficiencies.

The EOR meeting was held on June 9, 2010, and MannKind submitted a Complete Response on June 29, 2010. In this submission, MannKind abandoned their MedTone inhalation device and instead sought FDA approval of their Gen 2C system. The Complete Response also included the Complete Study Report for Clinical Study MKC-TI-117 entitled, "*A Phase 3, Multicenter, Open-label, Randomized, Clinical Trial Evaluating the Efficacy and Safety of Technosphere® Insulin Inhalation Powder in Combination with Lantus® Versus Humalog® in Combination with Lantus® in Subjects with Type 1 Diabetes Mellitus Over a 16-week Treatment Period*". This trial was included to provide additional efficacy and safety data in patients with type 1 diabetes but used the MedTone system, not the Gen 2C system. FDA identified clinical, clinical pharmacology, product quality, device, and labeling deficiencies and issued a Complete Response letter on January 18, 2011. On February 11, 2011, MannKind requested an EOR meeting.

MannKind's purpose for this second EOR meeting was to discuss selected portions of FDA's January 18, 2011, Complete Response letter to achieve clarity on the adequacy of the proposed clinical studies to support approval of the Gen 2C system and to discuss the regulatory path for resubmission. Their expected outcome is agreement on the proposed protocol designs and definition of the path for approval of Afrezza.

The EOR meeting was initially scheduled for April 15, 2011, and an internal meeting to prepare preliminary responses was initially scheduled for April 8, 2011. At approximately 9 pm on April 7, 2011, all FDA meeting attendees were instructed to begin identifying the required actions needed to effect an orderly government shutdown that was expected to occur at midnight on April 9, 2011.

Because of the required preparations for a potential government shutdown, the internal meeting could not be held as scheduled on April 8. FDA informed MannKind on April 8 that the internal meeting had to be cancelled and that we would, therefore, need to reschedule the April 15 meeting. FDA also said the meeting would be rescheduled as soon as possible. The government shutdown was subsequently averted and FDA returned to normal operations on Monday, April 11. FDA informed MannKind on Tuesday, April 12 that the April 15, 2011, EOR meeting had been rescheduled to May 4, 2011.

2. DISCUSSION

The summarized background and associated questions included in your March 16, 2011, meeting package appear below followed by our preliminary responses (in **bold)** that were sent to you via email on April 29, 2011. Your pre-meeting follow-up comments sent via email on May 3, 2011,

are shown in *underlined italics*. A summary of the discussion at the meeting is shown in *italics*. Post-meeting comments are shown in underlined regular font. No discussion is shown for those questions where neither MannKind nor FDA raised any additional issues.

Head-to-head Comparison of Pulmonary Safety

MKC proposes a head-to-head comparison of pulmonary safety of MedTone C and Gen2C inhaler through added arms of MedTone C from (b) (4) (Type 1: MKC-TI-171 (b) (4) [redacted]

[redacted] (b) (4)

Question 1: Does the proposed approach for assessing pulmonary safety of MedTone C and Gen2C inhaler provide sufficient head-to-head comparison data to bridge the pulmonary safety data of Gen2C to the extensive Phase 3 pulmonary safety data with MedTone C?

FDA Response: We have concerns with your proposal (b) (4) [redacted] **.**

We agree with inclusion of MedTone C treatment arms (b) (4) **to allow for the head-to-head safety comparison of the Gen2C to the MedTone C. In order to establish a bridge to the MedTone C safety data, we recommend, at a minimum,** (b) (4) [redacted] **be powered for a comparison of the Gen2C to the MedTone C utilizing the primary safety endpoint FEV1. Provide justification for the sample size and**

propose a margin for the comparison including justification of the margin. Final determination of the adequacy of the pulmonary safety bridging data will be a review issue.

Performing chest x-rays in the proposed clinical trials is at your discretion, but is not required for the proposed studies.

MannKind May 3, 2011:
We propose a trial (b) (4)

(b) (4)

1 Page(s) has been Withheld in Full as B4 (CCI/TS) immediately following this page

(b) (4)

Discussion: MannKind clarified that the design of this trial differs from the trial designs proposed in the meeting package. FDA stated that we would not be able to provide full feedback or agreements during the meeting on new proposals submitted one day before the scheduled meeting, as any new proposal would first need to be discussed internally. If MannKind subsequently decides to pursue one of the new proposals, we recommend that the modified proposal be submitted to FDA for review prior to implementation.

Mannkind stated that it was under the impression that FDA was requiring a third study to bridge pulmonary safety. FDA corrected this misperception by reading directly from the January 18, 2011, Complete Response letter the following passage:

"Therefore, you should conduct two randomized, controlled phase 3 trials with Gen2device, one in patients with type 1 diabetes and the other in patients with type 2 diabetes. At least one of these trials should include a treatment group using the MedTone C inhaler so that we can obtain a head-to-head comparison of the pulmonary safety data for the two devices……"

FDA emphasized that the letter required that only one of these two trials provide the comparative pulmonary safety data between the two devices and FDA also clarified that it was not our intent to imply that safety should be the primary endpoint in one or both of the pivotal Gen2C trials. FDA stated that the primary endpoint of these trials should still be efficacy based on HbA1c. Our intent was to ensure that the trials are sufficiently powered so that the pulmonary safety of the Gen2C inhaler could be adequately evaluated. FDA informed MannKind that although the data they had provided in support of a FEV1 non-inferiority margin of (b) (4) *was appreciated, we would not be able to accept this margin as FDA currently has not determined an acceptable non-inferiority margin for FEV1. The pulmonary safety analysis in the original Afrezza program has primarily been descriptive; therefore, it is anticipated that the analysis of the pulmonary safety data to bridge the two devices would also be descriptive. FDA agreed to provide a post-meeting comment if there was any additional guidance.*

MannKind clarified that they will also evaluate pulmonary safety in their type 2 diabetes trial but that trial will not include a MedTone C arm. MannKind stated that they are proposing the MedTone C arm for the type 1 diabetes trial in case they decide to seek initial approval for Afrezza only in patients with type 1 diabetes (in accordance with FDA's Additional Comment k). FDA stated that the FEV1 results for MedTone C were similar in the type 1 and type 2 diabetes populations and, therefore, FDA finds it acceptable to include MedTone C in only the type 1 diabetes trial.

Post-meeting comment: After further internal discussion, as stated in the meeting we cannot agree to the proposed non-inferiority approach or margin for the assessment of pulmonary safety data. The primary concern is that the trial(s) conducted to evaluate pulmonary safety for Gen2 have reasonable power to bridge to the pulmonary safety data from the MedTone C system. It is anticipated that the analysis of the pulmonary safety data will be descriptive in nature. MannKind's proposal to obtain pulmonary safety data in at least (b) (4) patients per treatment group

(MedTone C, Gen 2 and control) in at least one 24 week study should provide sufficient data to compare the pulmonary safety of MedTone C and the Gen 2; however, whether the results will adequately bridge the pulmonary safety of the two devices will depend upon the results of the study and will ultimately be a review issue.

Question 2: Is the Agency in agreement that the proposed PFT assessment and analysis plan is adequate? If not, please provide further guidance.

FDA Response: We have the following comments regarding PFT assessment and the PFT analysis plan:

Pulmonary Function Test Assessment:

a. Your proposed plan for [redacted] (b) (4) is concerning. In your original registration program, all PFTs were conducted at MannKind Corporation-certified pulmonary function laboratories (PFLs). Certification was based on successful completion of initial on-site equipment verification and training, and on-going quality control of the precision and accuracy of test procedures. A change to the PFT assessment protocol introduces significant risk and uncertainty into the reliability/quality of PFT measurements at a critical time in your development program. For this reason, we strongly recommend that you maintain the same PFT procedures (measurement only in PFLs) in your newly proposed protocols (MKC-TI-171 [redacted] (b) (4)

MannKind May 3, 2011:
As advised by the Agency, MKC will conduct pulmonary function tests (spirometry) at MKC certified Pulmonary Function Laboratories only - similar to the original registration trials.

b. In the original clinical program, body plethysmography (TLC) and diffusion capacity (DLco) did not provide different or additional information over that which was provided from the spirometry (e.g. FEV1) measurements. For this reason, omission of TLC and DLco measurements [redacted] (b) (4) would be acceptable from a pulmonary safety review standpoint.

c. The majority of the decline in FEV1, based on data from the original program, occurs by 12 weeks. [redacted] (b) (4) Amend your protocols to provide for more frequent PFT assessments.

MannKind May 3, 2011:
We acknowledge the suggested advice for more frequent PFT assessments and propose an additional measurement at Week 12. PFT assessments in the proposed trials now will be, similar to the original Phase 3, conducted at: screening, randomization, Week 12, Week 24 (end of the randomized treatment period), and Week 28 (follow-up Visit).

Discussion: FDA stated that this revised proposal is reasonable.

Statistical Analysis of Pulmonary Safety

d. Your analysis plan should include comparison of MedTone C and Gen2 pulmonary safety data as described in the response to question #1.

Insulin Glargine Twice Daily Injections

We propose to use insulin glargine [redacted] (b) (4) as the basal treatment with prandial TI as well as with the prandial SC comparator in protocol MKC-TI-171 (Type 1 diabetes mellitus study) to allow for an optimized basal insulin treatment regimen.

Question 3: Is the use of basal insulin glargine [redacted] (b) (4) in Type 1 DM patients acceptable?

FDA Response: No, this is not acceptable. As you note in your background package, use of [redacted] (b) (4) is not universal in patients with type 1 diabetes and is used by a minority of these patients according to some of the diabetologists you contacted. Note also that insulin glargine is not labeled for [redacted] (b) (4) raising concerns about labeling this unapproved regimen in your Afrezza package insert. In addition, [redacted] (b) (4) glargine further complicates your titration algorithms compared to a once-daily glargine regimen. Based on all these considerations, you should use a similar approach to glargine in your type 1 trial as you are doing in your type 2 trial. Specifically, patients who are already on twice-daily glargine pre-trial can continue this regimen whereas all others should enter the trial on once-daily glargine. Like in your type 2 trial, patients can be permitted to split the glargine dose if there is recurrent hypoglycemia (although both protocols should be clarified that splitting of the glargine dose should be based on hypoglycemia that is presumed to be related to glargine and not due to the prandial insulin). Similarly, both trials could specify that patients can be permitted to split the glargine dose if there is recurrent evening hyperglycemia attributed to waning of the morning glargine dose.

MannKind May 3, 2011:
MKC notes the Agency's position in the use of insulin glargine in the type 1 diabetes mellitus trial. Alternatively MKC proposes [redacted] (b) (4) for use in all subjects. Does the Agency agree?

Discussion: MannKind clarified that, from their examination of the literature, roughly 30% of patients with type 1 diabetes require twice-daily glargine while a higher percentage, 40-50%, require twice-daily detemir to optimize glycemic control. To improve generalizability of the results, FDA suggested considering a trial design in which patients remain on their pre-enrollment basal insulin therapy (i.e. either glargine or detemir) rather than having all patients switch to the same basal insulin therapy at the start of the trial. If this approach is used, FDA recommended stratifying randomization by type of basal insulin.

Post meeting comment: As stated at the meeting, we recommend that you consider a trial design in which patients remain on their pre-enrollment basal insulin because this may improve generalizability of the results. (b) (4) we recommend that your trial include patients using detemir once-daily and patients using detemir twice-daily. Our rationale is that twice daily detemir is used in only 40-50% of patients in clinical practice (per your literature review) and, therefore, using only twice-daily detemir in your trial will limit generalizability of the study results.

Special Safety Assessments

Special safety assessments for AEs of interest in the trials will include, apart from pulmonary function testing as described above, hypoglycemia, diabetic ketoacidosis, immunogenicity, eye events and device related performance issues as described in the protocols.

Question 4: Please confirm the adequacy of our proposed safety assessment plans as specified in the protocol summary.

FDA Response: The primary analyses of severe hypoglycemia event should include all cases requiring assistance regardless of blood glucose levels. Supportive analyses may include cases requiring assistance OR blood glucose <36 mg/dL as you proposed in the protocols.

Your plan for assessment of eye events is adequate. For diabetic ketoacidosis and immune-related adverse events, clarify how these events will be defined and captured. Please also see our response to question 6.

MannKind May 3, 2011:
The data collection for severe hypoglycemia will permit the primary analysis of events that require assistance regardless of blood glucose levels.

Diabetic ketoacidosis will be defined according to the ADA Consensus Statement 2009 (Kitabchi AE, et al. Hyperglycemic Crisis in Adult Patients with Diabetes. Diabetes Care, 2009; 32 (7):p1335 -1343).

We expect events of diabetic ketoacidosis will be reported as Serious Adverse Events. However, we will introduce an active questioning at clinic visits, such as: "Have you been hospitalized or medically treated for very high BG since last visit?"

Independent of the route of reporting we will request investigators to report such events in an expedited fashion to MKC, and a specific systematic data collection will be performed, including requests for laboratory data and potential precipitating factors.

Immune related events are defined according to MedDRA coding, and will be captured through the protocol defined AE reporting process, consistent with the original phase 3 program.

Post meeting comment: You should pre-define in your protocols specific Standardised MedDRA Queries and/or Preferred Terms that you will use to analyze immune-related adverse events.

In clinical trials (MKC-TI-171 (b) (4)) it is planned to record all episodes of hypoglycemia (non-severe and severe) that meet the hypoglycemia definitions specified in the protocols.

Question 5: Does the Agency agree with the proposed safety assessment plans of hypoglycemia, in particular the definition of hypoglycemia?

FDA Response: See response to question 4.

Patient Use and Device Robustness

In the proposed trials (MKC-TI-171 (b) (4) MKC expects to distribute over 2400 Gen2C inhalers and will evaluate all complaint inhalers including AE related complaints. A full summary of these data will be reported in the resubmission. A total of 100 non-complaint related devices has been evaluated previously; no additional random sampling and assessment of non-complaint devices is planned.

Question 6: Does the agency agree with this proposal for evaluation of device robustness?

FDA Response: Yes, we agree, provided that no changes were made to the device since the 100 non-complaint related devices were manufactured. However, if you make any modifications to the previously evaluated device, then you should provide complete evaluation of the new device. All complaint inhalers including adverse event-related complaints retained from trials MKC-TI-171 (b) (4) should be evaluated for the following parameters to the extent possible: physical deterioration, resistance, mouthpiece retention, force to open, emitted dose and aerodynamic particle size distribution. Furthermore, for each complaint inhaler, including adverse event-related complaints identified in your proposed clinical trials, provide the following additional information: root cause analysis; Failure Mode and Event Analysis (FMEA); mitigation plan; and verification and validation testing.

In addition, you did not respond to deficiencies 8 through 14 in our Complete Response letter dated January 18, 2011. These deficiencies must be resolved prior to approval.

MannKind May 3, 2011:
MKC confirms that there have been no further modifications to the device that impact the device robustness. However, as suggested in previous FDA advice, we will introduce a change in color of the mouth piece cover from (b) (4) to purple and previously suggested labeling of the device.

Furthermore, we will comply with the requests for evaluation of inhalers associated with a complaint (including those related to an adverse event) during trial conduct.

The device related deficiencies noted as numbers 8 thru 14 in the CRL (dated 18Jan2011) as well as the CMC related deficiencies noted as numbers 4 thru 7 are planned to be addressed separately. MKC will be requesting a separate meeting request for CMC/device topics.

Post Meeting Comment: You stated that you made no further modification to the device that impacts the device robustness. However, it is unclear if you made any other modifications to the previously evaluated device. Confirm that you made no other modifications to the previously evaluated device other than changing the color of the mouth piece cover. If you made any other modifications, provide complete evaluation of the new device. In addition, provide updated device labeling for review.

Immunogenicity

The Agency has requested that immunogenicity be assessed in the two requested Phase 3 clinical trials. The proposed clinical trials will have a 24-week treatment period (TI or comparator). IAB titers are not expected to plateau during this treatment period. Also, the follow-up after treatment discontinuation is likely to be too short to show the return of the titers to baseline values. It is MKC's expectation that, while these studies will provide limited data, the information obtained would enable bridging to the long term Phase 3 studies conducted with MedTone C.

The validated Kronus radioimmunoassay will be used to measure IAB levels (IgG, exclusively).

Question 7: Does the agency agree with this proposal for evaluation of immunogenicity?

FDA Response: We agree with your proposal for evaluation of immunogenicity pending clarification that the radioimmunoassay to be used in the two Phase 3 trials is the same as that used in your original NDA clinical development program.

MannKind May 3, 2011:
We can confirm that the radioimmunoassay to be used will be the same as used in the original NDA.

Additional Comments:

a. Except where noted in our responses to your questions and our additional comments, the overall plan for evaluation of efficacy and safety with the Gen2 device appears adequate. Actual study conduct, including adequate titration of insulins will be a critical factor in determining interpretability of the results.

MannKind May 3, 2011:
MKC requests clarification on the statement "…review of glucose data while the trials are ongoing with feedback with investigators…" from the Complete Response Letter (dated 18 Jan 2011; page 2 paragraph 2) regarding blood glucose review and titration of insulins.

> Inadequate titration of insulin doses has been an important limitation of all phase 3 clinical trials conducted with the MedTone inhaler to date. Therefore, your phase 3 trials with the Gen2 inhaler should ensure that appropriate titration of insulin doses occurs. Strategies include use of a titration algorithm, investigator training with frequent reminders about titrating insulin doses, and review of glucose data while the trials are ongoing with feedback to investigators when there is evidence of inadequate titration.

Post-meeting comment: The statement *"…review of glucose data while the trials are ongoing with feedback to investigators…"* is a suggestion for sponsor involvement in reviewing fingerstick glucose data and changes to the insulin regimen soon after the data are uploaded into an electronic database. With this approach, MannKind can provide feedback to investigators who appear to be inappropriately deviating from the titration algorithm. This would provide another safeguard for ensuring adequate titration of insulin in your trials rather than leaving the responsibility for ensuring adequate titration up to individual investigators alone.

b. It would be acceptable for patients to remain on their DPP-4 inhibitor therapy during the type 2 diabetes trial. Also, saxagliptin is an acceptable DPP-4 inhibitor for inclusion.

c. Clarify why the conversion dose of glargine for patients who were on insulin detemir will be 60% of the insulin detemir dose, while NPH will be converted in a 1:1 ratio.

MannKind May 3, 2011:
Review of the literature (list below) suggests higher doses of insulin detemir are required to achieve comparable HbA1c reductions to those seen with insulin glargine. The dose of insulin glargine can range from 43 % to 75 % of the total detemir dose. In addition, the mean dose of detemir was 2.3 times higher as compared to the dose of NPH. We therefore believe the conversion of detemir to glargine on a 1:1 basis may increase the risk of hypoglycemia in these patients. Is our current approach acceptable?

Hermansen K, et al. Comparison of the Soluble Basal Insulin Analog Insulin Determir with NPH. Diabetes Care 2001; 24(2):296-301.

Heller S, et al. Comparison of Insulin Detemir and Insulin Glargine in a Basal-Bolus regimen, with insulin aspart as the mealtime insulin in patients with type 1 diabetes mellitus: a 52 week, multinational, randomized openlabel, parallel-group treat-to-target non-inferiority trial. Clin Ther 2009; 31(10):2086-2097.

Dailey G, et al. Relationship of Insulin Dose, A1c lowering, and Weight in type 2 Diabetes: comparing Insulin Glargine & Insulin Detemir. Diabetes Technol Ther 2010;12(12):1019-1027.

Rosenstock J, et al. A randomized, 52 week, treat-to-target trial comparing insulin detemir with insulin glargine when administered as add-on to glucose-lowering drugs in insulin-naïve people with Type 2 diabetes. Diabetologia 2008;51(3):408-416.

Hollander P, et al. A 52 week, multinational, open-label, parallel-group, noninferiorty, treat-to-target trial comparing insulin detemir with insulin glargine in a basal-bolus regimen with mealtime insulin aspart in patients with Type 2 Diabetes. Clin Ther 2008;30(11):1976-1987.

Post meeting comment: Your conversion dose is acceptable provided that you can ensure adequate titration of the basal insulin dose over the basal insulin titration phase of the trial. In addition, please see our response to Question 3.

d. Increase the baseline HbA1c for inclusion and/or actively enroll patients in the upper range of the HbA1c inclusion criterion to help ensure that the mean baseline HbA1c will not be too low to be able to show a meaningful improvement in HbA1c over the duration of the study.

MannKind May 3, 2011:
Please clarify whether the Agency is suggesting we increase the lower HbA1c entry criteria. Does the Agency have advice in regards to a specific mean baseline HbA1c?

Our trial design currently does not include a stratification strategy for enrolling patients in the upper range of HbA1c. Please clarify if stratification is necessary and if so will the Agency accept an enrollment stratification only?

Discussion: FDA explained that the goal of this comment was to inform the sponsor that a high enough baseline HbA1c to be able to show meaningful improvement in HbA1c over the duration of the study is critical to the interpretation of study results and to suggest possible strategies to increase the mean HbA1c above that seen in Trial 117. MannKind asked if FDA required a particular strategy. FDA responded, no, these are suggested strategies but stated that stratification would likely be the most effective strategy. Stratification by baseline HbA1c is not required for interpretation of a valid study but can be used to increase the precision of estimates particularly if baseline HbA1c is expected to be strongly correlated with the change from baseline. FDA stated that a mean baseline HbA1c of roughly 8.5% or above would likely be adequate.

e. In clinical practice most patients use premeal glucose to determine the prandial insulin dose. Justify your plan for titration based on post-prandial glucose levels for both Afrezza and NovoLog.

MannKind May 3, 2011:
We agree that insulin aspart can be titrated based on pre-next meal blood glucose levels. However, the TI dosing titration must be based on the post-prandial blood glucose levels since

the distinct pharmacological profile of TI and the clinical trial data support such an approach. Please clarify any specific concerns with this approach and we suggest to discuss these during the meeting.

Discussion: MannKind clarified that they will revise the trials so that insulin aspart is titrated based on the pre-next meal blood glucose concentrations, which is consistent with how insulin aspart is typically used in clinical practice. FDA stated that titrating insulin aspart based on pre-meal glucose levels and titrating Afrezza based on post-prandial blood glucose concentrations is acceptable. FDA stated that Afrezza will be labeled according to how it is studied in the clinical trials.

f. Your dosing guidelines instruct patients to inject Novolog (b) (4) minutes before a meal, but the Novolog package insert instructs patients to inject immediately before the meal (within 5-10 minutes). Your instructions for Novolog administration should conform to its package insert.

MannKind May 3, 2011:
We agree.

g. Clarify what is the maximum permitted pre-meal and supplemental dose of your inhaled insulin via the Gen2 and MedTone C inhalers. In addition, clarify the maximum daily dose that can be administered with the Gen2 device (currently you state the maximum dose is (b) (4) units but this dose cannot be achieved with increments of the 10-unit and 20-unit Gen2 cartridges).

MannKind May 3, 2011:
We agree the maximum dose of (b) (4) U for Gen2C cannot be achieved with the current cartridge strengths. Therefore the total daily maximum cartridge dose for Gen2C should be 300 U for an average 75 kg adult. We recommend the maximum pre-meal dose for the TI Gen2C is 60 U per meal and MedTone C is 90 U.

Discussion: MannKind clarified that the maximum permitted dose of Afrezza is based on non-clinical studies and exposure to the excipient FDKP. FDA asked whether these dose caps will limit the ability to adequately titrate Afrezza in the clinical trials. MannKind responded that it would not (i.e., that most patients will not need Afrezza doses above these dose caps).

h. (b) (4)

MannKind May 3, 2011:
(b) (4) *In addition, we would propose the following:*

(b) (4)

We recognize the Agency's concerns (b) (4) *Therefore we would like to discuss an alternative type 2 diabetes mellitus trial design with the Agency. In this design we would propose* (b) (4) *. We recognize that the Agency currently has only very limited information on such an approach, but we would highly appreciate the Agency's preliminary thoughts and advice and discuss them during the meeting.*

Discussion: FDA asked MannKind to clarify their intended target patient population for Afrezza among patients with type 2 diabetes. MannKind stated that the most likely users of Afrezza would be type 2 diabetes patients already using injectable basal/bolus insulin therapy. FDA stated that other possible Afrezza users may be patients with type 2 diabetes who have failed oral antidiabetic medications and who prefer to add an inhaled insulin product with the goal of delaying the need for injectable antidiabetic therapy. FDA stated that, overall, the type 2 diabetes trial should focus on the most likely users of Afrezza among type 2 diabetes patients so that results can be the most generalizable. Although various potential comparators were mentioned (e.g., (b) (4) *), no final agreement was reached on a specific study design. FDA suggested that MannKind submit a revised proposal to FDA for comment prior to finalizing or initiating the trial.*

i. Clarify why you are obtaining Doppler echocardiograms in your trials.

MannKind May 3, 2011:
In a scientific advice from CHMP in 2005, prior to the Phase 3 program, the Agency suggested to explore the possible effects of TI on pulmonary arterial pressure in a small subset of patients (n = 50 to 100) using Doppler echocardiogram.

Post meeting comment: From FDA's perspective, it is acceptable – but not mandatory – to conduct the Doppler echocardiograms.

j. We note that in your End of Review meeting package briefing document, you did not address all of the deficiencies listed in the Complete Response letter, including deficiencies related to the device (see response to question 6). All the deficiencies in the Complete Response letter will need to be satisfactorily addressed before your application can be approved. Clarify your plans for addressing the remaining deficiencies.

MannKind May 3, 2011:
MKC is planning to discuss all remaining deficiencies (device related deficiencies noted as numbers 8 thru 14 as well as the CMC related deficiencies noted as numbers 4 thru 7) in a separate meeting.

k. Your original NDA proposed an indication for the use of Afrezza in the treatment of Type 1 and Type 2 diabetes mellitus. Although separate trials are required for approval of use in both these patient populations, FDA will accept the results of a trial performed in T1DM for consideration of initial approval only in patients with T1DM. Data supporting use of Afrezza in T2DM may be submitted as an efficacy supplement to your NDA, if approved.

MannKind May 3, 2011:
We note the Agency's position on a limited indication in type 1 diabetes mellitus only for an initial approval. We would like to understand and discuss the implications of such an approach.

Discussion: No discussion occurred.

l. For the type 2 diabetes trial, clarify why you are proposing (b) (4)

MannKind May 3, 2011:
We would like to discuss this comment in conjunction with our alternative type 2 study design as mentioned above.

Discussion: See our response to Additional Comment h.

3.0 ISSUES REQUIRING FURTHER DISCUSSION

Since the May 4, 2011 End-of-Review meeting, FDA has held additional internal discussions with senior managers regarding the clinical development program of Afrezza with the Gen2 device. We note that in your original NDA application, a dose-response with higher insulin doses administered via the Model C device was not observed in the placebo-controlled Study 005. The overall short trial duration and design limiting duration of use at higher doses may have contributed to the lack of a dose-response; however, we are unaware of a similarly conducted study involving the Gen2 device which can ensure us that with increasing doses of insulin administered via this new device, greater efficacy can be achieved. Has Mannkind conducted a clinical study with the Gen2device proposed for marketing that establishes a dose-response with escalating doses of insulin?

4.0 ATTACHMENTS AND HANDOUTS

There were no attachments or handouts for the meeting minutes.

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

/s/

RACHEL E HARTFORD
05/26/2011

DEPARTMENT OF HEALTH AND HUMAN SERVICES

Food and Drug Administration
Silver Spring MD 20993

NDA 022472

MEETING PRELIMINARY COMMENTS

MannKind Corporation
Attention: Patricia R. Mayer, Ph.D.
Vice President, WWRA & Clinical Compliance
61 South Paramus Road
Paramus, NJ 07652

Dear Dr. Mayer:

Please refer to your New Drug Application (NDA) submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act (FDCA) for Afrezza (insulin human [rDNA origin]) Inhalation Powder and Inhaler.

We also refer to your correspondence dated and received February 11, 2011, requesting an End-of-Review Meeting.

This material consists of our preliminary responses to your questions and any additional comments in preparation for the discussion at the meeting scheduled for May 4, 2011. We are sharing this material to promote a collaborative and successful discussion at the meeting. The meeting minutes will reflect agreements, important issues, and any action items discussed during the meeting and may not be identical to these preliminary comments following substantive discussion at the meeting. However, if these answers and comments are clear to you and you determine that further discussion is not required, you have the option of cancelling the meeting (contact me). If you choose to cancel the meeting, this document will represent the official record of the meeting. If you determine that discussion is needed for only some of the original questions, you have the option of reducing the agenda and/or changing the format of the meeting (e.g., from face to face to teleconference). It is important to remember that some meetings, particularly milestone meetings, can be valuable even if the premeeting communications are considered sufficient to answer the questions. Note that if there are any major changes to your development plan, the purpose of the meeting, or the questions based on our preliminary responses, we may not be prepared to discuss or reach agreement on such changes at the meeting although we will try to do so if possible. If any modifications to the development plan or additional questions for which you would like CDER feedback arise before the meeting, contact me to discuss the possibility of including these items for discussion at the meeting

Your background and questions are repeated below, followed by our responses in **bold**.

Head-to-head Comparison of Pulmonary Safety

MKC proposes a head-to-head comparison of pulmonary safety of MedTone C and Gen2C inhaler through added arms of MedTone C from (b) (4) (Type 1: MKC-TI-171 (b) (4)

(b) (4)

Question 1: Does the proposed approach for assessing pulmonary safety of MedTone C and Gen2C inhaler provide sufficient head-to-head comparison data to bridge the pulmonary safety data of Gen2C to the extensive Phase 3 pulmonary safety data with MedTone C?

FDA Response: We have concerns with your proposal (b) (4) **.**

We agree with inclusion of MedTone C treatment arms (b) (4) **to allow for the head-to-head safety comparison of the Gen2C to the MedTone C. In order to establish a bridge to the MedTone C safety data, we recommend, at a minimum,** (b) (4) **should be powered for a comparison of the Gen2C to the MedTone C utilizing the primary safety endpoint FEV1. Provide justification for the sample size and propose a margin for the comparison including justification of the margin. Final determination of the adequacy of the pulmonary safety bridging data will be a review issue.**

Performing chest x-rays in the proposed clinical trials is at your discretion, but is not required for the proposed studies.

Question 2: Is the Agency in agreement that the proposed PFT assessment and analysis plan is adequate? If not, please provide further guidance.

FDA Response: We have the following comments regarding PFT assessment and the PFT analysis plan:

Pulmonary Function Test Assessment:

a. Your proposed plan for [redacted] (b) (4) is concerning. In your original registration program, all PFTs were conducted at MannKind Corporation-certified pulmonary function laboratories (PFLs). Certification was based on successful completion of initial on-site equipment verification and training, and on-going quality control of the precision and accuracy of test procedures. A change to the PFT assessment protocol introduces significant risk and uncertainty into the reliability/quality of PFT measurements at a critical time in your development program. For this reason, we strongly recommend that you maintain the same PFT procedures (measurement only in PFLs) in your newly proposed protocols (MKC-TI-171 [redacted] (b) (4)

b. In the original clinical program, body plethysmography (TLC) and diffusion capacity (DLco) did not provide different or additional information over that which was provided from the spirometry (e.g. FEV1) measurements. For this reason, omission of TLC and DLco measurements [redacted] (b) (4) would be acceptable from a pulmonary safety review standpoint.

c. The majority of the decline in FEV1, based on data from the original program, occurs by 12 weeks. [redacted] (b) (4) Amend your protocols to provide for more frequent PFT assessments.

Statistical Analysis of Pulmonary Safety

d. Your analysis plan should include comparison of MedTone C and Gen2 pulmonary safety data as described in the response to question #1.

<u>Insulin Glargine Twice Daily Injections</u>

We propose to use insulin glargine [redacted] (b) (4) as the basal treatment with prandial TI as well as with the prandial SC comparator in protocol MKC-TI-171 (Type 1 diabetes mellitus study) to allow for an optimized basal insulin treatment regimen.

Question 3: Is the use of basal insulin glargine [redacted] (b) (4) in Type 1 DM patients acceptable?

FDA Response: No, this is not acceptable. As you note in your background package, use of [redacted] (b) (4) is not universal in patients with type 1 diabetes and is used by a minority of these patients according to some of the diabetologists you contacted. Note also that insulin glargine is not labeled for [redacted] (b) (4) raising concerns

about labeling this unapproved regimen in your Afrezza package insert. In addition, (b) (4) glargine further complicates your titration algorithms compared to a once-daily glargine regimen. Based on all these considerations, you should use a similar approach to glargine in your type 1 trial as you are doing in your type 2 trial. Specifically, patients who are already on twice-daily glargine pre-trial can continue this regimen whereas all others should enter the trial on once-daily glargine. Like in your type 2 trial, patients can be permitted to split the glargine dose if there is recurrent hypoglycemia (although both protocols should be clarified that splitting of the glargine dose should be based on hypoglycemia that is presumed to be related to glargine and not due to the prandial insulin). Similarly, both trials could specify that patients can be permitted to split the glargine dose if there is recurrent evening hyperglycemia attributed to waning of the morning glargine dose.

Special Safety Assessments

Special safety assessments for AEs of interest in the trials will include, apart from pulmonary function testing as described above, hypoglycemia, diabetic ketoacidosis, immunogenicity, eye events and device related performance issues as described in the protocols.

Question 4: Please confirm the adequacy of our proposed safety assessment plans as specified in the protocol summary.

FDA Response: The primary analyses of severe hypoglycemia event should include all cases requiring assistance regardless of blood glucose levels. Supportive analyses may include cases requiring assistance OR blood glucose <36 mg/dL as you proposed in the protocols.

Your plan for assessment of eye events is adequate. For diabetic ketoacidosis and immune-related adverse events, clarify how these events will be defined and captured. Please also see our response to question 6.

In clinical trials (MKC-TI-171 (b) (4) it is planned to record all episodes of hypoglycemia (non-severe and severe) that meet the hypoglycemia definitions specified in the protocols.

Question 5: Does the Agency agree with the proposed safety assessment plans of hypoglycemia, in particular the definition of hypoglycemia?

FDA Response: See response to question 4.

Patient Use and Device Robustness

In the proposed trials (MKC-TI-171 (b) (4) MKC expects to distribute over 2400 Gen2C inhalers and will evaluate all complaint inhalers including AE related complaints. A full summary of these data will be reported in the resubmission. A total of 100 non-complaint related

devices has been evaluated previously; no additional random sampling and assessment of non-complaint devices is planned.

Question 6: Does the agency agree with this proposal for evaluation of device robustness?

FDA Response: Yes, we agree, provided that no changes were made to the device since the 100 non-complaint related devices were manufactured. However, if you make any modifications to the previously evaluated device, then you should provide complete evaluation of the new device. All complaint inhalers including adverse event-related complaints retained from trials MKC-TI-171 (b) (4) should be evaluated for the following parameters to the extent possible: physical deterioration, resistance, mouthpiece retention, force to open, emitted dose and aerodynamic particle size distribution. Furthermore, for each complaint inhaler, including adverse event-related complaints identified in your proposed clinical trials, provide the following additional information: root cause analysis; Failure Mode and Event Analysis (FMEA); mitigation plan; and verification and validation testing.

In addition, you did not respond to deficiencies 8 through 14 in our Complete Response letter dated January 18, 2011. These deficiencies must be resolved prior to approval.

Immunogenicity

The Agency has requested that immunogenicity be assessed in the two requested Phase 3 clinical trials. The proposed clinical trials will have a 24-week treatment period (TI or comparator). IAB titers are not expected to plateau during this treatment period. Also, the follow-up after treatment discontinuation is likely to be too short to show the return of the titers to baseline values. It is MKC's expectation that, while these studies will provide limited data, the information obtained would enable bridging to the long term Phase 3 studies conducted with MedTone C.

The validated Kronus radioimmunoassay will be used to measure IAB levels (IgG, exclusively).

Question 7: Does the agency agree with this proposal for evaluation of immunogenicity?

FDA Response: We agree with your proposal for evaluation of immunogenicity pending clarification that the radioimmunoassay to be used in the two Phase 3 trials is the same as that used in your original NDA clinical development program.

Additional Comments:

a. Except where noted in our responses to your questions and our additional comments, the overall plan for evaluation of efficacy and safety with the Gen2 device appears adequate. Actual study conduct, including adequate titration of insulins will be a critical factor in determining interpretability of the results.

b. It would be acceptable for patients to remain on their DPP-4 inhibitor therapy during the type 2 diabetes trial. Also, saxagliptin is an acceptable DPP-4 inhibitor for inclusion.

c. Clarify why the conversion dose of glargine for patients who were on insulin detemir will be 60% of the insulin detemir dose, while NPH will be converted in a 1:1 ratio.

d. Increase the baseline HbA1c for inclusion and/or actively enroll patients in the upper range of the HbA1c inclusion criterion to help ensure that the mean baseline HbA1c will not be too low to be able to show a meaningful improvement in HbA1c over the duration of the study.

e. In clinical practice most patients use premeal glucose to determine the prandial insulin dose. Justify your plan for titration based on post-prandial glucose levels for both Afrezza and NovoLog.

f. Your dosing guidelines instruct patients to inject Novolog (b) (4) minutes before a meal, but the Novolog package insert instructs patients to inject immediately before the meal (within 5-10 minutes). Your instructions for Novolog administration should conform to its package insert.

g. Clarify what is the maximum permitted pre-meal and supplemental dose of your inhaled insulin via the Gen2 and MedTone C inhalers. In addition, clarify the maximum daily dose that can be administered with the Gen2 device (currently you state the maximum dose is (b) (4) units but this dose cannot be achieved with increments of the 10-unit and 20-unit Gen2 cartridges).

h. (b) (4)

i. Clarify why you are obtaining Doppler echocardiograms in your trials.

j. We note that in your End of Review meeting package briefing document, you did not address all of the deficiencies listed in the Complete Response letter, including deficiencies related to the device (see response to question 6). All the deficiencies in the Complete Response letter will need to be satisfactorily addressed before your application can be approved. Clarify your plans for addressing the remaining deficiencies.

k. Your original NDA proposed an indication for the use of Afrezza in the treatment of Type 1 and Type 2 diabetes mellitus. Although separate trials are required for approval of use in both these patient populations, FDA will accept the results of a trial performed in T1DM for consideration of initial approval only in patients with T1DM. Data supporting use of Afrezza in T2DM may be submitted as an efficacy supplement to your NDA, if approved.

l. For the type 2 diabetes trial, clarify why you are proposing (b) (4)

Provide a hardcopy or electronic version of any materials (i.e., slides or handouts) to be presented and/or discussed at the meeting.

If you have any questions, call me at (301) 796-0331.

Sincerely,

{See appended electronic signature page}

Rachel Hartford
Regulatory Project Manager
Division of Metabolism and Endocrinology Products
Office of Drug Evaluation II
Center for Drug Evaluation

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

/s/

RACHEL E HARTFORD
04/29/2011

Hartford, Rachel

From: Hartford, Rachel
Sent: Tuesday, April 12, 2011 12:45 PM
To: 'Mayer, Patricia'
Subject: Rescheduled End-of-Review Meeting

Hello Patricia,

The End-of-Review meeting is re-scheduled as follows:

Date: **May 4, 2011**
Time: **8:00 – 9:00 am**
Location: **10903 New Hampshire Avenue**
White Oak Building 22, Conference Room: 1313
Silver Spring, Maryland 20903

Please send revised Foreign Visitor Data Request Forms at least two weeks prior to the meeting.

Regards,

Rachel

Rachel E. Hartford
Regulatory Project Manager
Division of Metabolism and Endocrinology Products
Center for Drug Evaluation and Research
Food and Drug Administration
rachel.hartford@fda.hhs.gov
301-796-0331 (phone)
301-796-9712 (fax)

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

/s/

RACHEL E HARTFORD
04/12/2011

DEPARTMENT OF HEALTH AND HUMAN SERVICES

Food and Drug Administration
Silver Spring MD 20993

NDA 022472

MEETING REQUEST GRANTED

MannKind Corporation
Attention: Patricia R. Mayer, Ph.D.
Vice President Liaison, Worldwide Regulatory Affairs
61 South Paramus Road
Paramus, NJ 07652

Dear Mayer:

Please refer to your New Drug Application (NDA) submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act (FDCA) for Afrezza (insulin human [rDNA origin]) Inhalation Powder and Inhaler.

We also refer to your February 11, 2011, correspondence requesting an End-of-Review Meeting. Based on the statement of purpose, objectives, and proposed agenda, we consider the meeting a type B meeting.

The meeting is scheduled as follows:

Date:	**April 15, 2011**
Time:	**11:00 – 12:00 am**
Location:	**10903 New Hampshire Avenue** **White Oak Building 22, Conference Room: 1313** **Silver Spring, Maryland 20903**

CDER participants: (alphabetic) (tentative)

John Bishai, Ph.D.	Safety Project Manager, Division of Metabolism and Endocrinology Products (DMEP)
Amy Egan, M.D.	Deputy Director (Safety), DMEP
Enid Galliers	Chief Project Management Staff, DMEP
Rachel Hartford	Regulatory Project Manager, DMEP
Hylton Joffe, M.D., M.Sc.	Diabetes Team I Leader, DMEP

Banu Karimi-Shah, M.D.	Medical Officer, Division of Pulmonary, Allergy, and Rheumatology Products (DPARP)
Mary H. Parks, M.D.	Director, DMEP
Todd Sahlroot, Ph.D.	Statistics Team Leader, Division of Biometrics II
Sally Seymour, M.D.	Deputy Division Director (Safety), DPARP
Lisa Yanoff, M.D.	Medical Officer, DMEP

Please e-mail me any updates to your attendees at rachel.hartford@fda.hhs.gov, at least one week prior to the meeting. For each foreign visitor, complete and email me the enclosed Foreign Visitor Data Request Form, at least two weeks prior to the meeting. A foreign visitor is defined as any non-U.S. citizen or dual citizen who does not have a valid U.S. Federal Government Agency issued Security Identification Access Badge. If we do not receive the above requested information in a timely manner, attendees may be denied access.

Please have all attendees bring valid photo identification and allow 15-30 minutes to complete security clearance. Upon arrival at FDA, provide the guards with either of the following numbers to request an escort to the conference room: Rachel Hartford x60331; Lena Staunton x62290.

Submit background information for the meeting (three paper copies **or** one electronic copy to the application and 20 desk copies to me) at least four weeks prior to the meeting. If the materials presented in the information package are inadequate to prepare for the meeting or if we do not receive the package by March 16, 2011, we may cancel or reschedule the meeting.

Submit the 20 desk copies to the following address:

If sending via USPS, please send to:

Rachel Hartford
Food and Drug Administration
Center for Drug Evaluation and Research
White Oak Building 22, Room: 3118
10903 New Hampshire Avenue
Silver Spring, Maryland 20993

If sending via any carrier other than USPS (e.g., UPS, DHL), please send to:

Rachel Hartford
Food and Drug Administration
Center for Drug Evaluation and Research
White Oak Building 22, Room: 3118
10903 New Hampshire Avenue
Silver Spring, Maryland 20903

If you have any questions, call me at (301) 796-0331.

Sincerely,

{See appended electronic signature page}

Rachel Hartford
Regulatory Health Project Manager
Division of Metabolism and Endocrinology Products
Office of Drug Evaluation II
Center for Drug Evaluation and Research

ENCLOSURE: Foreign Visitor Data Request Form

FOREIGN VISITOR DATA REQUEST FORM

VISITORS FULL NAME (First, Middle, Last)	
GENDER	
COUNTRY OF ORIGIN/CITZENSHIP	
DATE OF BIRTH **(MM/DD/YYYY)**	
PLACE OF BIRTH **(city and country)**	
PASSPORT NUMBER COUNTRY THAT ISSUED PASSPORT ISSUANCE DATE: EXPIRATION DATE:	
VISITOR ORGANIZATION/EMPLOYER	
MEETING START DATE AND TIME	April 15, 2011 – 11:00am
MEETING ENDING DATE AND TIME	April 15, 2011 – 12:00am
PURPOSE OF MEETING	End-of-Review Meeting
BUILDING(S) & ROOM NUMBER(S) TO BE VISITED	WO 22, RM 1313
WILL CRITICAL INFRASTRUCTURE AND/OR FDA LABORATORIES BE VISITED?	NO
HOSTING OFFICIAL **(**name, title, office/bldg, room number, and phone number)	Rachel Hartford Regulatory Project Manager WO 22, RM 3118 X60331
ESCORT INFORMATION (If different from Hosting Official)	

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

/s/

RACHEL E HARTFORD
03/03/2011

DEPARTMENT OF HEALTH & HUMAN SERVICES

Public Health Service

Food and Drug Administration
Silver Spring, MD 20993

NDA 022472

PROPRIETARY NAME REQUEST
CONDITIONALLY ACCEPTABLE

MannKind Corporation
61 South Paramus Road
Paramus, NJ 07652

Attention: Patricia R. Mayer, Ph.D.
Vice President Liaison, Worldwide Regulatory Affairs

Dear Dr. Mayer:

Please refer to your New Drug Application (NDA) resubmission dated June 29, 2010, received June 29, 2010, submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act for Insulin Monomer Human [rDNA origin] Inhalation Powder 4 Units and 8 Units Cartridges.

We also refer to your September 23, 2010, correspondence, received September 24, 2010, requesting review of your proposed proprietary name, Afrezza. We have completed our review of the proposed proprietary name, Afrezza and have concluded that it is acceptable.

The proposed proprietary name, Afrezza, will be re-reviewed 90 days prior to the approval of the NDA. If we find the name unacceptable following the re-review, we will notify you.

If **any** of the proposed product characteristics as stated in your September 23, 2010, submission are altered prior to approval of the marketing application, the proprietary name should be resubmitted for review.

If you have any questions regarding the contents of this letter or any other aspects of the proprietary name review process, contact Margarita Tossa, Safety Regulatory Project Manager in the Office of Surveillance and Epidemiology, at margarita.tossa@fda.hhs.gov or at (301) 796-4053. For any other information regarding this application contact the Office of New Drugs (OND) Regulatory Project Manager Rachel Hartford at (301) 796-0331.

Sincerely,

{See appended electronic signature page}

Denise P. Toyer, Pharm.D.
Deputy Director
Division of Medication Error Prevention and Analysis
Office of Surveillance and Epidemiology
Center for Drug Evaluation and Research

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

/s/

DENISE P TOYER
12/13/2010

Hartford, Rachel

From: Hartford, Rachel
Sent: Monday, December 06, 2010 5:30 PM
To: 'Mayer, Patricia'
Subject: CMC Information Requests

Hello Patricia,

We have the following CMC Information Requests:

1. Continue to implement the following limits as part of the drug product specification for lot release and stability testing:

A-21 desamido insulin:	**NMT (b) (4) %**
Insulin Adducts group:	**NMT (b) (4) %**
Individual Unspecified Impurity:	**NMT (b) (4) %**
Total Others:	**NMT (b) (4) %**

2. In addition, we have been unable to contact the holder of DMF (b) (4) by telephone to request clarifications which are needed immediately. Please ask the DMF (b) (4) holder's representative to contact Dr. Alan Schroeder at 301-796-1749.

Thank you,

Rachel

Rachel E. Hartford
Regulatory Project Manager
Division of Metabolism and Endocrinology Products
Center for Drug Evaluation and Research
Food and Drug Administration
rachel.hartford@fda.hhs.gov
301-796-0331 (phone)
301-796-9712 (fax)

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

/s/

RACHEL E HARTFORD
12/07/2010

Hartford, Rachel

From: Hartford, Rachel
Sent: Thursday, October 28, 2010 6:17 PM
To: 'Mayer, Patricia'
Subject: Device Information Request

Hello Patricia,

Please respond to the Device related Information Requests below. After you have a chance to review, please provide an estimated response timeframe.

Thank you,

Rachel

1. It is unclear what Gen2 System version was used in all tests. Clarify whether version A, B or C was used in all test results presented in 3.2.P.2.4, 3.2.P.5.6 and 3.2.P.8 of your submission. If test results are from versions other than C, the finished product, provide a rationale to why the results are applicable to version C in each case.

2. The Gen2C Inhaler mouthpiece now has [redacted] (b) (4) and a new mouthpiece cover. Biocompatibility test reports could not be found for these components. Provide biocompatibility test reports in accordance to FDA General Program Memorandum #G95-1 (Required Biocompatibility Training and Toxicology Profiles for Evaluation of Medical Devices), which recommends the use of ISO 10993-1 (Biological evaluation of medical devices: Evaluation and Testing).

3. The area under pressure time curve (AUC) and peak pressure within the first two seconds of inhalation (PIP) criteria presented in 3.2.P.2.4.3.2 are unclear. On page 23 of this section, you stated that both AUC (≥ 1.2 kPa·s) and PIP (≥ 2.0 kPa) thresholds must be satisfied to achieve consistent *in vitro* particle performance; however, according to Table 4, there appears to be at least two test profiles where AUC or PIP thresholds were not met, but the volumetric median geometric particle diameter criterion was met. Explain this discrepancy.

4. In 3.2.P.2.4.3.1, Flow Mechanics for the Container Closure System, you theorized that (b) (4) [redacted] However, for Gen2 System complaints listed in Table 6 (3.2.P.2.4.4), a complaint of "A lot of residue build-up" was "evaluated/reviewed" to be "Powder confirmed in inhaler housing not mouthpiece. Likely caused by patient exhaling through the device." Explain the discrepancy between your theory and review of complaints from actual use, and provide scientific evidence that inadvertent exhalation through the Gen2 System will not affect the safety and effectiveness of your device.

5. The aerodynamic particle size distribution (APSD) and emitted dose criteria for the Gen2 System are less than that of equivalent doses with the MedTone inhaler. While you provided a justification in 3.2.P.5.6, your discussion did not clearly compare the equivalence of particle performance emitted from the two systems. Provide a side-by-side tabular comparison of each test criteria for the Gen2 System and MedTone inhaler with rationale for any differences.

   In addition, you reported that APSD determination with the Next Generation Impactor (NGI) for the Gen2 System is equivalent with that of Andersen Cascade Impactor (ACI) for the MedTone inhaler. However, this needs further explanation and/or testing. According to the logarithmic graphs

presented in Figures 5 and 6 of 3.2.P.5.6, comparing APSD for the Gen2 System with NGI and ACI, it appears NGI consistently exhibited greater cumulative distribution of insulin over the entire range of aerodynamic diameter detected than with ACI. However, in APSD comparison of Gen2 System with NGI to MedTone inhaler with ACI, presented in Figures 26 and 27 of 3.2.P.2.4, it appears that Gen2 System tested with NGI delivered less insulin units than that of the MedTone inhaler tested with ACI, especially in the respirable range of particle diameter less than (b) (4) Therefore, it appears that there may be a greater disparity between the two inhalers in the cumulative insulin dose delivered in the respirable size range. Provide a comparative APSD test report that directly compares the Gen2 System and MedTone inhaler performance using the same test method. Alternatively, provide further scientifically valid explanation on why your APSD results for the Gen2 System tested with NGI are equivalent to that of the MedTone inhaler tested with ACI.

6. For the Varied Flow Study results presented in 3.2.P.2.4.5.1, it appears that for (b) (4) kPa or (b) (4) LPM condition, the discharge time would be (b) (4) seconds. The physiological relevance of these parameters is unclear. Provide the discharge time associated with each flow/pressure tested and their physiological relevance.

7. In the Orientation Study provided in 3.2.P.2.4.5.2, it appears condition 6 (pitch 0°, Cant 180° or upside down orientation) did not meet your APSD criterion. Explain how this risk is mitigated.

8. In the inhaler stability discussion provided in 3.2.P.8.1, you stated that real time testing at 25 and 5°C and accelerated testing at 50°C were being conducted. Address the following issues regarding these tests:

   a. Clarify the storage condition range of the Gen2 System. Note that the performance of your device should be tested after storage at the two extreme conditions of this range.

   b. It is unclear how you qualified 50°C as the accelerated testing condition without published scientific evidence that your material decomposes with similar mechanisms at elevated and standard temperatures or validation of your accelerated stability data with real-time aging stability data. Accelerated aging process assumes identical decomposition mechanisms at standard and elevated temperatures. We believe that accelerated aging can only be used for product stability testing, if there is published scientific evidence that your material decomposes with similar mechanisms at elevated and standard temperatures or the accelerated stability data has been validated with real-time aging stability data. Provide real-time stability data or accelerated aging stability data with scientific literature or validation with real-time aging stability data that supports the use of accelerated aging for your device for the claimed shelf-life of (b) (4).

   c. Provide the test report for each of the design verification tests conducted in 3.2.P.8.1. Note the test report should include the test objective, setup, equipment under test, methods, pass/fail criteria with rationale, results, and conclusion. Also, indicate whether test numbers 1 to 6 were conducted with the cartridge.

   d. In 3.2.P.5.6.6, you stated that the flow rate used in emitted dose testing was modified to (b) (4) L/min in TM5557 for the Gen2 System from (b) (4) L/min in TM5514 for the MedTone inhaler. However, for the life cycle testing presented in 3.2.P.8.3, you stated that "All cartridge discharges occurred at (b) (4) LPM." Clarify this discrepancy.

   e. Provide a complete mouthpiece retention test report, as noted in part c above, after storage in extreme storage conditions and simulated use. Alternatively, provide a scientifically valid rationale why such test is not necessary to demonstrate (b) (4)

[redacted] (b) (4) over claimed shelf-life and use.

f. Provide the APSD minimum, maximum and standard deviation values for the mouthpiece buildup values presented in Table 28.

Human Factors Related Issues

9. While you have provided information on risk analysis and identified simulated and high risk use scenarios, a clear description of user tasks, their relative priority, a rationale for why they were selected for the study, and how they relate to the use related risk analysis were not provided. We believe that the tasks selected are those that are of highest priority and have potential results of inadequate performance based on the use related risk analysis. To evaluate the method you used, please provide:
   i. description of user tasks,
   ii. relative priority of user tasks,
   iii. rationale for why you selected those tasks, and
   iv. how these tasks are directly related to your risk analysis.

10. Address the following issues regarding the Summative Usability Test of AFREZZA Insulin Inhalation System Report, which discusses use errors:

    a. You included a risk table for the discussions of two use errors: "Delivered wrong insulin dose (used wrong type/number of cartridges)" and "Mistook used cartridges as new, and vice versa." However, the remaining 11 errors you discussed were not accompanied by a risk table. Provide a risk table for the remaining errors discussed. In these tables, clearly state the related tasks, and provide an explanation of risk index and risk priority numbers that were selected. Also, for each error type, include the root cause analysis, clinical impact discussion and mitigation strategy.

    b. The results from this study indicate that there are a number of use errors committed. In some instances, up to 12 participants committed the same error repeatedly. A pattern of similar problems indicate design flaws, which can include labeling, or training inadequacies. A summative study should provide the validation for the final product by demonstrating that it has fully met the needs of the intended users, and is safe and effective in the hands of intended users. Provide justification as to why all of the use errors detected in your study should be considered acceptable. Alternatively, submit test results of a usability study that demonstrates acceptable user performance.

    c. On pages 34 – 35 of 3.2.P.2, Appendix I on Human Factors Study Report, you proposed several mitigations based on user reported errors - added labeling on cartridges to identify cartridge strength, future updates to instructions for use (IFU) to emphasize the instruction for Mouthpiece Cover removal and revise front cover image to illustrate proper inhaler orientation during use. Address the following concerns regarding this report:

       i. It is unclear how the proposed mitigations will address all of the use errors reported in your study. Provide a discussion on how the proposed mitigation strategies address all use errors.

       ii. A validation study is needed to demonstrate the effectiveness of the proposed mitigation strategies to address use errors. Your study report did not include this information. Provide a study report that validates the effectiveness of your mitigation strategies or provide a valid scientific justification to why such study is not needed to validate the use errors are mitigated with your proposed steps.

Appears this way on original

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

/s/

RACHEL E HARTFORD
12/01/2010

Hartford, Rachel

From: Hartford, Rachel
Sent: Monday, November 08, 2010 2:54 PM
To: 'Mayer, Patricia'
Subject: CMC Information Request

Hello Patricia,

We have two additional CMC information requests:

1.) Provide additional data regarding the levels of the unidentified insulin-related degradant [redacted] (b) (4) as measured in lots of the Gen2 TI drug product that have been tested, to support your assertion that the [redacted] (b) (4) species is [redacted] (b) (4) % of the adduct peak area. If this degradant has been detected in lots of Gen1 drug product (e.g. under accelerated conditions or at room termperature), provide those data.

2.) Provide updated stability data, including the most recent data collected at 5 degrees, for the 6 registration lots of the drug product (Gen2). Include levels of the [redacted] (b) (4) impurity where measured. You have justified the observed increases in the FDKP adducts group impurities as being a consequence of [redacted] (b) (4)

Thanks,

Rachel

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

/s/

RACHEL E HARTFORD
11/09/2010

Hartford, Rachel

From: Hartford, Rachel
Sent: Tuesday, November 02, 2010 9:00 AM
To: 'Mayer, Patricia'
Subject: CMC IR

Hello Patricia,

Please respond to the following from Chemistry, Manufacturing, and Controls:

1. Figure 11 of 3.2.P.2.4 depicts the resistance of Gen2 inhaler at different flow rates. Provide data and graphs to corroborate your claim that resistance in the Gen2 system (inhaler plus cartridge) is linear (constant) at flow rates between about (b) (4) LPM and (b) (4) LPM.

2. Provide data to corroborate your claim that the design of Gen2 inhaler can effectively (b) (4)

3. Provide data to demonstrate that under the worst case in-use scenario, the powder build-up in the mouthpiece will not adversely impact the emitted dose and aerodynamic particle size distribution of subsequent drug administrations through the proposed 15 days of in-use period without clean-up.

4. Provide appropriate statistical analyses for data from which figures 26-29 were generated, to demonstrate that the emitted dose and APSD profiles of Gen2 and Medtone are statistically equivalent.

5. All your environmental study (3.2.P.2.4.5.3) and suitability for use (3.2.P.2.4.6.2), including the shipping impact study, were conducted on 20 U cartridges only. Provide similar data collected from 10 U cartridges, which might be more adversely affected percentage wise, or provide justifications for lack of such data.

6. Include lot numbers of inhalers in all tables in 3.2.P.5.4 (Batch analyses).

7. In figure 5 and 6 of 3.2.P.5.6.7 (Justification of specification (Technosphere Insulin)), you provide comparative APSD profiles from 5 Gen 2 development batches, measured by both Anderson impactor and Next Generation impactors. Please provide comparative graphic APSD profiles generated by the two impactors in terms of micrograms, i.e., the y axis is in micrograms (or IU) and the x axis is in microns. The graphs should display both individual measurements and fitted curve of the mean. Provide appropriate statistical analyses to demonstrate whether the results obtained from the two impactors are statistically equivalent, or whether system correction factors are needed to correlate testing results of Gen2 and Medtone inhalers measured by two methods: i.e., the NGI and ACI. Provide tabulated raw data (all stages and groupings) from which figure 5 and 6 were generated.

8. Conduct APSD testing on both Gen2 and Medtone inhalers, each with appropriate and comparable sample sizes, using NGI, and provide statistical analyses to demonstrate that whether the results obtained from the two type of inhalers are statistically equivalent.

Thank you,

Rachel

Rachel E. Hartford
Regulatory Project Manager
Division of Metabolism and Endocrinology Products
Center for Drug Evaluation and Research
Food and Drug Administration
rachel.hartford@fda.hhs.gov
301-796-0331 (phone)
301-796-9712 (fax)

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

/s/

RACHEL E HARTFORD
11/02/2010

DEPARTMENT OF HEALTH & HUMAN SERVICES

Public Health Service

Food and Drug Administration
Silver Spring, MD 20993

NDA 022472

PROPRIETARY NAME REQUEST WITHDRAWN

MannKind Corporation
61 South Paramus Rd.
Paramus, NJ 07652

Attention: Patricia Mayer, PhD
Vice President, Worldwide Regulatory Affairs

Dear Dr. Mayer:

Please refer to your New Drug Application resubmission (NDA) dated June 29, 2010, received June 29, 2010, submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act for Insulin Monomer Human [rDNA origin] Inhalation Powder, 4 Units and 8 Units single use cartridges.

We acknowledge receipt of your August 27, 2010, correspondence, on August 27, 2010, notifying us that you are withdrawing your request for a review of the proposed proprietary name, Afrezza (b) (4) Inhaler. This proposed proprietary name request is considered withdrawn as of August 27, 2010.

If you have any questions regarding the contents of this letter or any other aspects of the proprietary name review process, contact Margarita Tossa, Regulatory Project Manager in the Office of Surveillance and Epidemiology, at (301) 796-4053. For any other information regarding this application, contact the Office of New Drugs (OND) Regulatory Project Manager Rachel Hartford at (301) 796-0331.

Sincerely,

{See appended electronic signature page}

Carol Holquist, RPh
Director
Division of Medication Error Prevention and Analysis
Office of Surveillance and Epidemiology
Center for Drug Evaluation and Research

Application Type/Number	Submission Type/Number	Submitter Name	Product Name
NDA-22472	ORIG-1	MANNKIND CORP	Afrezza (insulin) inhalation powder

---

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

/s/

CAROL A HOLQUIST
09/14/2010

DEPARTMENT OF HEALTH AND HUMAN SERVICES
Public Health Service
Food and Drug Administration
Center for Drug Evaluation and Research

Memorandum

Date: September 10, 2010

From: Raymond Chiang, Regulatory Project Manager

Subject: CMC Information request—NDA 022472

From: Chiang, Raymond
Sent: Friday, September 10, 2010 11:09 AM
To: 'pmayer@mannkindcorp.com'
Cc: Hartford, Rachel
Subject: RE: CMC Information Request NDA 022472
Importance: High

Hi Patricia,

As per our phone conversation, I am emailing you another CMC information request (in black font below) and request that you respond ASAP.

Please contact the DMF (b) (4) holder as soon as possible to ask for an updated LOA including the date of submission for the referenced information? T his was part of our original July 13, 2010 request. This is a large DMF and we need the date of submission to be able to locate the information.

Please confirm receipt of this request. Please send your response to me and Rachel and submit it as an official amendment to the NDA.

thanks!
ray

From: Mayer, Patricia [mailto:pmayer@mannkindcorp.com]
Sent: Wednesday, August 04, 2010 4:23 PM
To: Hartford, Rachel
Subject: RE: CMC Information Request

Hello Rachel,
Attached please find the updated LOA for DMF (b) (4) that was provided to us. Although we have repeatedly asked the company (b) (4) to include section and/or page numbers as requested, they declined our request. The company claims that all of the (b) (4) are on one page in the DMF and that therefore, a page number is not necessary. I am sorry that this may create an inconvenience, but, at this point, there is

really not much we can do. Please let me know if you can think of anything that would allow us to facilitate the review.
Best regards,
Patricia

P.S.: we will now submit all the LOAs requested officially to the NDA.

Patricia R. Mayer, PhD
Vice President
Worldwide Regulatory Affairs - Liaison
Office: 201-983-5228
Cell: (b) (6)

From: Hartford, Rachel [mailto:Rachel.Hartford@fda.hhs.gov]
Sent: Wednesday, July 21, 2010 1:51 PM
To: Mayer, Patricia
Subject: RE: CMC Information Request

Thank you so much.

From: Mayer, Patricia [mailto:pmayer@mannkindcorp.com]
Sent: Wednesday, July 21, 2010 10:45 AM
To: Hartford, Rachel
Subject: RE: CMC Information Request

Hello Rachel,
In response to your request below, the updated LOAs for DMF (b) (4) are attached. We are still waiting for the LOA for DMF (b) (4)
We will submit the LOAs, once we have all of them, to the NDA promptly.
Best regards,
Patricia

Patricia R. Mayer, PhD
Vice President
Worldwide Regulatory Affairs - Liaison
Office: 201-983-5228
Cell: (b) (6)

From: Hartford, Rachel [mailto:Rachel.Hartford@fda.hhs.gov]
Sent: Tuesday, July 13, 2010 10:43 AM
To: Mayer, Patricia
Subject: CMC Information Request

Hello Patricia,

Please request updated letters of authorization (LOAs) from the following DMF holders, to include dates of submissions and page numbers for information relevant to your NDA for each DMF: DMF (b) (4), DMF (b) (4). These updated LOAs should be provided to the respective DMFs in the normal manner by the DMF holders, with copies sent to you to submit to NDA 022472.

Thank you,

Rachel

Rachel E. Hartford
Regulatory Project Manager

Division of Metabolism and Endocrinology Products
Center for Drug Evaluation and Research
Food and Drug Administration
rachel.hartford@fda.hhs.gov
301-796-0331 (phone)
301-796-9712 (fax)

Application Type/Number	Submission Type/Number	Submitter Name	Product Name
NDA-22472	ORIG-1	MANNKIND CORP	Afrezza (insulin) inhalation powder

---

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

/s/

RAYMOND S CHIANG
09/10/2010

DEPARTMENT OF HEALTH AND HUMAN SERVICES

Food and Drug Administration
Silver Spring MD 20993

NDA 022472 **ACKNOWLEDGE CLASS 2 RESPONSE**

MannKind Corporation
Attention: Patricia R. Mayer, Ph.D.
Vice President Liaison, Worldwide Regulatory Affairs
61 South Paramus Road
Paramus, NJ 07652

Dear Dr. Mayer:

We acknowledge receipt on June 29, 2010, of your resubmission to your new drug application for Afrezza (insulin human [rDNA origin]) Inhalation Powder and Inhaler.

We consider this a complete, class 2 response to our March 12, 2010, action letter. Therefore, the user fee goal date is December 29, 2010.

If you have any questions, call me at (301) 796-0331.

Sincerely,

{See appended electronic signature page}

Rachel Hartford
Regulatory Project Manager
Division of Metabolism and Endocrinology Products
Office of Drug Evaluation II
Center for Drug Evaluation and Research

Application Type/Number	Submission Type/Number	Submitter Name	Product Name
NDA-22472	ORIG-1	MANNKIND CORP	Afrezza (insulin) inhalation powder

---

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

/s/

RACHEL E HARTFORD
07/19/2010

Hartford, Rachel

From: Hartford, Rachel
Sent: Monday, July 19, 2010 12:31 PM
To: 'Mayer, Patricia'
Subject: CMC Information Request

Hello Patricia,

Regarding the submission dated 28-JUN-2010, clarify your statement in Form FDA 356h "Awaiting report from site inspection" regarding the testing facility [redacted] (b) (4) at the address [redacted] (b) (4) and indicate the tests that are performed at this facility for this NDA. Provide the date of FDA's most recent inspection of this facility and the names of the inspectors. If the GMP inspection was conducted by a non-FDA entity, provide detailed information on this inspection.

Thank you,

Rachel

Rachel E. Hartford
Regulatory Project Manager
Division of Metabolism and Endocrinology Products
Center for Drug Evaluation and Research
Food and Drug Administration
rachel.hartford@fda.hhs.gov
301-796-0331 (phone)
301-796-9712 (fax)

Application Type/Number	Submission Type/Number	Submitter Name	Product Name
NDA-22472	ORIG-1	MANNKIND CORP	Afrezza (insulin) inhalation powder

---

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

/s/

RACHEL E HARTFORD
07/19/2010

Hartford, Rachel

From: Hartford, Rachel
Sent: Tuesday, July 13, 2010 10:43 AM
To: 'Mayer, Patricia'
Subject: CMC Information Request

Hello Patricia,

Please request updated letters of authorization (LOAs) from the following DMF holders, to include dates of submissions and page numbers for information relevant to your NDA for each DMF: DMF (b) (4) DMF (b) (4). These updated LOAs should be provided to the respective DMFs in the normal manner by the DMF holders, with copies sent to you to submit to NDA 022472.

Thank you,

Rachel

Rachel E. Hartford
Regulatory Project Manager
Division of Metabolism and Endocrinology Products
Center for Drug Evaluation and Research
Food and Drug Administration
rachel.hartford@fda.hhs.gov
301-796-0331 (phone)
301-796-9712 (fax)

Application Type/Number	Submission Type/Number	Submitter Name	Product Name
NDA-22472	ORIG-1	MANNKIND CORP	Afrezza (insulin) inhalation powder

---

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

/s/

RACHEL E HARTFORD
07/13/2010

DEPARTMENT OF HEALTH & HUMAN SERVICES

Public Health Service

Food and Drug Administration
Rockville, MD 20857

NDA 022472 **MEETING PRELIMINARY COMMENTS**

Mannkind Corporation
Attention: Patricia R. Mayer, Ph.D.
Vice President Liaison, Worldwide Regulatory Affairs
61 South Paramus Road
Paramus, NJ 07652

Dear Dr. Mayer:

Please refer to your New Drug Application (NDA) submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act (FDCA) for Afrezza (insulin human [rDNA origin] Inhalation Powder and Inhaler.

We also refer to your March 26, 2010, correspondence, requesting an End-of-Review meeting.

This material consists of our preliminary responses to your questions and any additional comments in preparation for the discussion at the meeting scheduled for June 9, 2010, 4:00 – 5:00pm, White Oak Building 22. We are sharing this material to promote a collaborative and successful discussion at the meeting. The meeting minutes will reflect agreements, important issues, and any action items discussed during the meeting and may not be identical to these preliminary comments following substantive discussion at the meeting. However, if these answers and comments are clear to you and you determine that further discussion is not required, you have the option of cancelling the meeting (contact the regulatory project manager (RPM)). If you choose to cancel the meeting, this document will represent the official record of the meeting. If you determine that discussion is needed for only some of the original questions, you have the option of reducing the agenda and/or changing the format of the meeting (e.g., from face to face to teleconference). It is important to remember that some meetings, particularly milestone meetings, can be valuable even if the premeeting communications are considered sufficient to answer the questions. Note that if there are any major changes to your development plan, the purpose of the meeting, or the questions based on our preliminary responses, we may not be prepared to discuss or reach agreement on such changes at the meeting although we will try to do so if possible. If any modifications to the development plan or additional questions for which you would like CDER feedback arise before the meeting, contact the RPM to discuss the possibility of including these items for discussion at the meeting

REGULATORY

MannKind will prepare a resubmission as a response to the Complete Response Letter, which will include information that addresses all deficiencies in:

- Clinical
  - o New clinical data available from study MKC-TI-117
  - o Additional analyses of clinical data previously submitted in NDA 22-472
- Clinical Pharmacology
  - o New data to support bioequivalence (study MKC-TI-142) of the new Gen2 Inhalation System with the MedTone Inhalation System in accordance with prior FDA guidance
- CMC and Device
  - o New data from clinical use of the Gen2 inhaler generated according to previous FDA advice (study MKC-TI-158 and MKC-TI-159)
  - o A Usability Validation Study on the Gen2 Inhalation System as part of the overall Human Factors Evaluation
  - o CMC data to support the Gen2 inhalation system
- Updated Labeling
- Updated REMS
- Safety update
- Updated Pediatric Plan

Question A: Does the Agency agree that the proposed contents for resubmission address all deficiencies contained in the Complete Response Letter?

FDA Response: No. Please see our responses to your other questions. The deficiencies were directed towards the MedTone product submitted in the NDA, not to the Gen2 inhaler device. As explained below, additional controlled, clinical data will be needed to support the Gen2 inhaler device, which differs substantially in design from the MedTone device.

It is our assumption that the resubmission is a Class 2 resubmission with a PDUFA goal review time of 6 months.

Question B: Does the Agency concur?

FDA Response: Not necessarily. It is possible that the Gen2 inhaler product might need to be submitted as a separate NDA and that a Complete Response submission to the MedTone NDA may not be a possible regulatory pathway for the Gen2 device.

CLINICAL

In the Complete Response Letter, the Agency raised a question regarding the clinical utility of Afrezza and suggested that MannKind document how the currently available clinical data support the clinical utility of Afrezza in the marketplace. MannKind intends to provide new clinical data and new analyses of previously submitted data.

Question C: Does the Agency agree that MannKind's presented approach of new data from MKC-TI-117 and new analyses of data presented in the original NDA is adequate and complete for a successful resubmission to address the clinical utility of AFREZZA with the Gen2 inhaler?

FDA Response: New analyses of data presented in the original NDA are not adequate to address the clinical utility of Afrezza, because these data were already taken into consideration during the review of the original NDA. New data from study MKC-TI-117 may be adequate to support the MedTone device but this will be a review issue. Given your intention to proceed with the Gen2 inhaler, there will be further clinical requirements for resubmission. For example, clinical evidence of pulmonary safety and evidence of adequate glycemic effect (based on HbA1c) will be required with the new device. The extent of clinical data needed can be discussed at the End-of-Review meeting.

BIOEQUIVALENCE

MannKind completed a new bioequivalence (BE) study, MKC-TI-142, with the following specifics: 1) the new study compared the Gen2 and MedTone® Model C devices; 2) the protocol followed the Agency's analysis recommendations (Advice Letter, dated 13Nov2009); and, 3) utilized the ECLIA method which completely incorporated the DSI inspector's recommendations. In addition, the serum samples are being analyzed by RIA.

Question D: Does the Agency reaffirm the proposed BE approach to demonstrate that the MedTone Model C inhaler and the Gen2 inhaler are bioequivalent? And, if bioequivalence is demonstrated, does the Agency agree that the clinical data generated with MedTone Model C supplemented with the Gen2 Inhalation System data would serve as the basis for approving AFREZZA with the Gen2 inhaler?

FDA Response: The proposed BE approach is acceptable. However, the BE assessment should be based on the pharmacokinetic parameters generated from a reliable bioanalytical study. Regarding the basis for approving Gen2 inhaler, in addition to the BE study see the responses to Questions C and F.

In the Complete Response Letter, the Agency provided a comprehensive list of tables for the safety update. We would like to discuss this list, present and agree on the scope of the safety update.

Question E: Is the Agency in agreement with MannKind's proposal for the Safety Update?

FDA Response: Your proposal for the safety update will need to be updated to reflect the additional clinical data that will be needed for the Gen2 device.

CMC/DEVICE

The Agency had a number of questions/comments regarding the originally planned commercial device MedTone Model D and also the recommendation that a Human Factors evaluation should be performed following the FDA Guidance on Medical Device Use- Safety and Human Factors.

MannKind designed a Usability Validation study based upon the above referenced guidance and our evaluation indicates that the CMC documentation for Gen2 will address all the comments and recommendation in your Complete Response Letter.

In the resubmission, MannKind will include a revised Module 3, including complete CMC documentation for the Gen2 Inhalation System, which incorporates a Human Factors evaluation. The protocol for the summative usability test was submitted to IND 61,729 as SN 0351, 05Feb2010.

Question F: Based on the information provided in the Briefing Document does the Agency agree that this information will sufficiently address the design and use of the new Gen2 Inhalation System?

FDA Response: The CMC information provided in the briefing package is not complete in order for us to evaluate your proposal. We remind you to provide in the NDA the complete information on the drug product system using the Gen2 inhaler, including the sections Description and Composition, Pharmaceutical development, Manufacture, Control of Drug Product, Container Closure System (including Letters Of Authorizations to Drug Master Files), Stability, etc.

The following comments are relevant to your Gen2 device proposal:

Regarding the information provided in your IND 061729 amendment dated 28-AUG-2009:

1. Submit complete stability data for the Gen2 inhaler as recommended for new drug products in the International Conference on Harmonisation (ICH) Q1A(R2) Stability Testing of New Drug Substances and Products (http://www.fda.gov/downloads/RegulatoryInformation/Guidances/ucm128204.pdf) and Q1E Evaluation of Stability Data (http://www.fda.gov/downloads/RegulatoryInformation/Guidances/ucm128122.pdf) guidelines, including 12 months of long-term data and 6 months accelerated data. Provide data for a minimum of 3 batches for each dosage strength and formulation to support the proposed expiration dating in this product, which contains new components and materials as compared to the MedTone inhaler. Bracketing and matrixing designs may be used for stability studies where appropriately justified, as per ICH Q1D Bracketing and Matrixing Designs for Stability Testing of New Drug Substances and Products (http://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/ucm073379.pdf).

2) As you have proposed, provide stability data to support the proposed in-use period of the device. Note that these data should be sufficient for statistical evaluation of the drug product stability for periods that exceed the recommended use period (by a factor of 2) and should include data collected under accelerated conditions as appropriate.

3.) Provide comparative in vitro performance data comparing the MedTone inhaler with the Gen2 inhaler. This includes aerodynamic particle size distribution (APSD) as well as

delivered dose uniformity (DDU). The data should be from sufficient samples as to be fully representative of performances of the two devices (including the to-be-marketed devices).

4.) Provide full drug product CMC data for the Gen2 inhaler, including but not limited to: drug product performance data; CMC information for the container closure system; extractables and leachables data for the inhaler device and for the cartridge; and letters of authorization to all drug master files for the device, its components, and its materials of construction.

5.) Provide a tabular point-by-point comparison listing all differences in the proposed marketed presentation of the Gen2 inhaler as compared to the MedTone inhaler, including all device and cartridge components, the Technosphere insulin drug product, and the insulin drug substance used. Please note that changes you have proposed to the Gen2 inhaler product in IND 061729 have not been fully addressed in the briefing information package. These changes will affect the amount of supporting CMC information required.

In addition:
6) In the 12-JAN-2010 amendment to IND 061729, you proposed (b) (4) [redacted] **described in the briefing information package you provided on 10-MAY-2010 for NDA 022472.** (b) (4) [redacted] **. Be advised that significant changes to the composition, manufacturing, in-process controls, and specifications for the Technosphere® particles and the Technosphere Insulin® bulk powder, relative to the drug product information submitted in NDA 022472, will require additional supporting CMC data, for example stability studies (see ICH Q5C Quality of Biotechnological Products: Stability Testing of Biotechnological/Biological Products (http://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/ucm073466.pdf), ICH Q5E Comparability of Biotechnological/Biological Products Subject to Changes in Their Manufacturing Process (http://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/ucm073476.pdf), and Q1A(R2)), and may require additional nonclinical and/or clinical studies.**

7.) In the 27-JAN-2010 amendment to IND 061729, you proposed to add a new insulin source to the IND, referencing DMF 16482. To qualify the new supplier of insulin drug substance for use in the same drug product, you will be required to demonstrate similarity between the drug substances from the different sources and the resulting drug products. An assessment of similarity between two protein products (i.e. drug substance and drug product) depends upon their full characterization, comparative physicochemical and biological studies, and preclinical studies (which may include bridging toxicology studies), Pharmacokinetic/Pharmacodynamic, and/or clinical data (which may include immunogenicity studies), as appropriate. This assessment also includes assessment of product-related substances and impurities, as well as process-related impurities (see ICH Q6B Specifications: Test Procedures and Acceptance Criteria for Biotechnological/Biological Products

(http://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/ucm073488.pdf). The USP insulin reference standard should be used as the reference standard in the analyses, as appropriate. The use of a different host cell and/or expression construct for each insulin drug substance as well as different manufacturing processes may result in protein impurity differences, which may have clinical consequences with regards to immunogenicity, particularly since insulin is a drug for chronic administration. We note that the holder of DMF 16482 is MannKind Corporation. Therefore, submit the assessment of similarity to your IND 061729 and future NDA submissions.

Comments from the Center for Devices and Radiological Health (CDRH) regarding the proposed Human Factors study plan and device verification and validation are as follows:

1. **We note that you have conducted a Human Factors study with 15 users to date and provided a brief descriptive summary of the results in section 11.7. However, without fully understanding the scope of the test plan and results, or agreement on the proposed test plan, we cannot comment on the adequacy of the study conducted to date.**

   While you have provided a Final Test Plan for Summative Usability Test of Gen2 Delivery System, additional Human Factors information is necessary to evaluate the safety and effectiveness of the device in the hands of representative users. Specifically, the submission does not indicate how you have systematically evaluated use-related risks and how you propose to validate user-performance on the highest-priority task pertinent to your device. To complete our review, we will need this information to assess the safety and effectiveness of your device in the hands of representative users. Address the following issues:

   a. **Submit a detailed description of the intended user population, use environment, user interfaces, and anticipated user interaction with the proposed device in the test plan.**

   b. **Submit a revised test plan that includes an evaluation of use-related hazards and relative risks associated with the use of the device that has been conducted as part of your Human Factors study. Provide this evaluation in the context of overall risk management of the device and mitigation strategies intended to reduce the risks associated with your device.**

   c. **You stated that Gen2 is a prescription device intended for use with or without prior instructions. For example, some users may receive training by a diabetes nurse educator and/or a physician, while others may receive no training. It does not appear that all representative users are captured in your study plan. You have only included "untrained" individuals as a "worst case' scenario in your proposed study plan. Although this kind of information can be useful early in the process of product development, we expect your study of the final device to include users with varying levels of training, unless you specify a training program that all users will receive. Your Human Factors study is expected to evaluate at least 15 typical users from each representative user group.**

We acknowledge that realistic time periods for "training decay" are difficult to build into a testing approach. However, a period of time is expected to elapse between training and testing. Incorporate a likely time interval into your study and justify the length of the interval. Also, provide information regarding training regime that will be provided when the device is on the market.

d. **The relative priority of the tasks you selected for testing is unclear. We expect the tasks selected to be those tasks that are the most difficult for users to perform. You stated in the test plan that participants will perform all tasks supported by the delivery system and no tasks would be excluded from the usability study. Based on this approach, you concluded that there was no need to rank the tasks based on their risks-related priority. However, the purpose of prioritizing the tasks is three-fold: (1) to develop conditions/use scenarios for which inadequate performance would occur, (2) to evaluate user performance on the tasks that could lead to use-related problems, and (3) to evaluate the effectiveness of the mitigation strategies developed to minimize use errors and patient harm. Indicate where in the final test plan you have addressed these concerns or revise your test plan to include the above information.**

e. **In the introduction section of the study plan (page 3), you indicated that testing will focus on high-risk use scenarios and use errors identified during prior analyses. However, the final test plan did not provide a description of the high-risk use scenarios. Provide detailed description of high-risks use scenarios, and include this information in the revised test plan.**

f. **The high priority use-related risk associated with users selecting cartridge(s) of correct dosage was not included in the directed tasks list or the instructions for use. It is also unclear how this user task will be evaluated. Provide clarification, and include this information in the revised test plan.**

g. **Direct your Human Factors analysis toward assessment of task failures. The analysis should determine the nature of failures based on objective and subjective data. Also separate and submit the results of the validation study into separate tables for each distinct user groups. These tables should include objective data based on user performing specific tasks, and subjective data based on user questionnaire for assessment of device performance.**

    i. **Pertaining to objective data, the table should show a list of prioritized use related tasks that have the highest potential occurrence of hazards, the results of user performance (i.e. pass or fail), risk evaluation for the failures in terms of clinical impact, root cause, mitigation, and how those mitigations have been re-evaluated or validated. Additionally, note that study results should be recorded as a success or failure to complete a critical task. If failures are identified, discuss how those failures are to be evaluated in terms of root cause analysis, clinical impact, and mitigation strategies. If the mitigation strategies involve modifications to user interface, please discuss how your strategies are reevaluated or validated for safety and effectiveness. The study report should**

describe how the design is reasonably safe and will meet user's needs based on a discussion of results of the usability testing and evaluations.

Furthermore, provide a summary of the results in a tabular format that identifies the types of users. The following information is needed for each user: number of errors per task, error rate per task, types of error for related tasks, risk evaluation of the clinical impact of each type of error, root cause, mitigation strategy, and how mitigation strategy will be evaluated and validated. Address this concern and provide a revised test plan for review.

ii. **Include in your subjective data, descriptions by test participants of difficulties encountered and their suggestions regarding device user interface characteristics, particularly the logic of device operation. Collection of subjective assessment of device use can identify problems encountered by test participants as "concerns" or "close calls", but did not manifest themselves as errors during use and/or did not affect measures of objective performance. Rating scales (e.g., Likert scales) that assess overall "ease of use" may be considered supportive information, but are not represent all of the subjective data necessary for an adequate Human Factors test. Include a detailed discussion of how you plan to incorporate user suggestions.**

h. **It appears that you intend to market Gen2 version 2C. However, your risk assessment was based on "GEN2 V1.5". Clarify the model used in the risk assessment and how it correlates to the version that you intend to market. Also clarify the version intended for use in the Human Factors study. We recommend that you use the final version that will be marketed in your study.**

i. **Provide a complete response to each of the deficiencies above and include any supporting documents as appendices. Also refer to FDA's Guidance on Medical Device Use-Safety: Incorporating Human Factors Engineering into Risk Management available at: http://www.fda.gov/downloads/MedicalDevices/DeviceRegulationandGuidance/GuidanceDocuments/ucm094461.pdf for further information.**

2. **During the initial review of the Gen2 inhaler under IND 061729, we provided nine additional device-related comments in an Advice/Information Request letter dated November 13, 2009. These comments should also be addressed in clarifying the Gen2 inhaler system in your future submission.**

3. **You have provided a new set of verification testing of the Gen2 inhaler system in Table 14. Provide a discussion of how these set of tests will address the verification and validation of the Gen2 inhaler system, and provide a complete test report for all tests conducted. A complete test report consists of a purpose, introduction, test setup, methods, pass/fail criteria, results, and conclusion is needed. In addition, provide a scientifically valid rationale for the pass/fail criteria selected for each test.**

The Agency outlined a number of deficiencies associated with the Afrezza labeling. All of these deficiencies have been addressed and solutions are incorporated into the Gen2 Inhalation System label.

Question G: Based on the proposed labeling described in the Briefing Document, does the Agency agree that all labeling concerns have been addressed?

FDA Response: No, we do not agree that our labeling concerns are addressed. We are awaiting the results of the Human Factors and Useablity studies which will inform our evaluation of the device design and labeling. We also have identified the following concerns.
-The proposal to state that [redacted] (b) (4)
requires further evaluation to determine the acceptability of this statement.
-The cartridges should include the full proprietary name 'Afrezza' [redacted] (b) (4)

Also, we request full color mock-ups of the cartridges with blister strips, overwrap and carton labeling.

ADDITIONAL COMMENTS:

1. **Due to the change in product characteristics (cartridge strengths to 10 units and 20 units), the proprietary name Afrezza will need to be resubmitted and evaluated by FDA for acceptability.**

2. **It is unusual for a device to have a 15-day recommended in-use period. A more typical in-use period is one month. Clarify the basis for the 15-day period.**

You should provide, to the Regulatory Project Manager, a hardcopy or electronic version of any materials (i.e., slides or handouts) to be presented and/or discussed at the meeting.

If you have any questions, call me at (301) 796-0331.

Sincerely,

{See appended electronic signature page}

Rachel Hartford
Regulatory Project Manager
Division of Metabolism and Endocrinology Products
Office of Drug Evaluation II
Center for Drug Evaluation and Research

Application Type/Number	Submission Type/Number	Submitter Name	Product Name
NDA-22472	GI-1	MANNKIND CORP	Afrezza (insulin) inhalation powder

---

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

/s/

RACHEL E HARTFORD
06/08/2010

DEPARTMENT OF HEALTH AND HUMAN SERVICES

Food and Drug Administration
Silver Spring MD 20993

NDA 022472 **MEETING REQUEST GRANTED**

MannKind Corporation
Attention: Patricia R. Mayer, Ph.D.
Vice President Liaison, Worldwide Regulatory Affairs
61 South Paramus Road
Paramus, NJ 07652

Dear Dr. Mayer:

Please refer to your New Drug Application (NDA) submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act (FDCA) for Afrezza (insulin human [rDNA origin]) Inhalation Powder and Inhaler.

We also refer to your March 26, 2010, correspondence requesting an End-of-Review meeting. Based on the statement of purpose, objectives, and proposed agenda, we consider the meeting a type C meeting.

The meeting is scheduled as follows:

Date:	**June 9, 2010**
Time:	**4:00 – 5:00 pm**
Location:	**10903 New Hampshire Avenue** **White Oak Building 22** **Silver Spring, Maryland 20903**

CDER participants (alphabetic) (tentative):

Theodore Carver, Ph.D.	Chemist, Office of New Drug Quality Assessment (ONDQA)
Melanie Choe, Ph.D.	Biomedical Engineer, Center for Devices and Radiological Health (CDRH), Office of Device Evaluation (ODE), Division of Anesthesiology, General Hospital, Infection Control, and Dental Devices (DAGID), Anesthesiology & Respiratory Devices Branch (ARDB)
Sally Choe, Ph.D.	Lead Pharmacologist, Division of Clinical Pharmacology II (DCP II)
Sang Chung, Ph.D.	Pharmacologist, DCPII

Karen Davis Bruno, Ph.D.	Supervisory Pharmacologist, Division of Metabolism and Endocrinology Products (DMEP)
Amy Egan, M.D.	Deputy Director (Safety), DMEP
Enid Galliers	Chief Project Management Staff, DMEP
Rachel Hartford	Regulatory Project Manager, DMEP
Hylton Joffe, M.D., M.Sc.	Diabetes Team I Leader, DMEP
Banu Karimi-Shah, M.D.	Medical Officer, Division of Pulmonary, Allergy, and Rheumatology Products (DPARP)
Cynthia Liu, Ph.D.	Statistician, Division of Biometrics II
Mary H. Parks, M.D.	Director, DMEP
Laura Pincock, R.Ph., Pharm D.	Acting Team Leader, Drug Safety Evaluator, Office of Surveillance and Epidemiology, Division of Medication Error and Prevention (DMEPA)
Prasad Peri, Ph.D.	Supervisory Chemist, ONDQA
Todd Sahlroot, Ph.D.	Statistics Team Leader, Division of Biometrics II
Sally Seymour, M.D.	Deputy Division Director (Safety), DPARP
Alan Schroeder, Ph.D.	Chemist, ONDQA
Lester Schultheis, M.D.	Director, CDRH/ODE/DAGID/ARDB
Kellie Taylor	Deputy Director, OSE/DMEPA
Rita Tossa	Safety Project Manager, OSE
Su Tran, Ph.D.	Product Assessment Lead, ONDQA
Miyun Tsai-Turton, Ph.D.	Pharmacologist, DMEP
Lisa Yanoff, M.D.	Medical Officer, DMEP

Please e-mail me any updates to your attendees at rachel.hartford@hhs.fda.com, at least one week prior to the meeting. For each foreign visitor, complete and email me the enclosed Foreign Visitor Data Request Form, at least two weeks prior to the meeting. A foreign visitor is defined as any non-U.S. citizen or dual citizen who does not have a valid U.S. Federal Government Agency issued

Security Identification Access Badge. If we do not receive the above requested information in a timely manner, attendees may be denied access.

Please have all attendees bring valid photo identification and allow 15-30 minutes to complete security clearance. Upon arrival at FDA, provide the guards with either of the following numbers to request an escort to the conference room: Rachel Hartford x60331; Penya Littleton x61180.

Submit background information for the meeting (three paper copies or one electronic copy to the application and 24 desk copies to me) at least **four** weeks prior to the meeting. If the materials presented in the information package are inadequate to prepare for the meeting or if we do not receive the package by **May 12, 2010**, we may cancel or reschedule the meeting.

Submit the 24 desk copies to the following address:

Rachel Hartford
Food and Drug Administration
Center for Drug Evaluation and Research
White Oak Building 22, Room: 3118
10903 New Hampshire Avenue
Silver Spring, Maryland 20903

If you have any questions, call me at (301) 796-0331.

Sincerely,

{See appended electronic signature page}

Rachel Hartford
Regulatory Health Project Manager
Division of Metabolism and Endocrinology Products
Office of Drug Evaluation II
Center for Drug Evaluation and Research

ENCLOSURE: Foreign Visitor Data Request Form

FOREIGN VISITOR DATA REQUEST FORM

VISITORS FULL NAME (First, Middle, Last)	
GENDER	
COUNTRY OF ORIGIN/CITZENSHIP	
DATE OF BIRTH **(MM/DD/YYYY)**	
PLACE OF BIRTH **(city and country)**	
PASSPORT NUMBER COUNTRY THAT ISSUED PASSPORT ISSUANCE DATE: EXPIRATION DATE:	
VISITOR ORGANIZATION/EMPLOYER	
MEETING START DATE AND TIME	June 9, 2010 @ 4:00pm
MEETING ENDING DATE AND TIME	June 9, 2010 @ 5:00pm
PURPOSE OF MEETING	End-of-Review Meeting
BUILDING(S) & ROOM NUMBER(S) TO BE VISITED	Building 22 Conference Room 1313
WILL CRITICAL INFRASTRUCTURE AND/OR FDA LABORATORIES BE VISITED?	NO
HOSTING OFFICIAL **(**name, title, office/bldg, room number, and phone number)	Rachel E. Hartford Regulatory Project Manager Rm 3118, WO Bldg 22 301-796-0331
ESCORT INFORMATION (If different from Hosting Official)	

Application Type/Number	Submission Type/Number	Submitter Name	Product Name
NDA-22472	GI-1	MANNKIND CORP	Afrezza (insulin) inhalation powder

---

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

/s/

RACHEL E HARTFORD
04/27/2010

Hartford, Rachel

From: Hartford, Rachel
Sent: Monday, February 15, 2010 7:28 PM
To: 'Mayer, Patricia'
Subject: Information Request

Hello Patricia,

We have another request for information:

Please clarify where in the NDA submission you provide the supporting information that shows that a 15-unit cartridge of Afrezza emits (b) (4) units of insulin and that this cartridge provides the equivalent of 4 units of subcutaneous regular or fast-acting insulin. Please also provide the corresponding information for the 30-unit cartridge. If this information is not clearly provided in the NDA, please submit this information now within a single document.

Thanks,

Rachel

Rachel E. Hartford
Regulatory Project Manager
Division of Metabolism and Endocrinology Products
Center for Drug Evaluation and Research
Food and Drug Administration
rachel.hartford@fda.hhs.gov
301-796-0331 (phone)
301-796-9712 (fax)

Application Type/Number	Submission Type/Number	Submitter Name	Product Name
NDA-22472	ORIG-1	MANNKIND CORP	Afrezza (insulin) inhalation powder

---

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

/s/

RACHEL E HARTFORD
02/15/2010

Hartford, Rachel

From: Hartford, Rachel
Sent: Monday, February 01, 2010 11:15 AM
To: 'Mayer, Patricia'
Subject: Information Request

Good Morning Patricia,

We have two additional information requests:

1. Which model of the Afrezza inhaler is being used in ongoing Study 134 (the trial in patients with underlying lung disease that was temporarily suspended)?
2. What were the doses (mean, SD, median, range) of Afrezza used in the patients who achieved HbA1c <=7% in Study 009 and in Study 014?

Thank you,

Rachel

Rachel E. Hartford
Regulatory Project Manager
Division of Metabolism and Endocrinology Products
Center for Drug Evaluation and Research
Food and Drug Administration
rachel.hartford@fda.hhs.gov
301-796-0331 (phone)
301-796-9712 (fax)

Application Type/Number	Submission Type/Number	Submitter Name	Product Name
NDA-22472	ORIG-1	MANNKIND CORP	Afrezza (insulin) inhalation powder

---

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

/s/

RACHEL E HARTFORD
02/01/2010

Aljuburi, Lina

From: Aljuburi, Lina
Sent: Wednesday, January 20, 2010 5:03 PM
To: 'Mayer, Patricia'
Cc: Hartford, Rachel
Subject: NDA 022472 Afrezza information request

Hi Patricia,

Re: NDA 022472 Afrezza (insulin human [rDNA origin]) Inhalation Powder and Inhaler

1. In the narrative for Patient 162/0465 (Study 030), the patient had biochemical Hy's Law (ALT 560 U/L, total bilirubin 3.0 mg/dL and normal alkaline phosphatase) in the setting of pancreatitis. The narrative mentions that he had a normal bile duct without evidence of intraductal stones or pathology on ERCP but that he subsequently underwent cholecystectomy. What did the surgical pathology results show? Did this patient have elevated liver tests (ALT, total bilirubin) at any other time while treated with TI?

2. For the patient with hepatotoxicity attributed to paracetamol and ibuprofen overdose, please clarify:

A. Whether the patient exceeded the maximum recommended dose of paracetamol and ibuprofen (e.g., did the patient take 1500 mg of paracetamol at one time each day or was that the total dose over the course of the day). The maximum recommended dose of paracetamol is 4000 mg/day (1000 mg every 4-6 hours). Therefore, use of 1500 mg over the course of a day is not an overdose. Also, clarify the timing of the elevated liver tests relative to the paracetamol dosing and provide published data on the timing of abnormal liver tests relative to paracetamol overdose.
B. What were the accompanying results for total bilirubin (include the reference range)?
C. Were any other tests conducted to evaluate the cause of the liver test abnormalities (e.g., viral hepatitis, etc.)?

Feel free to contact me if you have any questions.

Thanks,
Lina

Lina AlJuburi, Pharm.D., M.S.
Chief, Project Management Staff
Division of Metabolism and Endocrinology Products
Center for Drug Evaluation and Research
Food and Drug Administration
l.aljuburi@fda.hhs.gov
301-796-1168 (phone)
301-796-9712 (fax)

Application Type/Number	Submission Type/Number	Submitter Name	Product Name
NDA-22472	ORIG-1	MANNKIND CORP	Afrezza (insulin) inhalation powder

---

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

/s/

LINA ALJUBURI
01/20/2010

Aljuburi, Lina

From: Aljuburi, Lina
Sent: Tuesday, January 19, 2010 10:56 PM
To: 'Mayer, Patricia'
Cc: Hartford, Rachel
Subject: NDA 022472 Afrezza information request

Hi Patricia,

Re: NDA 022472 Afrezza (insulin human [rDNA origin]) Inhalation Powder and Inhaler

There were high rates of discontinuations from the phase 3 trials due to withdrawal of consent. Please clarify whether you reviewed the case report forms for all patients in the trials below to assess whether withdrawal was actually due to lack of efficacy or due to adverse events (e.g., the complete study report for Study 030 does not explicitly state that you did this). In addition, it appears that some of these numbers changed after we sent you an information request regarding withdrawals due to adverse events consistent with lack of efficacy. Please explain why those cases were not picked up during your initial review of the case report forms. Lastly, please provide a tabular summary of the reasons for withdrawal of consent for the patients in the table below. Show these data separately for TI and for comparator and separately by trial.

Table. Patient withdrawal of consent across the main phase 2/3 trials

	TI	Comparator
Type 1 diabetes		
Study 009	47/301 (15.6%)	19/288 (6.6%)
Study 030	79/269 (29.4%)	39/271 (14.4%)
Type 2 diabetes		
Study 014	10/151 (6.6%)	0
Study 030	13/669 (20.8%)	127/680 (18.7%)
Study 102	50/334 (15.0%)	32/343 (9.3%)
Study 103	20/175 (11.4%)[1]	10/170 (5.9%)[2]

[1]TI+metformin; [2]secretagogue+metformin

Feel free to contact me if you have questions regarding this request.

Thanks,
Lina

Lina AlJuburi, Pharm.D., M.S.
Chief, Project Management Staff
Division of Metabolism and Endocrinology Products
Center for Drug Evaluation and Research
Food and Drug Administration
l.aljuburi@fda.hhs.gov
301-796-1168 (phone)
301-796-9712 (fax)

Application Type/Number	Submission Type/Number	Submitter Name	Product Name
NDA-22472	ORIG-1	MANNKIND CORP	Afrezza (insulin) inhalation powder

---

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

/s/

LINA ALJUBURI
01/19/2010

Aljuburi, Lina

From: Aljuburi, Lina
Sent: Monday, January 18, 2010 11:05 PM
To: 'Mayer, Patricia'
Cc: Hartford, Rachel
Subject: NDA 022472 Afrezza information requests

Hi Patricia,

Re: NDA 022472 Afrezza (insulin human [rDNA origin]) Inhalation Powder and Inhaler

1. Please put all the following narratives in a single document:

   A. Serious adverse events of asthma, cough, hemoptysis, and respiratory failure

   B. The following adverse events leading to discontinuation - asphyxia, laryngospasm, painful respiration, throat tightness, creatinine phosphokinase increased, pruritis generalised

2. Is there any further follow-up information on the patients diagnosed with pulmonary nodules on CT imaging?

Feel free to contact Rachel or me if you have any questions regarding this information request.

Thanks,
Lina

Lina AlJuburi, Pharm.D., M.S.
Chief, Project Management Staff
Division of Metabolism and Endocrinology Products
Center for Drug Evaluation and Research
Food and Drug Administration
l.aljuburi@fda.hhs.gov
301-796-1168 (phone)
301-796-9712 (fax)

Application Type/Number	Submission Type/Number	Submitter Name	Product Name
NDA-22472	ORIG-1	MANNKIND CORP	Afrezza (insulin) inhalation powder

---

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

/s/

LINA ALJUBURI
01/19/2010

Hartford, Rachel

From: Hartford, Rachel
Sent: Thursday, January 14, 2010 3:44 PM
To: 'Mayer, Patricia'
Cc: Aljuburi, Lina
Subject: Information Request

Hello Patricia,

We have two additional information requests:

1. With regard to serious adverse events, there were 3 reports of “retinal detachment” and 1 report of “vitreous hemorrhage” among TI-treated patients and no reports among comparator although there are 2 reports of “eye hemorrhage” with comparator. Please provide narratives in a single document for all these patients. Also, were there any non-serious reports of eye/vitreous hemorrhage in the controlled phase 2/3 database (if yes, please provide narratives for these)?

2. With regard to serious adverse events, there are 4 reports of pancreatitis acute and 1 report each of pancreatitis and pancreatic cyst among TI-treated patients and no reports among comparator. Please provide narratives in a single document for all these patients. Also, were there any non-serious reports of pancreatitis in the controlled phase 2/3 database (if yes, please provide narratives for these).

Please send your response to Lina and me.

Thanks,

Rachel

Rachel E. Hartford
Regulatory Project Manager
Division of Metabolism and Endocrinology Products
Center for Drug Evaluation and Research
Food and Drug Administration
rachel.hartford@fda.hhs.gov
301-796-0331 (phone)
301-796-9712 (fax)

Application Type/Number	Submission Type/Number	Submitter Name	Product Name
NDA-22472	ORIG-1	MANNKIND CORP	Afrezza (insulin) inhalation powder

---

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

/s/

RACHEL E HARTFORD
01/14/2010

Aljuburi, Lina

From: Aljuburi, Lina
Sent: Wednesday, January 13, 2010 2:00 PM
To: 'Mayer, Patricia'
Cc: Hartford, Rachel
Subject: NDA 022472 Afrezza information requests

Hi Patricia,

Re: NDA 022472 Afrezza (insulin human [rDNA origin]) Inhalation Powder and Inhaler

We have the following information requests. Response is requested as soon as possible.

1. Please clarify how the formulations of TI used in Study 005 and 0008 differ from the formulation of TI used in the other phase 2/3 trials.

2. For Study 103, please show the doses of study medications used by each treatment group (TI alone, TI+metformin, secretagogue+metformin) at each clinic visit from baseline to Week 12. Present the data showing the mean, SD, median, and range. Show the data for the intent-to-treat population with last observation carried forward. This analysis should not take into account what happened to patients after the 12-week treatment period.

3. For Study 102 (comparison of TI+glargine vs. NovoLog 70/30), please provide the number (and percentage) of patients in each treatment group (safety population) who meet the following criteria (this pertains to analyses of hypoglycemia):

A. Had any measured BG <=36 mg/dL (2.0 mmol/L)

B. Had any measured BG <=36 mg/dL (2.0 mmol/L) but did NOT require the assistance of another person and did NOT have at least 1 cognitive neurological symptom

C. Required the assistance of another person AND exhibited at least 1 cognitive neurological symptom (memory loss, confusion, uncontrollable behavior, irrational behavior, unusual difficulty in awakening, seizure, loss of consciousness)

D. Met the protocol criteria for mild/moderate hypoglycemia AND met A above.

E. Met the protocol criteria for mild/moderate hypoglycemia and met B above.

4. Please complete the following table.

Table X. Number of patients exposed to Technosphere Insulin (safety population from all submitted studies)			
	Type 1 diabetes	**Type 2 diabetes**	**Combined**
At NDA filing			

≥24 weeks			
≥52 weeks			
≥76 weeks			
≥104 weeks			
At 120-day safety update			
≥24 weeks			
≥52 weeks			
≥76 weeks			
≥104 weeks			

5. Please complete the X's in the table below - this pertains to weight changes in the intent-to-treat population with last-observation carried forward.

Table X. Change from baseline in body weight (kg)

(intent-to-treat population with last-observation-carried-forward)

	N	Baseline±SD	Adjusted mean change±SE	Change with TI vs. Compa	
				Mean difference (95% CI)	
Study 014 (24-weeks)					
TI+glargine	X	X±X	X±X	X (X, X)	
Aspart+glargine	X	X±X	X±X	X (X, X)	
Study 103 (12 weeks)					
TI alone	177	86.1±15.6	-0.6±0.2	-0.2 (X, X)	
TI+metformin	169	83.9±13.9	-1.1±0.2	-0.8 (X, X)	
Secretagogue+met	162	84.2±16.2	-0.4±0.2		

Feel free to contact me if you have any questions regarding these requests.

Many thanks,
Lina

Lina AlJuburi, Pharm.D., M.S.
Chief, Project Management Staff
Division of Metabolism and Endocrinology Products
Center for Drug Evaluation and Research
Food and Drug Administration
l.aljuburi@fda.hhs.gov
301-796-1168 (phone)
301-796-9712 (fax)

Application Type/Number	Submission Type/Number	Submitter Name	Product Name
NDA-22472	ORIG-1	MANNKIND CORP	Afrezza (insulin) inhalation powder

---

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

/s/

LINA ALJUBURI
01/13/2010

Hartford, Rachel

From: Hartford, Rachel
Sent: Wednesday, January 06, 2010 10:45 AM
To: 'Mayer, Patricia'
Subject: AE Reporting IR

Hello Patricia,

At the 2 inspected Russian sites (Yakusevich site #507 and Shavarts site #527), some adverse events were reported by the investigator to you but were not contained in the line listings submitted in the NDA. Examples at Prof. Vladimir Yakusevich's site includes Subject 548 with hypertension, Subject 152 with acute pain in lower colon, and Subject 580 with upper respiratory illness. Examples at Prof Yury Shavarts' site includes Subject 054 with an ischemic event and Subject 409 with arterial hypertension. Please clarify whether these adverse events are included in your tables of adverse events in the NDA. If these events are not included, please clarify why they were missed and whether there could be similar underreporting of events to the NDA from other clinical sites.

Thank you,

Rachel

Rachel E. Hartford
Regulatory Project Manager
Division of Metabolism and Endocrinology Products
Center for Drug Evaluation and Research
Food and Drug Administration
rachel.hartford@fda.hhs.gov
301-796-0331 (phone)
301-796-9712 (fax)

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

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

/s/

RACHEL E HARTFORD
01/06/2010

DEPARTMENT OF HEALTH AND HUMAN SERVICES

Food and Drug Administration
Silver Spring MD 20993

NDA 022472 **GENERAL ADVICE**

MannKind Corporation
Attention: Patricia R. Mayer, Ph.D.
Vice President Liaison, Worldwide Regulatory Affairs
61 South Paramus Road
Paramus, NJ 07652

Dear Dr. Mayer:

Please refer to your New Drug Application (NDA) submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act for Afrezza (insulin human [rDNA origin]) Inhalation Powder and Inhaler.

We have reviewed your proposed Risk Evaluation and Mitigation Strategy (REMS) and have the following comments.

1. A REMS is intended to ensure that the benefits outweigh the risks of the drug. The serious risks for which a REMS is warranted need to be clearly identified in the REMS and REMS Supporting Document (SD).

2. REMS goals should target the achievement of a particular health outcome or knowledge related to known safety risks. Revise the proposed REMS to include goals that mitigate the identified serious risks associated with the use of Afrezza. Include these risks in the Afrezza communication and educational material.

   The use of Afrezza in the appropriate patient population is currently a goal of the Afrezza Inhalation System REMS. The REMS and SD provide limited information about patient selection. Revise the REMS and SD to describe important factors healthcare professionals should consider before prescribing Afrezza for their patients.

3. Clarify the target audience [redacted] (b) (4)

4. Refer to the REMS format provided by the Food and Drug Administration (in Appendix A) when determining the headings and subheadings for the proposed Afrezza REMS. Delete [redacted] (b) (4) from the proposed REMS. This heading is not an approved heading in the REMS template.

5. Remove [redacted] (b) (4)

6. (b) (4)

7. Revise the REMS (b) (4)

8. Section 3.1.6.1 of the REMS Supporting Document states (b) (4)

   a. (b) (4) is not a sufficient timeline to describe the dissemination plan for the communication material. Provide a more definitive timeline such as 'x days after approval'.

   b. The introductory letter for health professionals is not intended to continue over the lifetime of the product; it will function only to inform prescribers of the serious risk associated with Afrezza for a period of time. Provide a timeline in 'months' or 'years' that you intend to provide the introductory letters for health professionals, e.g. yearly after approval for a period of 3 years.

9. Include the Afrezza risk information in the Introductory Letter for Healthcare Professionals, realizing that this information may change once the final labeling is completed and the risks are more clearly identified.

10. Remove the (b) (4) .

11. (b) (4)

12. (b) (4) .

13. We have not included comments for the (b) (4). These comments will be provided with the full review of the REMS.

14. Submit for review a detailed plan to evaluate the providers' and patients' understanding of the safe use of Afrezza 90 days prior to conducting the survey. The submission should include, but is not limited to:

a) *Sample size and confidence interval associated with that sample size*
b) *How the sample will be determined (selection criteria)*
c) *The expected number of patients surveyed*
d) *How the participants will be recruited*
e) *How and how often the surveys will be administered*
f) *Explain controls used to minimize bias*
g) *Explain controls used to compensate for the limitations associated with their methodology*
h) *Survey instruments (questionnaires and moderator's guide).*
i) *Any background information on testing survey questions and the correlation to the educational materials, and an explanation of what will be done with the resulting data from the surveys.*

15. Submit the revised proposed REMS with appended materials and the REMS Supporting Document. Provide a track changes and clean version of all revised materials and documents. Submit your proposed REMS and other materials in WORD format. It is preferable that the entire REMS and appended materials be in a single WORD document.

If you have any questions, call Rachel Hartford, Regulatory Project Manager, at (301) 796-0331.

Sincerely,

{See appended electronic signature page}

Mary H. Parks, M.D.
Director
Division of Metabolism and Endocrinology Products
Office of Drug Evaluation II
Center for Drug Evaluation and Research

2 Page(s) have been Withheld in Full as B4 (CCI/TS) immediately following this page

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

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

/s/

MARY H PARKS
12/31/2009

Hartford, Rachel

From: Hartford, Rachel
Sent: Friday, December 18, 2009 3:37 PM
To: 'Mayer, Patricia'
Subject: More labeling comments

Hello Patricia,

We have two additional labeling comments:

(b) (4)

Thanks,

Rachel

Rachel E. Hartford
Regulatory Project Manager
Division of Metabolism and Endocrinology Products
Center for Drug Evaluation and Research
Food and Drug Administration
rachel.hartford@fda.hhs.gov
301-796-0331 (phone)
301-796-9712 (fax)

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

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

/s/

RACHEL E HARTFORD
12/29/2009

Hartford, Rachel

From: Hartford, Rachel
Sent: Monday, December 28, 2009 11:39 AM
To: 'Mayer, Patricia'
Subject: Afrezza cartridge labeling

Hello Patricia,

We do not agree that space limitations prohibit the inclusion of the proprietary name "Afrezza" on the cartridge. The Afrezza cartridge, as the immediate label of the product, should attempt to meet the requirements of 201.10(i). We agree that the space limitations on the cartridge make it impossible to add the established name, but the cartridge should bear the proprietary name (Afrezza) in addition to the strength and lot number for safety and identification reasons.

Thank you,

Rachel

Rachel E. Hartford
Regulatory Project Manager
Division of Metabolism and Endocrinology Products
Center for Drug Evaluation and Research
Food and Drug Administration
rachel.hartford@fda.hhs.gov
301-796-0331 (phone)
301-796-9712 (fax)

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

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

/s/

RACHEL E HARTFORD
12/29/2009

Hartford, Rachel

From: Hartford, Rachel
Sent: Friday, December 18, 2009 9:28 AM
To: 'Mayer, Patricia'
Subject: Labeling comments

Hello Patricia,

We have two more labeling comments:

* Revise the inhaler and inhaler carton labels to state " Store a [redacted] (b) (4) May be stored refrigerated but the inhaler must be at room temperature prior to use."

* Revise the drug carton and foil pack labels to state ' [redacted] (b) (4)

Thank you,

Rachel

Rachel E. Hartford
Regulatory Project Manager
Division of Metabolism and Endocrinology Products
Center for Drug Evaluation and Research
Food and Drug Administration
rachel.hartford@fda.hhs.gov
301-796-0331 (phone)
301-796-9712 (fax)

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

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

/s/

RACHEL E HARTFORD
12/18/2009

Hartford, Rachel

From: Hartford, Rachel
Sent: Friday, December 18, 2009 9:14 AM
To: 'Mayer, Patricia'
Subject: Information Request

Hello Patricia,

We have an additional information request. Submit data (or provide the location within the NDA submission) in which FEV1 was serially assessed immediately post-dosing of Afrezza. (For example, FEV1 at 5, 10, 15, 30, and 60 minutes after a subject inhaled Afrezza.)

Please respond ASAP and no later than COB Wed Dec 23.

Thanks,

Rachel

Rachel E. Hartford
Regulatory Project Manager
Division of Metabolism and Endocrinology Products
Center for Drug Evaluation and Research
Food and Drug Administration
rachel.hartford@fda.hhs.gov
301-796-0331 (phone)
301-796-9712 (fax)

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

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

/s/

RACHEL E HARTFORD
12/18/2009

DEPARTMENT OF HEALTH & HUMAN SERVICES

Public Health Service

Food and Drug Administration
Silver Spring, MD 20993

NDA 022472

PROPRIETARY NAME REQUEST
CONDITIONALLY ACCEPTABLE

MannKind Corporation
61 South Paramus Road
Paramus, NJ 07652

ATTENTION: Patricia R. Mayer, Ph.D.
Vice President Liaison, Worldwide Regulatory Affairs

Dear Dr. Mayer:

Please refer to your New Drug Application (NDA) dated March 16, 2009, received March 16, 2009, submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act for Insulin Monomer Human [rDNA origin] Inhalation Powder, 4 Units and 8 Units single use cartridges.

We also refer to your September 18, 2009, correspondence, received September 18, 2009, requesting review of your proposed proprietary name, Afrezza. We have completed our review of the proposed proprietary name, Afrezza and have concluded that it is acceptable.

The proposed proprietary name, Afrezza, will be re-reviewed 90 days prior to the approval of the NDA. If we find the name unacceptable following the re-review, we will notify you.

If **any** of the proposed product characteristics as stated in your September 18, 2009, submission are altered prior to approval of the marketing application, the proprietary name should be resubmitted for review.

If you have any questions regarding the contents of this letter or any other aspects of the proprietary name review process, contact Margarita Tossa, Safety Regulatory Project Manager in the Office of Surveillance and Epidemiology, at (301) 796-4053. For any other information regarding this application contact the Office of New Drugs (OND) Regulatory Project Manager Rachel Hartford at (301) 796-0331.

Sincerely,
{See appended electronic signature page}

Carol Holquist, RPh
Director
Division of Medication Error Prevention and Analysis
Office of Surveillance and Epidemiology
Center for Drug Evaluation and Research

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

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

/s/

CAROL A HOLQUIST
12/16/2009

Hartford, Rachel

From: Hartford, Rachel
Sent: Tuesday, December 15, 2009 3:08 PM
To: 'Mayer, Patricia'
Subject: Afrezza Pediatric Development Plan

Hello Patricia,

Please refer to your submission Pediatric Development Plan (Version 2.0) from 15 October, 2009.

We have discussed your pediatric plan with the Pediatric Review Committee (PeRC) and have the following requests. Please respond in writing.

Pediatric Waiver Request for ages 0 (b) (4)

Please decrease the upper age limit of the waiver request to 3 years 11 months. We will require pediatric studies in age 4 – 16 years 11 months. Your product should be aligned with subcutaneous insulins for which the Agency grants waivers for less than 4 years of age. You should assess feasibility of use of your product in this younger age group of children. If accrued data with your product show that children as low as 4 years of age cannot reliably use your product, this important information will be included in labeling and you will be released of the postmarketing requirement to study children in those younger age groups.

Pediatric Deferral Request for ages (b) (4) 17

Accordingly, please update the request to ages 4 – 16 years 11 months.

Pediatric Plan

Trial 143: Update protocol 143 to include children as young as 4 years of age. Please add another arm to your study for ages 4 – 5 such that the total number of subjects studied is increased by 12 to 15 subjects. The age group studied in your PK and efficacy/safety trials will still depend on the results of the feasibility study. However, you should determine feasibility in a younger age group.

(b) (4)

General recommendations regarding the Gen2 device: It is permissible to conduct your initial feasibility study (protocol 143) and single dose pharmacokinetic/pharmacodynamic studies in the pediatric population with the Gen2 device. However, we require Gen2 device data in adults prior to any longer term studies in children. If you choose to incorporate your Gen2 device in these short-term studies, you should first discuss with the Division whether an Investigational New Drug application (IND) is needed for the new device/drug combination product.

Thank you,

Rachel

Rachel E. Hartford
Regulatory Project Manager
Division of Metabolism and Endocrinology Products
Center for Drug Evaluation and Research
Food and Drug Administration
rachel.hartford@fda.hhs.gov
301-796-0331 (phone)

301-796-9712 (fax)

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

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

/s/

RACHEL E HARTFORD
12/15/2009

Hartford, Rachel

From: Hartford, Rachel
Sent: Friday, December 11, 2009 11:32 AM
To: 'Mayer, Patricia'
Subject: CMC Information request

Hello Patricia,

We have two more CMC information requests:

1. Justify the lack of dimensional specifications for the cartridge top and cartridge bottom to ensure the proper size and placement of the holes in the cartridge top and cartridge bottom. Alternatively, institute such specifications.

2. As previously requested, clarify that you are providing an agreement to confirm accelerated data with real time data to support the in use period. We are requesting a full one year study of the inhaler device, since you have proposed an in use life of one year, with the device to be operated on a typical patient use regimen.

Thank you,

Rachel

Rachel E. Hartford
Regulatory Project Manager
Division of Metabolism and Endocrinology Products
Center for Drug Evaluation and Research
Food and Drug Administration
rachel.hartford@fda.hhs.gov
301-796-0331 (phone)
301-796-9712 (fax)

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

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

/s/

RACHEL E HARTFORD
12/11/2009

Hartford, Rachel

From: Hartford, Rachel
Sent: Monday, December 07, 2009 3:32 PM
To: 'Mayer, Patricia'
Subject: Additional CMC comments/requests

Hello Patricia,

We have a few more CMC comments/requests:

1. The following comment pertains to the drug product specification, specifically your November 30th response to Comment 5f. from our November 18th information request. For insulin-related compounds, remove the shelf life acceptance criteria from the drug product specification and provide a single set of acceptance criteria, including criteria of not more than (b) (4)% for A-21 desamido insulin, not more than (b) (4)% for Total Others, and not more than (b) (4)% for High Molecular Weight proteins. Per ICH Q6B, specifications should be based upon data obtained for lots used in preclinical and clinical studies. You have not provided acceptable justification for either separate acceptance criteria for shelf life or for the thresholds you propose for these impurities. Please note that modifying the drug product specification as described above is a very important consideration in review of this NDA.

The November 30, 2009 amendment:

2. Provide an agreement that as soon as it is feasible based on production levels, inhalers for commercial drug product (filled cartridges) release testing will be replaced with different batches of inhalers on a more frequent basis than annually (e.g., every three months). (Comment 1)

3. It is premature (for a new drug product) to delete stability time points in the post approval stability protocol. Modify Table 3 (Section 3.2.P.8.2 of the original NDA) to contain the same testing time points as Table 1.

4. As we previously requested, modify the post approval stability protocol to include foreign particles at multiple time points, since your current stability data are inconclusive as to whether foreign particles are increasing with time.

Please provide a response timeline.

Thank you,

Rachel

Rachel E. Hartford
Regulatory Project Manager
Division of Metabolism and Endocrinology Products
Center for Drug Evaluation and Research
Food and Drug Administration
rachel.hartford@fda.hhs.gov
301-796-0331 (phone)
301-796-9712 (fax)

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

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

/s/

RACHEL E HARTFORD
12/07/2009

Hartford, Rachel

From: Hartford, Rachel
Sent: Monday, December 07, 2009 10:41 AM
To: 'Mayer, Patricia'
Subject: RE: CMC labeling comments

Hello Patricia,

Thank you; the timeline you propose is acceptable. We have one additional comment:

Delete from all drug packaging labels the statement [redacted] (b) (4) because this statement is misleading; the shelf life of the product should be specific to the lot number.

Thanks again,

Rachel

From: Mayer, Patricia [mailto:pmayer@mannkindcorp.com]
Sent: Friday, December 04, 2009 4:36 PM
To: Hartford, Rachel
Subject: RE: CMC labeling comments

Dear Rachel,
We will implement all changes listed below and will submit updated labels. However, we will not have these updated labels available before the week of 14th Dec.. I hope that it is ok for you and the team. Please let me know if we have to find other, faster alternatives.
Have a great weekend.
Patricia

Patricia R. Mayer, PhD
Vice President
Worldwide Regulatory Affairs - Liaison
Office: 201-983-5228
Cell: [redacted] (b) (6)

From: Hartford, Rachel [mailto:Rachel.Hartford@fda.hhs.gov]
Sent: Thursday, December 03, 2009 4:29 PM
To: Mayer, Patricia
Subject: CMC labeling comments

Hello Patricia,

Please address the following CMC labeling comments:

Carton and cartridge labeling comments from CMC:

- Revise all drug packaging labels to have the correct dosage strengths "15 units" and "30 units" and revise the storage instruction on the carton and foil pack labels to state "[redacted] (b) (4)

For the drug carton label:

- Repeat the number of doses per carton on the top flap of the carton label as well as on all the panels that show the drug name and strength. Do the same for the statement "For Oral Inhalation with [NAME] Inhaler Only".
- Increase the prominence (e.g., font size, color) of the statement "For Oral Inhalation with [NAME] Inhaler Only".
- Clarify the location of the lot number and expiration date on the carton label.

(b) (4)

Thanks,

Rachel

Rachel E. Hartford
Regulatory Project Manager
Division of Metabolism and Endocrinology Products
Center for Drug Evaluation and Research
Food and Drug Administration
rachel.hartford@fda.hhs.gov
301-796-0331 (phone)
301-796-9712 (fax)

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

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

/s/

RACHEL E HARTFORD
12/07/2009

Hartford, Rachel

From: Hartford, Rachel
Sent: Thursday, December 03, 2009 4:29 PM
To: 'Mayer, Patricia'
Subject: CMC labeling comments

Hello Patricia,

Please address the following CMC labeling comments:

Carton and cartridge labeling comments from CMC:

- Revise all drug packaging labels to have the correct dosage strengths "15 units" and "30 units" and revise the storage instruction on the carton and foil pack labels to state "[redacted] (b) (4)

For the drug carton label:

- Repeat the number of doses per carton on the top flap of the carton label as well as on all the panels that show the drug name and strength. Do the same for the statement "For Oral Inhalation with [NAME] Inhaler Only".
- Increase the prominence (e.g., font size, color) of the statement "For Oral Inhalation with [NAME] Inhaler Only".
- Clarify the location of the lot number and expiration date on the carton label.

[redacted] (b) (4)

Thanks,

Rachel

Rachel E. Hartford
Regulatory Project Manager
Division of Metabolism and Endocrinology Products
Center for Drug Evaluation and Research
Food and Drug Administration
rachel.hartford@fda.hhs.gov
301-796-0331 (phone)
301-796-9712 (fax)

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

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

/s/

RACHEL E HARTFORD
12/03/2009

Hartford, Rachel

From: Hartford, Rachel
Sent: Friday, November 20, 2009 10:42 AM
To: 'Mayer, Patricia'
Subject: CDRH requests

Hello Patricia,

Please address the following CDRH requests:

1.In the Failure Mode Effect Analysis presented in your response to FDA request for the human factors study report received on September 25, 2009, corrective modes for several failure modes were not conducted. You stated that Risk Priority Number of 64 or greater triggered corrective actions; however, according to the report provided in Appendix II of this document, several failure modes were not mitigated, such as line item numbers 10, 11, 29, 30, 39, 68, 69, 81, 86-88, 105, 110, and 112. Please explain why these failure modes were not mitigated and how you concluded these were acceptable risks.

2. For the Inhaler Life Cycle Testing, please clarify whether the inhaler was physically manipulated from the dosage to cartridge load positions between each discharge. If not, please explain how the simulated Inhaler Life Cycle Testing is valid as the mechanical manipulation of the device in real use could affect the performance of the device.

3. You reported improvements of [redacted] (b) (4) etc. in Model D over Model C. For these design changes, please provide a validation report to demonstrate the improvement of Model D over Model C in a side-by-side comparison.

4. In the labeling, the storage temperature is stated to be "[redacted] (b) (4) and no operational temperatures are listed. Please specify and include the range of validated storage and operation temperatures in the labeling for the device.

5. Please clarify why the user is instructed to [redacted] (b) (4)

Thanks,

Rachel

Rachel E. Hartford
Regulatory Project Manager
Division of Metabolism and Endocrinology Products
Center for Drug Evaluation and Research
Food and Drug Administration
rachel.hartford@fda.hhs.gov
301-796-0331 (phone)
301-796-9712 (fax)

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

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

/s/

RACHEL E HARTFORD
11/22/2009

Hartford, Rachel

From: Hartford, Rachel
Sent: Friday, November 20, 2009 6:57 AM
To: 'Mayer, Patricia'
Subject: Clinical Information Request

Hello Patricia,

We have the following additional clinical information requests:

1. Please submit figures for trials 102 and 009 showing Mean (SE) HbA1c % by visit and by treatment group similar to Figure 5 in the trial 102 study report, however, instead including the ITT population **with LOCF.**

2. Trial 103 table 7 indicates the safety population to have a total of 181 subjects in the TI alone arm, 166 in the M + S arm and 174 in the TI + M arm, but the safety tables in section 12 indicate the safety population to have 177 subjects in the TI alone arm, 166 in the M + S arm and 177 in the TI + M arm. Consequently the numbers of discontinuations due to AEs are not the same in table 7 and in the tables in section 12. Please explain this difference.

3. For trial 103, the AEs leading to discontinuation include 3 subjects in the TI alone arm, 1 in the M + S arm and 2 in the TI + M arm. It is not clear how these cases are different than the "lack of efficacy" subjects listed in table 6.7 in the trial 103 tables and figures appendix.

4. For trial 009 there are 17 subjects listed as discontinued due to an AE in table 6, but 16 subjects listed as discontinued due to an AE in section 12 starting with table 36. Please clarify which is correct.

Thanks,

Rachel

Rachel E. Hartford
Regulatory Project Manager
Division of Metabolism and Endocrinology Products
Center for Drug Evaluation and Research
Food and Drug Administration
rachel.hartford@fda.hhs.gov
301-796-0331 (phone)
301-796-9712 (fax)

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

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

/s/

RACHEL E HARTFORD
11/20/2009

Hartford, Rachel

From: Hartford, Rachel
Sent: Friday, November 20, 2009 7:00 AM
To: 'Mayer, Patricia'
Subject: CMC Information Request

Good Morning Patricia,

Please address the following CMC information request:

Your drug product methods #TM5514 and TM5516 for Emitted Dose and APSD both call for the use of a (b) (4) prior to running the performance tests. Provide representative data under varying humidities, including low humidities, to demonstrate the performance of the drug product in these tests when the cartridge is (b) (4) (as in a patient use situation). Justify the use of the (b) (4)

Thanks,

Rachel

Rachel E. Hartford
Regulatory Project Manager
Division of Metabolism and Endocrinology Products
Center for Drug Evaluation and Research
Food and Drug Administration
rachel.hartford@fda.hhs.gov
301-796-0331 (phone)
301-796-9712 (fax)

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

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

/s/

RACHEL E HARTFORD
11/20/2009

Hartford, Rachel

From: Hartford, Rachel
Sent: Wednesday, November 18, 2009 10:23 AM
To: 'Mayer, Patricia'
Subject: CMC Information Request

Hello Patricia,

Please respond to the CMC information requests below by November 30, 2009.

Thanks,

Rachel

NDA 022472 CMC Information Request

1. This pertains to your October 30, 2009 response to our Comment 7 in our October 13, 2009 Information Request. For the 6 example inhalers in your response, provide their Aerodynamic Particle Size Distribution (APSD) profiles compared to their varied device resistances. If these example inhalers are not available, provide comparative APSD data using inhalers that differ in resistance, including those which fail the resistance specification. The purpose of this request is to seek additional data to support your proposal for the use of inhaler resistance as a discriminating test for the inhaler.

2. Provide summary data based on a significant number of drug product batches which are representative of the to be marketed drug product, to justify the targets that you have chosen for emitted dose and for APSD stage groupings for each strength of the drug product. Use these data to demonstrate dose proportionality of the two strengths of the drug product, both in terms of emitted dose and APSD.

3. The following comments pertain to your 8/14/2009 amendment, and specifically to the (b) (4) Bridging Stability data in section 3.2.P.8.3 (section 1.10 (b) (4)).

   a. Briefly explain how this test for (b) (4) was performed. Indicate the number of cartridges tested and the number of devices used for the results on each graph. Provide the units represented by the y-axis of the graphical results, and indicate the practical significance of the results in terms of a person's ability to turn the cartridge in the device.

   b. You have stated that "the Model D cartridges used in the bridging study were produced with a (b) (4) than seen with the Model C cartridges. (b) (4) is now in place and Model D cartridge (b) (4) is equivalent to Model C." Specify the differences between the Model D cartridge used in the bridging study and the Model D cartridge intended for marketing and provide a comparison of performance test data between these two cartridge types (e.g., APSD and emitted dose uniformity).

4. We note that the (b) (4) bridging stability studies used cartridges manufactured by (b) (4) for both Model C and Model D inhalers. This is based on drug product batch information provided in your 9/29/2009 amendment. Provide data to demonstrate that Model C cartridges manufactured by (b) (4) are equivalent in performance to Model C cartridges manufactured by (b) (4) since (b) (4) was the cartridge manufacturer for the primary stability batches and the clinical batches.

5. The following comments pertain to drug product specifications:

   a. Provide a post-approval agreement to propose acceptance criteria for (b) (4)

t (b) (4) Provide supportive data in tabular and graphical summaries. This agreement should be completed within one year after approval. This should be submitted as a prior approval supplement.

b. Provide a post-approval agreement to propose acceptance criteria for the (b) (4) Provide supportive data in tabular and graphical summaries. This agreement should be completed within one year after approval. This should be submitted as a prior approval supplement.

c. Provide a post-approval agreement to re-evaluate the acceptance criteria for Aerodynamic Particle Size Distribution test, based on additional data. This agreement should be completed within one year after approval. This should be submitted as a prior approval supplement.

d. Revise the regulatory drug product specification to specify the number of sample units tested for each test.

e. Your data appear to permit tightening the mean acceptance criterion for emitted dose uniformity to (b) (4)% of label claim (target dose) for the proposed shelf life storage conditions. Modify this acceptance criterion accordingly. Your data also appear to support tighter acceptance criteria for individual values of emitted dose uniformity. Revise the acceptance criteria based on your data so that (b) (4) determinations are within (b) (4)% of label claim, and that all (b) (4) determinations are within (b) (4)% of label claim.

f. Include appropriate acceptance criteria for Insulin-Related Compounds and High-Molecular Weight proteins. The current acceptance criteria are not justified by your analyses of clinical and nonclinical batches of drug product. Acceptance criteria of not more than (b) (4)% for A-21 desamido insulin, not more than (b) (4)% for Total Others, and not more than (b) (4)% for HMW proteins are recommended based on the data you have submitted.

g. Provide the final version of the regulatory drug product specification.

6. Revise your (b) (4) specification for aerodynamic particle size distribution to include multiple stage groupings to control the distribution.

7. Provide samples of the (b) (4) cartridge and provide samples of the device (b) (4).

8. We remind you of your commitment to retain the method for FDKP-related substances as a stability-indicating test at all time points in the drug product stability protocols and in the ongoing stability studies, including the studies of the first 3 production batches from the validated process.

9. The following comments pertain to your drug product stability protocols in section 3.2.P.8.2 of the original NDA.

a. Modify the Post Approval Stability Protocol (Table 3) as follows:

(1) Ensure that it contains the same testing time points as Table 1.

(2) Include testing for foreign particulates for multiple size ranges, as previously discussed.

(3) Clarify the number of sample units tested on stability for each attribute as part of the

stability protocol or specify that the same number is tested as indicated in the drug product specifications.

10. Based upon the stability and other data submitted for the drug product, no more than [redacted] (b) (4) of storage at 25°C beyond the refrigerated shelf life is justified. Revise all labeling to state that the product must be stored under refrigeration and it must be discarded if not used within [redacted] (b) (4) of storage at room temperature.

11. Summarize your data supporting the stability of the finished drug product when subjected to temperature cycling between [redacted] (b) (4) °C.

12. Provide a summary of the differences in manufacturing processes used for historical batches of drug product for which supporting data have been submitted in the NDA. Specifically, provide additional information regarding the [redacted] (b) (4) and relate these steps to the proposed commercial manufacturing process for Technosphere insulin powder.

Rachel E. Hartford
Regulatory Project Manager
Division of Metabolism and Endocrinology Products
Center for Drug Evaluation and Research
Food and Drug Administration
rachel.hartford@fda.hhs.gov
301-796-0331 (phone)
301-796-9712 (fax)

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

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

/s/

RACHEL E HARTFORD
11/18/2009

Hartford, Rachel

From: Hartford, Rachel
Sent: Thursday, November 12, 2009 10:07 AM
To: 'Mayer, Patricia'
Subject: RE: Clinical Information Requests

Hello Patricia,

Thank you for offering to perform the additional analyses listed below. These analyses are no longer needed based on your comments and on our preliminary review of the laboratory data from your phase 2/3 program. Therefore, you can disregard the prior request.

Please note that it is an extremely labor-intensive and time consuming task for MannKind to present tables including subjects from our entire controlled database. There are many datasets complicated by the fact that lab ranges are missing from some of the earlier studies. For these we will need to refer to the lab manuals and manually input the normal ranges. In addition, the studies outside of the pooled Phase 2/3 studies mostly very short term exposures (1 to 13 days) either. Given the small number of subjects we found in the long term studies, it is highly unlikely that an acute toxicity signal will appear in the short term studies. **In order to provide these tables we need to ask for additional time.** The full extent of the effort is difficult to estimate at this point, but we will update you on a regular basis.

Thanks,

Rachel

From: Mayer, Patricia [mailto:pmayer@mannkindcorp.com]
Sent: Tuesday, November 10, 2009 9:20 AM
To: Hartford, Rachel
Cc: Mayer, Patricia
Subject: RE: Clinical Information Requests

Hi Rachel,
Here is the response to the statistical request dated 02Nov2009.

Patricia

P.S.: Whenever we generated new tables or narratives they are attached. However, when our response refers to sections of the NDA, you will find the link in the original submission to the NDA only which is to follow shortly.
P.P.S.: The tables generated for question #1 will be send separately in a zip file, and as stated in the original submission.

Patricia R. Mayer, PhD
Vice President
Worldwide Regulatory Affairs - Liaison
Office: 201-983-5228
Cell: (b) (6)

From: Hartford, Rachel [mailto:Rachel.Hartford@fda.hhs.gov]
Sent: Monday, November 02, 2009 1:56 PM
To: Mayer, Patricia
Subject: FW: Clinical Information Requests

Patricia,

Please disregard question 3 below.

Thank you,

Rachel

From: Hartford, Rachel
Sent: Friday, October 30, 2009 2:08 PM
To: 'Mayer, Patricia'
Subject: Clinical Information Requests

Good Afternoon Patricia,

We have the following Clinical Information Requests:

1. In section 3.6.3 of the ISS, the tables of Serious Adverse events for both type 1 and type 2 combined and then separate (starting with table 28). Do these tables include deaths? Deaths were discussed in the previous section separately, but your definition of an SAE includes any fatal event. Therefore, it seems subjects who died were counted in both sections. If this is the case please resubmit your tables of SAEs excluding subjects who died.

2. For Trial 102 - CSR – page 107 – in the section discussing fasting plasma glucose results: It is not clear if the MMRM and ANCOVA models used the ITT populations with or without LOCF imputation for missing data. This is actually a consistent problem across many trials where it is unclear if any imputation was used.

3. Please update (provide an addendum for) the table of clinical studies with any new studies started after NDA submission (for example trial 134).

4. For trial 009, did subjects begin taking IMPs at week -1 or did they use empty inhalers and empty Pens until week 0? You mention a 10-week run-in period. What happens (or doesn't happen during the run in phase). Is it simply titration of IMPs?

5. In table 41 in the ISS, data for basophils, MCH, MCH (pg), and MCV are missing.

6. Please submit a table showing the number of patients (n, %) meeting these various cutpoints for outlier analyses. Include patients regardless of whether the baseline value is normal or not. First present tables including subjects from your entire controlled database. Then present tables including only subjects from the pooled controlled phase 2/3 trials. Include narratives for patients with ALT >5x ULN, for patients with total bilirubin >5x ULN, and for patients with serum creatinine >2x ULN.

ALT

- > ULN and ≤ 3 X ULN
- > 3X ULN and ≤ 5 X ULN
- > 5 X ULN and ≤ 10 X ULN
- > 10 X ULN

Total bilirubin

- > ULN and ≤ 2 X ULN
- > 2X ULN and ≤ 5 X ULN
- > 5 X ULN and ≤ 10 X ULN
- > 10 X ULN

Serum creatinine

- >ULN and ≤ 1.5 X ULN
- > 1.5 X ULN and ≤ 2 X ULN
- > 2 X ULN

7. Provide narratives for patients in your entire controlled database who met any of the following definitions for Hy's Law.

Hy's Law

- ALT > 3X ULN and total bilirubin > 2X ULN and alk phos < 2.5 X ULN
- ALT >3X ULN and total bili >2x ULN (regardless of alk phos)

Thank you,

Rachel

Rachel E. Hartford
Regulatory Project Manager
Division of Metabolism and Endocrinology Products
Center for Drug Evaluation and Research
Food and Drug Administration
rachel.hartford@fda.hhs.gov
301-796-0331 (phone)
301-796-9712 (fax)

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

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

/s/

RACHEL E HARTFORD
11/12/2009

Hartford, Rachel

From: Hartford, Rachel
Sent: Tuesday, November 10, 2009 10:02 AM
To: 'Mayer, Patricia'
Subject: Clinical Information Request

Follow Up Flag: Follow up
Flag Status: Blue

Attachments: 2009 11 10 IR email.pdf

Hello Patricia,

I received both of your responses this morning. Thank you.

Additional Clinical Information requests are in the attached pdf.

Thanks,

Rachel

2009 11 10 IR email.pdf (80 KB...

Rachel E. Hartford
Regulatory Project Manager
Division of Metabolism and Endocrinology Products
Center for Drug Evaluation and Research
Food and Drug Administration
rachel.hartford@fda.hhs.gov
301-796-0331 (phone)
301-796-9712 (fax)

Information Request - November 10, 2009

1) Please explain how you were able to give 6 U of TI in trial 0008 when in all other trials the minimum dose was 15 U.

2) Please fill in the following tables using the **LOCF method** for missing data. Models should include treatment and pooled investigator site as fixed effects and baseline value as covariate.
The corresponding table from the study reports using ITT observed data is included in the bottom row of each table for your reference.

Trial 102 Treatment Difference in HbA1c (%) Responder Rates at Week 52 (ITT Population with LOCF)					
	TI + glargine	70/30	TI + glargine vs. 70/30		
Responder Category	n (%)	n (%)	Odds Ratio	95% CI	p Value
HbA1c ≤ 6.5% at Week 52					
HbA1c ≤ 7.0% at Week 52					
HbA1c ≤ 8.0% at Week 52					
Table 19, Trial 102 CSR					

Trial 009 Treatment Difference in HbA1c (%) Responder Rates at Week 52 (ITT with LOCF Population)					
	TI + Glargine	Insulin Aspart + Glargine	TI + Glargine vs. Insulin Aspart + Glargine		
Responder Category	n (%)	n (%)	Odds Ratio	95% CI	p Value
HbA1c ≤ 6.5% at Week 52					
HbA1c ≤ 7.0% at Week 52					
HbA1c ≤ 8.0% at Week 52					
Table 18, Trial 009 CSR					

Trial 102 ANCOVA of Change in Body Weight (kg) at Week 52, ITT Population with LOCF				
Time Point	Statistic	TI	70/30 Mix	TI vs. 70/30 Mix
Baseline	N			
	Mean			
	SD			
	95% CI			
Week 52	N			
	Mean			
	SD			
	95% CI			
Change from Baseline to Week 52	N			
	LS Mean			
	SE			
	95% CI			
Table 28, Trial 102 CSR				

Trial 009 ANCOVA of Change in Body Weight (kg) at Week 52, ITT Population with LOCF				
Time Point	Statistic	TI	Insulin Aspart	TI vs. Insulin Aspart
Baseline	N			
	Mean			
	SD			
	95% CI			
Week 52	N			
	Mean			
	SD			
	95% CI			
Change from Baseline to Week 52	N			
	LS Mean			
	SE			
	95% CI			
Table 28, Trial 009 CSR				

Trial 103 - Mean Change from Baseline to Week 12 in Body Weight (kg) (ITT Population with LOCF)				
		TI Alone	Metformin + Secretagogue (MS)	TI + Metformin (TM)
Baseline (Week 0)	N			
	Mean			
	SD			
Endpoint (Week 12)	N			
	Mean			
	SD			
Change from Baseline	Mean			
	SD			
Between Group	Comparison	TI vs. MS	TM vs. MS	TM vs. TI
	Estimate			
	P value			
Within Group	P value			

3) I could not find any updated total exposure data in the 120 day safety update. Please indicate where that information can be found if it was submitted. If it was not submitted please complete the following table for subject exposure to TI as of the cutoff date of 31 May 2009. Include all subjects exposed to TI (i.e. include phase 1, 2, and 3 studies) not just the safety population. Do not include comparator-treated patients.

Diabetes Type	All subjects exposed to TI (n)	Mean and median exposure time (days)	At least 3 month (n) (>=80d)	At least 6 month (n) (>=165d)	At least 12 month (n) (>=330d)	At least 18 month (n) (>=510d)	At least 24 month (n) (>=660d)
Type 1							
Type 2							
Total							

4) There are inconsistencies in the numbers in tables 15/18 and 16/19. The numbers in the "overall" section of tables 18 and 19 do not match the corresponding total numbers in 15 and 16.

For example: in table 18 the overall number adds up to 608 although the heading and table 15 say there are 614 subjects.
We also note that there is no row for > 300 here. Please indicate if this was intentional.

Exposure Duration (Months)	Average Daily Dose of TI (U)	Number of Subjects Exposed to TI (n = 614)
Overall	≤ 60	47 (7.7)
	> 60-120	223 (36.3)
	> 120-180	189 (30.8)
	> 180-240	103 (16.8)
	> 240-300	46 (7.5)

5) Please present the duration of diabetes (mean (SD), median, and range) for the type 2 diabetes pooled safety population and then for the type 1 diabetes pooled safety population.

6) For trials 009 and 102 we request further analyses of patient disposition. Please create separate tables for trial 009 and 102 with categories like the example presented here. Subjects who discontinued due to lack of efficacy should be reported separately from other adverse events. For subjects who "withdrew consent" and withdrew for "investigator decision", please further subcategorize by reason. Some example reasons are listed in the table. <u>However, add as many categories as needed to properly categorize all subjects.</u> If the reason was "not happy with treatment" please attempt to provide a reason. Do not include an "other" category; instead list the investigator verbatim reason for discontinuation for subjects who were in the "other" category. Please include all events regardless of severity (i.e. include both serious and non-serious events).

	TI n (5)	Comparator n (%)
Randomized		
Safety Population		
Completed 52 weeks		
Prematurely Discontinued		
• Adverse event of hyperglycemia, blood glucose increased, or Diabetes mellitus inadequate control, ketoacidosis, diabetic ketoacidosis, or any other preferred term representing inadequate glycemic control and any other withdrawal due to lack of efficacy including investigator decisions that upon examination appear to be due to lack of efficacy		
• Adverse Event other than those related to hyperglycemia		
• Protocol Violation		
• Subject Withdrew Consent		

• Moved		
• Randomization choice		
• New occupation		
• Subject Died		
• Investigator Decision		
• Reason		
• reason		
• Lost to Follow-up		
• Unknown		

7) In the integrated summary of safety, please explain why table 35 includes events under the categories of psychotic disorders and skin and subcutaneous tissue disorders but table 31 does not include these events.

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

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

/s/

RACHEL E HARTFORD
11/10/2009

Hartford, Rachel

From: Hartford, Rachel
Sent: Friday, November 06, 2009 10:05 AM
To: 'Mayer, Patricia'
Subject: Clinical Information Requests

Attachments: FDA 26Oct requests_clinical +Agency clarification requests_04Nov.doc; 2009 11 06 Clinical IR.doc

Good Morning Patricia,

We have additional clinical information requests (2009 11 06 Clinical IR.doc) and a clarification request for a previous response (FDA 26Oct requests_clinical + Agency clarification_requests 04Nov.doc). The clarification request is in bold maroon font.

Thank you,

Rachel

FDA 26Oct equests_clinical +A.

2009 11 06 Clinical IR.doc (36...

Rachel E. Hartford
Regulatory Project Manager
Division of Metabolism and Endocrinology Products
Center for Drug Evaluation and Research
Food and Drug Administration
rachel.hartford@fda.hhs.gov
301-796-0331 (phone)
301-796-9712 (fax)

1) Please give the duration of diabetes in years (mean, median and range) for trial 101.

2) We have a follow up question related to question 8A: ***Was severe hyperglycemia a withdrawal criterion in other trials besides 0008?***

Your response: There were 7 other trials were hyperglycemia was a criteria for withdrawal.

For some of the trials (005, 026) it was stated that hyperglycemia was classified as lack of efficacy rather than an AE. However, none of the subject disposition tables in the CSRs include a row for discontinuation due to lack of efficacy. Were there no discontinuations due to lack of efficacy in these trials?

Additionally your response is inconsistent with the following table from trial 005 which show that hyperglycemia was reclassified as adverse events not as lack of efficacy.

Table 11. Reclassified as Adverse Events Leading to Discontinuation

Subject Number	Treatment Group	Original Classification	Reason for Withdrawal
2905	TI 14 U	Other	Lack of efficacy – hyperglycemia
4680	TI 28 U	Other	Hyperglycemia
5298	TI 42 U	Physician Decision	Hyperglycemia > 27.5 mmol/L
5382	TI 56 U	Withdrew Consent	Patient was dissatisfied with blood sugar and adverse events (chest discomfort, pharyngolaryngeal pain, nocturnal dyspnoea, nasopharyngitis)
7607	TI 14 U	Other	Continuous hyperglycemia; metabolic decompensation

Data Source: Appendix 2, Listing 1 and Listing 51.

Additionally, please explain how hyperglycemia related withdrawals were coded for trials 0008, 010, and 101.

3) Were there any criteria for discontinuation due to lack of efficacy in trial 102 or 009? If so what were they? How many subjects if any discontinued due to lack of efficacy in these two trials?

4) In trial 0008, there were 5 patients excluded from the ITT population. Please provide the reasons for these exclusions.

Title:	Response to FDA Request for Information dated 26Oct2009
NDA Number:	22-472
Product Name:	Technosphere® Insulin Inhalation Powder
Drug Substance:	Insulin Human Recombinant
Indication:	Diabetes Mellitus
Sponsor:	MannKind Corporation 61 South Paramus Rd Paramus, NJ 07652

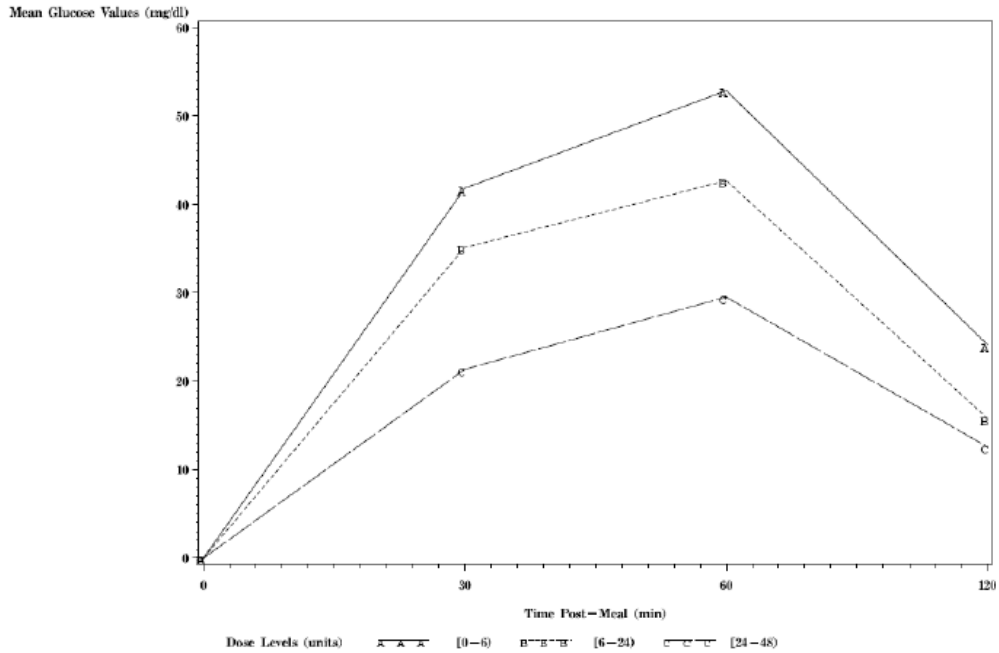
Confidentiality Statement

Please refer to the MannKind's NDA 22-472 for Technosphere Insulin® Inhalation Powder and the email request submitted to MannKind Corporation on 26Oct2009.

The Agency's requests are noted in ***bold, italic*** font. MannKind's response immediately follows the request in normal font.

1) ***On page 90 of the trial PDC-INS-0008 report it states that: Based on Time 0-corrected laboratory glucose values, increasing the TI Inhalation Powder dose lowered mean postprandial glucose values over time (Figure 7). Hence, a dose response was demonstrated. This is unclear. Please explain.***

Figure 7: Mean Time 0-corrected Laboratory Glucose Values by Weighted Average Dose Level Over Time Post-meal (ITT Population)



Data Source: Section 14.2, Figure 7

Figure 7 of the PDC-INS-0008 CSR (Section 11.5.1.2 – Secondary Efficacy Results – Effect on postprandial glucose control) represents the mean Time 0 corrected blood glucose values that were measured during the meal challenges at the visits 3,6,8 and 9. Curve "A" represents the mean blood glucose values for subjects treated with 6 U of Technosphere Insulin. Curve "B" represents those subjects on a meal time dose of between 6 – 24 U and curve "C" represents those subjects on a meal time dose of 24 -48 U. At each of the meal challenge time points (30 minutes, 60 minutes and 120 minutes), time 0 corrected blood glucose levels (i.e. post meal blood glucose excursions) were lowest in subjects on the highest doses of TI (i.e curve "C") and highest for those on the lowest dose of TI (curve "A"), with blood glucose levels for the group with the intermediate dose (curve "B") falling in between C and A. Thus, subjects treated with

higher doses of TI had smaller post-prandial blood glucose excursion during the meal challenge testing than those on lower doses of TI.

2) It is unclear how metformin and gliclazide could be concomitant medications in trial MKC-TI-005 because subjects were supposed to discontinue oral antidiabetic medications at the start of the trial.

Metformin and gliclazide were considered concomitant medications according to the definition in section 5.3.7 – Prior and concomitant therapy (page 31 of the clinical study report [CSR]) and were to be discontinued at visit 4 (week 5). – See text from CSR:

5.3.7 Prior and Concomitant Therapy

Prior medications are defined as medications stopped prior to the day of the first administration of TP at Visit 3 (Week 4). Concomitant medications are defined as medications taken prior to Visit 3 and continued thereafter, as well as those started after the day of the first TP administration. (Lantus® was not considered a concomitant medication.)

Any medications known to modify glucose metabolism or the ability to recover from hypoglycemia were discontinued at Visit 4 (Week 5); they are considered concomitant medications as they would have been concomitant with TP. Such medications include: oral, parenteral and inhaled steroids, oral anti-hyperglycemic medications, or > 25 mg of hydrochlorothiazide daily. Subjects could not take another investigational drug within 3 months prior to trial entry or during the trial.

3) ***Trial MKC-TI-005 study report table 22, please re-presents using U.S. units. (mg/dL)***

See TBL_FBG_SUMM_mg_dL.pdf

4) ***For trial 0008 figure 5 we would like to see the time response curve for each dose separately (i.e. 8 lines instead of 3) and then another time response graph with four categories instead of 3. Please include graphs using ITT with LOCF and ITT observed data.***

In response to request #4 below, we have generated 4 figures presenting mean change in HbA1c, by visit and different dose or dose groups, for ITT population and ITT population with LOCF applied.

1. Figures F-A1c-001 (ITT) and F-A1c-002 (ITT with LOCF): these two figures are presenting mean change of HbA1c from baseline to each post-baseline visit, by the actual dose level taken on the HbA1c measurement visit day; there are 8 dose levels and thus 8 lines are presented

2. Figures F-DOSE-001 (ITT) and F-DOSE-002 (ITT with LOCF): these two figures are presenting mean change of HbA1c from baseline to each post-baseline visit, by the exposure weighted average dose level - there are 4 dose groups as selected and thus 4 lines are presented.
For the exposure weighted average dose level, it is derived for each of the 3 time intervals (visit 3 to visit 6, visit 6 to visit 8 and visit 8 to visit 9) and calculated as:
Exposure weighted average dose in each interval = Total dose taken in each interval divided by total exposure in each time interval.

Please refer to your response above. Please clarify why the N's for number of patients exposed at each dose are different than in the original analysis presented in the NDA (Figure 5 in the trial 0008 CSR). Specifically, why is the total N at visit 9 110 in figure 5, but only 54 in figure F-DOSE-001 (ITT)? We note that the N for visit 3 was not presented in the new figure, and the N for visit 6 and 8 were not presented in the original figure.

4) Were all HbA1c measurements performed by a central laboratory?

HbA1c measurements within each study were performed by a central lab. Except for one study (PDC-INS-0008) all HbA1c measurements in all studies were performed by one central lab (b) (4).

STUDY	LAB USED
PDC-INS-0008	(b) (4)
MKC-TI-005	
MKC-TI-009	
MKC-TI-010	
MKC-TI-014	
MKC-TI-026	
MKC-TI-030	
MKC-TI-101	
MKC-TI-102	
MKC-TI-103	

6) ***Glucose data for the meal tolerance test in all studies should be presented in mg/dL units instead of mmol/L***

We have reviewed all trials and only Study MKC-TI-005 includes tables with the meal challenge glucose data that require a presentation in mg/dL.

While we did the conversion in the SAS tables, we recognized that 3 of the original tables in mmol/L had been mislabeled.

The errors found in these 3 original tables are:

T-004-002-03D: this table contains the result from an incorrect population. The population presented in the original table was 'Randomized Subjects' while it should have been the 'Per-Protocol Population'. This table has been redone with the correct PP-population. The results from these tables had not been discussed in the CSR, but referenced only. No result interpretation or conclusions changed.

T-004-002-02B.pdf: the title should not read as 'Baseline Corrected AUC'; instead it should be just 'AUC' . The table has now the corrected title and also the appropriate unit in the title was added. The CSR text is correct.

T-004-002-03B.pdf: the unit is missing in the original table and it was added

The corrected tables are provided in the original unit: mmol/L .

The corresponding mg/dL tables are the tables labeled with an 'x' at the end T-004-002-02BX.pdf, T-004-002-03BX.pdf, T-004-002-03DX.pdf and T-004-003-001X.pdf. We kept the same table numbers so that they can be easily related to the submitted original tables.

7) ***For trials where the HbA1c entry criteria state HbA1c "between" certain values (trials 0008, 005, and 026) is the range inclusive of the upper and lower bounds or not inclusive?***

7A) Clarification request: In the question, the meaning of the word inclusive was intended to be 'including the upper and lower bounds'. Therefore if, for example, For study MKC-TI-005, the inclusion criteria "HbA1c between 7.0% and 12%" was defined as HbA1c >7.0% and <12% then the Hba1c values would be non-inclusive of the upper and lower bounds. Is this correct? Inclusive of the upper and lower bounds would be ≥ 7.0% and ≤ 12%.

Yes, HbA1c >7.0% and <12% means that the HbA1c values would be non-inclusive of the upper and lower bounds. Inclusive of the upper and lower bounds would be ≥ 7.0% and ≤ 12%.

MKC-TI-005:

For study MKC-TI-005, the inclusion criteria "HbA1c between 7.0% and 12%" was defined as HbA1c >7.0% and <12%.

PDC-INS-0008:

For study PDC-INS-0008, the inclusion criteria "HbA1c between 6.6% and 10.5%" was defined as HBA1c >6.6 and <10.5, non inclusive.

MKC-TI-026:

For study MKC-TI-026, the inclusion criteria "HbA1c between 7.5% and 12%" was defined as HbA1c >7.5% and <12%.
The investigators and the site coordinators/staff were instructed that HbA1c values should be between the bounds. Therefore, there were 5 approved protocol exemptions for HbA1c values outside that range (subjects with screening values of 7.4%, 7.5%, 7.5%, 12%, 12.7%).

8) For trial 0008 withdrawal criteria include "The patient experienced one episode of severe hyperglycemia." Is this supposed to read "hypoglycemia"?

No, section 9.3.3 should read "the patient experienced one episode of severe hyper – or hypoglycemia. Both conditions labeled as "severe" led to withdrawal of the patient (Discontinuation due to severe hypoglycemia protocol section 4.5.1, discontinuation due to severe hyperglycemia, protocol section 4.1)

8A) Was severe hyperglycemia a withdrawal criterion in other trials besides 0008?

There were 7 other trials were hyperglycemia was a criteria for withdrawal
In MKC-TI-010, it was designated as "severe" as it was in 0008.

MKC-TI-010- CSR Page 32

hyperglycemia." Likewise, any finding of a plasma glucose level of > 27.5 mmol/L (495 mg/dL) will constitute an automatic designation of "severe hyperglycemia."

Any finding of a "severe hyperglycemia" was to result in the automatic withdrawal of the subject from the trial.

MKC-TI-005- CSR Page 35

NOTE ON HYPERGLYCEMIA

Hyperglycemia was classified as lack of efficacy rather than an AE unless specifically designated as an AE by the Investigator. Unless specifically reported as AEs by the Investigator, such events are not included in the AE listings and summaries but are separately listed and summarized. Hyperglycemia was defined as a fasting glucose value > 15.0 mmol/L (270 mg/dL) or a non-fasting glucose value > 22 mmol/L (396 mg/dL). Discontinuation of a subject's participation in the trial due to hyperglycemia was at the discretion of the Investigator. However, any glucose reading > 27.5 mmol/L (495 mg/dL) was to result in automatic withdrawal of the subject from the trial.

MKC-TI-101- CSR Page 33

Hyperglycemia: Hyperglycemia was defined as a FBG concentration > 270 mg/dL (> 15.0 mmol/L) or a nonfasting blood glucose > 396 mg/dL (> 22 mmol/L). Discontinuation of a subject's participation in the study because of hyperglycemia was at the discretion of the Investigator, except that any glucose concentration of > 495 mg/dL (> 27.5 mmol/L) was to result in immediate discontinuation. Hyperglycemia occurring after meal ingestion and treatment with the investigational drug might also be considered as lack of efficacy.

MKC-TI-014- CSR Page 37

discretion of the Investigator. However, if despite increases in TI Inhalation Powder to 60 U per meal, the measured fasting glucose levels were repeatedly ≥270 mg/dL, subjects were to be permanently discontinued from the trial. Additionally, any BG reading of >495 mg/dL (27.5 mmol/L) was to result in automatic withdrawal of the subject from the trial.

MKC-TI-026- CSR Page 29

Hyperglycemia

Hyperglycemia was classified as lack of efficacy rather than an AE unless specifically designated as an AE by the Investigator. It was also analyzed separately from other events in the trial. Unless specifically reported as AEs by the Investigator, such events are not included in the AE listings and summaries but are separately listed and summarized. Hyperglycemia was defined as a fasting glucose value greater than 15.0 mmol/L (270 mg/dL) or a non-fasting glucose value greater than 22 mmol/L (396 mg/dL). Discontinuation of a subject's participation in the trial because of hyperglycemia was at the discretion of the Investigator. However, any glucose reading of greater than 27.5 mmol/L (495 mg/dL) was to result in automatic withdrawal of the subject from the trial.

MKC-TI-104- CSR. Page 30

NOTE ON HYPERGLYCEMIA

Hyperglycemia was classified as lack of efficacy rather than an AE unless specifically designated as an AE by the Investigator. Unless specifically reported as AEs by the Investigator, such events are not included in the AE listings and summaries but are separately listed and summarized. Hyperglycemia was defined as a fasting glucose value greater than 15.0 mmol/L (270 mg/dL) or a non-fasting glucose value greater than 22 mmol/L (396 mg/dL). Discontinuation of a subject's participation in the study due to hyperglycemia was at the discretion of the Investigator. However, any glucose reading of greater than 27.5 mmol/L (495 mg/dL) was to result in automatic withdrawal of the subject from the study. Hyperglycemia that occurred after meal ingestion and treatment with the investigational drug could be considered as a lack of efficacy.

MKC-TI-027- CSR- Page 31

to be withdrawn from the trial.

Discontinuation of a subject's participation in the clinical trial due to hyperglycemia was at the discretion of the PI however, any BG > 495 mg/dL (27.5 mmol/L) was to result in automatic withdrawal of the subject from the clinical trial.

9) ***For Trial 009 Table 9 in the CSR is unclear. If all subjects were taking insulin at study entry, why does the table indicate 91% for the TI group and 88% in the insulin aspart group were using insulin?***

Table 9. Diabetes Treatments Taken at Screening (Safety Population)

Diabetes Treatment Taken	TI (n = 293) n (%)	Insulin Aspart (n = 272) n (%)
Insulin and analogues	267 (91.1) [a]	240 (88.2) [a]
Premixed	6 (2.0)	4 (1.5)
Fast-acting + intermediate-acting	72 (24.6)	68 (25.0)
Fast-acting + long-acting	174 (59.4)	154 (56.6)

[a] All subjects were using insulin at trial entry.
Medications were coded using the WHO Drug Dictionary Version 2003Q4.
Percentages are based on the number of subjects in each treatment group in the Safety Population.
Data Source: Table 6.3.3 and Listing 6.5.1

All patients fulfilled the requirement of being on insulin at screening, but the information on the type of insulin was not available in all patients. That missing information for some patients accounts for the total not adding up to 100%.

10) ***The following table indicates that trial 026 had comparator subjects using insulin. However, according to the study report it does not appear that any subjects were using subcutaneous insulin. Please explain.***

Table 2: Comparator Group Trial Contributions

Trial	Comparator Group	Comparator Treatment
MKC-TI-102	Insulin	Premix analog 70/30
MKC-TI-014	Insulin	insulin aspart
MKC-TI-030	Insulin	Usual care subjects who took insulin
MKC-TI-026	Insulin	Usual care subjects who took insulin
MKC-TI-103	Non-insulin	Metformin + secretagogue
MKC-TI-030	Non-insulin	Usual care subjects who did not take insulin
MKC-TI-026	Non-insulin	Usual care subjects who did not take insulin

Data Source: Statistical Analysis Plan.

We recognize that the table appears unclear.

In study MKC-TI-026 there were five subjects, three subjects in the TI group (subjects Nos. 269, 357 and 790) and two subjects in the comparator group (subjects Nos. 356 and 677) who had reported previous exposures to insulin. The exposure was for very short periods (between 7 days up to 1 month) and prior to participation in the study (Listing 4, Diabetes History, Randomized Subjects). There were no subjects treated with sc insulin during the trial (Listing 21. Concomitant Medications Randomized Subjects).

10A) Therefore, is it correct to state that trial 026 did not contribute any patients to the "insulin" group for the hypoglycemia analyses or any of the other integrated summaries of safety that compared TI patients to "insulin" patients?

Yes, it is a correct statement. 026 did not contribute any patients to the "insulin" control group in any of the integrated summaries. Table 2 from the ISS is incorrect, as 026 is listed both under "comparator group insulin" and "comparator group non-insulin", it should only figure as "comparator group non-insulin".

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

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

/s/

RACHEL E HARTFORD
11/06/2009

Hartford, Rachel

From: Hartford, Rachel
Sent: Wednesday, November 04, 2009 10:52 AM
To: 'Mayer, Patricia'
Subject: Clinical Information Request

Attachments: Analysis request for trial 005.doc

Hello Patricia,

Please see the attachment for additional Clinical Information Requests for trial 005.

Thank you,

Rachel

Analysis request for trial 005...

Rachel E. Hartford
Regulatory Project Manager
Division of Metabolism and Endocrinology Products
Center for Drug Evaluation and Research
Food and Drug Administration
rachel.hartford@fda.hhs.gov
301-796-0331 (phone)
301-796-9712 (fax)

Analysis request for trial 005

1) Please fill in the following table for each of these variables

HbA1c
AUCglucose 0-300
Fasting plasma glucose

Treatment Group	N	Baseline value (raw mean) and (SD)	Final value (raw mean) and (SD)	Change from baseline LS Mean and (%)	95% CI for the LS Mean change from baseline	Difference from TP LS Mean and (%)	P value from t test with stepdown procedure
TP							
TI 14 U							
TI 28 U							
TI 42 U							
TI 56 U							

Use the visit 5 value as the baseline and use the visit 12 value as the final value.

In the ANCOVA model include treatment and baseline value (at visit 5) as a covariate. Do not include site.

2) Please fill in the table again with an ANCOVA analysis for each of the three variables listed in #1 except this time include time adjusted Lantus exposure (TALE) and the TALE x treatment interaction effect in the model.

3) Table 19 in the CSR for trial 005:
We believe the title has the units mislabeled and it should be mmol/L. Please confirm

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

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

/s/

RACHEL E HARTFORD
11/04/2009

Hartford, Rachel

From: Hartford, Rachel
Sent: Monday, November 02, 2009 1:56 PM
To: 'Mayer, Patricia'
Subject: FW: Clinical Information Requests

Patricia,

Please disregard question 3 below.

Thank you,

Rachel

From: Hartford, Rachel
Sent: Friday, October 30, 2009 2:08 PM
To: 'Mayer, Patricia'
Subject: Clinical Information Requests

Good Afternoon Patricia,

We have the following Clinical Information Requests:

1. In section 3.6.3 of the ISS, the tables of Serious Adverse events for both type 1 and type 2 combined and then separate (starting with table 28). Do these tables include deaths? Deaths were discussed in the previous section separately, but your definition of an SAE includes any fatal event. Therefore, it seems subjects who died were counted in both sections. If this is the case please resubmit your tables of SAEs excluding subjects who died.

2. For Trial 102 - CSR – page 107 – in the section discussing fasting plasma glucose results: It is not clear if the MMRM and ANCOVA models used the ITT populations with or without LOCF imputation for missing data. This is actually a consistent problem across many trials where it is unclear if any imputation was used.

3. **Please update (provide an addendum for) the table of clinical studies with any new studies started after NDA submission (for example trial 134).**

4. For trial 009, did subjects begin taking IMPs at week -1 or did they use empty inhalers and empty Pens until week 0? You mention a 10-week run-in period. What happens (or doesn't happen during the run in phase). Is it simply titration of IMPs?

5. In table 41 in the ISS, data for basophils, MCH, MCH (pg), and MCV are missing.

6. Please submit a table showing the number of patients (n, %) meeting these various cutpoints for outlier analyses. Include patients regardless of whether the baseline value is normal or not. First present tables including subjects from your entire controlled database. Then present tables including only subjects from the pooled controlled phase 2/3 trials. Include narratives for patients with ALT >5x ULN, for patients with total bilirubin >5x ULN, and for patients with serum creatinine >2x ULN.

   ALT
   - > ULN and ≤ 3 X ULN
   - > 3X ULN and ≤ 5 X ULN
   - > 5 X ULN and ≤ 10 X ULN
   - > 10 X ULN

   Total bilirubin
   - > ULN and ≤ 2 X ULN
   - > 2X ULN and ≤ 5 X ULN
   - > 5 X ULN and ≤ 10 X ULN
   - > 10 X ULN

Serum creatinine

- >ULN and ≤ 1.5 X ULN
- > 1.5 X ULN and ≤ 2 X ULN
- > 2 X ULN

7. Provide narratives for patients in your entire controlled database who met any of the following definitions for Hy's Law.

Hy's Law

- ALT > 3X ULN and total bilirubin > 2X ULN and alk phos < 2.5 X ULN
- ALT >3X ULN and total bili >2x ULN (regardless of alk phos)

Thank you,

Rachel

Rachel E. Hartford
Regulatory Project Manager
Division of Metabolism and Endocrinology Products
Center for Drug Evaluation and Research
Food and Drug Administration
rachel.hartford@fda.hhs.gov
301-796-0331 (phone)
301-796-9712 (fax)

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

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

/s/

RACHEL E HARTFORD
11/03/2009

Hartford, Rachel

From: Hartford, Rachel
Sent: Tuesday, November 03, 2009 11:39 AM
To: 'Mayer, Patricia'
Subject: Statistical Requests

Hello Patricia,

Please respond to the following statistical requests:

1. In your response on August 28, 2009 to the FDA's question No. 3, the 19 subjects that you identified were not the same subjects this reviewer referred to. Specifically, in this study (MKC-TI-103), there were some subjects (this reviewer noticed at least 18) who were randomized but early terminated (ET) with a baseline and post-baseline (ET) HbA1c recorded. However, the early termination values were not flagged for the primary efficacy analysis in the ITT/LOCF population (for example, subject no. 1073, 1116, 1145. etc.). Please verify and send the corrected data set ASAP.

2. In your response on October 27, 2009 to the FDA's question for Study MKC-TI-014, you mentioned below,

Regarding the request on the pooled site information, we are not sure what to provide. We have checked through all the related documents including analysis datasets and we could not find any pooled site that was used or referenced in any of submitted analysis. Can you provide more information on this request, e.g. in which analysis the reviewer has identified that the pooled site was used?

Please see your CSR for this study, page 75, Section 7.1.1.5. Also, in that section, it talks about "Attachments, Ad hoc Output 2", which was unable to be located by this reviewer.

3. For Study MKC-TI-005, the baseline values in the hba005.xpt (HBA_BASE) file are different from those in the adhba1cr.xpt (NVALUE5) file. The errors were reflected on the results (for example, Tables 15 and 17 were generated using adhba1cr.xpt file, while Table 16 was generated using hba005.xpt file) in the CSR. Please clarify and make any necessary corrections. In addition, please clarify the sample size per group for the ITT population and ITT/LOCF population.

Thank you,

Rachel

Rachel E. Hartford
Regulatory Project Manager
Division of Metabolism and Endocrinology Products
Center for Drug Evaluation and Research
Food and Drug Administration
rachel.hartford@fda.hhs.gov
301-796-0331 (phone)
301-796-9712 (fax)

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

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

/s/

RACHEL E HARTFORD
11/03/2009

Hartford, Rachel

From: Hartford, Rachel
Sent: Monday, November 02, 2009 11:43 AM
To: 'Mayer, Patricia'
Subject: Clinical Information Requests

Attachments: 2009 11 02 Clinical IR email.pdf

Hello Patricia,

Please see the attached pdf for additional Clinical Information Requests.

Thank you,

Rachel

2009 11 02 Clinical IR email.p...

Rachel E. Hartford
Regulatory Project Manager
Division of Metabolism and Endocrinology Products
Center for Drug Evaluation and Research
Food and Drug Administration
rachel.hartford@fda.hhs.gov
301-796-0331 (phone)
301-796-9712 (fax)

Afrezza Questions for Sponsor 3

1. In the ISS it states that subject (MKC-TI-102-2487) was receiving BPR 70/30 and discontinued due to anemia. However, the link to the case narrative leads to what appears to be the correct patient, but there is no mention of discontinuation due to anemia. Instead it states **Neoplasm Cardiovascular** and under Withdrawn due to Adverse Event it says "no"

2. In this table from the ISS the numbers for comparator treated patients do not match what is in the text which reads ". . . . with 1552 of these 1944 subjects receiving other (nonTI) insulin treatment and 392 receiving oral agents only."

Table 8. Disposition of Subjects With Type 1 or Type 2 Diabetes Mellitus (Safety Population – Pooled Controlled Phase 2/3 Trials)

			Comparator		
	TI	TP	Other insulin	Non-insulin	All
	n (%)	n (%)	n (%)	n (%)	n (%)
Randomized subjects	2453	108			1978
Safety population	2409	114	1541	403	1944
Completed study treatment	1539 (63.9)	0	1208 (78.4)	281 (69.7)	1489 (76.6)
Prematurely discontinued	870 (36.1)	21 (18.4)	333 (21.6)	122 (30.3)	455 (23.4)
Reasons for discontinuation from study					
Adverse events[a]	185 (7.7)	2 (1.8)[b]	22 (1.4)	5 (1.2)	27 (1.4)
Protocol violation	50 (2.1)	3 (2.6)	24 (1.6)	5 (1.2)	29 (1.5)
Subject withdrew consent	380 (15.8)	11 (9.6)	162 (10.5)	69 (17.1)	231 (11.9)
Subject died	8 (0.3)	0	5 (0.3)	0	5 (0.3)
Investigator decision	64 (2.7)	1 (0.9)	16 (1.0)	6 (1.5)	22 (1.1)
Lost to follow-up	69 (2.9)	0	78 (5.1)	33 (8.2)	111 (5.7)
Other	113 (4.7)	4 (3.5)	26 (1.7)	4 (1.0)	30 (1.5)
Unknown	1 (0.0)	0	0	0	0

TI = Technosphere® Insulin; TP = Technosphere® Inhalation Powder.

[a] Including laboratory abnormalities

[b] Includes subjects MKC-TI-014/016, MKC-TI-014/804, MKC-TI-030/0299, MKC-TI-030/1053, MKC-TI-030/1198, MKC-TI-030/1283, MKC-TI-030/2627, MKC-TI-030/3058, MKC-TI-030/3398, MKC-TI-102/1126, MKC-TI-102/1338, MKC-TI-102/1498, MKC-TI-102/1653, MKC-TI-103/1309, MKC-TI-103/1789, MKC-TI-103/2249, MKC-TI-103/2263, MKC-TI-103/2281, and PDC-INS-0008/374 who were recorded on the subject summary page as discontinuing because of an adverse event but did not have a TEAE recorded as leading to discontinuation from trial.

Note(s): Percentages are based on the total number of subjects in the Safety Population in each treatment group.

Data Source: Table G.3.1

3. Please clarify whether the "b" superscript is in the right place in the following table. Also for each of the subjects listed after the "b" superscript in the key please provide the site number.

Table 10. Disposition of Subjects With Type 2 Diabetes Mellitus (Safety Population – Pooled Controlled Phase 2/3 Trials)

	TI n (%)	TP n (%)	Comparator		
			Other insulin n (%)	Non-insulin n (%)	All n (%)
Randomized subjects	1829	108	NA	NA	1363
Safety population	1795	114	953	392	1345
Completed study treatment	1166 (65.0)	0	733 (77.8)	281 (69.7)	1014 (75.4)
Prematurely discontinued	629 (35.0)	21 (18.4)	214 (22.2)	117 (29.8)	331 (24.6)
Reasons for discontinuation from study					
Adverse events[a]	142 (7.9)	2 (1.8)[b]	19 (2.0)	5 (1.3)	24 (1.8)
Protocol violation	37 (2.1)	3 (2.6)	8 (0.8)	5 (1.3)	13 (1.0)
Subject withdrew consent	251 (14.0)	11 (9.6)	106 (11.1)	67 (17.1)	173 (12.9)
Subject died	7 (0.4)	0	4 (0.4)	0	4 (0.3)
Investigator decision	42 (2.3)	1 (0.9)	9 (0.9)	6 (1.5)	15 (1.1)
Lost to follow-up	53 (3.0)	0	53 (5.6)	30 (7.7)	83 (6.2)
Other	97 (5.4)	4 (3.5)	15 (1.6)	4 (1.0)	19 (1.4)
Unknown	0	0	0	0	0

NA = Not applicable; TI = Technosphere® Insulin; TP = Technosphere® Powder.

Note(s): Percentages are based on the total number of subjects in the Safety Population in each treatment group.

[a] Including laboratory abnormalities

[b] Includes subjects MKC-TI-014/016, MKC-TI-014/804, MKC-TI-030/0299, MKC-TI-030/1053, MKC-TI-030/1198, MKC-TI-030/1283, MKC-TI-030/2627, MKC-TI-030/3058, MKC-TI-030/3398, MKC-TI-102/1126, MKC-TI-102/1338, MKC-TI-102/1498, MKC-TI-102/1653, MKC-TI-103/1309, MKC-TI-103/1789, MKC-TI-103/2249, MKC-TI-103/2263, MKC-TI-103/2281, and PDC-INS-0008/374 who were recorded on the subject summary page as discontinuing because of an adverse event but did not have a TEAE recorded as leading to discontinuation from trial.

Data source: Table G.2.1.

4. In studies 0008 and 005 tables of prior medications: How is it possible that roughly 80% of subjects were taking metformin and/or sulfonylureas, and also that roughly 40 – 60% were treated with diet/exercise alone?

5. Please present data (mean, median, and range) for duration of diabetes, by treatment group, for the ITT populations in trial 005 and trial 0008 and trial 026.

6. Please present mean and range BMI, by treatment group, for the ITT populations in trial 005 and 0008.

7. In one of the summaries it states that LOCF was the pre-specified method of imputation applied to data from trials MKC-TI-102, MKC-TI-009, MKC-TI-026 and MKC-TI-103. No method of imputation was employed in the primary analysis for the other trials. However, you have presented (for example Table 9) LOCF data for trial 005. Please explain this discrepancy.

8. Please provide the intersubject coefficient of variation for the Hba1c assay from (b) (4)

9. In table 18 in the CSR for trial 005 which states it includes the ITT population (total n=212), the N's for the 14 U TI group and the 28 U TI group are 43 and 43, respectively and the total patients add up to 210 instead of 212. In table 17 the N's for the 14 U TI group and the 28 U TI group are listed as 44 and 44, respectively and the total patients do add up to 212. The same issue exists for

Tables 23 and 24 25, 26, and 27 for trial 005 where the individual N's do not add up to 212. Also in the Table 4.2.1AX of fasting plasma glucose that was sent in on Friday 10.30 as a response to clinical questions, the total number of patients adds up to 211. Please explain the discrepancies in your numbers throughout this trial.

10. In trial 005, tables 15 and 16 show the change in HbA1c from baseline to study endpoint in the ITT population, and in the ITT population with LOCF method for imputation of missing data. It is unclear why the mean HbA1c at baseline should be different in the two tables for the several of the groups.

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

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

/s/

RACHEL E HARTFORD
11/02/2009

Hartford, Rachel

From: Hartford, Rachel
Sent: Monday, November 02, 2009 11:35 AM
To: 'Mayer, Patricia'
Subject: Additional Clarification Requests for 30Oct09 email

Attachments: Response to FDA 26Oct requests_clinical Agency clarification requests.doc

Hello Patricia,

The attached document sent via email on 30Oct09 contains additional clarification requests in red text.

Thank you,

Rachel

Response to FDA 26Oct requests...

Rachel E. Hartford
Regulatory Project Manager
Division of Metabolism and Endocrinology Products
Center for Drug Evaluation and Research
Food and Drug Administration
rachel.hartford@fda.hhs.gov
301-796-0331 (phone)
301-796-9712 (fax)

Title:	Response to FDA Request for Information dated 26Oct2009
NDA Number:	22-472
Product Name:	Technosphere® Insulin Inhalation Powder
Drug Substance:	Insulin Human Recombinant
Indication:	Diabetes Mellitus
Sponsor:	MannKind Corporation 61 South Paramus Rd Paramus, NJ 07652

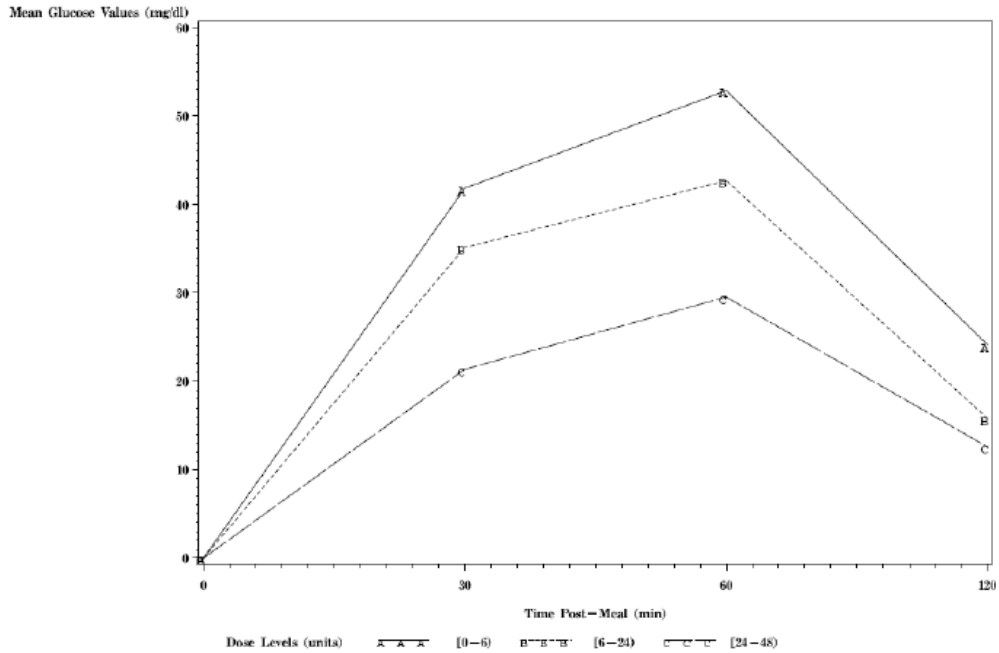
Confidentiality Statement

Please refer to the MannKind's NDA 22-472 for Technosphere Insulin® Inhalation Powder and the email request submitted to MannKind Corporation on 26Oct2009.

The Agency's requests are noted in ***bold, italic*** font. MannKind's response immediately follows the request in normal font.

1) ***On page 90 of the trial PDC-INS-0008 report it states that: Based on Time 0-corrected laboratory glucose values, increasing the TI Inhalation Powder dose lowered mean postprandial glucose values over time (Figure 7). Hence, a dose response was demonstrated. This is unclear. Please explain.***

Figure 7: Mean Time 0-corrected Laboratory Glucose Values by Weighted Average Dose Level Over Time Post-meal (ITT Population)



Data Source: Section 14.2, Figure 7

Figure 7 of the PDC-INS-0008 CSR (Section 11.5.1.2 – Secondary Efficacy Results – Effect on postprandial glucose control) represents the mean Time 0 corrected blood glucose values that were measured during the meal challenges at the visits 3,6,8 and 9. Curve "A" represents the mean blood glucose values for subjects treated with 6 U of Technosphere Insulin. Curve "B" represents those subjects on a meal time dose of between 6 – 24 U and curve "C" represents those subjects on a meal time dose of 24 -48 U. At each of the meal challenge time points (30 minutes, 60 minutes and 120 minutes), time 0 corrected blood glucose levels (i.e. post meal blood glucose excursions) were lowest in subjects on the highest doses of TI (i.e curve "C") and highest for those on the lowest dose of TI (curve "A"), with blood glucose levels for the group with the intermediate dose (curve "B") falling in between C and A. Thus, subjects treated with

higher doses of TI had smaller post-prandial blood glucose excursion during the meal challenge testing than those on lower doses of TI.

2) It is unclear how metformin and gliclazide could be concomitant medications in trial MKC-TI-005 because subjects were supposed to discontinue oral antidiabetic medications at the start of the trial.

Metformin and gliclazide were considered concomitant medications according to the definition in section 5.3.7 – Prior and concomitant therapy (page 31 of the clinical study report [CSR]) and were to be discontinued at visit 4 (week 5). – See text from CSR:

5.3.7 Prior and Concomitant Therapy

Prior medications are defined as medications stopped prior to the day of the first administration of TP at Visit 3 (Week 4). Concomitant medications are defined as medications taken prior to Visit 3 and continued thereafter, as well as those started after the day of the first TP administration. (Lantus® was not considered a concomitant medication.)

Any medications known to modify glucose metabolism or the ability to recover from hypoglycemia were discontinued at Visit 4 (Week 5); they are considered concomitant medications as they would have been concomitant with TP. Such medications include: oral, parenteral and inhaled steroids, oral anti-hyperglycemic medications, or > 25 mg of hydrochlorothiazide daily. Subjects could not take another investigational drug within 3 months prior to trial entry or during the trial.

3) ***Trial MKC-TI-005 study report table 22, please re-presents using U.S. units. (mg/dL)***

See TBL_FBG_SUMM_mg_dL.pdf

4) ***For trial 0008 figure 5 we would like to see the time response curve for each dose separately (i.e. 8 lines instead of 3) and then another time response graph with four categories instead of 3. Please include graphs using ITT with LOCF and ITT observed data.***

We will provide the appropriate figures early next week.

4) Were all HbA1c measurements performed by a central laboratory?

HbA1c measurements within each study were performed by a central lab. Except for one study (PDC-INS-0008) all HbA1c measurements in all studies were performed by one central lab ((b) (4)

STUDY	LAB USED
PDC-INS-0008	(b) (4)
MKC-TI-005	
MKC-TI-009	
MKC-TI-010	
MKC-TI-014	
MKC-TI-026	
MKC-TI-030	
MKC-TI-101	
MKC-TI-102	
MKC-TI-103	

6) ***Glucose data for the meal tolerance test in all studies should be presented in mg/dL units instead of mmol/L***

We have reviewed all trials and only Study MKC-TI-005 includes tables with the meal challenge glucose data that require a presentation in mg/dL.

While we did the conversion in the SAS tables, we recognized that 3 of the original tables in mmol/L had been mislabeled.

The errors found in these 3 original tables are:

T-004-002-03D: this table contains the result from an incorrect population. The population presented in the original table was 'Randomized Subjects' while it should have been the 'Per-Protocol Population'. This table has been redone with the correct PP-population. The results from these tables had not been discussed in the CSR, but referenced only. No result interpretation or conclusions changed.

T-004-002-02B.pdf: the title should not read as 'Baseline Corrected AUC'; instead it should be just 'AUC' . The table has now the corrected title and also the appropriate unit in the title was added. The CSR text is correct.

T-004-002-03B.pdf: the unit is missing in the original table and it was added

The corrected tables are provided in the original unit: mmol/L .

The corresponding mg/dL tables are the tables labeled with an 'x' at the end T-004-002-02BX.pdf, T-004-002-03BX.pdf and T-004-002-03DX.pdf. We kept the same table numbers so that they can be easily related to the submitted original tables.

7) ***For trials where the HbA1c entry criteria state HbA1c "between" certain values (trials 0008, 005, and 026) is the range inclusive of the upper and lower bounds or not inclusive?***

For the three trials PDC-INS-0008, MKC-TI-005 and MKC-TI-026 the ranges were all given inclusive the lower and upper bounds:

MKC-TI-005:

For study MKC-TI-005, the inclusion criteria "HbA1c between 7.0% and 12%" was defined as HbA1c >7.0% and <12%.

PDC-INS-0008:

In order to provide a consistent answer we need to do some final check and it will be reported early next week

MKC-TI-026:

For study MKC-TI-026, the inclusion criteria "HbA1c between 7.5% and 12%" was defined as HbA1c >7.5% and <12%.
There were 5 approved protocol exemptions for HbA1c values outside that range (subjects with screening values of 7.4%, 7.5%, 7.5%, 12%, 12.7%).

Clarification request: In the question, the meaning of the word inclusive was intended to be 'including the upper and lower bounds'. Therefore if, for example, For study MKC-TI-005, the inclusion criteria "HbA1c between 7.0% and 12%" was defined as HbA1c >7.0% and <12% then the Hba1c values would be non-inclusive of the upper and lower bounds. Is this correct?
Inclusive of the upper and lower bounds would be ≥ 7.0% and ≤ 12%.

8) For trial 0008 withdrawal criteria include "The patient experienced one episode of severe hyperglycemia." Is this supposed to read "hypoglycemia"?

No, section 9.3.3 should read "the patient experienced one episode of severe hyper – or hypoglycemia. Both conditions labeled as "severe" led to withdrawal of the patient (Discontinuation due to severe hypoglycemia protocol section 4.5.1, discontinuation due to severe hyperglycemia, protocol section 4.1)

Was severe hyperglycemia a withdrawal criterion in other trials besides 0008?

9) ***For Trial 009 Table 9 in the CSR is unclear. If all subjects were taking insulin at study entry, why does the table indicate 91% for the TI group and 88% in the insulin aspart group were using insulin?***

Table 9. Diabetes Treatments Taken at Screening (Safety Population)

Diabetes Treatment Taken	TI (n = 293) n (%)	Insulin Aspart (n = 272) n (%)
Insulin and analogues	267 (91.1) [a]	240 (88.2) [a]
Premixed	6 (2.0)	4 (1.5)
Fast-acting + intermediate-acting	72 (24.6)	68 (25.0)
Fast-acting + long-acting	174 (59.4)	154 (56.6)

[a] All subjects were using insulin at trial entry.
Medications were coded using the WHO Drug Dictionary Version 2003Q4.
Percentages are based on the number of subjects in each treatment group in the Safety Population.
Data Source: Table 6.3.3 and Listing 6.5.1

All patients fulfilled the requirement of being on insulin at screening, but the information on the type of insulin was not available in all patients. That missing information for some patients accounts for the total not adding up to 100%.

10) ***The following table indicates that trial 026 had comparator subjects using insulin. However, according to the study report it does not appear that any subjects were using subcutaneous insulin. Please explain.***

Table 2: Comparator Group Trial Contributions

Trial	Comparator Group	Comparator Treatment
MKC-TI-102	Insulin	Premix analog 70/30
MKC-TI-014	Insulin	insulin aspart
MKC-TI-030	Insulin	Usual care subjects who took insulin
MKC-TI-026	Insulin	Usual care subjects who took insulin
MKC-TI-103	Non-insulin	Metformin + secretagogue
MKC-TI-030	Non-insulin	Usual care subjects who did not take insulin
MKC-TI-026	Non-insulin	Usual care subjects who did not take insulin

Data Source: Statistical Analysis Plan.

Appears this way on original

We recognize that the table appears unclear.

In study MKC-TI-026 there were five subjects, three subjects in the TI group (subjects Nos. 269, 357 and 790) and two subjects in the comparator group (subjects Nos. 356 and 677) who had reported previous exposures to insulin. The exposure was for very short periods (between 7 days up to 1 month) and prior to participation in the study (Listing 4, Diabetes History, Randomized Subjects). There were no subjects treated with sc insulin during the trial (Listing 21. Concomitant Medications Randomized Subjects).

Therefore, is it correct to state that trial 026 did not contribute any patients to the "insulin" group for the hypoglycemia analyses or any of the other integrated summaries of safety that compared TI patients to "insulin" patients?

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

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

/s/

RACHEL E HARTFORD
11/02/2009

Hartford, Rachel

From: Hartford, Rachel
Sent: Monday, November 02, 2009 11:26 AM
To: 'Mayer, Patricia'
Subject: Statistical Clarification Request

Hello Patricia,

An analysis of the ISS dataset ADHY subsetting on MKC-TI-030 yielded different numbers than the same analysis using the ADHY dataset provided with the study report for MKC-TI-030.

This analysis counted the number of patients having at least 1 severe hypoglycemic event. An example of the discrepancy between the analyses is that 42 T1/TI pts were identified in the MKC-TI-030 dataset (matching Table 43 of the report) while 40 were identified using the ISS dataset.

Please explain the discrepancy. To assess severe hypoglycemia in the ISS, what dataset did you use?

Thank you,

Rachel

Rachel E. Hartford
Regulatory Project Manager
Division of Metabolism and Endocrinology Products
Center for Drug Evaluation and Research
Food and Drug Administration
rachel.hartford@fda.hhs.gov
301-796-0331 (phone)
301-796-9712 (fax)

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

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

/s/

RACHEL E HARTFORD
11/02/2009

Hartford, Rachel

From: Hartford, Rachel
Sent: Friday, October 30, 2009 2:08 PM
To: 'Mayer, Patricia'
Subject: Clinical Information Requests

Good Afternoon Patricia,

We have the following Clinical Information Requests:

1. In section 3.6.3 of the ISS, the tables of Serious Adverse events for both type 1 and type 2 combined and then separate (starting with table 28). Do these tables include deaths? Deaths were discussed in the previous section separately, but your definition of an SAE includes any fatal event. Therefore, it seems subjects who died were counted in both sections. If this is the case please resubmit your tables of SAEs excluding subjects who died.

2. For Trial 102 - CSR – page 107 – in the section discussing fasting plasma glucose results: It is not clear if the MMRM and ANCOVA models used the ITT populations with or without LOCF imputation for missing data. This is actually a consistent problem across many trials where it is unclear if any imputation was used.

3. Please update (provide an addendum for) the table of clinical studies with any new studies started after NDA submission (for example trial 134).

4. For trial 009, did subjects begin taking IMPs at week -1 or did they use empty inhalers and empty Pens until week 0? You mention a 10-week run-in period. What happens (or doesn't happen during the run in phase). Is it simply titration of IMPs?

5. In table 41 in the ISS, data for basophils, MCH, MCH (pg), and MCV are missing.

6. Please submit a table showing the number of patients (n, %) meeting these various cutpoints for outlier analyses. Include patients regardless of whether the baseline value is normal or not. First present tables including subjects from your entire controlled database. Then present tables including only subjects from the pooled controlled phase 2/3 trials. Include narratives for patients with ALT >5x ULN, for patients with total bilirubin >5x ULN, and for patients with serum creatinine >2x ULN.

   ALT
   - > ULN and ≤ 3 X ULN
   - > 3X ULN and ≤ 5 X ULN
   - > 5 X ULN and ≤ 10 X ULN
   - > 10 X ULN

   Total bilirubin
   - > ULN and ≤ 2 X ULN
   - > 2X ULN and ≤ 5 X ULN
   - > 5 X ULN and ≤ 10 X ULN
   - > 10 X ULN

   Serum creatinine
   - >ULN and ≤ 1.5 X ULN
   - > 1.5 X ULN and ≤ 2 X ULN
   - > 2 X ULN

7. Provide narratives for patients in your entire controlled database who met any of the following definitions for Hy's Law.

   Hy's Law
   - ALT > 3X ULN and total bilirubin > 2X ULN and alk phos < 2.5 X ULN
   - ALT >3X ULN and total bili >2x ULN (regardless of alk phos)

Thank you,

Rachel

Rachel E. Hartford
Regulatory Project Manager
Division of Metabolism and Endocrinology Products
Center for Drug Evaluation and Research
Food and Drug Administration
rachel.hartford@fda.hhs.gov
301-796-0331 (phone)
301-796-9712 (fax)

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

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

/s/

RACHEL E HARTFORD
10/30/2009

Hartford, Rachel

From: Hartford, Rachel
Sent: Thursday, October 29, 2009 1:11 PM
To: 'Mayer, Patricia'
Subject: Urgent information request

Hello Patricia,

We have an urgent information request:

Clarify whether the Model C cartridge was always used with the Model C inhaler, and the Model D cartridge was always used with the Model D inhaler. This pertains to any data in the NDA, including for example, characterization data (section 3.2.P.2.4.2.3 pp. 42-48), stability data, etc.

Please provide a response timeframe.

Thank you,

Rachel

Rachel E. Hartford
Regulatory Project Manager
Division of Metabolism and Endocrinology Products
Center for Drug Evaluation and Research
Food and Drug Administration
rachel.hartford@fda.hhs.gov
301-796-0331 (phone)
301-796-9712 (fax)

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

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

/s/

RACHEL E HARTFORD
10/29/2009

Hartford, Rachel

From: Hartford, Rachel
Sent: Monday, October 26, 2009 9:41 AM
To: 'Mayer, Patricia'
Subject: Afrezza NDA 22-472 Clarification Requests

Patricia,

We have the following clarification requests:

1) On page 90 of the trial PDC-INS-0008 report it states that: Based on Time 0-corrected laboratory glucose values, increasing the TI Inhalation Powder dose lowered mean postprandial glucose values over time (Figure 7). Hence, a dose response was demonstrated. This is unclear. Please explain.

2) It is unclear how metformin and gliclazide could be concomitant medications in trial MKC-TI-005 because subjects were supposed to discontinue oral antidiabetic medications at the start of the trial.

3) Trial MKC-TI-005 study report table 22, please re-present using U.S. units. (mg/dL)

4) For trial 0008 figure 5 we would like to see the time response curve for each dose separately (i.e. 8 lines instead of 3) and then another time response graph with four categories instead of 3. Please include graphs using ITT with LOCF and ITT observed data.

5) Were all HbA1c measurements performed by a central laboratory?

6) Glucose data for the meal tolerance test in all studies should be presented in mg/dL units instead of mmol/L

7) For trials where the HbA1c entry criteria state HbA1c "between" certain values (trials 0008, 005, and 026) is the range inclusive of the upper and lower bounds or not inclusive?

8) For trial 0008 withdrawal criteria include "The patient experienced one episode of severe hyperglycemia." Is this supposed to read "hypoglycemia"?

9) For Trial 009 Table 9 in the CSR is unclear. If all subjects were taking insulin at study entry, why does the table indicate 91% for the TI group and 88% in the insulin aspart group were using insulin?

10) The following table indicates that trial 026 had comparator subjects using insulin. However, according to the study report it does not appear that any subjects were using subcutaneous insulin. Please explain.

Thank you,

Rachel

Rachel E. Hartford
Regulatory Project Manager
Division of Metabolism and Endocrinology Products
Center for Drug Evaluation and Research
Food and Drug Administration
rachel.hartford@fda.hhs.gov
301-796-0331 (phone)
301-796-9712 (fax)

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

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

/s/

RACHEL E HARTFORD
10/26/2009

Hartford, Rachel

From: Hartford, Rachel
Sent: Monday, October 26, 2009 9:09 AM
To: 'Mayer, Patricia'
Subject: Statistical Information Request - Afrezza NDA 22-472

Patricia,

We have an additional statistical information request. For Study MKC-TI-014, please advise where the pooled site data and TALE (or insulin glargine exposure) data are. If they were not in the original submission, please provide the electronic data sets ASAP.

Thank you,

Rachel

Rachel E. Hartford
Regulatory Project Manager
Division of Metabolism and Endocrinology Products
Center for Drug Evaluation and Research
Food and Drug Administration
rachel.hartford@fda.hhs.gov
301-796-0331 (phone)
301-796-9712 (fax)

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

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

/s/

RACHEL E HARTFORD
10/26/2009

Hartford, Rachel

From: Hartford, Rachel
Sent: Tuesday, October 20, 2009 3:40 PM
To: 'Mayer, Patricia'
Subject: NDA 22-472 Statistical Information Request

Hello Patricia,

For Study MKC-TI-005, the statistical reviewer was able to match the results presented in Table 16, but not the results presented in Table 17 and Table 18 of the CSR using HBA005.xpt and TALE.xpt data sets. Please submit the SAS codes for generating the information in those 2 tables. Also, please clarify whether the "site" effect in your ANCOVA model was a pooled site effect or not and if it was, please advise how they were pooled and where to find the data. Lastly, in the TALE.xpt file, how was TALE variable derived? TALE is not = exp_time / sdosetm in the data set.

Thanks,

Rachel

Rachel E. Hartford
Regulatory Project Manager
Division of Metabolism and Endocrinology Products
Center for Drug Evaluation and Research
Food and Drug Administration
rachel.hartford@fda.hhs.gov
301-796-0331 (phone)
301-796-9712 (fax)

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

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

/s/

RACHEL E HARTFORD
10/20/2009

Hartford, Rachel

From: Hartford, Rachel
Sent: Tuesday, October 13, 2009 10:37 AM
To: 'pmayer@mannkindcorp.com'
Subject: CMC Information Request

Good Morning Dr. Mayer,

My name is Rachel Hartford and I am now the project manager for your NDA (see below for contact information). After you review the following CMC requests, please provide an expected response timeframe.

Cascade impactor data for Aerodynamic Particle Size Distribution for both product strengths:

1) Summarize the differences between the methods # TM5445 and TM5516 for Aerodynamic Particle Size Distribution and provide concise summary data supporting their equivalence.
2) Clarify the reason for some of the [redacted] (b) (4) observed for the primary stability batches compared to the other batch data provided in Figures 3 and 7.
3) Describe any differences in these primary stability batches relative to the other batches. This also applies to the related data for [redacted] (b) (4)
4) Clarify the reason for the [redacted] (b) (4) for batches analyzed with method TM5516 relative to the other batches analyzed with method TM5445; clarify if this is related to the analytical method or to the particular batches. (This comment is referenced to your response to our Comment 8 sent on May 5, 2009, in your June 11, 2009, amendment.)

Clarification for the first part of our previous Comment 6 in our letter dated May 21, 2009 (and it also pertains to your response in your July 22, 2009 amendment).

5) Indicate whether representative multiple batches of devices were employed in the generation of release and stability performance data for the drug product in this NDA.

The following pertain to your response to our Comment 7 in your amendment dated July 22, 2009.

6) Clarify the release and stability testing to be performed for the cartridges for the uniformity of emitted dose and aerodynamic particle size distribution specifications: specify how the inhaler device batches will be selected for each cartridge batch for release (and as appropriate, stability testing), as well as the sampling plan performed to assure that the devices are representative of each batch.
7) A review of the minutes of the pre-NDA meeting (section 2.6, pages 16-17) which took place on July 14, 2008 does not appear to suggest that the Agency agreed to accept [redacted] (b) (4) for release of the device. Develop and institute an additional inhaler device specification for emitted mass, at a minimum.

Additional Requests:

8) Provide the identity of the [redacted] (b) (4) if known.
9) Provide an estimate of the limit of quantitation for measuring [redacted] (b) (4).
10) Provide summary information for the [redacted] (b) (4) analytical procedure as well as summarize any data generated from experiments conducted to show that the method is valid.
11) Clarify whether the [redacted] (b) (4) (This comment is referenced to your response to our Comment 10 sent on May 21, 2009, in your July 22, 2009, amendment.)

Thank you,

Rachel

Rachel E. Hartford
Regulatory Project Manager
Division of Metabolism and Endocrinology Products
Center for Drug Evaluation and Research
Food and Drug Administration
rachel.hartford@fda.hhs.gov
301-796-0331 (phone)
301-796-9712 (fax)

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

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

/s/

RACHEL E HARTFORD
10/13/2009

From: Mayer, Patricia
To: Seymour, Haley;
Subject: RE: NDA 22-472/Afrezza Pediatric plan
Date: Friday, October 09, 2009 9:57:12 AM

Patricia R. Mayer, PhD
Vice President
Worldwide Regulatory Affairs - Liaison
Office: 201-983-5228
Cell: (b) (6)

From: Seymour, Haley [mailto:Haley.Seymour@fda.hhs.gov]
Sent: Thursday, October 01, 2009 2:52 PM
To: Mayer, Patricia; Suh, Sandy; Gale, Donna; Wyka, Eileen
Subject: NDA 22-472/Afrezza Pediatric plan

Dr. Mayer,

Please refer to you submission dated September 28, 2009. Your pediatric plan is incomplete. While we agree with starting your pediatric assessment with a feasibility study (refer to submission from Sept. 28, 2009) we require a more complete proposal for pediatric assessment comprised of your future plans including pharmacokinetic/pharmacodynamic studies and efficacy/ safety studies in the pediatric population (with the understanding that these plans are dependent upon results of the initial feasibility studies). We also refer you to FDA Guidance for Industry "How to Comply with the Pediatric Research Equity Act."

Please send this information electronically, via email, by close of business on Wednesday, October 14, 2009. You should also submit it officially to the NDA (reference NDA 22-472).

Please provide a synopsis for each of your of proposed pediatric PK/PD and efficacy safety studies including:

Drug information:

- **Route of administration:**
- **Formulation:**
- **Dosage:**
- **Regimen:**

  Types of studies/ Study Design:

Age group and population in which study will be performed:

Number of patients to be studied or power of study to be achieved:

Entry criteria:

Clinical endpoints:

Timing of assessments:

Statistical information (statistical analyses of the data to be performed):
Sample size calculations

Statistical methods

Timeframe for submitting reports of the studies:

Comments on Drug safety:

Please also provide updated information if any regarding your pediatric

deferral and/or waiver requests including:

1. Age group(s) included in deferral request

2. If requesting a waiver for certain age groups, include a rationale for why these age groups are not being deferred.

3. Reason(s) for requesting deferral of pediatric studies.
4.Timelines for each proposed pediatric trial that includes the date (day, month, year) by when the final protocol will be submitted to FDA, the date by when the study will be completed (i.e., last patient last visit), and the date by when the complete study report will be submitted to FDA.

Please confirm receipt of this email.

Thank you.
Haley Seymour

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

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

/s/

HALEY H SEYMOUR
10/09/2009

Executive CAC
Date of Meeting: September 29, 2009

Committee: David Jacobson-Kram, Ph.D., OND IO, Chair
Paul Brown, Ph.D., OND IO, Member
John Leighton, Ph.D., OODP, Alternate Member
Karen Davis-Bruno, Ph.D., DMEP, Pharm/Tox Supervisor
Miyun Tsai-Turton, Ph.D., M.P.H., DMEP, Presenting Reviewer

Author of Draft: Miyun Tsai-Turton

The following information reflects a brief summary of the Committee discussion and its recommendations.

NDA #: 22-472
Drug Name: Afresa (inhaled insulin)
Sponsor: MannKind Corporation

Background: Afresa acts as fast acting insulin to treat T1DM and T2DM in adults. It consists of Technosphere® Insulin (TI) Inhalation Powder pre-metered into unit dose cartridges and the MedTone® inhaler. TI is comprised primarily of insulin and a novel excipient, fumaryl diketopiperazine (FDKP). The sponsor submitted two carcinogenicity studies in their NDA application. The carcinogenicity of both Technosphere® particles (FDKP) and Technosphere® insulin (FDKP+insulin) were evaluated in 2-year rat study (inhalation) and 6-month transgenic rasH2 mouse study (subcutaneous injection).

Rat Carcinogenicity Study: Spraque-Dawley rats (60/sex/group) were dosed one daily by inhalation for 104 weeks with test articles (Technosphere® Insulin) or vehicle article (Technosphere® particles – FDKP). Dose selections were based on 25X AUC for FDKP and MTD for insulin, which ECAC concurred with in 2004. Findings: Both Technosphere® particles (up to 46 mg/kg/day) and Technosphere® Insulin (up to 1.23 mg/kg/day) were well-tolerated. The survival over the course of the study was acceptable between 62-73% and comparable across all groups. No test article related pre-neoplasia and/or neoplastic findings were seen in the lung with either Technosphere® particles or Technosphere® Insulin above concurrent controls. Observed tumor findings included adrenal cortical carcinoma (high-dose TI females), malignant astrocytoma (low- and high-dose T males), malignant schwannoma in nasal cavity (low-dose T males), fibroma in the skin/subcutis (low-dose TI males and females), and pituitary adenoma/carcinoma (low-dose TI males). However, these tumor incidences were not statistically significant. In addition, mammary tumors (adenoma, fibroadenoma, and adenocarcinoma) were found in females across all treatment groups, suggesting an association with background incidence which was not attributable to insulin treatment. Based on these findings, there were no indications that Technosphere® particles or Technosphere® Insulin had carcinogenic potential.

Tg.rasH2 Mouse Carcinogenicity Study: Transgenic rasH2 mice (25/sex/group) were dosed one daily by SC injection for 26 weeks with test article (Technosphere® Insulin or Technosphere® particles - FDKP) or control (sham, vehicle, or positive – MNU). Dose selections were based on MFD for FDKP and MTD for insulin, which ECAC concurred with in 2007. Findings: There was no evidence of increased oncogenicity associated with Technosphere® particles (25 or 75 mg/kg/day) or with Technosphere® Insulin (2.5 and 5 mg/kg/day in males or 0.6 and 1.25 mg/kg/day in females). In females, Technosphere® Insulin at doses of 2.5 and 5 mg/kg/day exceeded the MTD as evidenced by the required dose adjustment on Day 77 due to hypoglycemia. TK analysis showed systemic bioavailability for both T and TI at all groups. There were neoplastic findings, such as bronchiolar-alveolar adenoma/carcinoma in the lung, hemangioma/hemangiosarcoma (primarily spleen), Harderian gland adenoma/carcinoma, squamous cell neoplasms (multiple sites including stomach and skin/subcutis), and myeloproliferative neoplasia, found with low incidences across all groups which were considered non-treatment related. Based on these findings, the sponsor concluded that there were no indications that Technosphere® particles or Technosphere® Insulin had carcinogenic potential.

Executive CAC Recommendations and Conclusions:

Rat:

- The Committee concluded that the study was adequate, noting prior Exec CAC concurrence.

- The Committee concluded that the study was negative for carcinogenicity.

Tg.rasH2 mouse:

- The Committee concluded that the study was adequate, noting prior Exec CAC concurrence.

- The Committee concluded that the study was negative for carcinogenicity.

David Jacobson-Kram, Ph.D.
Chair, Executive CAC

cc:\
/Division File, DMEP
/Karen Davis-Bruno, Ph.D., Pharm/Tox Supervisor, DMEP
/Miyun Tsai-Turton, Ph.D., M.P.H., Reviewer, DMEP
/Haley Seymour, Project Manager, DMEP
/Adele Seifried, OND IO

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

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

/s/

ADELE S SEIFRIED
10/01/2009

DAVID JACOBSON KRAM
10/01/2009

Hi again Jena!

If MannKind insists that they were "not sure that info/data concerning the operation of contractors should have been included in the submission", please let them know that - **Information on the actual operations of a contractor and all data obtained by the contractor would be considered confidential as part of a DMF, but the identity of the contractor (name, address, contact info) is required as part of the NDA for FDA's GMP enforcement actions such as inspections.**

Thanks again!
Su

From: Weber, Jena M
Sent: Wednesday, August 12, 2009 12:08 PM
To: Tran, Suong T; Al Hakim, Ali H; Carver, Theodore
Cc: Aljuburi, Lina; Galliers, Enid M
Subject: FW: Coverage during my absence

See below. This really doesn't address anything. I called Dr. Mayer, and the company will attempt to provide the information requested today. However, the sub-contractors are located in (b) (4), so it may be tomorrow until a response is provided. Mankind was not sure that info/data concerning the operation of contractors should have been included in the submission.

Thanks,
Jena

From: Tran, Suong T
Sent: Wednesday, August 12, 2009 9:58 AM
To: Weber, Jena M
Cc: Seymour, Haley; Carver, Theodore; Al Hakim, Ali H; Galliers, Enid M; Aljuburi, Lina
Subject: URGENT: Please send to Applicant of NDA 22-472 insulin inhalation
Importance: High

Hi Jena-

Thanks for covering for Haley!

Please send this statement to MannKind, the applicant of NDA 22-472 insulin inhalation as soon as you can and demand (yes, demand!) an immediate response from MannKind:

In our Information Letter dated 09-MAY-2009, we asked you for a confirmation 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,…"

In your amendment dated 11-JUN-2009, you confirmed 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…"
Be advised that three additional testing facilities have been identified in the Drug Master File (b) (4), and none of these facilities is included in the NDA CMC section or Form 356h. Clarify the functions of these facilities and indicate whether they are essential in the manufacturing and testing of your drug. If they are essential but were not disclosed in the initial submission of the NDA, this finding may affect the review clock of the NDA.

Thanks so much!

Su

From: Mayer, Patricia [mailto:pmayer@mannkindcorp.com]
Sent: Wednesday, August 12, 2009 11:41 AM
To: Weber, Jena M
Subject: FW: Coverage during my absence

Dear Jena,
I am sorry, but I was under the impression that Haley is back. Please see below my message to her. I would highly appreciate if we could get an answer to the question about the Advisory Committee.
Thank you very much.
Patricia

Patricia R. Mayer, PhD
Vice President
Worldwide Regulatory Affairs - Liaison
Office: 201-983-5228
Cell: (b) (6)

From: Mayer, Patricia
Sent: Monday, August 10, 2009 6:15 PM
To: 'Seymour, Haley'
Subject: Coverage during my absence

Dear Haley,
As indicated in my voicemail last week I will be out of the office starting Friday 14Aug and will return Tuesday 01Sept. Since I will not have access to email during that time, please address any requests to Sandy Suh (ssuh@mannkindcorp.com, phone:201-983-5023, cell: 203-512-4702) and Donna Gale (dgale@mannkindcorp.com, cell: 203-512-1371) and they will assist you.

Also, maybe we can touch base some time this week (Wednesday). We really would like to know for sure if we can cancel our activities in preparing for an Advisory Committee Meeting. I would highly appreciate if we could get a definitive answer before Friday.
Thank you and talk to you soon.
Patricia

Patricia R. Mayer, PhD
Vice President
Worldwide Regulatory Affairs - Liaison
Office: 201-983-5228
Cell: (b) (6)

Thanks. I checked with one of the team leaders here, and they said as of now, no AC will be held.

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

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

/s/

JENA M WEBER
09/24/2009

DEPARTMENT OF HEALTH AND HUMAN SERVICES

Food and Drug Administration
Silver Spring MD 20993

NDA 22-472 **INFORMATION REQUEST**

MannKind Corporation
Attention: Patricia Mayer, Ph.D.
Vice President Liaison, WW Regulatory Affairs
61 South Paramus Road
Paramus, New Jersey 07652

Dear Dr. Mayer:

Please refer to your New Drug Application (NDA) dated March 16, 2009, received March 16, 2009, submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act for (insulin human [rDNA origin]) Inhalation Powder and Inhaler.

We also refer to your submissions dated June 15 and July 22, 2009 and your e-mail response sent on August 21, 2009.

We are reviewing the Chemistry, Manufacturing and Controls section of your submissions and have the following comments and information requests. We request a prompt written response in order to continue our evaluation of your NDA.

1. Modify the fumaryl diketopiperazine (FDKP) specification to include a general test for heavy metals, such as USP <231>.

2. Provide a representative certificate of analysis for the excipient Polysorbate 80.

3. Provide additional data supporting the proposed [redacted] (b) (4) in the manufacturing of the drug product. These data should include results from all stability-indicating assays for insulin-related substances in your drug product stability protocol, such as insulin adducts, HMW degradants, and any degradants above the reporting limit. Report the total insulin-related degradants as well as insulin purity.

4. Provide additional data supporting the proposed [redacted] (b) (4) including results from all stability-indicating assays for FDKP-related substances in your drug product stability protocol. Provide a description of the assay used to monitor microbial growth.

5. This comment concerns the FDKP-related impurity detected in the analytical method TM5504, the high molecular weight impurities method. Provide data to show that this

impurity can be detected by the analytical method for FDKP-related substances. One approach could be to prepare FDKP samples enriched in this impurity from method TM5504, analyze them using the FDKP-related substances method, and compare the resulting profiles to profiles of unenriched FDKP samples.

6. Provide data from analysis of multiple batches of Technosphere® Insulin particles to justify the absence of specifications for individual Insulin-FDKP adducts, (b) (4) You state that (b) (4) then individual as well as total amounts of these impurities should also be reported.

7. Provide data for batches of Technosphere® or Technosphere® Insulin particles demonstrating that (b) (4)

8. Summarize your data providing assurance of the comparability of batches of bulk Technosphere® Insulin powder manufactured using the pilot and commercial scale manufacturing processes. In particular, provide data regarding the appearance, (b) (4) and size distribution of the powder particles.

9. Provide a summary of batch analysis data indicating (b) (4) . You state that impurity (b) (4) is converted to the (b) (4) impurity during drug product manufacturing. Based on the information provided, specifications for the (b) (4) impurity, unspecified FDKP-related substances, and total FDKP-related substances (to be determined from testing of the drug product) should be added to the drug product specification, or their absence should be justified.

10. Justify the exclusion of testing for (b) (4) from the bulk TI powder or finished drug product specifications.

11. Provide representative certificates of analysis for the MedTone Inhaler device (b) (4) .

12. Clarify how you ensure that the manufacturer of cartridge components will not change the process and will not make other changes (e.g., (b) (4))

13. Describe testing and acceptance criteria on the (b) (4) at (b) (4) (including identity testing).

14. Provide comparative data in graphical format for pressure drop vs. flow rate for the Model C inhaler and cartridge vs. the Model D inhaler and cartridge.

15. Provide additional proof of the similarity of the two model inhalers (D and C), i.e. in their performance with the drug formulation (i.e., aerodynamic particle size distribution and emitted dose), at multiple flow rates that are represented in the values achieved by the patient population. As you have stated, flow rate primarily affects de-agglomeration of the drug particles and therefore it influences the aerodynamic particle size distribution of the delivered drug.

16. Clarify which inhaler model was used for the clinical study MKC-TI-129 to characterize flow rates achieved by diabetic patients (section 3.2.P.2.4.2.1.3 of the NDA).

17. Clarify if the relative differences in mean emitted dose between the Model D and Model C inhalers as described in Tables 7 and 8 of section 3.2.P.2.4 of your NDA are consistent over a larger database (e.g., multiple batches of cartridges and inhalers) and provide summary data. Provide summary data for a comparison of the aerodynamic particle size distribution for Models C and D over a larger database (e.g., multiple batches of cartridges and inhalers).

18. Clarify your rationale for the specific target analytes selected for the extractable specifications for the cartridge top and cartridge bottom components, out of the list of substances observed in the controlled extraction studies (including, for example, (b) (4)). Describe how the acceptance criteria for extractables were determined. Provide the weights of the cartridge top and bottom, and show example calculations for the "Analytical Evaluation Threshold" for the extractable present in the greatest amount, based on the PQRI proposal for extractables and leachables in orally inhaled and nasal drug products which you have referenced. Clarify the basis for the decision that the (b) (4) chosen for routine analysis are optimal.

19. Provide specifications for the (b) (4) cartridge (e.g., integrity testing of the (b) (4)).

20. This pertains to your characterization study of orientation of drug product performance. Provide dose delivery and MMAD data to show the affects of possible patient use that deviate substantially from the orientations which were studied (e.g., horizontal but inverted, or a pitch of -60 degrees, for example).

21. Express the quantitation limits and detection limits of the (b) (4) method (Method M4548) for volatile extractables of the cartridge top and bottom, in terms of concentration (ppm) in the plastic components as well as in terms of concentration in the extracts. Set minimum limits for the cartridge bottom extractables (b) (4) See page 72 (Table 3-33) of the validation report for Method M4548.

22. Provide adequate and representative in vitro data, including device test data and drug product performance data, to compare the Model D MedTone Inhaler using plastic components manufactured by [redacted] (b) (4) (and intended for marketing) compared to the earlier Model D model which used most of its plastic components manufactured by subsuppliers. Demonstrate that the manufacture of these components by different manufacturers provides a consistent product. Similarly compare the device [redacted] (b) (4). Demonstrate with data that eliminating [redacted] (b) (4) will not adversely result in potential microbial, particulate, or other residual contamination on the surfaces of device components.

23. This pertains to [redacted] (b) (4) for the device. Demonstrate identity testing, integrity testing of the [redacted] (b) (4). Provide a Certificate of Analysis.

24. This pertains to your in-use studies to support a [redacted] (b) (4) in-use period of the inhaler. Clarify what the accelerated conditions and time points actually were for the accelerated time points (e.g., [redacted] (b) (4)). Provide individual stage and component data for the APSD testing in this study. Provide an agreement to confirm accelerated data with real time data to support the in use period.

25. Clarify method TM5516 for aerodynamic particle size distribution, to specify the [redacted] (b) (4)

26. Provide an identification specification for the [redacted] (b) (4).

27. This pertains to specifications for the cartridge top and cartridge bottom (section 3.2.P.7 for the Technosphere Insulin Inhalation Powder), particularly for Table 2 (Visual Attributes for Cartridge Tops and Bottoms). Provide justifications for the various AQL acceptance criteria which allow a certain number of failures depending on lot size. Provide an interpretation of the AQLs used (e.g., numbers of samples tested for different batch sizes, number of failures permitted for each attribute).

If you have any questions, call Haley Seymour, Regulatory Project Manager, at (301) 796-2443.

Sincerely,

{See appended electronic signature page}

Ali Al Hakim, Ph.D.
Branch Chief
Division of Pre-Marketing Assessment I
Office of New Drug Quality Assessment
Center for Drug Evaluation and Research

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

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

/s/

ALI H AL HAKIM
09/16/2009

MannKind Corporation Responses to CMC Questions received from FDA 19Aug2009

The Agency's requests are noted in ***bold, italic*** font. MannKind's responses immediately follow the FDA request in normal font.

1. **FDA:** ***Provide additional information regarding the specified FDKP-related impurity designated*** (b) (4) ***during the drug product manufacturing process.*** (b) (4) [redacted] ***, one of which is an FDKP impurity that has already been identified.***

MannKind response:

(b) (4)

[redacted]

2. **FDA:** ***Revise the drug product release specification to include testing for FDKP-related degradants. We note that testing for FDKP-related substances is included in your drug product stability specification, and that therefore, you have a validated assay available for this purpose. Refer to ICH Q3B(R2) for guidance regarding reporting of FDKP-related substances. FDKP-related degradants should be evaluated using the criteria from ICH Q3B(R2) for evaluating degradants related to the drug substance. It is not necessary to include acceptance criteria for specified FDKP-related impurities in the release specification, unless these impurities are also degradants..***

MannKind response:

With acknowledgement of the ICH Q3b(R2) guidance, MannKind understands it is not necessary to include specified FDKP-related impurities in the drug product specification unless these impurities are also degradants. On June 11 MannKind provided a response to the FDA Information Request Letter dated 5 May 2009, agreeing to FDA's request to include FDKP impurities in the drug product release specifications. The acceptance criteria will be the same as for the FDKP raw material and the data reported will be obtained from the batches of FDKP used to manufacture the lot of drug product. As noted in the response, MannKind has demonstrated that the FDKP-related impurities observed in the drug product either remain at the same level as present in the FDKP raw material or are reduced during the manufacture of Technosphere Insulin Inhalation Powder.

A Stability Update was provided to the FDA on August 16, 2009. The level of FDKP Total Impurities does not change on stability (see Figures 1-3 below). Since there are no specified FDKP-related degradants in the drug product, MannKind will maintain the drug product specification included in NDA 22-472 submitted on 16 March 2009. The drug product specification will not include specified FDKP-related impurities.

Figure 1. FDKP Related Compounds

As found in 3.2.P.8.3 (b) (4) Primary Stability (Technosphere® Insulin) Update August 2009, pg 19

Proposed Specification	None
Batch Numbers	PM6317A, PM6325A, PM6338A, PM6339A, PM6340A, PM6341A
Storage Conditions	(b) (4)

(b) (4)

Figure 2. FDKP Related Compounds

As found in 3.2.P.8.3 (b) (4) Primary Stability (Technosphere® Insulin) Update August 2009, pg 20

Proposed Specification	None
Batch Numbers	PM7030A, PM7031A, PM7032A, PM7033A, PM7036A, PM7037A
Storage Conditions	(b) (4)

(b) (4)

Figure 3. FDKP Related Compounds

As found in 3.2.P.8.3 (b) (4) Bridging Stability (Technosphere® Insulin) Update August 2009, pgs 15-16 with newly plotted (b) (4) data.

Proposed Specification	None
Batch Numbers	PPT2008.27, PPT2008.28, PPT2008.29, PPT2008.30, PPT2008.31, PPT2008.32
Storage Conditions	(b) (4)

(b) (4)

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

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

/s/

HALEY H SEYMOUR
09/14/2009

From: Seymour, Haley
Sent: Wednesday, August 19, 2009 3:43 PM
To: Seymour, Haley; 'Mayer, Patricia'; 'ssuh@mannkindcorp.com'; 'dgale@mannkindcorp.com'
Subject: RE: NDA 22-472

Clin Pharmology requests:

Please submit an electronic individual insulin plasma concentrations for the pivotal BE study (MKC-TI-138) or if you already submitted it please locate.

(Typical file for the data such as 'Lab.xpt' is blank in the study dataset section).

From: Seymour, Haley
Sent: Wednesday, August 19, 2009 3:12 PM
To: 'Mayer, Patricia'; 'ssuh@mannkindcorp.com'; 'dgale@mannkindcorp.com'
Subject: RE: NDA 22-472

CMC information requests:

1. Provide additional information regarding the specified FDKP-related impurity designated (b) (4) **during the drug product manufacturing process.** (b) (4) **ne of which is an FDKP impurity that has already been identified.**

2. Revise the drug product release specification to include testing for FDKP-related degradants. We note that testing for FDKP-related substances is included in your drug product stability specification, and that therefore, you have a validated assay available for this purpose. Refer to ICH Q3B(R2) for guidance regarding reporting of FDKP-related substances. FDKP-related degradants should be evaluated using the criteria from ICH Q3B(R2) for evaluating degradants related to the drug substance. It is not necessary to include acceptance criteria for specified FDKP-related impurities in the release specification, unless these impurities are also degradants.

From: Seymour, Haley
Sent: Wednesday, August 19, 2009 12:59 PM
To: 'Mayer, Patricia'; 'ssuh@mannkindcorp.com'; 'dgale@mannkindcorp.com'
Subject: RE: NDA 22-472

I have an additional question:

Did you do any toxicology studies with the aged product to qualify any degradants that are FDKP or drug related?

Thank you.

From: Seymour, Haley

Sent: Wednesday, August 19, 2009 11:49 AM
To: 'Mayer, Patricia'; 'ssuh@mannkindcorp.com'; 'dgale@mannkindcorp.com'
Subject: NDA 22-472

NDA 22-472/(insulin human [rDNA origin]) Inhalation Powder and Inhaler

Please provide the levels of impurities in the drug batches used for toxicology testing.

Thanks.

Haley

Linked Applications	Submission Type/Number	Sponsor Name	Drug Name / Subject
NDA 22472	ORIG 1	MANNKIND CORP	INSULIN HUMAN (RDNA ORIG)INH POWDER

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

/s/

HALEY H SEYMOUR
08/21/2009

From: Seymour, Haley
To: "Mayer, Patricia";
cc: Seymour, Haley;
Subject: NDA 22-472
Date: Tuesday, July 21, 2009 9:48:27 AM

Dear Mayer,

Please clarify the information presented with regard to subject disposition in Table 7 on page 57 of the MKC-TI-014 study report. The table reports that of the 151 patients in the TI safety population, 30 discontinued prematurely, and therefore 123 completed the study. If 30 subjects discontinued, then it should be 121 subjects who completed. Please provide the correct numbers or explanation as to why the current numbers are accurate. If changes are made, please submit a revised Table 7.

If you have any questions, please contact me.

Haley

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

/s/

Haley Seymour
7/21/2009 10:02:25 AM
CSO

From: Seymour, Haley
To: "Mayer, Patricia";
cc: Seymour, Haley;
Subject: NDA 22-472
Date: Tuesday, July 21, 2009 9:43:49 AM

Dr. Mayer,

You submitted the tumor data sets of a rat study and a mouse study to the agency on March 16, 2009, for our review. By design the rat study should have 60 animals per group and the mouse study should have 25 animals per group. However the submitted data showed the following number of animals per group in the rat and the mouse studies:

Number of Animals in the Submitted Data Sets

Rat			Mouse		
Dose-Group	Male	Female	Dose-Group	Male	Female
1	44	50	1	25	25
2	43	48	2	25	25
3	42	43	3	25	25
4	46	49	4	25	25
5	34	50	5	25	25
			6	25	25
			7	18	18

According to our guidance, you are suppose to submit data of all animals in each group, irrespective of an animal ever grew any tumor or died before the end of study. A partial data can not be used in a statistical review for meaningful interpretations. You are, therefore, requested to resubmit the data of both the rat and the mouse studies with information of all animals or give the reasons why the agency should accept the data in its present form for analysis.

If you have any questions, please contact me. Thank you.

Haley

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

/s/

Haley Seymour
7/21/2009 09:59:55 AM
CSO

DEPARTMENT OF HEALTH & HUMAN SERVICES

Public Health Service

Food and Drug Administration
Rockville, MD 20857

NDA 22-472

PROPRIETARY NAME REQUEST
- UNACCEPTABLE

MannKind Corporation
61 South Paramus Road
Paramus, NJ 07652

ATTENTION: Patricia R. Mayer, Ph.D.
Vice President, Worldwide Regulatory Affairs

Dear Dr. Mayer:

Please refer to your New Drug Application (NDA) dated March 16, 2009, received March 16, 2009, submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act for insulin monomer human (rDNA origin) inhalation powder, 4 unit and 8 unit single use cartridges.

We also refer to your March 31, 2009, correspondence, received April 2, 2009, requesting review of your proposed proprietary name, Afresa. We have completed our review of this proposed proprietary name and have concluded that Afresa is unacceptable because the proposed name has a similar product characteristic profile and orthographic similarity to the currently marketed product Apidra.

Orthographic similarities in conjunction with the similar product characteristic profiles between the products Apidra and Afresa increase the likelihood of medication errors in the usual practice setting between this name pair. The orthographic similarity of this name pair stems from the use of the same beginning and ending letter (a), same length, and downstrokes that appear in the same position of each name when scripted. Additionally, both products share the same indication of use (short-acting insulin used for treatment in diabetes), and can have overlapping numerical doses (in units) that can increase the potential for confusion. Afresa and Apidra will be administered as rapid acting insulin for diabetic patients to take just prior to meals and both products will be used on a chronic and ongoing basis. Thus a medication error is less likely to be detected by the pharmacist. We are particularly concerned with the potential for confusion between these two products because although they are both short-acting insulin products, they are not interchangeable. Administering a dose (in units) of one product when the dose was intended for the other product could result in serious harm to the patient as a result of an overdose or under dose of insulin. Given the overwhelming similarity of the product characteristics, and similarity of this name pair when scripted, we do not recommend the use of Afresa.

We note that you have not proposed an alternate proprietary name for review. If you intend to have a proprietary name for this product, we recommend that you submit a new request for a proposed proprietary name review. (See the draft Guidance for Industry, *Complete Submission for the Evaluation of Proprietary Names,* HTTP://www.fda.gov/cder/guidance/7935dft.pdf and "PDUFA Reauthorization Performance Goals and Procedures Fiscal Years 2008 through 2012".)

If you have any questions regarding the contents of this letter or any other aspects of the proprietary name review process, call Mildred Wright, Safety Regulatory Project Manager in the Office of Surveillance and Epidemiology, at (301) 796-1027. For any other information regarding this application contact the Office of New Drugs (OND) Regulatory Project Manager.

Sincerely,

{See appended electronic signature page}

Carol Holquist, RPh
Director
Division of Medication Error Prevention and Analysis
Office of Surveillance and Epidemiology
Center for Drug Evaluation and Research

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

/s/

Carol Holquist
6/30/2009 04:36:01 PM

DEPARTMENT OF HEALTH & HUMAN SERVICES

Public Health Service

Food and Drug Administration
Rockville, MD 20857

FILING COMMUNICATION

NDA 22-472

MannKind Corporation
Attention: Patricia Mayer, Ph.D.
Vice President Liaison, WW Regulatory Affairs
61 South Paramus Road
Paramus, New Jersey 07652

Dear Dr. Mayer:

Please refer to your new drug application (NDA) dated March 16, 2009, received March 16, 2009, submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act, for Afresa (insulin human [rDNA origin]) Inhalation Powder and Afresa Inhaler.

We also refer to your submission dated April 2, 2009.

We have completed our filing review and have determined that your application is sufficiently complete to permit a substantive review. Therefore, in accordance with 21 CFR 314.101(a), this application is considered filed 60 days after the date we received your application. The review classification for this application is **Standard.** Therefore, the user fee goal date is **January 16, 2010.**

We are reviewing your application according to the processes described in the *Guidance for Review Staff and Industry: Good Review Management Principles and Practices for PDUFA Products*. Therefore, we have established internal review timelines as described in the guidance, which includes the timeframes for FDA internal milestone meetings (e.g., filing, planning, mid-cycle, team and wrap-up meetings). Please be aware that the timelines described in the guidance are flexible and subject to change based on workload and other potential review issues (e.g., submission of amendments). We will inform you of any necessary information requests or status updates following the milestone meetings or at other times, as needed, during the process. If major deficiencies are not identified during the review, we plan to communicate proposed labeling and, if necessary, any postmarketing commitment requests by December 16, 2009.

During our filing review of your application, we identified the following potential review issues:

Clinical:

1. We note your request for a pediatric deferral for ages up to 18 years and plans to subsequently request a partial waiver for the youngest age groups after confirming the

youngest age at which children can safely use the product. We will make a determination on this request at a later date. Submit by September 28, 2009, a pediatric plan, including protocol synopses, for the pediatric studies you would like to defer. For each study, include a timeline, specifying when the final study protocol will be submitted to FDA, when the study will be completed, and when the final study report will be submitted to FDA.

Chemistry, Manufacturing and Controls (CMC):

2. For stability testing of the drug product, retain the method for FDKP-related substances as a stability-indicating test at all time points. It is premature to remove this test from the stability protocol.

3. Provide additional detail regarding the composition and structural characterization of the stability-limiting insulin-FDKP adducts that were formed during stability studies of the drug product.

4. Provide additional information regarding the composition of the 'FDKP-related species' eluting at < (b) (4) minutes in the drug product sample analyzed using the method for high molecular weight proteins (TM5504). Provide data to quantify this impurity for the lots of the drug product used in the batch analysis and report any amounts formed during stability studies of the drug product.

5. Present a summary of the stability data on a parameter-by-parameter basis, in tabular format. Provide summary graphical plots of the stability data for the most important (e.g., dose content uniformity (DCU), aerodynamic particle size distribution (APSD)) and any trending parameters for each storage condition and position. Include graphs with both mean and individual data. Separate the data for different lots in the graphical data. Include the proposed acceptance criteria limits on the plots (e.g., (b) (4) .

6. Provide clarification pertaining to the devices used for the drug product release and stability testing for this NDA, for performance parameters such as aerodynamic particle size distribution, uniformity of emitted dose and (b) (4) testing. The drug product is a drug device combination and it is expected that both the device and the drug formulation in the cartridge are stored under the same stability conditions and tested at the same time points.

7. Clarify the assignment of lot numbers to the drug product. Lot numbers of the drug product should be linked to lot numbers for the device and for the cartridge. If multiple device lots are to be marketed with a single cartridge lot (as a single drug product lot), then performance characteristics for that lot of drug product are to be tested according to the specifications for each lot of the device. This presumes that the device lot is smaller than the cartridge lot. If the reverse is true, then the same principle applies for testing.

8. Provide a reference to the characterization of foreign particulates, or provide the information.

9. Provide release and stability APSD data for a combined grouping of stages 3-5. Provide these data also in graphical summaries.

10. Provide long term stability data for leachables [redacted] (b) (4) [redacted]. Alternatively, justify (with data) the lack of this information.

11. The following comment pertains to the Aerodynamic Particle Size Distribution test using the cascade impactor. In addition to the comment previously conveyed to you, provide release and stability data to show the amounts of insulin deposited on each stage and component (e.g., [redacted] (b) (4)) and stage grouping. Provide graphical data summarizing the overall stability data and showing the aerodynamic particle size distribution profile in terms of the amount of drug per cascade impactor stage and component, and the variability of that data.

12. In addition to the comment previously conveyed to you regarding foreign particulates, institute testing and develop a specification for foreign particulates in the drug product for diameters equal to or greater than [redacted] (b) (4) µm and greater than [redacted] (b) (4) µm.

13. Provide comparison data for the varied flow study for the Technosphere Insulin Inhalation System, for both model C and model D. (Refer to section 3.2.P.2.4.4.1.)

<u>The following issues were previously conveyed in our letter dated May 5, 2009:</u>

14. The established name should be "insulin human [rDNA]" instead of your proposed "insulin monomer human [rDNA]".

15. The labeled dosage strength should be the pre-metered dose of the drug substance: "15 units" or "30 units" per cartridge.

16. Provide the 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 [redacted] (b) (4) present in the product.

17. [redacted] (b) (4)

18. Justify the lack of testing for particulates larger than [redacted] (b) (4) µm in the drug product specification.

19. Revise the drug product specification to include the FDKP-related impurities that are present in the drug product.

20. You state that [redacted] (b) (4) [redacted]" 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.
21. Regarding the Aerodynamic Particle Size Distribution test by the cascade impactor, provide data to show the amounts of insulin deposited on each stage, [redacted] (b) (4) [redacted]. In addition, provide a representative plot of the mean deposition vs. each accessory and each stage.
22. Submit additional stability data for Batches PPT2008.31 and PPT2008.32 (formulated with the commercial [redacted] (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 [redacted] (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.
23. Provide information (or the location of this information in the NDA) to support [redacted] (b) (4) [redacted]
24. 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.

Microbiology:

25. USP <61> Microbiological Examination of Nonsterile Products: Microbial Enumeration Tests requires that the ability of the test to detect microorganisms in the presence of the product must be established (method suitability). Please provide the method suitability testing report for this product.

26. USP <62> Microbiological Examination of Nonsterile Products: Tests for Specified Microorganisms requires that the ability of the test to detect microorganisms in the presence of the product to be tested must be established (method suitability). Please provide the method suitability report for the detection of *Pseudomonas aeruginosa*, *Staphylococcus aureus* and Bile-tolerant gram negative bacteria.

Device:

27. You stated that a human factors study was conducted in section 3.2.P.2.4.2.1 of "Technosphere Insulin Inhalation Powder-Inhalation Powder-MannKind Corporation", but we could not find the study report. Please provide the study report that includes the protocol, pass/fail criteria, results, and conclusion for review.

28. You provided the results of the stability test for shelf-life and life cycle in section 3.2.P.8 of "Med Tone Inhaler-Not Applicable- (b) (4) for MannKind Corporation". Please provide the protocol, pass/fail criteria and conclusion for review.

We are providing the above comments to give you preliminary notice of potential review issues. Our filing review is only a preliminary evaluation of the application and is not indicative of deficiencies that may be identified during our review. Issues may be added, deleted, expanded upon, or modified as we review the application.

REQUIRED PEDIATRIC ASSESSMENTS

Under the Pediatric Research Equity Act (PREA) (21 U.S.C. 355c), all applications for new active ingredients, new indications, new dosage forms, new dosing regimens, or new routes of administration are required to contain an assessment of the safety and effectiveness of the product for the claimed indication in pediatric patients unless this requirement is waived, deferred, or inapplicable.

Pediatric studies conducted under the terms of section 505B of the Federal Food, Drug, and Cosmetic Act (the Act) may also qualify for pediatric exclusivity under the terms of section 505A of the Act. If you wish to qualify for pediatric exclusivity please consult the Division of Metabolism and Endocrinology Products. Please note that satisfaction of the requirements in section 505B of the Act alone may not qualify you for pediatric exclusivity under 505A of the Act.

We acknowledge receipt of your request for a full deferral of pediatric studies for this application. Once we have received your plan for the deferred pediatric studies and reviewed your request, we will notify you if the full deferral request is granted.

If you have any questions, call Haley Seymour, Regulatory Project Manager, at (301) 796-2443.

Sincerely,

{See appended electronic signature page}

Mary H. Parks, M.D.
Director
Division of Metabolism and Endocrinology Products
Office of Drug Evaluation II
Center for Drug Evaluation and Research

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

/s/

Mary Parks
5/21/2009 12:57:54 PM

DEPARTMENT OF HEALTH & HUMAN SERVICES

Food and Drug Administration
Silver Spring, MD 20993

NDA 22-472 **INFORMATION REQUEST LETTER**

MannKind Corporation
Attention: Patricia Mayer, Ph.D.
Vice President Liaison, WW Regulatory Affairs
61 South Paramus Road
Paramus, New Jersey 07652

Dear Dr. Mayer:

Please refer to your March 16, 2009 new drug application (NDA) submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act for Afresa insulin human [rDNA origin] Inhalation Powder) and Afresa Inhaler, 15 unit and 30 unit/cartridge.

We are reviewing the Chemistry, Manufacturing and Controls section of your submission and have the following comments and information requests. We request a prompt written response to the following comments by June 15, 2009, in order to continue our evaluation of your NDA. Please notify us as soon as possible if you need an extension of this timeline to complete a specific study.

1. The established name should be "insulin human [rDNA]" instead of your proposed "insulin monomer human [rDNA]".
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 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. (b) (4)
5. Justify the lack of testing for particulates larger than (b) (4) µm 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 [redacted] (b) (4) 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. Regarding the Aerodynamic Particle Size Distribution test by the Cascade Impactor, provide data to show the amounts of insulin deposited on each stage, [redacted] (b) (4). In addition, provide a representative plot of the mean deposition vs. each accessory and each stage.
9. Submit additional stability data for Batches PPT2008.31 and PPT2008.32 (formulated with the commercial [redacted] (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 [redacted] (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. Provide information (or the location of this information in the NDA) to support the [redacted] (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.

If you have any questions, call Haley Seymour, Regulatory Health Project Manager, at (301) 796-2443.

Sincerely,

Ali Al Hakim, Ph.D.
Chief, Branch II
Division of Pre-Marketing Assessment I
Office of New Drug Quality Assessment
Center for Drug Evaluation and Research

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

```
 /s/
----------------------
Ali Al-Hakim
5/5/2009 03:23:12 PM
```

DEPARTMENT OF HEALTH & HUMAN SERVICES

Public Health Service

Food and Drug Administration
Rockville, MD 20857

NDA 22-472

NDA ACKNOWLEDGMENT

MannKind Corporation
Attention: Patricia Mayer, Ph.D.
Vice President Liaison, WW Regulatory Affairs
61 South Paramus Road
Paramus, New Jersey 07652

Dear Dr. Mayer:

We have received your new drug application (NDA) submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act (FDCA) for the following:

Name of Drug Product: Afresa (insulin monomer human [rDNA origin]) Inhalation Powder) and Afresa Inhaler

Date of Application: March 16, 2009

Date of Receipt: March 16, 2009

Our Reference Number: NDA 22-472

Unless we notify you within 60 days of the receipt date that the application is not sufficiently complete to permit a substantive review, we will file the application on May 16, 2009, in accordance with 21 CFR 314.101(a).

If you have not already done so, promptly submit the content of labeling [21 CFR 314.50(l)(1)(i)] in structured product labeling (SPL) format as described at http://www.fda.gov/oc/datacouncil/spl.html. Failure to submit the content of labeling in SPL format may result in a refusal-to-file action under 21 CFR 314.101(d)(3). The content of labeling must conform to the content and format requirements of revised 21 CFR 201.56-57.

The NDA number provided above should be cited at the top of the first page of all submissions to this application. Send all submissions, electronic or paper, including those sent by overnight mail or courier, to the following address:

Food and Drug Administration
Center for Drug Evaluation and Research
Division of Metabolism and Endocrinology Products
5901-B Ammendale Road
Beltsville, MD 20705-1266

All regulatory documents submitted in paper should be three-hole punched on the left side of the page and bound. The left margin should be at least three-fourths of an inch to assure text is not obscured in the fastened area. Standard paper size (8-1/2 by 11 inches) should be used; however, it may occasionally be necessary to use individual pages larger than standard paper size. Non-standard, large pages should be folded and mounted to allow the page to be opened for review without disassembling the jacket and refolded without damage when the volume is shelved. Shipping unbound documents may result in the loss of portions of the submission or an unnecessary delay in processing which could have an adverse impact on the review of the submission. For additional information, please see http:www.fda.gov/cder/ddms/binders.htm.

If you have any questions, call me at (301) 796-2443.

Sincerely,

{See appended electronic signature page}

Haley Seymour
Regulatory Project Manager
Division of Metabolism and Endocrinology Products
Office of Drug Evaluation II
Center for Drug Evaluation and Research

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

/s/

Haley Seymour
3/24/2009 11:10:20 AM