CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

022472Orig1s000

OTHER REVIEW(S)

DEPARTMENT OF HEALTH AND HUMAN SERVICES **M E M O R A N D U M**

Food and Drug Administration
Respiratory Devices Branch
Division of Anesthesiology, General Hospital, Respiratory, Infection Control and Dental Device
Office of Device Evaluation
10903 New Hampshire Avenue
Silver Spring, MD 20993

NDA 022-472 – Regulatory Device Consult

Date: March 21, 2014

To: Mr. Richard Whitehead, Regulatory Project Manager (OND/ODEII/DMEP)

From: Mr. Sugato De, M.S., Biomedical Engineer (ODE/DAGID/ARDB), Lead Reviewer

Through: Anya Harry, M.D., Ph.D., Chief, Respiratory Devices Branch

Through: Tejashri Purohit Sheth, M.D. Clinical Deputy Director, Division of Anesthesia, General Hospital, Respiratory, Infection Control and Dental Devices

Applicant: MannKind Corporation

Product Name: AFREZZA (Insulin Human [rDNA Origin] Inhalation Powder

Indication: Improve glycemic control in adults with Type 1 and Type 2 diabetes mellitus (DM).

A. Executive Summary

In NDA 022-472, MannKind Corporation has proposed a novel formulation of insulin human (rDNA origin) inhalation powder (AFREZZA), an ultra-rapid-acting prandial insulin developed for the treatment of Type 1 and Type 2 diabetes mellitus (DM) in adults). AFREZZA is a combination product consisting of Technosphere Insulin (TI) Inhalation Powder and the 2nd generation (Gen2) inhaler. TI Inhalation Powder is a dry powder formulation of recombinant human insulin pre-metered into unit dose cartridges that patients self-administer by oral inhalation. Cartridges containing either 0.35 mg (10 units) or 0.7 mg (20 units) of insulin are available. The Gen2 inhaler is used for 15 days and discarded. The 10 unit (U) cartridge approximates 3 U of injected insulin and the 20 U cartridge approximates 6 U of injected insulin. For commercialization, labeling of AFREZZA will be prominently expressed as "approximates 3 units (or 6 units) of injected insulin."

The original TI Inhalation Powder development program submitted to FDA (SN 0000 NDA in March 26, 2009) did not use the Gen2 inhaler but rather an earlier model (MedTone Inhaler). The NDA provided data on the clinical efficacy and safety of TI Inhalation powder delivered using the MedTone Inhaler for the treatment of Type 1 and Type 2 DM in adult patients. On March 26, 2010, FDA provided a Complete Response Letter citing the need to establish the clinical utility of TI Inhalation Powder in the treatment of DM. In the June 29, 2010 Amendment submitted by the applicant (SN 0045), MannKind Corporation switched the inhalation delivery system to the to-be-marketed Gen2 inhaler based on bioequivalence (MKC-TI-142) between the MedTone and Gen2 inhalers. The switch was made to reduce the number of steps required for an effective inhalation and to address an issue with de-agglomeration with the MedTone Inhaler. FDA subsequently requested in vitro bridging data utilizing the MedTone and Gen2 inhalers to establish relative equivalence in terms of particle size, delivered dose and respirable dose. To provide further validation of the new drug-device configuration, FDA also requested additional clinical data and other information such as usability testing on TI Inhalation Powder with the Gen2 inhaler in a second Complete Response Letter dated January 18, 2011. The current 2013 NDA Resubmission addresses FDA's requests by presenting new information including comparative in vitro performance data and clinical data intended to demonstrate the safety and efficacy of TI Inhalation Powder administered using the Gen2 inhaler to support the registration of TI Inhalation Powder. These clinical studies were conducted after submission of the 2010 Amendment. The 2013 NDA Resubmission (October 15, 2013) also includes data

demonstrating a comparison of pulmonary safety between the MedTone and Gen2 devices.
This review memorandum focuses on the device element of the proposed combination product and does not cover the clinical data submitted by the applicant in support of safety and effectiveness. Specifically, this review covers (1) the design attributes of the proposed inhalational system, (2) the in vitro performance of the device in terms of particle size, delivered dose and respirable dose, (3) stability of the combination product in both storage and simulated use conditions and (4) the biocompatibility considerations associated with the device.

RECOMMENDATION: The sponsor has provided a range of descriptive information and comparative analyses to establish relative equivalence between the originally proposed combination product that includes the MedTone Inhaler and the to-be-marketed configuration that uses the Gen2 Inhaler. Collectively, these tests are sufficient to demonstrate that the to-be-marketed drug-device configuration (Gen 2 Inhaler and TI Inhalation Powder) reliably administers a delivered dose of (b) (4) U from the 10 U cartridge (0.35 mg insulin , 3.3 mg TI Inhalation Powder) and (b) (4) from the 20 U (0.7 mg insulin, 6.7 mg TI Inhalation Powder). These results are within the emitted dose acceptance criterion of (b) (4) % of nominal dose that was specified by the applicant and was deemed to be safe and effective by the Center for Drug Evaluation and Research (CDER). The measured mass-median aerosol diameters for the 10 U and 20 U cartridges were approximately (b) (4) µm ((b) (4) % respirable fraction) and (b) (4) µm ((b) (4) % respirable fraction), respectively.

In order to demonstrate stability of the device, the applicant conducted long term, accelerated, and extension study to determine recommended storage conditions and specifications for shelf-life and use duration. The results of these studies were sufficient to validate a shelf life of 24 months when stored at refrigerated conditions (2-8 ˚C) and a (b) (4) day user period.

The Respiratory and Pulmonary Device Branch (RPDB) in CDRH considers devices that contact the patient gas pathway to be externally communicating devices with tissue contact. This is primarily due to the potential for chemical leachants from the device entering the patient's airway. Accordingly, the Branch consistently recommends that biocompatibility testing be selected in accordance with ISO 10993-1 with careful consideration of the appropriate duration and level of contact of the device, and that the cumulative duration of use be considered in determining the duration of patient contact.

In accordance with the present version of ISO 10993-1, externally communicating devices with either prolonged (24 hours – 30 days) or permanent (>30 days) tissue contact require cytoxicity sensitization, irritation or intracutaneous reactivity, systemic toxicity, subchronic toxicity, genotoxicity and implantation tests. As described in Section C below, the sponsor has provided acceptable test results in accordance with the aforementioned standard for cytoxicity, sensitization, irritation and acute systemic toxicity. However, the remaining tests as outlined above were not conducted. As such, the conducted tests in isolation would not be considered sufficient to validate biocompatibility for an externally communicating device with tissue contact when utilizing ISO 10993-1.

However, in the present submission, the sponsor has supplemented the ISO 10993-1 biocompatibility tests provided previously in 2009 with controlled extraction studies to ensure that the molded components contacting the TI Inhalation Powder do not affect safety and quality. These tests detected what appear to be low levels of (b) (4)
Small amounts of (b) (4) CDRH believes that the cumulative information provided for review is not sufficient to make a definitive determination of biocompatibility for the proposed device. CDRH is currently not aware of validated acceptance criteria to describe safe levels of extractables, leachables, and volatile organic compounds and therefore defers to CDER to determine whether the observed levels of (b) (4) are safe.

Dr. Miyun Tsai-Turton, the pharmacological-toxicological reviewer on the present NDA submission, reviewed on extraction studies referenced above in conjunction with local and systemic animal

toxicological studies provided by the sponsor to evaluate tissue and physiological responses from the combination product. Based on her review, she concludes that the totality of the information provided is sufficient to demonstrate biocompatibility for the proposed drug-device combination. With consideration of this assessment, CDRH believes that the biocompatibility of the proposed device has been sufficiently supported by 10993-1 tests, extractables testing, and toxicological testing in animals.

In conclusion, the sponsor has adequately validated the proposed drug-device combination product in terms of in vitro performance and stability. Accordingly, if CDER determines the biocompatibility information provided is sufficient and that the clinical study information provided for review provides a sufficient basis for safety and effectiveness, CDRH recommends approval of the proposed drug-device combination.

CDRH strongly believes that relevant measured specifications (e.g. emitted dose, respirable dose, particle size) for the drug-device combination are necessary whenever recommended doses and/or device specifications are listed in labeling. This information is useful to prescribers and physicians to distinguish between a recommended dose specification and the actual measured dose specification. The importance of this information is dependent on the observed difference between the recommended and measured values and also on the therapeutic index of the drug under consideration.

B. Device Description

Overview:

The Gen2 Inhaler has been designed and developed by MannKind for use with the Technosphere Insulin filled cartridge. It is a dry powder inhaler device intended to provide drug to the pulmonary tract. It is a mechanical device consisting of custom plastic injection molded components assembled with an ultrasonic weld. The inhaler is non-sterile and is characterized by the following attributes:

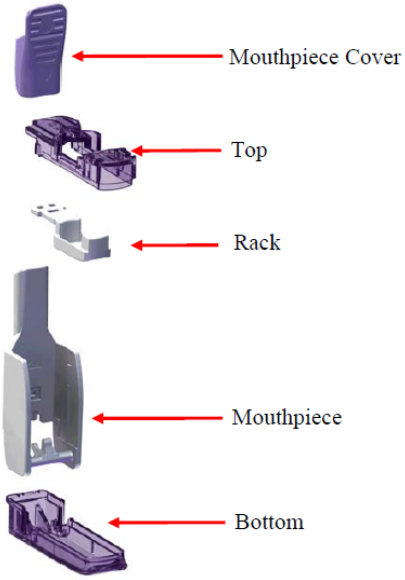
- Breath powered
- Re-usable for 15 Days
- High flow resistance

Figure 1 depicts the assembled Gen2 inhaler. The components of the assembly are depicted in an exploded schematic within Figure 2. A contract manufacturer assembles the components and supplies MannKind finished devices.

Figures 1 and 2: Gen 2 Inhaler, Exploded Schematic of the Gen 2 Inhaler

Figure 1. Gen2 Inhaler

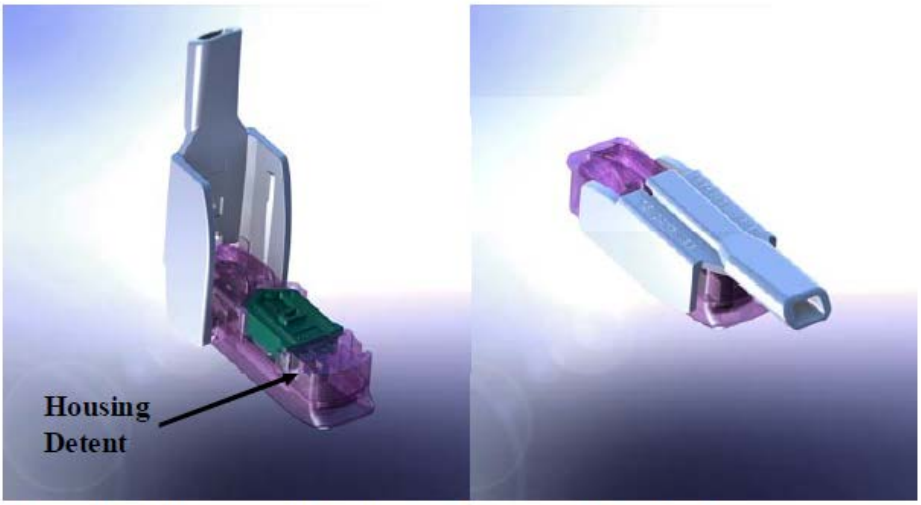
Figure 2. Exploded Schematic of the Gen2 Inhaler



The Gen2 Inhaler (shown in Figure 1) is a mechanical device consisting of four custom plastic injection molded components assembled and held together with an ultrasonic weld. A fifth part, the Mouthpiece Cover, protects the lumen of the Mouthpiece from dust and debris during storage. These components can be seen in an exploded view in Figure 2. The inhaler can be generally described as having two distinct, but non-separable components, a Mouthpiece and Housing. The Mouthpiece is white and is the external portion of the device users put in their mouth during inhalation. The Housing is translucent purple and serves as a grasping surface by which users can hold and manipulate the device. The Mouthpiece Cover is purple to differentiate it from the Mouthpiece. Text is provided on the Mouthpiece to remind users of the in-use period.

The Mouthpiece rotates about a hinge point at the rear of the Housing, allowing users to move the device between the Load and Dose Positions. The Load Position allows users to insert or remove a cartridge (shown in Figure 3). To achieve the Load Position, users must exert minimal force to overcome the housing detents that keep the inhaler closed. The Mouthpiece cannot be rotated beyond 90 degrees.

Figure 3: Inhaler Configurations



Load Position – cartridge installed **Dose Position**

The cartridge contents are inhaled from the Dose Position that is achieved by closing the inhaler. A tactile snap is felt when the Mouthpiece moves over the housing detents. The device is also stored in this position. A removable Mouthpiece Cover can be used to minimize foreign particulate collection in the Mouthpiece opening.

The primary container closure for Technosphere Insulin Powder in the Gen2 Inhalation System is the cartridge, consisting of two plastic injection molded components, the Lid and Cup. Figure 4 depicts the individual components and an assembled cartridge. Cartridge Lids are color coded. Green Cartridge Lids are used for cartridges which contain 0.7 mg (20 U) insulin (6.7 mg TI Inhalation Powder) and blue Cartridge Lids for cartridges which contain 0.35 mg (10 U) insulin (3.3 mg TI Inhalation Powder). Cartridge Lids will be molded with the product name, “afrezza”, and the appropriate cartridge identifier, i.e., “6 units” will be molded on the green Cartridge Lids and “3 units” will be molded on the blue Cartridge Lid. The cartridge is manually placed into the Gen2 Inhaler when the inhaler is in the Load Position.

Figure 4: Cartridge Components and Assembly

Green Gen2 Cartridge Lid

Blue Gen2 Cartridge Lid

Gen2 Cartridge Cup

Green Gen2 Cartridge

Blue Gen2 Cartridge

Device Development

In an effort to improve user appeal and delivery performance, MannKind activities were focused on the development of a next generation inhalation system (Gen2 Inhaler) to replace the previously proposed MedTone Inhaler. The development effort was guided by the following primary design criteria:

(b) (4)

The Gen2 inhalation system was developed to maintain all performance characteristics of the previously proposed MedTone system while providing additional patient benefit. Both devices are breath-powered, re-usable, high resistance inhalers that rely on air flow balance to empty the cartridge and deagglomerate the powder. It is important to note that the same TI powder is used in the MedTone and Gen2 inhalation systems. The same powder (b) (4) has been used throughout the Phase 3 program. Both inhalation systems comprise a cartridge container closure and operate at a comparable high resistance. The Gen2 inhalation system incorporates cosmetic improvements and removes non-essential elements. The resulting device is smaller, can be operated in fewer steps, requires only one inhalation per cartridge, and requires minimal cleaning because it is replaced after 15 days of use. A comparison of the two systems is provided in Table 1 below:

Table 1: Comparison of MedTone Inhaler and Gen2 Inhaler

Product Element	MedTone® ("Gen 1")	Gen2
API (Unchanged)	Insulin Human Rec [redacted] DMF [redacted]	Insulin Human Rec [redacted] DMF [redacted]
Composition (Qualitative and Quantitative) (Unchanged)	3U insulin/mg	3U insulin/mg
Method of Manufacture (Unchanged)	[redacted]	
Cartridge Content	15 U Nominal fill 5 mg TI powder 30 U Nominal fill 10 mg TI powder	10 U (0.35 mg insulin) Nominal fill 3.3 mg TI powder 20 U (0.7 mg insulin) Nominal fill 6.7 mg TI powder
Drug Product Controls	Per original application	Parameters, methodology, acceptance criteria unchanged with the exception of: [redacted]

Product Element	MedTone® ("Gen 1")	Gen2
Primary Container Closure	[redacted]	Two-Part Pre-metered Cartridge [redacted] Extractable & Biocompatibility Tested
Secondary Container Closure		[redacted] Blister Foil Overwrap
Device Element	**MedTone® ("Gen 1")**	**Gen2**
Resistance	[redacted]	High Resistance ranging from [redacted]
Simplicity		- Load Position (place cartridge) - Dose Position
Ease of use		4 steps 1 inhalation per cartridge
Cleaning		No cleaning required 15 days (disposable)
Inhaler Mouthpiece		[redacted]

In the previously proposed MedTone system, [redacted] The Gen2 system employs the [redacted] flow path principles. In the MedTone system, [redacted] In Gen2, [redacted] reducing the size of the device. The schematics in Figure 5 illustrate the common flow path in both devices.

The materials for (b) (4) were changed to (b) (4) The biocompatibility of the new materials were assessed via ISO 10993-1 testing and extractables testing as a part of the 2009 NDA submission.

As seen in Figure 6, the inhaler has (b) (4)

Figure 5: Gen2 Inhaler and MedTone Inhaler Flow Paths

(b) (4)

Figure 6: Air Control Volume Prospective View with Simulated Particle Flow

(b) (4)

Both the Gen2 and MedTone systems employ a de-agglomeration mechanism and associated geometry that are characterized as having a flow resistance of (b) (4) (b) (4) (b) (4) In the MedTone Inhaler, In the Gen2 device, (b) (4) improved the performance of the de-agglomeration mechanism as shown by aerodynamic particle size (APSD) testing.

Flow Mechanics

(b) (4)

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

C. Device Performance

During development, emitted dose (ED) and aerodynamic particle size distribution (APSD/NGI) testing of TI Gen2 cartridges have been conducted to assess variability. Both 10 U and 20 U cartridges were used in the powder performance assessments. Early testing of the Gen2 system showed greater consistency over MedTone. The following studies were conducted to establish a baseline in the Gen2 system.

ED testing was conducted per ATM 360-003 (TM5557) and utilized an acceptance criterion of (b) (4) % for individuals (10 U: (b) (4); 20 U: (b) (4)). Thirty (30) different inhalers were tested with 10 U cartridges and 40 different inhalers were used with 20 U cartridges. Table 2 provides the summary data. The acceptance criteria are the same as agreed to for the "Gen 1", MedTone inhalation system in terms of individual percent of target.

Table 2: Gen2 Emitted Dose Testing Results

	10 U Cartridge (U) [a]	20 U Cartridge (U) [a]
N	30	40
AVG	(b) (4)	
STD		
Max		
Min		
[a] each inhaler tested with 1 cartridge		

APSD testing was conducted per ATM 360-005 (TM5558) and utilized an acceptance criterion for Cups 3-MOC (10 U: (b) (4) 20 U: (b) (4) Twenty one (21) different inhalers were tested with 10 U cartridges and 23 different inhalers were used with 20 U cartridges. Figure 9 and Figure 10 show the 10 U and 20 U particle size distribution results, respectively. Table 3 provides the summary data for the 10 and 20 U particle size distribution results. The data demonstrate the powder performance (ED and APSD) is consistent.

Figure 9: APSD Profile for Gen2 (10 U)

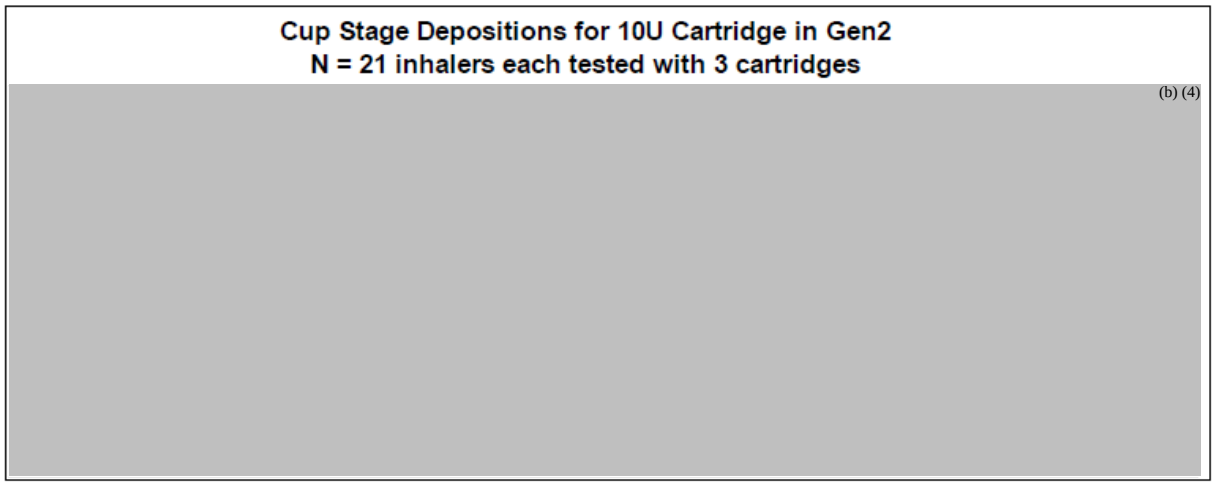


Figure 10: APSD Profile for Gen2 (20 U)

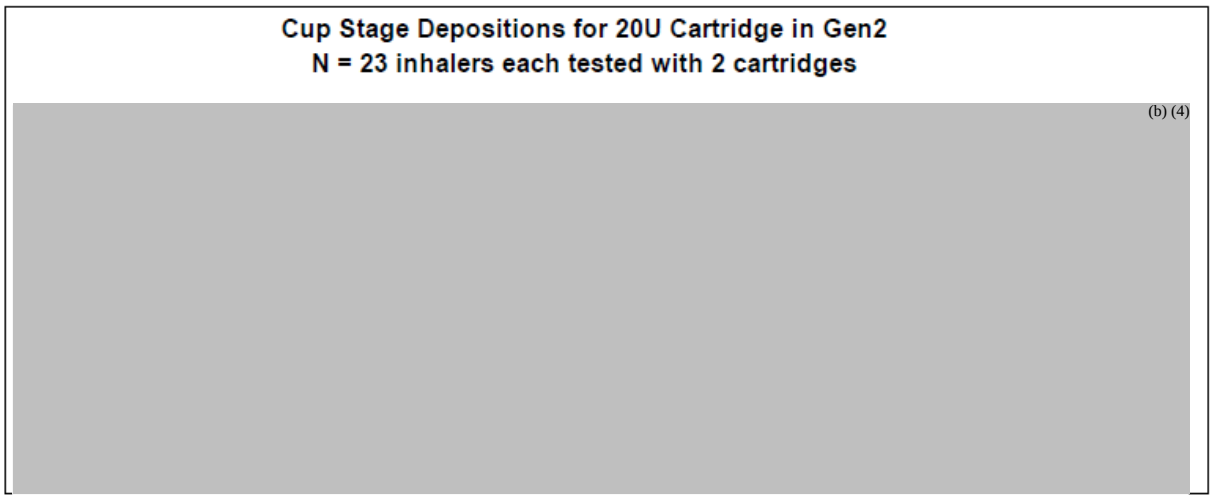


Table 3: APSD Summary for Gen2

	10 U[a]		20 U[b]	
	AVG (U)	**STD (U)**	**AVG (U)**	**STD (U)**
Mouthpiece	(b) (4)			
IP				
Cup 1				
Cup 2				
Cup 3				
Cup 4				
Cup 5				
Cup 6				
Cup 7				
MOC				
Total Dose (IP - MOC)				
APSD (Cups 3 - MOC)				

[a] each inhaler tested with 3 cartridges
[b] each inhaler tested with 2 cartridges

Comparison of Gen2 Inhaler and MedTone Inhaler

Aerodynamic particle size distribution (APSD) can provide an assessment on comparable fine particle dose and distribution of particle size in the respirable range. Aerodynamic particle size distribution (APSD) for the Gen2 Inhalation System is collected on the Next Generation Impactor (NGI) whereas Andersen Cascade Impactor (ACI) was used for the MedTone Inhalation System. Both NGI and ACI provide comparable APSD profiles. A flow rate of (b) (4) LPM is used for both test methodologies which provides good resolution, consistency, and sensitivity for quality control but has no link to in-vivo performance. Historical MedTone APSD performance (b) (4) per cartridge has been compared to recent Gen2 APSD performance using one discharge (Figure 11 and Figure 12). This data was pulled from batch analysis for the two inhalation systems. These representations reflect insulin collected at the various cut off diameters from MedTone and Gen2 batches. The data shows that the particle size distributions in the respirable range are comparable. These data show that 33% less powder in the Gen2 Inhalation System provides the same respirable amount of Technosphere Insulin as the MedTone system.

Figure 11: APSD Comparison Gen2 (20 U) vs. MedTone (30 U)

Figure 12: APSD Comparison Gen2 (10 U) vs. MedTone (15 U)

Emitted Dose (ED) data can provide an assessment of variability within the Gen2 Inhalation System (one inhalation per cartridge) and the MedTone Inhalation System (two inhalations per cartridge). Historical MedTone ED performance using (b) (4) per cartridge has been compared to recent Gen2 ED performance using one discharge (Figure 13 and Figure 14). This representation reflects individual data from MedTone and Gen2 provided in batch analysis. The variability of emitted dose for Gen2 is less than that historically seen for MedTone batches. The Gen2 ED values are expected to be lower than the MedTone ED values because the starting insulin content in the Gen2 cartridge is lower (i.e. 20 U in Gen2 cartridge compared to 30 U in MedTone cartridge)

Figure 13: Emitted Dose Variability Gen2 (20 U) vs. MedTone (30 U)

Figure 14: Emitted Dose Variability Gen2 (10 U) vs. MedTone (15 U)

To further study the comparability of Gen2 to MedTone, a study was done comparing the same powder with the same methodology on the two devices. Data was collected from batches utilized in study MKC-TI-141. A compendial standard (b) (4) LPM flow rate was used and results are presented in Figure 15 and Figure 16. Again, MedTone inhalation system testing was conducted with (b) (4) per cartridge and Gen2 inhalation system testing was conducted with one discharge per cartridge.

As seen in Figure 15 and Figure 16 insulin units contained within Cup 4 through MOC are similar for both MedTone and Gen2 Inhalation Systems even though the amount of TI powder in the Gen2 cartridges was 33% less than that in the Medtone cartridges (10 mg MedTone vs. 6.7 mg Gen2; 5mg MedTone vs. 3.3 mg Gen2). These data confirm the hypothesis that the Gen2 Inhalation System requires less powder per cartridge than the MedTone inhalation system. Data from pharmacokinetic study MKCTI-141 shows these batches are biocomparable for both Insulin and FDKP.

Figure 15: NGI Data, MedTone (15 U) vs. Gen2 (10 U)

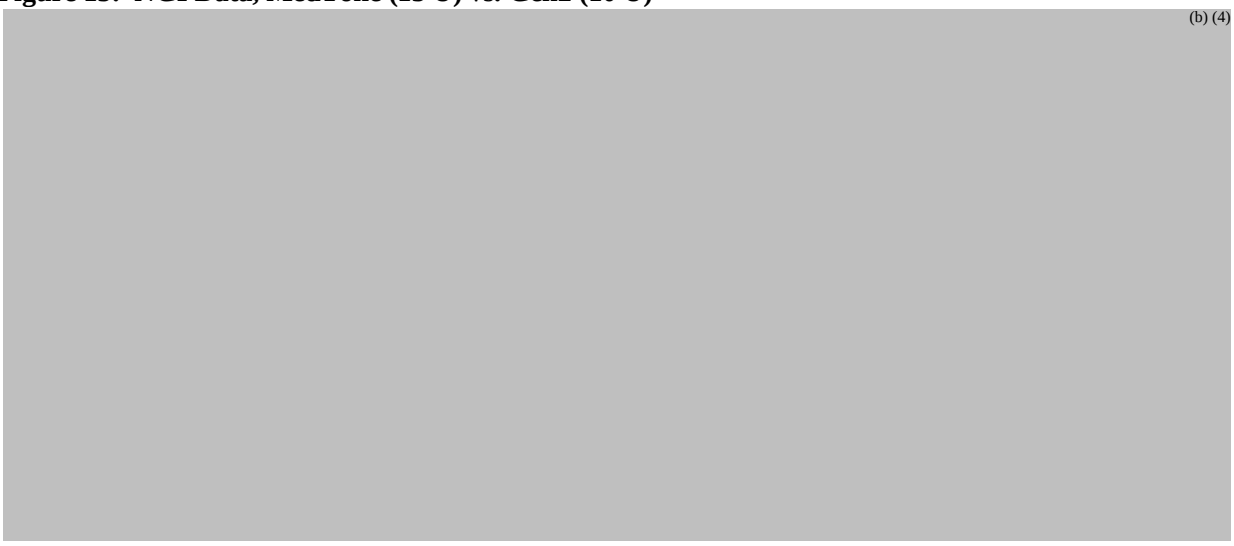


Figure 16: NGI Data, MedTone (30 U) vs. Gen2 (20 U)

(b) (4)

(b) (4)

Therefore, a (b) (4) kPa pressure drop was selected for testing.

Therefore, additional comparative data using the NGI was collected on the two device systems using samples from the MKC-TI-142 (pivotal bioequivalence) supplies run at (b) (4) kPa. The 30 U MedTone and 20 U Gen2 cartridges were compared using three different inhalers each. MedTone testing was conducted using (b) (4) per cartridge while Gen2 used a single discharge per cartridge.

To account for differences from the standard flow rate, the particle size cut-off diameters at each NGI cup were corrected using CITDAS software (Copley Inhaler Testing Data Analysis Software). The corrections were based on the following equation:

Equation 2:

$$D_{50} = A \times \left(\frac{60}{Q} \right)^{B}$$

Where D50 is the impactor cup stage cut-off size

A and B are pre determined constants, and

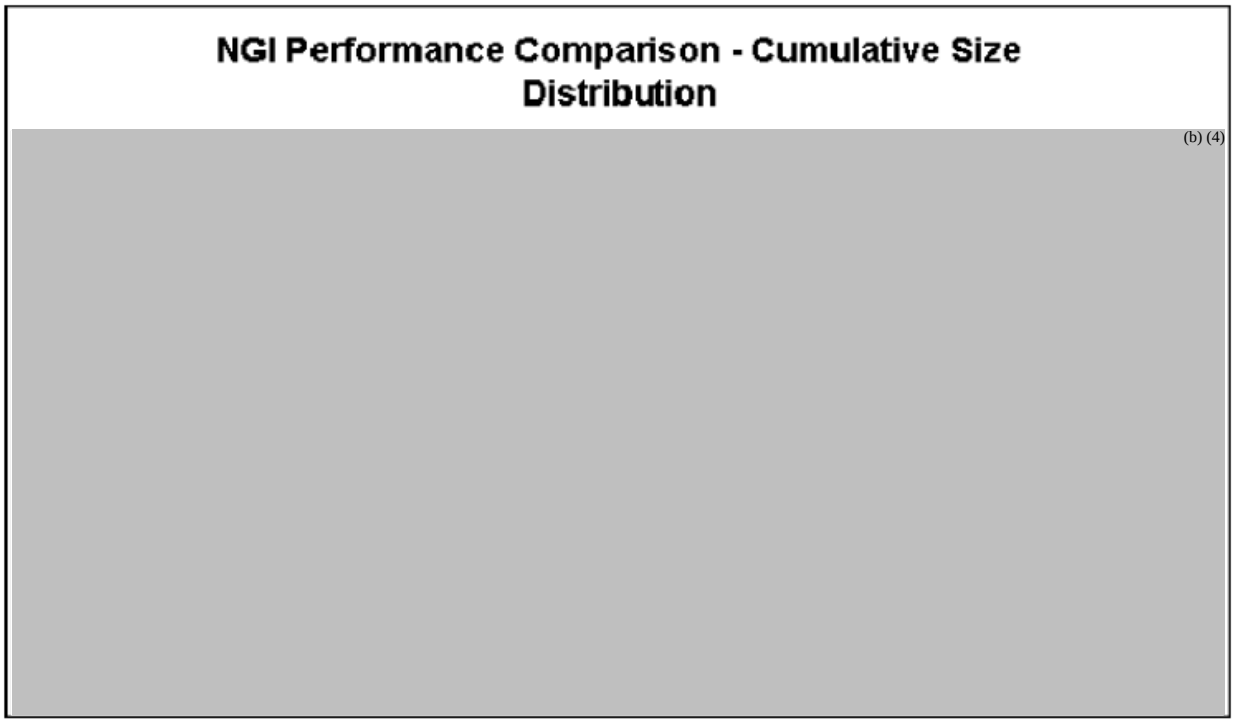
Q is the total volumetric flow rate through the impactor cup stages.

The uncorrected deposition profiles are shown in Figure 17. The CITDAS corrected results shown in Figure 18 and Figure 19. Here, the fine particle dose ((b) (4) microns) is comparable even though 33% less powder is used in the Gen2 system. This appears to reflect an overall efficiency improvement. Importantly, these NGI deposition profiles confirm the delivery of TI in the Gen2 system occurs without the larger particle agglomerates that are prone to throat depositions (never reaching the lung). In the MedTone system, (b) (4) As a result the fine particle fraction (fine particle dose/delivered dose) in Gen2 is significantly higher.

Figure 17: Comparative Deposition Profile Using Constant Pressure (MedTone vs. Gen2)

Figure 18: APSD Comparison by NGI at Constant Pressure (CITDAS Corrected) (MedTone vs. Gen2)

Figure 19: APSD Comparison by NGI at Constant Pressure (CITDAS Corrected) Cumulative Size Distribution (MedTone vs. Gen2)



Results confirm the hypothesis that less powder per cartridge is required in the Gen2 Inhalation System compared to the MedTone Inhalation System. Assessment of Emitted Dose (ED) data shows the Gen2 results with one discharge per cartridge are less variable than the MedTone ED with (b) (4) per cartridge. Aerodynamic particle size distribution (APSD) shows comparable fine particle dose and distribution of particle size in the respirable range.

Characterization Studies

One-time characterization studies were performed on the Gen2 Inhalation System to assess the possible impact of actual in-use conditions on powder performance. These included a varied flow study and an environmental study. All emitted dose (ED) testing during characterization studies were conducted on six inhalers (per cartridge) each discharged with 3 cartridges. Methodology as described in ATM 360-003 (TM5557) was used. All aerodynamic particle size distribution (APSD) testing utilized the procedure described in ATM 360-005 (TM5558) but with only three replicates per inhaler.

The effects of varied flow rates on powder performance of 10 U and 20 U cartridges were investigated in the Gen2 system. The varied flow study was performed according to FDA guidance (Draft MDI/DPI Guidance). High speed videography of device discharges shows that the powder generally leaves the Mouthpiece within 1 second (b) (4) During the varied flow study, a minimum discharge volume of (b) (4) was used to set the test duration (Table 4). This volume established consistency in the testing and represents a physiologically relevant inhalation volume.

Table 4: Varied Flow Parameters

Flow Rate	Time	Volume
(b) (4)		

Emitted dose (ED), aerodynamic particle size distribution (APSD) by NGI, and geometric particle size distribution (GPSD) by laser diffraction were assessed at flow rates generated by pressures of 2, 4, 6, and 8 kPa. Results of the ED testing are shown in Table 5. Increases in pressure and the accompanying increases in flow rate did not significantly affect the emitted dose for either the 10 U or 20 U cartridges.

Table 5: Gen2 ED Testing and Varied Flows/Pressures

(b) (4)

Assessment of APSD at varied flow rates was performed using the NGI and CITDAS software (Copley Inhaler Testing Data Analysis Software). Effective cut-off diameters (ECDs) for the cup stages (Table 6) were corrected by the software based on Equation 2 (see Page 15 above).

Table 6: Gen 2 Effective Cut-Off Diameters (µm) in Varied Flow Study

(b) (4)

During the NGI testing, either three 10 U or two 20 U cartridges were discharged through each inhaler. Mass median aerodynamic diameter (MMAD), geometric standard deviation (GSD), fine particle dose less than (b) (4) microns (FPD), and fine particle fraction (FPF = FPD/Delivered Dose) were determined. CITDAS software was utilized for interpolation of data. Table 7 depicts the MMAD, GSD, FPD, and FPF for the two cartridges at the tested pressures/flow rates. Cumulatively, these results demonstrate that expected variations in flow and pressure do not significantly affect particle specifications.

Table 7: Gen2 APSD Summary Data at Varied Flows

	10 U	20 U
Pressure (kPa)	(b) (4)	
Flow (LPM)		
MMAD (µm) (range)		
GSD (range)		
FPD (U) (range)		
FPF, % (range)		

The effects of variation in environmental conditions on powder performance were evaluated in the Gen2 Inhalation System using 10 U and 20 U cartridges. Emitted dose (ED) and aerodynamic particle size testing (APSD) by NGI were conducted under conditions of low temperature, low humidity (5°C /25% RH) and high temperature, high humidity (40°C /75% RH) in a controlled chamber (glove box). During testing, the inhaler and packaged cartridges were acclimated to the environmental condition. The cartridges were removed from the secondary packaging just prior to discharging. ED was unaffected by discharging at environmental extremes (Table 30). The lowest data points (b) (4) U for the 10 U cartridge and (b) (4) U for the 20 U cartridge) were still within (b) (4)% of the target dose (b) (4) U for the 10 U cartridge and (b) (4) U for the 20 U cartridge). Accordingly, expected variations in environmental use conditions do not significantly affect particle specifications.

Table 30: ED Test Results in Gen2 at Varied Environmental Conditions

Environment	5°C/25%RH	40°C/75%RH	5°C/25%RH	40°C/75%RH
Inhaler	ED (U) [10 U cartridge]		ED (U) [20 U cartridge]	
1	[redacted] (b) (4)			
2				
3				
4				
5				
6				
AVG				
STD				
MAX				
MIN				
Conducted with six (6) inhalers each tested with 3 cartridges				

Stability Testing

To support the long term shelf life and 15 day in use period of the Gen2 Inhaler, stability and lifecycle testing programs were initiated to verify inhaler functionality is maintained.

The stability report for Technosphere Insulin (TI) Inhalation Powder Gen2 cartridges comprises data from 6 registration batches. The batches on stability represent the commercial products of 0.35 mg (10 U) of insulin per cartridge and 0.7 mg (20 U) of insulin per cartridge. The samples were stored according to the ICH Q1A (R2) *Stability Testing of New Drug Substances and Products.*

Samples were stored at 5°C for up to 36 months. Samples for the "extension" or "end use" study were obtained from the 5°C chamber after the 21, 24 and 36 month time points. End-use samples with and without foil overwrap were stored at 25°C/60% relative humidity (RH) for up to 30 days or at 30°C/65%RH for up to 10 days. All test parameters in the extension studies were obtained from samples stored at accelerated conditions without foil overwrap. The Seal Integrity (Leak Test) was also performed on samples stored with overwrap because that test is a test of the overwrap, not of the cartridge.

Also included are data from samples stored 3 months at 25°C/60%RH, 3 months at 30°C/65%RH and 2 months at 25°C/75%RH. These data were obtained early on during the stability studies to get an indication of the extent of degradation at these accelerated storage conditions and to use for extrapolation purposes. However, now that real time data from the extension studies are available, the real time data is the focus of the stability discussion. The real time room temperature (25°C/60%RH) extension study data exhibits a similar extent of degradation as was previously observed with the initial accelerated room temperature (25°C/60%RH) samples. Data demonstrated that chemical stability is the most important stability indicating parameter and considered the most relevant for the assignment of shelf life. Technosphere Insulin Inhalation Powder exhibited minimal degradation at 5ºC. At room temperature insulin loss and increase in degradation was observed. However, no trends were observed with the physical stability (APSD, ED, Moisture, and Foreign Particulates).

A 48 month shelf life has been established for the inhaler. The shelf life period is supported by a design verification program with assessments at three storage conditions: real time aging at standard temperature of 25°C, real time aging at refrigerated temperature of 5°C, and accelerated aging at elevated temperature of 50°C. Powder performance and specific functional/mechanical assessments, including resistance testing are included within the verification. The program is on-going. Age related performance effects have not been observed. To date, inhalers have been tested after storage at the following conditions:

- 50°C for 26 weeks (equivalent to 48 month storage at 25°C)
- 25°C for 24 months
- 5°C for 24 months

As part of the Gen2 Inhaler design verification program, life cycle testing was conducted to confirm suitability of the design to meet the in-use period of 15 days. After storage at the conditions outlined above, fifteen inhalers were subjected to 180 discharges to mimic real time use. Three cartridges were discharged at each of four approximate meal times (breakfast, lunch, dinner and a snack). Powder performance and specific functional assessments, including resistance testing were performed. Data to date includes performance evaluations of pre and post life cycling on inhalers stored at the following conditions: time zero, up to 26 weeks exposure at 50°C (equivalent to 48 month storage at 25°C), up to 24 months exposure at 25°C, and up to 24 months exposure at 5°C. All results passed acceptance criteria.

CDRH considers the stability testing performed to date sufficient to validate the proposed shelf-life and lifetime of use.

Biocompatibility

The sponsor has completed a range of biocompatibility tests intended to demonstrate the safety of materials that are either in contact with the skin or the mucosa for a duration less than 30 days. The biocompatibility assessments provided in this submission are identical to those submitted with the original NDA (March 26, 2009). The new materials in the Gen2 device were assessed at this time in accordance with ISO 10993-1. These assessments were reviewed at that time, and there do not appear to be any outstanding concerns regarding biocompatibility as of the January 19, 2011 Complete Response Letter.

In summary, components used in the manufacture of the mouthpiece, lid and medication cups underwent cytoxicity, sensitization, intracutaneous reactivity and delayed hypersensitivity tests in accordance with ISO 10993-1.

In the present submission, the sponsor has supplemented the ISO 10993-1 biocompatibility tests provided previously in 2009 with controlled extraction studies to ensure that the molded components contacting the TI Inhalation Powder do not affect safety and quality. These tests detected what appear to be (b) (4) . Small amounts of (b) (4) and associated degradants were also observed. CDRH believes that the

cumulative information provided for review is not sufficient to make a definitive determination of biocompatibility for the proposed device. CDRH is currently not aware of validated acceptance criteria to describe safe levels of extractables, leachables, and volatile organic compounds and therefore defers to CDER to determine whether the observed levels of volatile alkenes are safe.

As discussed further below, these tests are different from what CDRH currently accepts in support of biocompatibility for respiratory drug delivery devices submitted via the 510(k) Premarket Notification process. However, it appears that based on CDER's pharmacology-toxicology assessment of the extractables testing and animal toxicology testing, biocompatibility has been sufficiently supported by the combination of ISO 10993-1 tests, extractables tests and animal toxicology reports.

D. Review Conclusions and Recommendation

The sponsor has provided a range of descriptive information and comparative analyses to establish relative equivalence between the originally proposed combination product that includes the MedTone Inhaler and the to-be-marketed configuration that uses the Gen2 Inhaler. Collectively, these tests are sufficient to demonstrate that the to-be-marketed drug-device configuration (Gen 2 Inhaler and TI Inhalation Powder) reliably administers a delivered dose of (b) (4) U from the 10 U cartridge (0.35 mg insulin , 3.3 mg TI Inhalation Powder) and (b) (4) from the 20 U (0.7 mg insulin, 6.7 mg TI Inhalation Powder). These results are within the emitted dose acceptance criterion of (b) (4) % of nominal dose that was specified by the applicant and was deemed to be safe and effective by the Center for Drug Evaluation and Research (CDER). The measured mass-median aerosol diameters for the 10 U and 20 U cartridges were approximately (b) (4) µm ((b) (4) % respirable fraction) and (b) (4) µm (b) (4) % respirable fraction), respectively.

In order to demonstrate stability of the device, the applicant conducted long term, accelerated, and extension study to determine recommended storage conditions and specifications for shelf-life and use duration. The results of these studies were sufficient to validate a shelf life of 24 months when stored at refrigerated conditions (2-8 ˚C) and a 15 day user period.

The Respiratory and Pulmonary Device Branch (RPDB) in CDRH considers devices that contact the patient gas pathway to be externally communicating devices with tissue contact. This is primarily due to the potential for chemical leachants from the device entering the patient's airway. Accordingly, the Branch consistently recommends that biocompatibility testing be selected in accordance with ISO 10993-1 with careful consideration of the appropriate duration and level of contact of the device, and that the cumulative duration of use be considered in determining the duration of patient contact.

In accordance with the present version of ISO 10993-1, externally communicating devices with either prolonged (24 hours – 30 days) or permanent (>30 days) tissue contact require cytoxicity sensitization, irritation or intracutaneous reactivity, systemic toxicity, subchronic toxicity, genotoxicity and implantation tests. As described in Section C below, the sponsor has provided acceptable test results in accordance with the aforementioned standard for cytoxicity, sensitization, irritation and acute systemic toxicity. However, the remaining tests as outlined above were not conducted. As such, the conducted tests in isolation would not be considered sufficient to validate biocompatibility for an externally communicating device with tissue contact when utilizing ISO 10993-1.

However, in the present submission, the sponsor has supplemented the ISO 10993-1 biocompatibility tests provided previously in 2009 with controlled extraction studies to ensure that the molded components contacting the TI Inhalation Powder do not affect safety and quality. These tests detected what appear to be (b) (4)
Small amounts of (b) (4) and associated degradants were also observed. CDRH believes that the cumulative information provided for review is not sufficient to make a definitive determination of biocompatibility for the proposed device. CDRH is currently not aware of validated

acceptance criteria to describe safe levels of extractables, leachables, and volatile organic compounds and therefore defers to CDER to determine whether the observed levels of volatile alkenes are safe.

Dr. Miyun Tsai-Turton, the pharmacological-toxicological reviewer on the present NDA submission, reviewed on extraction studies referenced above in conjunction with local and systemic animal toxicological studies provided by the sponsor to evaluate tissue and physiological responses from the combination product. Based on her review, she concludes that the totality of the information provided is sufficient to demonstrate biocompatibility for the proposed drug-device combination. With consideration of this assessment, CDRH believes that the biocompatibility of the proposed device has been sufficiently supported by 10993-1 tests, extractables testing, and toxicological testing in animals.

In conclusion, the sponsor has adequately validated the proposed drug-device combination product in terms of in vitro performance and stability. Accordingly, if CDER determines the biocompatibility information provided is sufficient and that the clinical study information provided for review provides a sufficient basis for safety and effectiveness, CDRH recommends approval of the proposed drug-device combination.

CDRH strongly believes that relevant measured specifications (e.g. emitted dose, respirable dose, particle size) for the drug-device combination are necessary whenever recommended doses and/or device specifications are listed in labeling. This information is useful to prescribers and physicians to distinguish between a recommended dose specification and the actual measured dose specification. The importance of this information is dependent on the observed difference between the recommended and measured values and also on the therapeutic index of the drug under consideration.

_____ _____

Mr. Sugato De, M.S., Lead Reviewer Date

_____ _____

Dr. Anya Harry, RPDB Branch Chief Date

_____ _____

Dr. Tejashri Purohit-Sheth, Clinical Deputy Director 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

07/02/2014

This CDRH Regulatory Device Consult is being checked into DARRTS by RPM for Sugato De, M.S., Biomedical Engineer (ODE/DAGID/ARDB), Lead Reviewer

PMR/PMC Development Template

This template should be completed by the PMR/PMC Development Coordinator and included for ***each*** PMR/PMC in the Action Package.

NDA/BLA #	NDA 022472
Product Name:	Afrezza (insulin human) Inhalation Powder
PMR/PMC Description:	An open-label, pharmacokinetic (PK), and multiple-dose safety and tolerability dose-titration trial of Afrezza in pediatric patients ages 4 to 17 years (inclusive) with type 1 diabetes (Part 1), followed by a prospective, multicenter, open-label randomized, controlled trial comparing the efficacy and safety of prandial Afrezza to prandial, subcutaneous, insulin aspart used in combination with subcutaneous basal insulin in pediatric patients 4 to 17 years old (inclusive) with type 1 or type 2 diabetes (Part 2). Part 2 of the trial should include a 4-week run-in phase and a 52-week randomized intervention phase.

PMR/PMC Schedule Milestones:		
	Final Protocol Submission:	January 2015
	Study/Trial Completion:	July 2020
	Final Report Submission:	January 2021
	Other:	

1. During application review, explain why this issue is appropriate for a PMR/PMC instead of a pre-approval requirement. Check type below and describe.

- ☐ Unmet need
- ☐ Life-threatening condition
- ☐ Long-term data needed
- ☐ Only feasible to conduct post-approval
- ☐ Prior clinical experience indicates safety
- ☐ Small subpopulation affected
- ☐ Theoretical concern
- ☒ Other

Afrezza is ready for approval for use in adults. However, pediatric studies have been deferred until adequate safety data are available.

2. Describe the particular review issue and the goal of the study/clinical trial. If the study/clinical trial is a FDAAA PMR, describe the risk. If the FDAAA PMR is created post-approval, describe the "new safety information."

Part 1: This is a deferred pediatric study under the Pediatric Research Equity Act (PREA) to evaluate the pharmacokinetics (PK), and safety and tolerability of Afrezza dose-titration in pediatric patients ages 4 to 17 years (inclusive).

Part 2: This is a deferred pediatric study under the Pediatric Research Equity Act (PREA) to determine the efficacy and safety of Afrezza in pediatric patients ages 4 to 17 years (inclusive).

3. If the study/clinical trial is a **PMR**, check the applicable regulation.
If not a PMR, skip to 4.

- **Which regulation?**

☐ Accelerated Approval (subpart H/E)
☐ Animal Efficacy Rule
☒ Pediatric Research Equity Act
☐ FDAAA required safety study/clinical trial

- **If the PMR is a FDAAA safety study/clinical trial, does it: (check all that apply)**

☐ Assess a known serious risk related to the use of the drug?
☐ Assess signals of serious risk related to the use of the drug?
☐ Identify an unexpected serious risk when available data indicate the potential for a serious risk?

- **If the PMR is a FDAAA safety study/clinical trial, will it be conducted as:**

☐ Analysis of spontaneous postmarketing adverse events?
Do not select the above study/clinical trial type if: such an analysis will not be sufficient to assess or identify a serious risk

☐ Analysis using pharmacovigilance system?
Do not select the above study/clinical trial type if: the new pharmacovigilance system that the FDA is required to establish under section 505(k)(3) has not yet been established and is thus not sufficient to assess this known serious risk, or has been established but is nevertheless not sufficient to assess or identify a serious risk

☐ Study: all other investigations, such as investigations in humans that are not clinical trials as defined below (e.g., observational epidemiologic studies), animal studies, and laboratory experiments?
Do not select the above study type if: a study will not be sufficient to identify or assess a serious risk

☐ Clinical trial: any prospective investigation in which the sponsor or investigator determines the method of assigning investigational product or other interventions to one or more human subjects?

4. What type of study or clinical trial is required or agreed upon (describe and check type below)? If the study or trial will be performed in a subpopulation, list here.

Part 1: Open-label, pharmacokinetic (PK), and multiple-dose safety and tolerability dose-titration trial in pediatric patients ages 4 to 17 years (inclusive) with type 1 diabetes.

Part 2: Prospective, multi-center, open-label, randomized, controlled trial comparing the efficacy and safety of prandial Afrezza to prandial, subcutaneous, insulin apsart used in combination with subcutaneous basal insulin in pediatric patients 4 to 17 years old (inclusive) with type 1 or type 2 diabetes. Part 2 of the trial should include a 4-week run-in phase and a 52-week randomized intervention phase.

Required

☐ Observational pharmacoepidemiologic study
☐ Registry studies
☐ Primary safety study or clinical trial
☐ Pharmacogenetic or pharmacogenomic study or clinical trial if required to further assess safety
☐ Thorough Q-T clinical trial
☐ Nonclinical (animal) safety study (e.g., carcinogenicity, reproductive toxicology)
☐ Nonclinical study (laboratory resistance, receptor affinity, quality study related to safety)
☒ Pharmacokinetic studies or clinical trials
☐ Drug interaction or bioavailability studies or clinical trials
☐ Dosing trials
☐ Additional data or analysis required for a previously submitted or expected study/clinical trial (provide explanation)

_____

☐ Meta-analysis or pooled analysis of previous studies/clinical trials
☐ Immunogenicity as a marker of safety
☐ Other (provide explanation)

Agreed upon:

☐ Quality study without a safety endpoint (e.g., manufacturing, stability)
☐ Pharmacoepidemiologic study not related to safe drug use (e.g., natural history of disease, background rates of adverse events)
☐ Clinical trials primarily designed to further define efficacy (e.g., in another condition, different disease severity, or subgroup) that are NOT required under Subpart H/E
☐ Dose-response study or clinical trial performed for effectiveness
☐ Nonclinical study, not safety-related (specify)

_____

☐ Other

_____

5. Is the PMR/PMC clear, feasible, and appropriate?

☒ Does the study/clinical trial meet criteria for PMRs or PMCs?
☒ Are the objectives clear from the description of the PMR/PMC?
☒ Has the applicant adequately justified the choice of schedule milestone dates?
☒ Has the applicant had sufficient time to review the PMRs/PMCs, ask questions, determine feasibility, and contribute to the development process?

☐ Check if this form describes a FDAAA PMR that is a randomized controlled clinical trial

If so, does the clinical trial meet the following criteria?

☐ There is a significant question about the public health risks of an approved drug
☐ There is not enough existing information to assess these risks
☐ Information cannot be gained through a different kind of investigation
☐ The trial will be appropriately designed to answer question about a drug's efficacy and safety, and
☐ The trial will emphasize risk minimization for participants as the protocol is developed

---

PMR/PMC Development Coordinator:

☒ *This PMR/PMC has been reviewed for clarity and consistency, and is necessary to further refine the safety, efficacy, or optimal use of a drug, or to ensure consistency and reliability of drug quality.*

_____

(signature line for BLAs)

PMR/PMC Development Template

This template should be completed by the PMR/PMC Development Coordinator and included for ***each*** PMR/PMC in the Action Package.

NDA/BLA #	NDA 022472
Product Name:	Afrezza (insulin human) Inhalation Powder
PMR/PMC Description:	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 are adequately captured and characterized. Compare the dose-response curves for Afrezza and subcutaneous insulin noting the dose at which the response become curvilinear for each. These data may impact labeling recommendations for dosing and thereby mitigate the risk of diabetic ketoacidosis, which has been observed with Afrezza.

PMR/PMC Schedule Milestones:	Final Protocol Submission:	January 2015
	Study/Trial Completion:	June 2016
	Final Report Submission:	March 2017
	Other:	

1. During application review, explain why this issue is appropriate for a PMR/PMC instead of a pre-approval requirement. Check type below and describe.

   ☐ Unmet need
   ☐ Life-threatening condition
   ☐ Long-term data needed
   ☐ Only feasible to conduct post-approval
   ☐ Prior clinical experience indicates safety
   ☐ Small subpopulation affected
   ☐ Theoretical concern
   ☒ Other

   Only the patients requiring higher doses of insulin will be affected by lack of this knowledge. Even in those patients, insulins can be titrated to clinical benefit. However, availability of this knowledge will help in performing the up-titrations in a guided manner.

2. Describe the particular review issue and the goal of the study/clinical trial. If the study/clinical trial is a FDAAA PMR, describe the risk. If the FDAAA PMR is created post-approval, describe the "new safety information."

The goal of this study is to get a more reliable determination of the dosing regimen for patients switching from subcutaneous insulin to Afrezza.

Data from PK/PD studies and from a fixed dose Phase 2 study suggest that the glucose lowering benefit of Afrezza is less-than dose proportional in the therapeutic dosing range. Although it is known that the glucose lowering effect of subcutaneously administered insulin is also less-than dose proportional, loss of dose-proportionality is usually observed outside the therapeutic dosing range for subcutaneously delivered insulin. The data in the application suggest the maximum PD response for Afrezza occurs at a lower dose relative to subcutaneous insulin. An adequate characterization of the difference in dose response between Afrezza and subcutaneous insulin is important for safety reasons. If it is known that above a certain dose Afrezza would not be expected to result in added glucose lowering benefit, patients could be saved from being unnecessarily exposed to high glucose levels by being switched to a more effective form of therapy. The adverse event of diabetic ketoacidosis (DKA) with Afrezza was observed in the clinical program and further knowledge about the PK-PD relationship for Afrezza relative to subcutaneous insulin could potentially mitigate this risk.

3. If the study/clinical trial is a **PMR**, check the applicable regulation.
If not a PMR, skip to 4.

- **Which regulation?**

☐ Accelerated Approval (subpart H/E)
☐ Animal Efficacy Rule
☐ Pediatric Research Equity Act
☒ FDAAA required safety study/clinical trial

- **If the PMR is a FDAAA safety study/clinical trial, does it: (check all that apply)**

☒ Assess a known serious risk related to the use of the drug?
☐ Assess signals of serious risk related to the use of the drug?
☐ Identify an unexpected serious risk when available data indicate the potential for a serious risk?

- **If the PMR is a FDAAA safety study/clinical trial, will it be conducted as:**

☐ Analysis of spontaneous postmarketing adverse events?
Do not select the above study/clinical trial type if: such an analysis will not be sufficient to assess or identify a serious risk

☐ Analysis using pharmacovigilance system?
Do not select the above study/clinical trial type if: the new pharmacovigilance system that the FDA is required to establish under section 505(k)(3) has not yet been established and is thus not sufficient to assess this known serious risk, or has been established but is nevertheless not sufficient to assess or identify a serious risk

☐ Study: all other investigations, such as investigations in humans that are not clinical trials as defined below (e.g., observational epidemiologic studies), animal studies, and laboratory experiments?
Do not select the above study type if: a study will not be sufficient to identify or assess a serious risk

☒ Clinical trial: any prospective investigation in which the sponsor or investigator determines the method of assigning investigational product or other interventions to one or more human subjects?

4. What type of study or clinical trial is required or agreed upon (describe and check type below)? If the study or trial will be performed in a subpopulation, list here.

The study will be a dose-ranging pharmacokinetic-pharmacodynamics (PK-PD) euglycemic clamp trial to characterize the dose-response of Afrezza relative to subcutaneous insulin in patients with type 1 diabetes. Three to four doses for each route of insulin administration will be selected to ensure both the linear and curvilinear portions of the dose response curves are adequately captured and characterized. The dose-response curves for Afrezza and subcutaneous insulin will be compared noting the dose at which the response becomes curvilinear for each.

Required

☐ Observational pharmacoepidemiologic study
☐ Registry studies
☐ Primary safety study or clinical trial
☐ Pharmacogenetic or pharmacogenomic study or clinical trial if required to further assess safety
☐ Thorough Q-T clinical trial
☐ Nonclinical (animal) safety study (e.g., carcinogenicity, reproductive toxicology)
☐ Nonclinical study (laboratory resistance, receptor affinity, quality study related to safety)
☒ Pharmacokinetic studies or clinical trials
☐ Drug interaction or bioavailability studies or clinical trials
☐ Dosing trials
☐ Additional data or analysis required for a previously submitted or expected study/clinical trial (provide explanation)

_____

☐ Meta-analysis or pooled analysis of previous studies/clinical trials
☐ Immunogenicity as a marker of safety
☐ Other (provide explanation)

_____

Agreed upon:

☐ Quality study without a safety endpoint (e.g., manufacturing, stability)
☐ Pharmacoepidemiologic study not related to safe drug use (e.g., natural history of disease, background rates of adverse events)
☐ Clinical trials primarily designed to further define efficacy (e.g., in another condition, different disease severity, or subgroup) that are NOT required under Subpart H/E
☐ Dose-response study or clinical trial performed for effectiveness
☐ Nonclinical study, not safety-related (specify)

_____

☐ Other

_____

5. Is the PMR/PMC clear, feasible, and appropriate?

☒ Does the study/clinical trial meet criteria for PMRs or PMCs?
☒ Are the objectives clear from the description of the PMR/PMC?
☒ Has the applicant adequately justified the choice of schedule milestone dates?
☒ Has the applicant had sufficient time to review the PMRs/PMCs, ask questions, determine feasibility, and contribute to the development process?

PMR/PMC Development Coordinator:

☒ *This PMR/PMC has been reviewed for clarity and consistency, and is necessary to further refine the safety, efficacy, or optimal use of a drug, or to ensure consistency and reliability of drug quality.*

_____

(signature line for BLAs)

PMR/PMC Development Template

This template should be completed by the PMR/PMC Development Coordinator and included for ***each*** PMR/PMC in the Action Package.

NDA/BLA #	022472
Product Name:	Afrezza (insulin human) Inhalation Powder
PMR/PMC Description:	A PK-PD eugylcemic glucose-clamp trial to characterize within-subject variability for Afrezza pharmacokinetic (PK) and pharmacodynamic (PD) parameters. These data may impact labeling recommendations for glucose monitoring and thereby mitigate the risk of hypoglycemia, which has been observed with Afrezza.

PMR/PMC Schedule Milestones:	Final Protocol Submission:	April 2015
	Study/Trial Completion:	April 2016
	Final Report Submission:	January 2017
	Other:	

1. During application review, explain why this issue is appropriate for a PMR/PMC instead of a pre-approval requirement. Check type below and describe.

   ☐ Unmet need
   ☐ Life-threatening condition
   ☐ Long-term data needed
   ☐ Only feasible to conduct post-approval
   ☐ Prior clinical experience indicates safety
   ☐ Small subpopulation affected
   ☐ Theoretical concern
   ☒ Other

   Insulin products are titrated to clinical benefit; therefore, patients can titrate the dose if desired glucose control is not achieved as a result of within-subject variability. However, if the within-subject variability is adequately characterized and reported in the label, it will make prescribers and patients aware of what to expect from the product with respect to variability in product performance for the same subject at different occasions and minimize any undue safety risk.

2. Describe the particular review issue and the goal of the study/clinical trial. If the study/clinical trial is a FDAAA PMR, describe the risk. If the FDAAA PMR is created post-approval, describe the "new safety information."

   The goal of this study is to characterize the within-subject variability for PK and PD parameters for Gen2 (the commercial device) delivered Afrezza insulin.

   In general, the clinical response to insulin treatment is associated with high between and within-subject variability. The within-subject variability in PK and PD parameters for Afrezza is not known. An insulin with high within subject variability may provide less reliable/predictable effects. Characterization of the within-subject variability for Afrezza PK and PD parameters may impact labeling recommendations for glucose monitoring and thereby mitigate the risks of hypoglycemia. Hypoglycemia was observed with Afrezza in the clinical program.

3. If the study/clinical trial is a **PMR**, check the applicable regulation.
If not a PMR, skip to 4.

- **Which regulation?**

☐ Accelerated Approval (subpart H/E)
☐ Animal Efficacy Rule
☐ Pediatric Research Equity Act
☒ FDAAA required safety study/clinical trial

- **If the PMR is a FDAAA safety study/clinical trial, does it: (check all that apply)**

☒ Assess a known serious risk related to the use of the drug?
☐ Assess signals of serious risk related to the use of the drug?
☐ Identify an unexpected serious risk when available data indicate the potential for a serious risk?

- **If the PMR is a FDAAA safety study/clinical trial, will it be conducted as:**

☐ Analysis of spontaneous postmarketing adverse events?
Do not select the above study/clinical trial type if: such an analysis will not be sufficient to assess or identify a serious risk

☐ Analysis using pharmacovigilance system?
Do not select the above study/clinical trial type if: the new pharmacovigilance system that the FDA is required to establish under section 505(k)(3) has not yet been established and is thus not sufficient to assess this known serious risk, or has been established but is nevertheless not sufficient to assess or identify a serious risk

☐ Study: all other investigations, such as investigations in humans that are not clinical trials as defined below (e.g., observational epidemiologic studies), animal studies, and laboratory experiments?
Do not select the above study type if: a study will not be sufficient to identify or assess a serious risk

☒ Clinical trial: any prospective investigation in which the sponsor or investigator determines the method of assigning investigational product or other interventions to one or more human subjects?

4. What type of study or clinical trial is required or agreed upon (describe and check type below)? If the study or trial will be performed in a subpopulation, list here.

The study will be a pharmacokinetic-pharmacodynamic (PK-PD) euglycemic clamp trial to characterize within-subject variability for Afrezza pharmacokinetic (PK) and pharmacodynamics (PD) parameters.

Required

☐ Observational pharmacoepidemiologic study
☐ Registry studies
☐ Primary safety study or clinical trial
☐ Pharmacogenetic or pharmacogenomic study or clinical trial if required to further assess safety
☐ Thorough Q-T clinical trial
☐ Nonclinical (animal) safety study (e.g., carcinogenicity, reproductive toxicology)

☐ Nonclinical study (laboratory resistance, receptor affinity, quality study related to safety)
☒ Pharmacokinetic studies or clinical trials
☐ Drug interaction or bioavailability studies or clinical trials
☐ Dosing trials
☐ Additional data or analysis required for a previously submitted or expected study/clinical trial (provide explanation)

_____

☐ Meta-analysis or pooled analysis of previous studies/clinical trials
☐ Immunogenicity as a marker of safety
☐ Other (provide explanation)

_____

Agreed upon:

☐ Quality study without a safety endpoint (e.g., manufacturing, stability)
☐ Pharmacoepidemiologic study not related to safe drug use (e.g., natural history of disease, background rates of adverse events)
☐ Clinical trials primarily designed to further define efficacy (e.g., in another condition, different disease severity, or subgroup) that are NOT required under Subpart H/E
☐ Dose-response study or clinical trial performed for effectiveness
☐ Nonclinical study, not safety-related (specify)

_____

☐ Other

_____

5. Is the PMR/PMC clear, feasible, and appropriate?

☒ Does the study/clinical trial meet criteria for PMRs or PMCs?
☒ Are the objectives clear from the description of the PMR/PMC?
☒ Has the applicant adequately justified the choice of schedule milestone dates?
☒ Has the applicant had sufficient time to review the PMRs/PMCs, ask questions, determine feasibility, and contribute to the development process?

PMR/PMC Development Coordinator:

☒ *This PMR/PMC has been reviewed for clarity and consistency, and is necessary to further refine the safety, efficacy, or optimal use of a drug, or to ensure consistency and reliability of drug quality.*

_____
(signature line for BLAs)

PMR/PMC Development Template

This template should be completed by the PMR/PMC Development Coordinator and included for ***each*** PMR/PMC in the Action Package.

NDA/BLA # 022472
Product Name: Afrezza (insulin human) Inhalation Powder

PMR/PMC Description: Conduct a 5-year, randomized, controlled trial in 8,000-10,000 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 to compare the incidence of pulmonary malignancy observed with Afrezza to that observed in the standard of care control group. Secondary endpoints should include mortality due to pulmonary malignancy and all-cause mortality. Randomization to Afrezza or standard of care 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-years). 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 issues should continue to be followed for the outcomes of interest and prospective measures to encourage subject retention and capture outcomes in patients who withdraw or are lost to follow-up should be in place. 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 (also with 1 to 1 randomization to either Afrezza or standard of care) 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.

PMR/PMC Schedule Milestones:

Final Protocol Submission:	April 2015
Study/Trial Completion:	April 2023
Final Report Submission:	December 2023
Other:	

1. During application review, explain why this issue is appropriate for a PMR/PMC instead of a pre-approval requirement. Check type below and describe.

   - ☐ Unmet need
   - ☐ Life-threatening condition
   - ☒ Long-term data needed
   - ☐ Only feasible to conduct post-approval
   - ☐ Prior clinical experience indicates safety
   - ☐ Small subpopulation affected
   - ☐ Theoretical concern
   - ☐ Other

The evaluation of the signal of a serious risk of pulmonary malignancy, the known risk of decline in pulmonary function, and the unexpected serious risk of cardiovascular events requires long-term safety data.

2. Describe the particular review issue and the goal of the study/clinical trial. If the study/clinical trial is a FDAAA PMR, describe the risk. If the FDAAA PMR is created post-approval, describe the "new safety information."

The goal of this trial is to evaluate a serious risk of pulmonary malignancy, the known risk of decline in pulmonary function, and the unexpected serious risk of cardiovascular events.

Regarding pulmonary malignancy, in clinical trials two cases of lung cancer were observed in participants exposed to Afrezza while no cases were observed in comparators. In both cases, a prior history of heavy tobacco use was identified as a risk factor. Two additional cases of lung cancer (squamous cell) occurred in non-smokers exposed to Afrezza and were reported by investigators after clinical trial completion.

Regarding decline in pulmonary function, Afrezza causes a decline in lung function over time as measured by FEV1. In clinical trials excluding patients with chronic lung disease and lasting up to 2 years, Afrezza treated patients experienced a small (40 mL) but greater FEV_1 decline than comparator treated patients. The effects of Afrezza on pulmonary function for treatment duration longer than 2 years has not been established.

Regarding cardiovascular events, there have been signals of a serious risk of cardiovascular events with some medications developed for the treatment of type 2 diabetes mellitus.

3. If the study/clinical trial is a **PMR**, check the applicable regulation.
If not a PMR, skip to 4.

- **Which regulation?**
  - ☐ Accelerated Approval (subpart H/E)
  - ☐ Animal Efficacy Rule
  - ☐ Pediatric Research Equity Act
  - ☒ FDAAA required safety study/clinical trial

- **If the PMR is a FDAAA safety study/clinical trial, does it: (check all that apply)**
  - ☒ Assess a known serious risk related to the use of the drug?
  - ☒ Assess signals of serious risk related to the use of the drug?
  - ☒ Identify an unexpected serious risk when available data indicate the potential for a serious risk?

- **If the PMR is a FDAAA safety study/clinical trial, will it be conducted as:**
  - ☐ Analysis of spontaneous postmarketing adverse events?
    Do not select the above study/clinical trial type if: such an analysis will not be sufficient to assess or identify a serious risk

☐ Analysis using pharmacovigilance system?
Do not select the above study/clinical trial type if: the new pharmacovigilance system that the FDA is required to establish under section 505(k)(3) has not yet been established and is thus not sufficient to assess this known serious risk, or has been established but is nevertheless not sufficient to assess or identify a serious risk

☐ Study: all other investigations, such as investigations in humans that are not clinical trials as defined below (e.g., observational epidemiologic studies), animal studies, and laboratory experiments?
Do not select the above study type if: a study will not be sufficient to identify or assess a serious risk

☒ Clinical trial: any prospective investigation in which the sponsor or investigator determines the method of assigning investigational product or other interventions to one or more human subjects?

4. What type of study or clinical trial is required or agreed upon (describe and check type below)? If the study or trial will be performed in a subpopulation, list here.

A randomized, controlled trial in 8,000-10,000 patients with type-2 diabetes. The primary objective of the trial should be to compare the incidence of pulmonary malignancy observed with Afrezza to that observed in the standard of care control group. Secondary endpoints should include mortality due to pulmonary malignancy and all-cause mortality. Randomization to Afrezza or standard of care 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-years). 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 issues should continue to be followed for the outcomes of interest and prospective measures to encourage subject retention and capture outcomes in patients who withdraw or are lost to follow-up should be in place. 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 included as part of the trial is a substudy (also with 1 to 1 randomization to either Afrezza or standard of care) evaluating 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.

Required

☐ Observational pharmacoepidemiologic study
☐ Registry studies
☒ Primary safety study or clinical trial
☐ Pharmacogenetic or pharmacogenomic study or clinical trial if required to further assess safety
☐ Thorough Q-T clinical trial
☐ Nonclinical (animal) safety study (e.g., carcinogenicity, reproductive toxicology)
☐ Nonclinical study (laboratory resistance, receptor affinity, quality study related to safety)
☐ Pharmacokinetic studies or clinical trials
☐ Drug interaction or bioavailability studies or clinical trials
☐ Dosing trials
☐ Additional data or analysis required for a previously submitted or expected study/clinical trial (provide explanation)

_____

☐ Meta-analysis or pooled analysis of previous studies/clinical trials
☐ Immunogenicity as a marker of safety

☐ Other (provide explanation)

_____

Agreed upon:

☐ Quality study without a safety endpoint (e.g., manufacturing, stability)
☐ Pharmacoepidemiologic study not related to safe drug use (e.g., natural history of disease, background rates of adverse events)
☐ Clinical trials primarily designed to further define efficacy (e.g., in another condition, different disease severity, or subgroup) that are NOT required under Subpart H/E
☐ Dose-response study or clinical trial performed for effectiveness
☐ Nonclinical study, not safety-related (specify)

_____

☐ Other

_____

5. Is the PMR/PMC clear, feasible, and appropriate?

☒ Does the study/clinical trial meet criteria for PMRs or PMCs?
☒ Are the objectives clear from the description of the PMR/PMC?
☒ Has the applicant adequately justified the choice of schedule milestone dates?
☒ Has the applicant had sufficient time to review the PMRs/PMCs, ask questions, determine feasibility, and contribute to the development process?

☒ Check if this form describes a FDAAA PMR that is a randomized controlled clinical trial

If so, does the clinical trial meet the following criteria?

☒ There is a significant question about the public health risks of an approved drug
☒ There is not enough existing information to assess these risks
☒ Information cannot be gained through a different kind of investigation
☒ The trial will be appropriately designed to answer question about a drug's efficacy and safety, and
☒ The trial will emphasize risk minimization for participants as the protocol is developed

---

PMR/PMC Development Coordinator:

☒ *This PMR/PMC has been reviewed for clarity and consistency, and is necessary to further refine the safety, efficacy, or optimal use of a drug, or to ensure consistency and reliability of drug quality.*

_____

(signature line for BLAs)

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

/s/

JENNIFER R PIPPINS
06/27/2014

REGULATORY PROJECT MANAGER
PHYSICIAN'S LABELING RULE (PLR) FORMAT REVIEW
OF THE PRESCRIBING INFORMATION

Complete for all new NDAs, BLAs, Efficacy Supplements, and PLR Conversion Labeling Supplements

Application: NDA 22472 AFREZZA

Application Type: New NDA **(Class 2 NDA resubmission)**

Name of Drug/Dosage Form: (insulin human) Inhalation Powder

Applicant: MannKind Corporation

Receipt Date: 10/15/13

Action Goal Date: June 27, 2014

1. Regulatory History and Applicant's Main Proposals

Class 2 NDA resubmission labeling

2. Review of the Prescribing Information

This review is based on the applicant's submitted Word format of the prescribing information (PI). The applicant's proposed PI was reviewed in accordance with the labeling format requirements listed in the "Selected Requirements for Prescribing Information (SRPI)" checklist (see the Appendix).

3. Conclusions/Recommendations

SRPI format deficiencies were identified in the review of this PI. For a list of these deficiencies see the Appendix.

Appendix

The Selected Requirement of Prescribing Information (SRPI) is a 42-item, drop-down checklist of important format elements of the prescribing information (PI) based on labeling regulations (21 CFR 201.56 and 201.57) and guidances.

Highlights

See Appendix A for a sample tool illustrating the format for the Highlights.

HIGHLIGHTS GENERAL FORMAT

NO 1. Highlights (HL) must be in a minimum of 8-point font and should be in two-column format, with ½ inch margins on all sides and between columns.

Comment: *Not in portrai and some font needs to be changed to 8-pointt*

NO 2. The length of HL must be one-half page or less unless a waiver has been granted in a previous submission. The HL Boxed Warning does not count against the one-half page requirement. Instructions to complete this item: If the length of the HL is one-half page or less, select "YES" in the drop-down menu because this item meets the requirement. However, if HL is longer than one-half page, select "NO" unless a waiver has been granted.

Comment:

NO 3. A horizontal line must separate HL from the Table of Contents (TOC). A horizontal line must separate the TOC from the FPI.

Comment:

YES 4. All headings in HL must be **bolded** and presented in the center of a horizontal line (each horizontal line should extend over the entire width of the column as shown in Appendix A). The headings should be in UPPER CASE letters.

Comment:

NO 5. White space should be present before each major heading in HL. There must be no white space between the HL Heading and HL Limitation Statement. There must be no white space between the product title and Initial U.S. Approval. See Appendix A for a sample tool illustrating white space in HL.

Comment: *No whitespace between boxed warning and Inications and Usage*

YES 6. Each summarized statement or topic in HL must reference the section(s) or subsection(s) of the Full Prescribing Information (FPI) that contain more detailed information. The preferred format is the numerical identifier in parenthesis [e.g., (1.1)] at the end of each summarized statement or topic.

Comment:

NO 7. Section headings must be presented in the following order in HL:

Section	Required/Optional
• **Highlights Heading**	Required
• **Highlights Limitation Statement**	Required
• **Product Title**	Required

Selected Requirements of Prescribing Information

• **Initial U.S. Approval**	Required
• **Boxed Warning**	Required if a BOXED WARNING is in the FPI
• **Recent Major Changes**	Required for only certain changes to PI*
• **Indications and Usage**	Required
• **Dosage and Administration**	Required
• **Dosage Forms and Strengths**	Required
• **Contraindications**	Required (if no contraindications must state "None.")
• **Warnings and Precautions**	Not required by regulation, but should be present
• **Adverse Reactions**	Required
• **Drug Interactions**	Optional
• **Use in Specific Populations**	Optional
• **Patient Counseling Information Statement**	Required
• **Revision Date**	Required

* RMC only applies to the BOXED WARNING, INDICATIONS AND USAGE, DOSAGE AND ADMINISTRATION, CONTRAINDICATIONS, and WARNINGS AND PRECAUTIONS sections.

Comment: *Revision date needs to ber on first page*

HIGHLIGHTS DETAILS

Highlights Heading

YES 8. At the beginning of HL, the following heading must be **bolded** and should appear in all UPPER CASE letters: **"HIGHLIGHTS OF PRESCRIBING INFORMATION"**.

Comment:

Highlights Limitation Statement

YES 9. The **bolded** HL Limitation Statement must include the following verbatim statement: "**These highlights do not include all the information needed to use (insert name of drug product) safely and effectively. See full prescribing information for (insert name of drug product).**" The name of drug product should appear in UPPER CASE letters.

Comment:

Product Title in Highlights

YES 10. Product title must be **bolded**.

Comment:

Initial U.S. Approval in Highlights

YES 11. Initial U.S. Approval in HL must be **bolded**, and include the verbatim statement "**Initial U.S. Approval:**" followed by the **4-digit year**.

Comment:

Boxed Warning (BW) in Highlights

YES 12. All text in the BW must be **bolded**.

Comment:

YES 13. The BW must have a heading in UPPER CASE, containing the word "**WARNING**" (even if more than one warning, the term, "**WARNING**" and not "**WARNINGS**" should be used) and other words to identify the subject of the warning (e.g., "**WARNING: SERIOUS INFECTIONS and ACUTE HEPATIC FAILURE**"). The BW heading should be centered.

Comment:

NO 14. The BW must always have the verbatim statement "***See full prescribing information for complete boxed warning***." This statement should be centered immediately beneath the heading and appear in *italics*.

Comment:

YES 15. The BW must be limited in length to 20 lines (this includes white space but does not include the BW heading and the statement "***See full prescribing information for complete boxed warning.***").

Comment:

Recent Major Changes (RMC) in Highlights

N/A 16. RMC pertains to only the following five sections of the FPI: BOXED WARNING, INDICATIONS AND USAGE, DOSAGE AND ADMINISTRATION, CONTRAINDICATIONS, and WARNINGS AND PRECAUTIONS. RMC must be listed in the same order in HL as the modified text appears in FPI.

Comment:

N/A 17. The RMC must include the section heading(s) and, if appropriate, subsection heading(s) affected by the recent major change, together with each section's identifying number and date (month/year format) on which the change was incorporated in the PI (supplement approval date). For example, "Warnings and Precautions, Acute Liver Failure (5.1) --- 9/2013".

Comment:

N/A 18. The RMC must list changes for at least one year after the supplement is approved and must be removed at the first printing subsequent to one year (e.g., no listing should be one year older than revision date).

Comment:

Indications and Usage in Highlights

YES 19. If a product belongs to an established pharmacologic class, the following statement is required under the Indications and Usage heading in HL: "(Product) is a (name of established pharmacologic class) indicated for (indication)".

Comment:

Dosage Forms and Strengths in Highlights

YES 20. For a product that has several dosage forms (e.g., capsules, tablets, and injection), bulleted subheadings or tabular presentations of information should be used under the Dosage Forms and Strengths heading.

Comment:

Contraindications in Highlights

YES

21. All contraindications listed in the FPI must also be listed in HL or must include the statement "None" if no contraindications are known. Each contraindication should be bulleted when there is more than one contraindication.

Comment:

Adverse Reactions in Highlights

YES 22. For drug products other than vaccines, the verbatim **bolded** statement must be present: "**To report SUSPECTED ADVERSE REACTIONS, contact (insert name of manufacturer) at (insert manufacturer's U.S. phone number) or FDA at 1-800-FDA-1088 or www.fda.gov/medwatch**".

Comment:

Patient Counseling Information Statement in Highlights

YES 23. The Patient Counseling Information statement must include one of the following three **bolded** verbatim statements that is most applicable:

If a product **does not** have FDA-approved patient labeling:

- **"See 17 for PATIENT COUNSELING INFORMATION"**

If a product **has** FDA-approved patient labeling:

- **"See 17 for PATIENT COUNSELING INFORMATION and FDA-approved patient labeling"**
- **"See 17 for PATIENT COUNSELING INFORMATION and Medication Guide"**

Comment:

Revision Date in Highlights

NO 24. The revision date must be at the end of HL, and should be **bolded** and right justified (e.g., "**Revised: 9/2013**").

Comment: *Is on page 2*

Contents: Table of Contents (TOC)

See Appendix A for a sample tool illustrating the format for the Table of Contents.

YES 25. The TOC should be in a two-column format.

Comment:

YES 26. The following heading must appear at the beginning of the TOC: **"FULL PRESCRIBING INFORMATION: CONTENTS"**. This heading should be in all UPPER CASE letters and **bolded**.

Comment:

NO 27. The same heading for the BW that appears in HL and the FPI must also appear at the beginning of the TOC in UPPER CASE letters and **bolded**.

Comment: *No BW information included in TOC*

YES 28. In the TOC, all section headings must be **bolded** and should be in UPPER CASE.

Comment:

YES 29. In the TOC, all subsection headings must be indented and not bolded. The headings should be in title case [first letter of all words are capitalized except first letter of prepositions (through), articles (a, an, and the), or conjunctions (for, and)].

Comment:

NO 30. The section and subsection headings in the TOC must match the section and subsection headings in the FPI.

Comment: *Section 7 subsections and Section 13subsections need to be updated*

YES 31. In the TOC, when a section or subsection is omitted, the numbering must not change. If a section or subsection from 201.56(d)(1) is omitted from the FPI and TOC, the heading "FULL PRESCRIBING INFORMATION: CONTENTS" must be followed by an asterisk and the following statement must appear at the end of TOC: "*Sections or subsections omitted from the full prescribing information are not listed."

Comment:

Full Prescribing Information (FPI)

FULL PRESCRIBING INFORMATION: GENERAL FORMAT

NO 32. The **bolded** section and subsection headings in the FPI must be named and numbered in accordance with 21 CFR 201.56(d)(1) as noted below (section and subsection headings should be in UPPER CASE and title case, respectively). If a section/subsection required by regulation is omitted, the numbering must not change. Additional subsection headings (i.e., those not named by regulation) must also be **bolded** and numbered.

BOXED WARNING
1 INDICATIONS AND USAGE
2 DOSAGE AND ADMINISTRATION
3 DOSAGE FORMS AND STRENGTHS
4 CONTRAINDICATIONS
5 WARNINGS AND PRECAUTIONS
6 ADVERSE REACTIONS
7 DRUG INTERACTIONS
8 USE IN SPECIFIC POPULATIONS
8.1 Pregnancy
8.2 Labor and Delivery
8.3 Nursing Mothers
8.4 Pediatric Use
8.5 Geriatric Use
9 DRUG ABUSE AND DEPENDENCE
9.1 Controlled Substance
9.2 Abuse
9.3 Dependence
10 OVERDOSAGE
11 DESCRIPTION
12 CLINICAL PHARMACOLOGY
12.1 Mechanism of Action
12.2 Pharmacodynamics
12.3 Pharmacokinetics
12.4 Microbiology (by guidance)
12.5 Pharmacogenomics (by guidance)
13 NONCLINICAL TOXICOLOGY
13.1 Carcinogenesis, Mutagenesis, Impairment of Fertility
13.2 Animal Toxicology and/or Pharmacology
14 CLINICAL STUDIES
15 REFERENCES
16 HOW SUPPLIED/STORAGE AND HANDLING
17 PATIENT COUNSELING INFORMATION

Comment: *Section 7 subsections and section 13 subsections should be corrected*

YES 33. The preferred presentation for cross-references in the FPI is the section (not subsection) heading followed by the numerical identifier. The entire cross-reference should be in *italics* and enclosed within brackets. For example, *"[see Warnings and Precautions (5.2)]*" or "[*see Warnings and Precautions (5.2)*]".

Comment:

N/A 34. If RMCs are listed in HL, the corresponding new or modified text in the FPI sections or subsections must be marked with a vertical line on the left edge.

Comment:

FULL PRESCRIBING INFORMATION DETAILS

FPI Heading

YES 35. The following heading must be **bolded** and appear at the beginning of the FPI: "**FULL PRESCRIBING INFORMATION".** This heading should be in UPPER CASE.

Comment:

BOXED WARNING Section in the FPI

YES 36. In the BW, all text should be **bolded**.

Comment:

YES 37. The BW must have a heading in UPPER CASE, containing the word "**WARNING**" (even if more than one Warning, the term, "**WARNING**" and not "**WARNINGS**" should be used) and other words to identify the subject of the Warning (e.g., "**WARNING: SERIOUS INFECTIONS and ACUTE HEPATIC FAILURE**").

Comment:

CONTRAINDICATIONS Section in the FPI

YES 38. If no Contraindications are known, this section must state "None."

Comment:

ADVERSE REACTIONS Section in the FPI

YES 39. When clinical trials adverse reactions data are included (typically in the "Clinical Trials Experience" subsection of ADVERSE REACTIONS), the following verbatim statement or appropriate modification should precede the presentation of adverse reactions:

"Because clinical trials are conducted under widely varying conditions, adverse reaction rates observed in the clinical trials of a drug cannot be directly compared to rates in the clinical trials of another drug and may not reflect the rates observed in practice."

Comment:

N/A 40. When postmarketing adverse reaction data are included (typically in the "Postmarketing Experience" subsection of ADVERSE REACTIONS), the following verbatim statement or appropriate modification should precede the presentation of adverse reactions:

"The following adverse reactions have been identified during post-approval use of (insert drug name). Because these reactions are reported voluntarily from a population of uncertain size, it is not always possible to reliably estimate their frequency or establish a causal relationship to drug exposure."

Comment:

PATIENT COUNSELING INFORMATION Section in the FPI

YES 41. Must reference any FDA-approved patient labeling in Section 17 (PATIENT COUNSELING INFORMATION section). The reference should appear at the beginning of Section 17 and

include the type(s) of FDA-approved patient labeling (e.g., Patient Information, Medication Guide, Instructions for Use).

Comment:

YES 42. FDA-approved patient labeling (e.g., Medication Guide, Patient Information, or Instructions for Use) must not be included as a subsection under section 17 (PATIENT COUNSELING INFORMATION). All FDA-approved patient labeling must appear at the end of the PI upon approval.

Comment:

Appendix A: Format of the Highlights and Table of Contents

HIGHLIGHTS OF PRESCRIBING INFORMATION
These highlights do not include all the information needed to use [DRUG NAME] safely and effectively. See full prescribing information for [DRUG NAME].

[DRUG NAME (nonproprietary name) dosage form, route of administration, controlled substance symbol]
Initial U.S. Approval: [year]

WARNING: [SUBJECT OF WARNING]
See full prescribing information for complete boxed warning.

- [text]
- [text]

----------RECENT MAJOR CHANGES----------
[section (X.X)] [m/year]
[section (X.X)] [m/year]

----------INDICATIONS AND USAGE----------
[DRUG NAME] is a [name of pharmacologic class] indicated for [text]

----------DOSAGE AND ADMINISTRATION----------
- [text]
- [text]

----------DOSAGE FORMS AND STRENGTHS----------
[text]

----------CONTRAINDICATIONS----------
- [text]
- [text]

----------WARNINGS AND PRECAUTIONS----------
- [text]
- [text]

----------ADVERSE REACTIONS----------
Most common adverse reactions (incidence > x%) are [text].

To report SUSPECTED ADVERSE REACTIONS, contact [name of manufacturer] at [phone #] or FDA at 1-800-FDA-1088 or *www.fda.gov/medwatch*.

----------DRUG INTERACTIONS----------
- [text]
- [text]

----------USE IN SPECIFIC POPULATIONS----------
- [text]
- [text]

See 17 for PATIENT COUNSELING INFORMATION [and FDA-approved patient labeling OR and Medication Guide].

Revised: [m/year]

FULL PRESCRIBING INFORMATION: CONTENTS*

*Sections or subsections omitted from the full prescribing information are not listed.

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
06/26/2014

Department of Health and Human Services
Public Health Service
Food and Drug Administration
Center for Drug Evaluation and Research
Office of Medical Policy

PATIENT LABELING REVIEW

Date:	June 25, 2014
To:	Jean-Marc Guettier, MD Director **Division of Metabolism and Endocrinology Products (DMEP)**
Through:	LaShawn Griffiths, MSHS-PH, BSN, RN Associate Director for Patient Labeling **Division of Medical Policy Programs (DMPP)** Melissa Hulett, MSBA, MSN, RN Team Leader, Patient Labeling **Division of Medical Policy Programs (DMPP)**
From:	Shawna Hutchins, MPH, BSN, RN Senior Patient Labeling Reviewer **Division of Medical Policy Programs (DMPP)** Ankur Kalola, Pharm.D. Regulatory Review Officer **Office of Prescription Drug Promotion (OPDP)**
Subject:	Review of Patient Labeling: Medication Guide (MG) and Instructions for Use (IFU)
Drug Name (established name):	AFREZZA (insulin human [rDNA origin])
Dosage Form and Route:	Inhalation Powder, for oral use
Application Type/Number:	NDA 22-472
Applicant:	Mankind Corporation

1 INTRODUCTION

On October 13, 2013, Mankind Corporation re-submitted for the Agency's review a New Drug Application (NDA 22472) for AFREZZA (insulin human [rDNA origin]) inhalation powder, for oral use, indicated to improve glycemic control in adults with type 1 or type 2 diabetes mellitus. This NDA was originally submitted on March 16, 2009, received a Complete Response (CR) Letter from the Agency on March 12, 2010, was re-submitted on June 29, 2010, but received a second CR Letter from the Agency on January 18, 2011.

This collaborative review is written by the Division of Medical Policy Programs (DMPP) and the Office of Prescription Drug Promotion (OPDP) in response to a request by the Division of Metabolism and Endocrinology Products (DMEP) on December 19, 2013, and June 20, 2014, respectively, for DMPP and OPDP to review the Applicant's proposed Medication Guide (MG) and Instructions for Use (IFU) for AFREZZA (insulin human [rDNA origin]) inhalation powder, for oral use.

DMPP conferred with the Division of Medication Error, Prevention, and Analysis (DMEPA) and a separate DMEPA review of the IFU was completed on January 30, 2014.

2 MATERIAL REVIEWED

- Draft AFREZZA (insulin human [rDNA origin]) MG and IFU received on October 15, 2013 and received by DMPP on June 19, 2014.
- Draft AFREZZA (insulin human [rDNA origin]) MG and IFU received on October 15, 2013 and received by OPDP on June 19, 2014.
- Draft AFREZZA (insulin human [rDNA origin]) Prescribing Information (PI) received on October 15, 2013, revised by the Review Division throughout the review cycle, and received by DMPP on June 19, 2014.
- Draft AFREZZA (insulin human [rDNA origin]) Prescribing Information (PI) received on October 15, 2013, revised by the Review Division throughout the review cycle, and received by OPDP on June 19, 2014.
- Humulin N (insulin human [rDNA origin]) isophane suspension) comparator labeling dated November 07, 2013.

3 REVIEW METHODS

To enhance patient comprehension, materials should be written at a 6th to 8th grade reading level, and have a reading ease score of at least 60%. A reading ease score of 60% corresponds to an 8th grade reading level. In our review of the MG and IFU the target reading level is at or below an 8th grade level.

Additionally, in 2008 the American Society of Consultant Pharmacists Foundation (ASCP) in collaboration with the American Foundation for the Blind (AFB) published *Guidelines for Prescription Labeling and Consumer Medication Information for People with Vision Loss*. The ASCP and AFB recommended using fonts such as Verdana, Arial or APHont to make medical information more

accessible for patients with vision loss. We have reformatted the MG document using Verdana font, size 10 and IFU document using Verdana font, size 11.

In our collaborative review of the MG and IFU we have:

- simplified wording and clarified concepts where possible
- ensured that the MG and IFU are consistent with the Prescribing Information (PI)
- removed unnecessary or redundant information
- ensured that the MG is free of promotional language or suggested revisions to ensure that it is free of promotional language
- ensured that the MG meets the Regulations as specified in 21 CFR 208.20
- ensured that the MG and IFU meets the criteria as specified in FDA's Guidance for Useful Written Consumer Medication Information (published July 2006)

4 CONCLUSIONS

The MG and IFU are acceptable with our recommended changes.

5 RECOMMENDATIONS

- Please send these comments to the Applicant and copy DMPP and OPDP on the correspondence.
- Our collaborative review of the MG and IFU are appended to this memorandum. Consult DMPP and OPDP regarding any additional revisions made to the PI to determine if corresponding revisions need to be made to the MG and IFU.

Please let us know if you have any questions.

33 Page(s) of Draft Labeling have 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/

SHAWNA L HUTCHINS
06/25/2014

ANKUR S KALOLA
06/25/2014

MELISSA I HULETT
06/25/2014

LASHAWN M GRIFFITHS
06/25/2014

FOOD AND DRUG ADMINISTRATION
Center for Drug Evaluation and Research
Office of Prescription Drug Promotion

****Pre-decisional Agency Information****

Memorandum

Date: June 20, 2014

To: Richard Whitehead, Regulatory Project Manager
Division of Metabolism and Endocrinology Products (DMEP)

From: Ankur Kalola, Regulatory Review Officer
Office of Prescription Drug Promotion (OPDP)

Subject: OPDP Labeling Consult Request
NDA 022472 AFREZZA® (insulin human) Inhalation Powder

On June 20, 2014, OPDP received a consult request from DMEP to review the proposed draft Prescribing Information (PI), Medication Guide (MG), Instructions for Use (IFU), and Carton and Container labeling for Afrezza. OPDP's comments on the proposed draft PI are based on the version sent via email by Richard Whitehead on June 19, 2014 and are provided below.

OPDP's review of the proposed Carton and Container labeling is based on the version obtained from Microsoft Sharepoint on June 20, 2014. We have no comments on the Carton and Container labeling at this time.

Additionally, OPDP will work collaboratively with DMPP to provide comments on the MG and IFU under separate cover.

Thank you for the opportunity to comment on these materials. If you have any questions, please contact Ankur Kalola at 301-796-4530 or Ankur.Kalola@fda.hhs.gov.

23 Page(s) of Draft Labeling have 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/

ANKUR S KALOLA
06/20/2014

M E M O R A N D U M

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

CLINICAL INSPECTION SUMMARY

DATE: April 16, 2014

TO: Richard Whitehead, Regulatory Project Manager
Lisa Yanoff, M.D., Medical Reviewer
Ali Mohamadi, M.D., Medical Team Leader
Division of Metabolism and Endocrinology Products

FROM: Janice Pohlman, M.D., M.P.H.
Team Leader
Good Clinical Practice Assessment Branch
Division of Good Clinical Practice Compliance
Office of Scientific Investigations

THROUGH: Kassa Ayalew, M.D., M.P.H.
Acting Branch Chief
Good Clinical Practice Assessment Branch
Division of Good Clinical Practice Compliance
Office of Scientific Investigations

SUBJECT: Evaluation of Clinical Inspections

NDA: 22472

APPLICANT: MannKind Corporation

DRUG: Afrezza Inhalation Powder and Inhaler (insulin human [rDNA origin])
NME: No
THERAPEUTIC CLASSIFICATION: NDA resubmission (6 month review)

INDICATIONS: To improve glycemic control in adults with type 1 or type 2 diabetes mellitus

CONSULTATION REQUEST DATE: January 3, 2013
INSPECTION SUMMARY GOAL DATE: March 21, 2014
DIVISION ACTION GOAL DATE: April 15, 2014
PDUFA DATE (original): April 15, 2014
PDUFA DATE (extension): July 15, 2014

I. BACKGROUND:

MannKind Corporation has resubmitted NDA 22472 for AFREZZA® (insulin human [rDNA origin] inhalation powder and inhaler), an inhaled ultra-rapid acting insulin for the treatment of adults with type 1 or type 2 diabetes mellitus (T1DM and T2DM, respectively) for the control of hyperglycemia.

The Technosphere® Insulin Inhalation System (AFREZZA®) is a combination product consisting of Technosphere® Insulin (TI) Inhalation Powder and the Gen2 Inhaler. TI Inhalation Powder is a dry powder formulation of recombinant human insulin. The powder is pre-metered in color-coded cartridges containing either 10 U or 20 U of insulin per cartridge. Patients self-administer TI Inhalation Powder by oral inhalation using the Gen2 inhaler.

The sponsor included two new Phase 3 studies, Study MKC-TI-171 and Study MKC-TI-175, in their resubmission of NDA 22472.

Study MKC-TI-171
This was a Phase 3, multicenter, open-label, randomized, forced titration, noninferiority study evaluating efficacy and safety in the TI-Gen2C and insulin aspart group in subjects with T1DM over a 24-week treatment period following a 4 week basal insulin optimization phase. Subjects were randomized to 1 of 3 treatment groups in a 1:1:1 scheme: insulin aspart in combination with a basal insulin, TI Inhalation Powder administered using the Gen2C inhaler in combination with a basal insulin, and TI Inhalation Powder administered using the MedTone C inhaler in combination with a basal insulin. The randomization was stratified based on region (North America, Latin America, and Eastern Europe) and type of basal insulin (insulin glargine, insulin detemir, and NPH insulin). The primary efficacy endpoint was the change in HbA1c (%) from the end of the basal insulin optimization phase at Visit 4 (Week 0, Randomization) to Visit 10 (Week 24) for the TI-Gen2C group and the insulin aspart group.

The study was conducted from September 19, 2011 to May 31, 2013.There were two formal protocol amendments and additional administrative changes/clarifications to the protocol. The Study Protocol was dated August 16, 2011, Protocol Amendment 1 dated November 4, 2011, and Protocol Amendment 2 dated March 26, 2012.

MKC-TI-175
This was a Phase 3, multicenter, randomized, double-blind, placebo-controlled clinical study evaluating the efficacy and safety of the addition of TI Inhalation Powder versus placebo administered using the Gen2C inhaler in insulin naïve subjects with T2DM who are suboptimally controlled on only metformin or a combination with optimal/maximally tolerated doses of two or more oral antidiabetes medications, one of which can be metformin. After screening, eligible subjects entered a 6-week run-in period during which they continued their pre-enrollment antidiabetes medications to stabilize their HbA1c values. Subjects with HbA1c $\geq$7.5% or fasting plasma glucose $\leq$ 270 mg/dL (15.0 mmol/L) were randomized in a 1:1 ratio to receive either TI Inhalation Powder or placebo in addition to their ongoing optimal/maximally tolerated stable dose of metformin or two or more oral antidiabetes medications for a 24-week

treatment phase. The primary efficacy endpoint was comparison of mean change in HbA1c value (%) from Randomization (Week 0) to Week 24 between treatment groups.

The study was conducted from November 30, 2011 to June 17, 2013.There were two formal protocol amendments and additional administrative changes/clarifications to the protocol. The Study Protocol was dated September 23, 2011 and Protocol Amendment 1 dated March 26, 2012.

Initially, two foreign sites were selected for inspection for both studies: Dr. Vadym Korpachev (Site #852, Kiev, Ukraine) and Dr. Denise Reiz Franco (Site 483, Sao Paulo, Brazil). However, due to current events in Ukraine, the inspection of Dr. Korpachev was cancelled. Given the short time-frame in which the consult needed to be completed, a site in the United States, Dr. Janet McGill (Site #28, St. Louis, MO), was selected as an alternate site. An inspection of Dr. Farid Marquez (Site #433, Hialeah, FL) had also been planned (b) (4) The inspection of Dr. Marquez was cancelled due to low enrollment in Study MKC-TI-175 (three subjects) and the time-frame in which the assignment needed to be completed. (b) (4) .

II. RESULTS (by Site):

Site # Name of CI	Protocol # and # of Subjects	Inspection Date	Final Classification
Site #483 Denise Reiz Franco Sao Paulo, Brazil	MKC-TI-171 23 subjects MKC-TI-175 16 subjects	March 17-28, 2014	Pending Preliminary VAI
Site #28 Janet McGill St. Louis, MO	MKC-TI-171 16 subjects MKC-TI-175 13 subjects	February 21-28, 2014	Pending Preliminary NAI

Key to Classifications

NAI = No deviation from regulations.
VAI = Deviation(s) from regulations.
OAI = Significant deviations from regulations. Data unreliable.
Pending = Preliminary classification based on information in 483 or preliminary communication with the field; EIR has not been received from the field, and complete review of EIR is pending.

III INSPECTION RESULTS

1. Denise Reiz Franco
   Rua Goias, 193 Higienopolis
   Sao Paulo 01244-030, Brazil

   a. What was inspected: At this site for Study MKC-TI-171, 70 subjects were screened, 23 subjects were randomized, and 6 subjects discontinued from the study after randomization. For MKC-TI-175, 85 subjects were screened, 16 subjects were randomized, and 15 subjects completed the study. The records of seven subjects were reviewed for each study.

      Records reviewed included, but were not limited to, informed consent forms, inclusion/exclusion criteria, randomization, source documents, case report forms, primary efficacy endpoint data, protocol deviations, and adverse events.

   b. General observations/commentary: The records were found to be in good condition. Worksheets were used extensively for study visits so they had prompts for all visit-specific tasks. There was also electronic transfer of data from patient diaries, laboratory studies, and pulmonary function tests.

      Primary efficacy endpoint data were verifiable. There was evidence that for Study 175 there was under-reporting of self-reported hypoglycemic events for two of seven subject records reviewed. (See Observation I, iii, below)

      In general, the clinical site followed good clinical practices. However, a Form FDA 483 was issued at the end of inspection. The observations included:

      Observation 1: An investigation was not conducted in accordance with the investigational plan.

      i) According to Protocol 171, the pulmonary function tests (PFTs) should not be performed within two hours of study medication administration (inhaled insulin) at Visits 8 and 10. Five of 17 completed subjects had a dose of study medication within two hours of the Visit 8 or 10 PFTs. Specifically:
      a) Subject #2139 had a dose of 20U at 14:32 on January 30, 2013 and the Visit 8 PFT was done at 15:35 (approximately 1 hour after dose)
      b) Subject #2198 had a dose of 45U at 13:00 on February 5, 2013 and the Visit 8 PFT was done at 14:14 (approximately 1 hour and 15 minutes after dose)
      c) Subject #2207 had a dose of 15U at 15:45 on January 30, 2013 and the Visit 8 PFT was done at 17:14 (approximately 1 hour and 30 minutes after dose)
      d) Subject #2212 had a dose of 10U at 8:44 on April 15, 2013 and the Visit 10

PFT was done at 9:14 (approximately one half hour after dose)
e) Subject #2261 had a dose of 20U at 8:29 on April 22, 2013 and the Visit 10 PFT was done at 8:56 (approximately one half hour after dose).

OSI Reviewer Comment: The rationale for not using study medication (inhaled insulin) within two hours prior to PFTs would seem to be to minimize the acute effects (or interference) of the inhaled product on PFTs collected over the longer 12- or 24-week time period. The impact of administering the study drug in the two hour period prior to PFTs, would likely result in increased negative effects of inhaled product on the lungs and therefore be a conservative estimate in terms of long-term pulmonary safety.

ii) According to the protocol for Study 175, subjects were to receive open-label rescue therapy when self-administered blood glucose (SMBG) was > 11.1 mmol/dL on three different days in at least two weeks after Visit #12 and then have a fasting plasma glucose (FPG) of > 11.1 mmol/dL confirmed by the central laboratory. Subject #4095 had SMBG > 11.1 mmol/dL on three days during the weeks of February 10-16, and 17-23, 2013. The FBG measured by the central laboratory was 11.93 mmol/dL on March 1, 2013. This subject did not receive open-label rescue therapy.

OSI Reviewer Comment: This appears to be an isolated event.

iii) According to the protocol for Study 175, symptoms of hypoglycemia that are relieved by self-administration of carbohydrates must be recorded in the e-diary only. For each of two of seven subjects reviewed, an episode of hypoglycemic symptoms (i.e. symptoms of hypoglycemia that are relieved by self-administration of carbohydrates) was not reported. In one of these patients (#4095), problems transmitting data from the e-diary was reported two days after this hypoglycemic event.

OSI Reviewer Comment: The ORA field investigator indicated that some patients (such as #4095) reported technical difficulties with the e-diary which may have had a negative impact (i.e. under-reporting) on self-reported episodes of hypoglycemia.

Observation 2: Failure to prepare or maintain adequate and accurate case histories with respect to observations and data pertinent to the investigation.

i) According to the protocol for Study 171, the PFTs were not to be performed within two hours of study medication administration (insulin) at Visits 8 and 10. The time of the insulin dose previous to the PFT was not reported for five of 23 randomized subjects.

OSI Reviewer Comment: The primary stipulation was that PFTs were to be performed at least two hours prior to the dose of study drug. As noted above, the rationale was (likely) to minimize impact of acute administration of product on lung function when trying to assess lung effects over the longer 12- and 24-week intervals. If inhaled insulin were taken within this window, it would likely have a negative impact on lung function and overestimate any decline in pulmonary function attributed to chronic administration.

ii) According to the adverse event report in the medical records for Subject #4304 (in Study 175), the evaluation of 'hoarseness" from January to March 2013 was changed from "not related" to "possibly related" on August 1, 2013 (after the data lock). The Clinical Trial Manager notified the sponsor of the change by e-mail dated August 8, 2013 which states the hoarseness is "related" to the study drug.

OSI Reviewer Comment: This appears to be an isolated event.

c. Assessment of data integrity: At this site, the observation was made that study drug (inhaled insulin) had been administered within the two hour window prior to PFTs performed at Visits 8 and 10 in 5 of 17 subjects and also that the timing of insulin dose prior to PFTs was not always documented (for 5 of 17 subjects completed). This may have allowed some acute pulmonary effects of the inhaled product to overlap changes seen with longer term (i.e. 12- or 24-week) administration. Additionally, in one of two subjects in whom an episode of self-recorded hypoglycemia was not reported, problems with transmitting data from the e-diary were noted two days after the event. Other than the potential for some acute pulmonary effects to overlap longer term administration, the studies appear to have been conducted adequately, and the efficacy data generated by this site appear acceptable in support of the respective indication.

Note: Observations noted above are based on the Form FDA 483 and communications with the field investigator; an inspection summary addendum will be generated if conclusions change upon receipt and review of the EIR.

2. Janet B. McGill, M.D.
4570 Childrens Place
St. Louis, MO 63110-1010

a. What was inspected: At this site for Study MKC-TI-171, 28 subjects were screened, 16 subjects were randomized, and 14 subjects completed the study. For MKC-TI-175, 20 subjects were screened, 13 subjects were randomized, and 10 subjects completed the study. The records of nine subjects were reviewed for Study MKC-TI-171 and eight subjects for MKC-TI-175. Records reviewed included, but were not limited to, informed consent forms, inclusion/exclusion criteria, randomization, source documents, case report forms, primary and secondary efficacy endpoints, protocol deviations, and adverse events. Also

reviewed were training records for study personnel, and sponsor and IRB correspondence.

b. General observations/commentary: Informed consent documents were signed and present for subjects' whose records were reviewed. Source documents were compared to case report forms and NDA data listings and verified. There was no under-reporting of adverse events. Most protocol deviations that occurred were minor and included out of window visits. On May 2, 2012, Subject #1366 participating in Study MKC-TI-171 had a reported SAE of seizure attributed to severe hypoglycemia. This event was downgraded to a non-SAE by the PI after noting that the subject reported experiencing shakiness and sweating and was able to drink orange juice to resolve the symptoms.

   Generally, this site was compliant with good clinical practices. No Form FDA 483, Inspectional Observations, was issued at the conclusion of the inspection.

c. Assessment of data integrity: At this site, the studies appear to have been conducted adequately, and the data generated by this site appear acceptable in support of the respective indication.

IV. OVERALL ASSESSMENT OF FINDINGS AND RECOMMENDATIONS

Two clinical sites participating in the two studies supporting the resubmission of NDA 22472 were inspected. The preliminary classification of the inspection of Dr. Janet McGill is No Action Indicated (NAI). The preliminary classification of the inspection of Dr. Reiz Franco is Voluntary Action Indicated (VAI).

Based on observations made by the ORA investigator during the inspection of Dr. Reiz Franco regarding administration of study drug (inhaled insulin) within the two hour window prior to PFTs or failure to record time of insulin dose prior to PFTs, the review division may wish to explore the timing (or lack of documentation of timing) of study drug (inhaled insulin) relative to performance of PFTs when evaluating acute versus chronic pulmonary effects of administration of inhaled insulin at the Visit 8 and 10 timepoints. Additionally, based on the observation that some subjects had technically difficulties with the e-diary (including replacement of a modem), the review division may wish to send an information request to the sponsor to see how pervasive problems with the e-diary were, as this may have resulted in problems with reporting of SMBG and episodes of self-reported hypoglycemia.

The studies at both sites do appear to have been conducted in accordance with good clinical practices. The data generated by both sites appear acceptable in support of the respective indication.

Note: Observations noted above are based on the Form FDA 483 and communications with

the field investigator and or preliminary review of the EIR; an inspection summary addendum will be generated if conclusions change upon receipt and/or final review of the EIR.

{See appended electronic signature page}

Janice Pohlman, M.D., M.P.H.
Team Leader
Good Clinical Practice Assessment Branch
Division of Good Clinical Practice Compliance
Office of Scientific Investigations

CONCURRENCE: ***{See appended electronic signature page}***

Kassa Ayalew, M.D., M.P.H.
Acting Branch Chief
Good Clinical Practice Assessment Branch
Division of Good Clinical Practice Compliance
Office of Scientific Investigations

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

/s/

JANICE K POHLMAN
04/16/2014

KASSA AYALEW
04/16/2014

Department of Health and Human Services
Public Health Service
Food and Drug Administration
Center for Drug Evaluation and Research
Office of Surveillance and Epidemiology (OSE)
Office of Pharmacovigilance and Epidemiology (OPE)

Epidemiology: Review of Sponsor Report

Date:	March 28, 2014
Reviewer:	Patricia L. Bright, M.S.P.H., Ph.D., Epidemiologist, Division of Epidemiology 1 (DEPI 1), Office of Pharmacovigilance and Epidemiology (OPE), Office of Surveillance and Epidemiology (OSE)
Team Leader:	Diane K. Wysowski, M.P.H., Ph.D., DEPI 1, OPE, OSE
Division Director:	Cunlin Wang, M.D., Ph.D., DEPI 1, OPE, OSE
Subject:	Review of the Sponsor's September 4, 2013, report on the "Incidence of Lung Cancer in Diabetes and in Clinical Studies of Afrezza"
Drug Name(s):	Afrezza (Technosphere Insulin Inhalation System)
Application Type/Number:	NDA 022472
Applicant/sponsor:	MannKind
OSE RCM #:	2014-332
TSI #:	Not Applicable

TABLE OF CONTENTS

EXECUTIVE SUMMARY

Afrezza (insulin, human [rDNA] inhalation powder) is an ultra-rapid acting inhaled insulin indicated for improving glycemic control in adults with type 1 and type 2 diabetes mellitus.

Following the second FDA Complete Response for NDA 022472, the FDA received a third submission for the product on October 15, 2013. The Division of Metabolism and Endocrinology Products (DMEP) requested the Division of Epidemiology 1 (DEPI 1) to evaluate the sponsor's report entitled "Incidence of Lung Cancer in Diabetes and in Clinical Studies of Afrezza."

During the clinical development program for Afrezza in which Afrezza use was compared primarily with other insulin use, two cases of pulmonary malignancies were identified in Afrezza-exposed patients: One involved neuro-endocrine oat cell type small cell lung cancer after 137 days of Afrezza treatment in a 61-year-old male subject with a 40 pack-year history of smoking[I]. The other involved a non-small cell bronchogenic carcinoma in a 66-year-old male subject exposed to 627 days of Afrezza in an uncontrolled trial who had a 54 pack-year history of smoking and a family history of lung cancer. Two additional lung cancers were spontaneously reported at 1.9 and 3.5 years after clinical trial discontinuation in a male and female nonsmoker, respectively. No lung cancer cases were reported in comparator-exposed patients. The reported lung cancer incidence rate for Afrezza use (based on the 2 cases and not including the spontaneous reports) was 0.80 per 1,000 person-years (PY).

To put the lung cancer cases in context, the sponsor provided a report summarizing lung cancer incidence rates in diabetic populations (stratifying by smoking history when feasible). The author(s) also included lung cancer incidence rates among nonsmokers and smokers in the general population and discussed the observed incidence of lung cancer in the Afrezza clinical trials.

There was limited published data on lung cancer incidence in patients with diabetes mellitus adjusted for smoking. In the Women's Health Initiative of postmenopausal women, those with self-reported treated type 2 diabetes, compared to women without diabetes, had a significantly higher risk of lung cancer (adjusted HR 1.27 [95% CI 1.02–1.59]) with risks increasing for women with diabetes requiring insulin treatment (1.71 [1.15–2.53]. When unadjusted, lung cancer risk was overwhelmed by smoking history. For participants treated for diabetes, the incidence rate was 0.6 per 1,000 PY for never smokers and 2.5 per 1,000 PY for ever smokers.

[I] The details of the pulmonary malignancy cases differs from our Feb 28, 2014, DEPI review on Afrezza postmarketing approaches (RCM 2014-304). The current review contains updated information from the Afrezza clinical development program from the reviewing medical officer.

The report included data from other sources on lung cancer incidence rates in the general population of smokers and non-smokers. However, the data were of questionable utility since the incidence rates were not for diabetic populations.

The report stated that the lung cancer incidence among Afrezza users, comprised of non-smokers and former smokers, lies between the incidence for postmenopausal women with diabetes who never smoked (0.5-0.7 per 1,000 person-years [PY]) and the incidence in diabetic populations that included smokers (1-2 per 1,000 PY).

The incidence rates for Afrezza in the clinical trial population are within the broad range of estimates for lung cancer in diabetes mellitus patients. However, lung cancer incidence rates generally reflect the proportion of smokers, previous smokers, and non-smokers in each population being studied. Comparing rates found in studies to the rate in the Afrezza clinical trial that had only a small number of subjects studied for a short duration does not provide reassurance that Afrezza does not increase the risk of lung cancer.

We are in agreement with the sponsor's report that states "The estimate of lung cancer incidence from the Afrezza studies, based on 2 cases, was quite imprecise and so it is difficult to make any definitive conclusions about the relative incidence among these subjects compared with external data sources."

1 INTRODUCTION

In March 2010 and January 2011, the FDA issued Complete Responses (CR) for a new drug application (NDA) submission for Afrezza. On October 15, 2013, MannKind, the sponsor resubmitted the application to the FDA, responding to the FDA's concerns. As part of this submission, the sponsor included a report summarizing lung cancer incidence in diabetes. The Division of Metabolism and Endocrinology Products (DMEP) requested the Office of Surveillance and Epidemiology, Office of Pharmacovigilance and Epidemiology, Division of Epidemiology1 (OSE/OPE/DEPI1) to review the sponsor's September 4, 2013, report entitled "Incidence of Lung Cancer in Diabetes and in Clinical Studies of Afrezza."

1.1 BACKGROUND

Brief Drug Description

Afrezza (insulin, human [rDNA] inhalation powder) is an ultra-rapid acting inhaled insulin with proposed indication of improving glycemic control in adults with type 1 and type 2 diabetes. The dry powder is administered at the beginning of a meal by a Gen2 inhaler with cartridges containing 10 units or 20 units of drug product. The sponsor has proposed in the Afrezza labeling that Afrezza be contraindicated in patients with a current diagnosis or history of asthma, chronic obstructive pulmonary disease (COPD) or other chronic lung disease. The sponsor also has proposed labeling under Warnings and Precautions that Afrezza not be recommended for current smokers and those who have

smoked in the last 6 months and that prior to initiating therapy with Afrezza, all patients should be clinically evaluated with a detailed medical history, physical examination and spirometry (FEV1) to identify potential underlying lung disease.

Lung cancer risk for inhaled insulins

- **Exubera**
  The FDA approved Exubera, another inhaled insulin, in January 2006, but Exubera was later withdrawn by the sponsor due to lower than expected sales. Prior to official withdrawal, however, the FDA required changes to the Exubera product labeling due to postmarketing pulmonary malignancies. The labeling noted that there were too few cases to determine whether the events were related to Exubera and that all patients who were diagnosed with lung cancer had a prior history of cigarette smoking.

  Since that time, results from an observational Follow-Up Study of patients previously enrolled in Exubera (referred to as FUSE) controlled clinical trials [1] found the following:
  - Primary lung cancer mortality -- Six cases were reported in 12,605.9 person-years (PY) in the Exubera group and 2 cases in 11,802.5 PY in the comparator group. The incidence density ratio (IDR) was 2.81 (95% CI: 0.50 - 28.46).
  - Primary lung cancer incidence -- Twelve cases were reported in 11,180.7 PY in the Exubera group and 3 cases in 10,467.9 PY in the comparator group. The IDR was 3.75 (95% CI: 1.01 - 20.68).
  - All-cause mortality -- The estimated rate was 6.0 per 1,000 PYs (76 deaths in 12,605.9 PY) in the Exubera group and 7.4 per 1000 PYs (87 deaths in 11,802.5 PY) in the comparator group. The hazard ratio (HR) was 0.81 (95% CI: 0.60 - 1.10).

- **Afrezza**
  During the clinical development program for Afrezza in which Afrezza use was compared primarily with other insulin use[II], two cases of pulmonary malignancies were identified in Afrezza-exposed patients: one involved neuroendocrine oat cell type small cell lung cancer after 137 days of Afrezza treatment in a 61-year-old male subject with a 40 pack-year history of smoking. The other involved a non-small cell bronchogenic carcinoma in a 66-year-old male subject exposed to 627 days of Afrezza in an uncontrolled trial who had a 54 pack-year history of smoking and a family history of lung cancer [2].

  Two additional lung cancer cases were spontaneously reported at 1.9 and 3.5 years, after clinical trial discontinuation in a male and female nonsmoker, respectively. No lung cancer cases were reported in comparator-exposed patients. The reported lung

[II] The comparators in most of the trials were generally insulin aspart or insulin lispro with a background basal insulin (typically insulin glargine) as compared to Afrezza with a background basal insulin. Some trials used placebo as a comparator in combination with metformin or two or more oral anti-diabetic agents.

cancer incidence ratio for Afrezza use (based on the 2 cases and not including the spontaneous reports) was 0.80 per 1,000 PY.

Sponsor's Report

To put the lung cancer cases in context, the sponsor provided a report summarizing lung cancer incidence rates in diabetic populations (stratifying by smoking history when feasible). The author also provided lung cancer incidence rates among smokers and nonsmokers in the U.S. general population and discussed the observed incidence of lung cancer in the Afrezza clinical trials. This report is the basis for the current review.

1.2 REGULATORY HISTORY (ABBREVIATED):

- December 22, 2000: IND 061729 submitted to the FDA.
- March 16, 2009: NDA 022472 submitted to the FDA.
- March 12, 2010: The FDA issued a Complete Response letter.
- June 29, 2010: The sponsor sent a class 2 resubmission for NDA 022472.
- January 18, 2011: The FDA issued another Complete Response letter.
- October 15, 2013: The sponsor sent a class 2 resubmission for NDA 022472.
- October 22, 2013: DMEP consulted DEPI1 on the sponsor's submission and requested a review of the sponsor's report on lung cancer incidence in diabetic populations.

1.3 PRODUCT LABELING

Afrezza has not yet been approved and product labeling has not been finalized. However, MannKind has proposed in the Afrezza labeling that Afrezza be contraindicated in patients with a current diagnosis or history of asthma, chronic obstructive pulmonary disease (COPD) or other chronic lung disease. The sponsor also has proposed labeling under Warnings and Precautions that Afrezza not be recommended for current smokers and those who have smoked in the last 6 months and that prior to initiating therapy with Afrezza, all patients should be clinically evaluated with a detailed medical history, physical examination and spirometry (FEV1) to identify potential underlying lung disease.

2 REVIEW METHODS AND MATERIALS

Following the second FDA Complete Response for NDA 022472, the FDA received a third submission for the product on October 15, 2013. DMEP requested that DEPI 1 review the sponsor's September 4, 2013, report entitled "Incidence of Lung Cancer in Diabetes and in Clinical Studies of Afrezza."

In conducting this review, DEPI staff sought to assess the adequacy of methods used for the literature summary such as the inclusion criteria and whether the summary's findings were consistent with interpretation in the published literature. However, DEPI staff did not review the studies included in the summary.

3 REVIEW RESULTS

3.1 SPONSOR'S LITERATURE REVIEW METHODS

The report stated that the author(s) conducted a Medline PubMed search and restricted the search to: 2003-present, humans, and no comments/letters/editorials. Key words for disease status included the following: lung neoplasm; lung/lungs and cancer/neoplasm/tumor/tumors/tumour; diabetes mellitus/diabetes/diabetic/diabetes complication. (For the full list of the Medline PubMed search criteria see Appendix A.)

The initial search methods identified fewer articles than anticipated so the author(s) dropped the requirement to specify diabetes type. Publications from Eastern Asia were excluded (since Afrezza trials were not conducted in that region), whereas literature from Western Europe was included.

The abstracts were screened by a doctoral level epidemiologist. Table 1 includes the screening keywords and criteria copied from the sponsor's report. Studies were further eliminated if they only included lung cancer mortality, incidence ratios, Asian populations (not included in Afrezza clinical trials), or ended follow-up before 2003.

Table 1. Publication Screening Criteria

Criterion	Specification	
Study setting	Members of the general population diagnosed with type 1 or type 2 diabetes	
Type of study subjects	Diagnosed with diabetes type 1 or type 2	
Age range of study subjects	Adults (aged ≥ 18 years)	
Study design	Longitudinal (cohort) study; follow-up ≥ 3 months, preferably longer; case-control studies were excluded[a]	
Outcome definition	Newly diagnosed primary lung cancer	
Frequency of lung cancer outcome	To obtain benchmark frequencies of outcomes for indirect comparison with frequencies in the Afrezza clinical program, the outcome frequencies had to be reported in units of cases per person-years (i.e., incidence) unless the duration of follow-up was the same as in the Afrezza clinical trials	
Ascertainment of outcome	Death records as a sole source of data were not acceptable; records of a cancer registry or hospital were acceptable	
Study size	Preferably large (e.g., > 1,000 per arm), if a sufficient number of such publications is available; otherwise smaller studies will be considered[b]	
Stratifications	By smoking status	By diabetes type: ▪ Type 1 diabetes ▪ Type 2 diabetes

[a] Because estimates of outcome frequencies can be derived only from longitudinal studies, included studies were required to be longitudinal (i.e., not case-control studies).

[b] A sufficient number of large studies was available, and it was not necessary to focus on smaller studies.

Source: MannKind. Incidence of Lung Cancer in Diabetes and in Clinical Studies of Afrezza, September 4, 2013.

3.2 SPONSOR'S LITERATURE REVIEW RESULTS

The sponsor's literature search identified 1,073 references (including duplicates). The researcher(s) removed duplicates and screened the articles by the characteristics listed in Table 1, resulting in 65 remaining abstracts. Three other references cited in review articles were included for a total of 68 publications.

Studies were further eliminated if they only included lung cancer mortality, incidence ratios, studies in Asian populations (not included in Afrezza clinical trials) or that ended follow-up before 2003. Fifteen studies remained: two in the type 1 diabetic population and 13 in the type 2 diabetic population.

Type 1 Diabetes Mellitus

The two studies conducted in the type 1 diabetic population were from the same source -- the national healthcare databases from Sweden. One study restricted inclusion to 24,052 patients hospitalized for diabetes at an age younger than 21 years and followed them for a median of 17 years, but identified only 3 cases of lung cancer [3]. In this population, the observed number of cases of lung cancer was not statistically different from the expected number of cases among the Swedish population without a history of type 1 diabetes (adjusted for age, gender, time, and residential area).

The second study restricted inclusion to patients 30 years or younger at the first age of diabetes diagnosis. Patients had a mean age of study entry at 17 years with mean duration of follow-up of 14.4 years [4]. The study identified 11 lung cancers. The incidence rate for lung cancer in this study also was not significantly higher than the incidence rate in the general population of Sweden. The unadjusted incidence rates for the two studies as listed in the sponsor report were 0.007 per 1,000 PY and 0.026 per 1,000 PY, respectively. The sponsor report stated that the relatively low incidence rates are probably due to the young age of participants.

Type 2 Diabetes Mellitus

Of the 13 studies in patients with type 2 diabetes, only one study stratified by smoking [5]. In the study, data were drawn from 145,765 postmenopausal women, ages 50-79, enrolled in the Women's Health Initiative. Data were stratified by diabetes and smoking. The unadjusted incidence rates are listed in Table 2.

Table 2: Unadjusted incidence of lung cancer per 1,000 PY stratified by smoking and type 2 diabetes mellitus in U.S. postmenopausal women

	Non-Diabetic* (cancer cases = 106)	Diabetic (cancer cases = 1,818)
Never Smoked	0.36	0.46
Smoked	2.02	2.24

* The sponsor's report did not include the incidence rates for the non-diabetic population.

Although not listed in the sponsor report, this publication [5] stated that after adjustment[III] "Compared with women without diabetes, women with self-reported treated diabetes had a significantly higher risk of lung cancer (HR 1.27 [95% CI 1.02–1.59]), with risks further increased for women with diabetes requiring insulin treatment (1.71 [1.15–2.53])."

Data from the 12 other studies [6-17] identified in the literature search are included in Table 3 of Appendix B. Table 3 is based on the sponsor's report, but adapted to include fewer study details and to incorporate the number of lung cancer cases and smoking information from each study.

The researchers summarized the overall data from the 12 studies as follows "…the incidence of lung cancer ranged between 1 and 2 cases per 1,000 person-years. A lower incidence of 0.5 cases per 1,000 person-years was reported from two arms in large clinical studies of rosiglitazone and comparator groups."

Lung cancer incidence (nonsmoking, non-diabetic population with European ancestry)
The report also provided estimates for the incidence of lung cancer among nonsmokers (defined as those who smoked < 100 cigarettes in their lifetime). Published incidence rates of lung cancer were pooled for nonsmokers of European descent, stratified by age and sex, across eight incidence studies from North America and Europe. The report author(s) used the overall age- and sex-adjusted incidence among these nonsmokers and weighted the rates by the age and sex distribution of the Afrezza users to calculate an estimate of 0.098 (95% CI 0.089–0.11) per 1,000 PY in the Afrezza clinical trial population.

Lung cancer incidence (smoking diabetic and non-diabetic population)
The report affirmed that the incidence of lung cancer was variable by age and the number of cigarettes smoked per day. The authors focused on the 45-69 age group of Afrezza users in the clinical development program, and reported that lung cancer incidence per 1,000 person-years in smokers was 0.4 in women and 1.9 in men in the U.S. Framingham Cohort Study [18] and was 2.2 in men and women combined in a study of members of the Kaiser Permanente Medical Care Program [19]. The report stated that in a third study that utilized population-based data identified through a New Mexico Tumor Registry "…the incidences were averaged over 2 levels of smoking and over ages 45-54 and 55-64 years, resulting in incidences of 1.8 per 1,000 PY in men and 1.5 cases per 1,000 PY in women" [20]. It should be noted, however, that two of these studies were published in 1993 and one in 1988. Secular trends in cigarette smoking behavior could make the data less relevant to the current period.

3.3 GENERAL CONCLUSIONS IN THE REPORT

- There was limited published data on the incidence of lung cancer among non-smokers and ex-smokers in patients with diabetes mellitus.

[III] Adjusted for age, ethnicity, education, current and former smoking, waist to hip ratio, physical activity, alcohol intake, present calories from fat, fruit intake, vegetable intake, and use of hormonal replacement therapy.

- For type 1 diabetes, published lung cancer incidence was based on a study population younger than the age distribution of Afrezza-exposed patients.
- A study that did provide smoking stratified data was based on a population of postmenopausal women in the U.S.
- The lung cancer incidence among the Afrezza users (never smokers and ex-smokers) appears to lie between the incidence in postmenopausal women who never smoked and the incidence in diabetic populations that included smokers.
- The report also stated that "Comparison of the incidence of lung cancer among patients in the Afrezza clinical trials to published incidences of lung cancer in other studies or in the general population should be interpreted with caution. Incidences estimated from studies of nonsmokers in the general population are likely to underestimate the expected incidence in the Afrezza trials because of the inclusion of ex-smokers in the Afrezza trials; on the other hand, most studies of lung cancer incidence in patients with diabetes, because of their inclusion of current and ex-smokers, are likely to overestimate the expected incidence in Afrezza studies." Current smokers were excluded from the Afrezza trials.
- The report stated that "The estimated incidence of lung cancer from the Afrezza studies is based on 2 cases, was quite imprecise and so it is difficult to make any definitive conclusions about the relative incidence among these subjects compared with external data sources.

4 DISCUSSION

Studies selected for inclusion

The authors appear to have used a reasonable approach to the literature search; however, no details were provided in the Results section on the numbers and corresponding reasons for exclusion of the originally identified articles (such as the number of duplicates, number that only included data on lung cancer mortality, etc.). The lack of detail would make it unfeasible to reproduce the methods as described.

Accuracy in Describing Literature Included in the Summary

The literature summary accurately reflected the referenced studies. However, the report only included information on the incidence of lung cancer in the diabetic population, although many of the studies contrasted the incidence in patients with diabetes to those without. Including incidence rates for both when available would have been more comprehensive, particularly because the report author(s) stated that "the incidence of lung cancer by smoking categories in the general population was used to provide a second set of benchmark rates." Incidence rates from smokers and non-smokers for the overall U.S. population were provided, yet the incidence rates from the non-diabetic patients from the same source population for each of the studies were not provided in the report even when available -- resulting in less comparable estimates.

Consistency of the Conclusions with the Literature

The report accurately characterized the literature on lung cancer incidence in the diabetic population.

The report also stated that the lung cancer incidence among the Afrezza users (0.80 per 1,000 PY), a group made up of nonsmokers and ex-smokers, lies between the incidence reported among postmenopausal women with diabetes who never smoked (0.5-0.7 per 1,000 person-years) and the incidence in cohorts of individuals with diabetes that included smokers (1-2 per 1,000 person-years).

The authors cautioned, however, that:

- A direct formal comparison between the clinical trial results and the published incidences in diabetes from population-based studies would minimally require adjustment for diabetes type, age, geographic region, and smoking status.

Incidence Rates in the general population for smokers and non-smokers

The report included data on lung cancer incidence in the general population stratified by smoking (nonsmokers or current smokers). However, the data are of questionable utility since the participants in the Afrezza clinical development program were a mix of nonsmokers and former smokers. Data from diabetic populations would be a better predictor for the proportion of expected nonsmokers and former smokers.

Also, the literature on smoking in the U.S. general population was published in 1993 and 1988. Secular trends in smoking behavior in the U.S. general population make the data less relevant to the current period.

5 CONCLUSION

- The sponsor's literature search methods appear appropriate, but the researchers included insufficient detail on article selection results.
- The literature summary accurately reflected the referenced studies.
- The report included data from the literature on the incidence of lung cancer in the diabetic population, but excluded data from the same studies that reported the incidence in those without diabetes. Instead, the report included lung cancer incidence in the general population stratified by smoking (nonsmokers or current smokers) from other sources. Such data is of questionable utility.
- The report's conclusions were appropriate.
- There was limited published data on the lung cancer incidence in patients with diabetes mellitus adjusted for nonsmokers and ex-smokers.
- Although restricted to postmenopausal women, data from the Women's Health Initiative compared women with diabetes to women without diabetes. The women with self-reported treated diabetes had a significantly higher risk of lung cancer (HR 1.27 [95% CI 1.02–1.59]) with risks increasing for women with diabetes requiring insulin treatment (1.71 [1.15–2.53]). If unadjusted, risk estimates for lung cancer are overwhelmed by confounding due to smoking. (The adjusted results comparing diabetic participants to non-diabetic participants were not listed in the sponsor's report, but were included in this review in Section 3.2 based on the information provided in the published article.)
- The incidence rates for Afrezza in the clinical trial population are within the broad range of estimates for lung cancer in diabetes mellitus patients. However, lung cancer incidence rates generally reflect the proportion of smokers, previous smokers,

and non-smokers in each study population. Comparing rates found in studies to the rate in the Afrezza clinical trial that only had a small number of subjects followed for a short duration does not provide reassurance that Afrezza does not increase the risk of lung cancer.

- We are in agreement with the sponsor report that states "The estimate of lung cancer incidence from the Afrezza studies, based on 2 cases, was quite imprecise and so it is difficult to make any definitive conclusions about the relative incidence among these subjects compared with external data sources."

6 RECOMMENDATIONS TO SPONSOR

DEPI has no regulatory recommendations for the sponsor.

7 REGULATORY RECOMMENDATIONS TO DMEP

Lung cancer incidence rates in the diabetic population primarily represent smoking history in the particular population.

The incidence rates for Afrezza in the clinical trial population are within the broad range of estimates for lung cancer in diabetes mellitus patients. However, lung cancer incidence rates generally reflect the proportion of current smokers, previous smokers, and non-smokers in each study population. Comparing rates found in studies to the rate in the Afrezza clinical trial that only had a small number of subjects followed for a short duration does not provide reassurance that Afrezza does not increase the risk of lung cancer.

8 REFERENCES

[1] Source: Gatto NM, Koralek DO, Bracken MB, Duggan WT, Lem J, Klioze SS, Jackson NC. Comparative lung cancer mortality with inhaled insulin or comparator: FUSE final results. ICPE, August 24, 2012.
[2] MannKind. A postmarketing observational cohort study to evaluate the long-term safety of Afrezza in the treatment of patients with diabetes mellitus. October 2013 resubmission of Afrezza NDA.
[3] Shu X, Ji J, Li X, Sundquist J, Sundquist K, Hemminki K. Cancer risk among patients hospitalized for type 1 diabetes mellitus: a population-based cohort study in Sweden. *Diabet Med* 2010;27(7):791-7.
[4] Zendehdel K, Nyrén O, Östenson CG, Adami HO, Ekbom A, Ye W. Cancer incidence in patients with type 1 diabetes mellitus: a population-based cohort study in Sweden. *J Natl Cancer Inst* 2003;95(23):1797-800.
[5] Luo J, Chlebowski R, Wactawski-Wende J, Schlecht NF, Tinker L, Margolis KL. Diabetes and lung cancer among postmenopausal women. *Diabetes Care* 2012;35(7):1485-91.
[6] Atchison EA, Gridley G, Carreon JD, Leitzmann MF, McGlynn KA. Risk of cancer in a large cohort of U.S. veterans with diabetes. *Int J Cancer* 2011;128(3):635-43.
[7] Buchs AE, Silverman BG. Incidence of malignancies in patients with diabetes mellitus and correlation with treatment modalities in a large Israeli health maintenance organization: a historical cohort study. *Metabolism* 2011;60(10):1379-85.
[8] Cartensen B, Witte DR, Friis S. Cancer occurrence in Danish diabetic patients: duration and insulin effects. *Diabetologia* 2012;55(4):948-58.
[9] Ehrlich SF, Quesenberry Jr CP, Van Den Eeden SK, Shan J, Ferrara A. Patients diagnosed with diabetes are at increased risk of asthma, chronic obstructive pulmonary disease, pulmonary fibrosis, and pneumonia but not lung cancer. *Diabetes Care* 2010;33(1):55-60.

[10] Ferrara A, Lewis JD, Quesenberry Jr CP, Peng T, Strom BL, Van Den Eeden SK, et al. Cohort study of pioglitazone and cancer incidence in patients with diabetes. *Diabetes Care* 2011; 34(4):923-9.
[11] Johnson JA, Bowker SL, Richardson K, Marra CA. Time-varying incidence of cancer after the onset of type 2 diabetes: evidence of potential detection bias. *Diabetologia* 2011;54(9):2263-71.
[12] Smiechowski BB, Azoulay L, Yin H, Pollak MN, Suissa S. The use of metformin and the incidence of lung cancer in patients with type 2 diabetes. *Diabetes Care* 2013;36(1):124-9.
[13] Van Staa TP, Patel D, Gallagher AM, de Bruin ML. Glucose-lowering agents and the patterns of risk for cancer: a study with the General Practice Research Database and secondary care data. *Diabetologia* 2012;55(3):654-65.
[14] Andersson C, Vaag A, Selmer C, Schmieglow M, Sørensen R, Lindhardsen J, et al. Risk of cancer in patients using glucose-lowering agents: a nationwide cohort study of 3.6 million people. *BMJ Open* 2012;2(3):1-6.
[15] Blin P, Lassalle R, Dureau-Pournin C, Ambrosino B, Bernard MA, Abouelfath A, et al. Insulin glargine and risk of cancer: a cohort study in the French National Healthcare Insurance Database. *Diabetologia* 2012 55(3):644-53.
[16] Home PD, Kahn SE, Jones NP, Noronha D, Beck-Nielsen H, Viberti G. Experience of malignancies with oral glucose-lowering drugs in the randomised controlled ADOPT (A Diabetes Outcome Progression Trial) and RECORD (Rosiglitazone Evaluated for Cardiovascular Outcomes and Regulation of Gycaemia in Diabetes) clinical trials. *Diabetologia* 2010;53(9):1838-45.
[17] Ruiter R, Visser LE, van Herk-Sukel MP, Coebergh JW, Haak HR, Geelhoed-Duijvestijn PH, et al. Risk of cancer in patients on insulin glargine and other insulin analogues in comparison with those on human insulin: results from a large population-based follow-up study. *Diabetologia* 2012;55(1):51-62.
[18] Freund KM, Belanger AJ, D'Agostino RB, Kannel WB. The health risks of smoking. The Framingham Study: 34 years of follow-up. *Ann Epidemiol* 1993;3(4):417-24.
[19] Sidney S, Tekawa IS, Friedman GD. A prospective study of cigarette tar yield and lung cancer. *Cancer Causes and Control* 1993;4:3-10.
[20] Samet JM, Wiggins CL, Humble CG, Pathak DR. Cigarette smoking and lung cancer in New Mexico. *Am Rev Respir Dis* 1988;137(5):1110-3.

cc: Calloway P/WysowskiD/WangC/DEPI
CanidaL/OSE
WhiteheadR/YanoffL/MohamadiA/PippinsJ/GuettierJM/DMEP
SeymourS/DPARP
WeaverJ/LaCivitaC/DRISK
Pai-ScherfL/DOP2/OHOP
XieD/LevensonM/DBVII

APPENDIX A

Table A-1. Search Terms for Medline PubMed

Search Parameters	Search Terms
Limits	2003-present; humans; no comments, letters, editorials
Disease	"Lung Neoplasms"[Mesh] OR (("lung"[Text Word] OR "lungs"[Text Word]) AND (cancer*[Text Word] OR neoplasm*[Text Word] OR carcinoma*[Text Word] OR tumor*[Text Word] OR "tumors"[Text Word] OR tumour*[Text Word])) "Diabetes Mellitus"[Mesh] OR "Diabetes Complications"[Mesh] OR "diabetes"[Text Word] OR diabetic*[Text Word]
Geographic areas	("North America"[Mesh] OR "United States"[Mesh] OR "Canada"[Mesh] OR "Mexico"[Mesh] OR "Brazil"[Mesh] OR "Europe, Eastern"[Mesh] OR North America*[Title/Abstract] OR "United States"[Title/Abstract] OR "USA"[Title/Abstract] OR "U.S.A."[Title/Abstract] OR Canada*[Title/Abstract] OR "Mexico"[Title/Abstract] OR Mexican*[Title/Abstract] OR Brazil*[Title/Abstract] OR Eastern Europe*[Title/Abstract] OR Albania*[Title/Abstract] OR Estonia*[Title/Abstract] OR Latvia*[Title/Abstract] OR Lithuania*[Title/Abstract] OR Bosnia- Herzegovina*[Title/Abstract] OR Bulgaria*[Title/Abstract] OR Croatia*[Title/Abstract] OR "Czech Republic"[Title/Abstract] OR "Hungary"[Title/Abstract] OR Hungarian*[Title/Abstract] OR Macedonia*[Title/Abstract] OR Moldova*[Title/Abstract] OR "Montenegro"[Title/Abstract] OR "Poland"[Title/Abstract] OR "Polish"[Title/Abstract] OR Belarus*[Title/Abstract] OR Romania*[Title/Abstract] OR Russia*[Title/Abstract] OR Serbia*[Title/Abstract] OR Slovakia*[Title/Abstract] OR Slovenia*[Title/Abstract] OR Ukrain*[Title/Abstract] OR Yugoslavia*[Title/Abstract] OR North America*[Affiliation] OR "United States"[Affiliation] OR "USA"[Affiliation] OR "U.S.A."[Affiliation] OR "US"[Affiliation] OR "U.S."[Affiliation] OR Canada*[Affiliation] OR "Mexico"[Affiliation] OR Mexican*[Affiliation] OR Brazil*[Affiliation] OR Eastern Europe*[Affiliation] OR Albania*[Affiliation] OR Estonia*[Affiliation] OR Latvia*[Affiliation] OR Lithuania*[Affiliation] OR Bosnia-Herzegovina*[Affiliation] OR Bulgaria*[Affiliation] OR Croatia*[Affiliation] OR "Czech Republic"[Affiliation] OR "Hungary"[Affiliation] OR Hungarian*[Affiliation] OR Macedonia*[Affiliation] OR Moldova*[Affiliation] OR "Montenegro"[Affiliation] OR "Poland"[Affiliation] OR "Polish"[Affiliation] OR Belarus*[Affiliation] OR Romania*[Affiliation] OR Russia*[Affiliation] OR Serbia*[Affiliation] OR Slovakia*[Affiliation] OR Slovenia*[Affiliation] OR Ukrain*[Affiliation] OR Yugoslavia*[Affiliation])
Study type	("Cohort Studies"[Mesh] OR "Follow-Up Studies"[Mesh] OR "Longitudinal Studies"[Mesh] OR "Prospective Studies"[Mesh] OR "Retrospective Studies"[Mesh] OR "Clinical Trials as Topic"[Mesh] OR "Clinical Trial"[Publication Type] OR cohort*[Text Word] OR "follow up"[Text Word] OR longitudinal*[Text Word] OR "prospective"[Text Word] OR "retrospective"[Text Word] OR trial*[Text Word] OR outcome*[Text Word] OR "population based"[Text Word] OR "smoking"[Text Word] OR smoker*[Text Word] OR "tobacco"[Text Word] OR "incidence"[Text Word] OR "prevalence"[Text Word] OR "morbidity"[Text Word] OR epidemiolog*[Text Word])

APPENDIX B

Table 3: Lung cancer incidence in sponsor identified publications (not including the studies involving the Women's Health Initiative and the type 1 diabetic populations since these were included in the text of the review).

Reference	Diabetic status (all type 2)	Smoking status	Lung Cancer Cases (n)	Lung Cancer Incidence per 1,000 person years (PY)	Comments
Atchison 2011(6)	Hospitalized for diabetes	Unknown	Not provided	1.89	US veterans
Buchs 2011 (7)_	Diabetes in healthcare database	Unknown	145 respiratory cancers	0.88 for respiratory cancers	Israel
Carstensen 2012 (8)	Diabetes versus general population	Unknown	2,741 lung, bronchus, and pleura	diabetes = 2.14 diabetes + insulin = 1.66	Denmark, National Cancer Registry
Ehrlich 2010 (Kaiser Permanente Northern California) (9)	Diabetic	Past-smoking 35.4%	Not provided	0.47 (95% CI 0.44–0.50)	Age and sex adjusted
Ferrara 2011 (Kaiser Permanente Northern California) (10)	KPNC Diabetes Registry	Approximately 19%	1,637 lung/bronchus	1.64	Unadjusted
Johnson 2011 (British Columbia Linked Health database) (11)	Diabetic ≤ 3 months since diabetes onset	Unknown	227	5.08 (95% CI 4.46–5.79)	Matched on sex, birth year, and index year (year of diabetes onset matched to year of health coverage registration in non-diabetic)
	Diabetic > 3 months since diabetes onset	Unknown	1,463	1.94 (95% CI 1.84–2.04)	
Smiechowski 2013	Diabetes with at least 1				Unadjusted; excluded those

(GPRD) (12)	prescription for oral antidiabetic drug	62%	1,061	2.0 (95% CI 1.90–2.0)	with insulin as first treatment
Van Staa 2012 (GPRD) (13)	Diabetes with at least 1 prescription for antidiabetic drug	Approximately 55%	1,673	1.9	0.19 in literature, but report assumes this to be per 100 PY
By Antidiabetic Type					
Andersson 2012 (14)	Dispensed insulin, SU, metformin, or TZD	Unknown	Metformin: 602 SU: 666 Insulin (insulatard): 132	Metformin: 1.7 SU: 2.0 Insulin (insulatard): 1.9	Danish National Hospitalization Registry
Blin 2012 (15)	Random sample of people using insulin	Unknown	11	Insulin glargine 1.9 (95% CI 0.70–4.2) Insulin glargine 2.1 (95% CI 0.70–5.0)	French National Health Care Insurance Database
Home 2010 (16)	Use of oral anti-diabetic 6 months prior to screening	Unknown	ADOPT: 18 RECORD: 21	ADOPT Metformin 1.2 Rosiglitazone 1.0 Glibenclamide 1.6 RECORD Metformin 0.5 Ros/SU 1.5 SU/MET 1.0 ROS/MET 0.5	Reanalysis from RECORD and ADOPT
Ruiter 2012 (17)	Any prescription for a hypoglycemic agent	Unknown	Respiratory cancer 81	"respiratory cancer" Glargine 1.64 Other insulin analogs 1.89 Human insulin 1.9	Dutch National Medical Register

---

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

/s/

PATRICIA L BRIGHT
03/28/2014

DIANE K WYSOWSKI
03/28/2014

CUNLIN WANG
03/28/2014

Department of Health and Human Services
Public Health Service
Food and Drug Administration
Center for Drug Evaluation and Research
Office of Surveillance and Epidemiology (OSE)
Office of Pharmacovigilance and Epidemiology (OPE)

Epidemiology: Review of Study Protocol

Date:	February 28, 2014
Reviewer(s):	Patricia L. Bright, M.S.P.H., Ph.D., Epidemiologist, Division of Epidemiology 1 (DEPI 1), Office of Pharmacovigilance and Epidemiology (OPE), Office of Surveillance and Epidemiology (OSE)
Team Leader:	Diane K. Wysowski, M.P.H., Ph.D., DEPI 1, OPE, OSE
Division Director:	Cunlin Wang, M.D., Ph.D., DEPI 1, OPE, OSE
Subject:	Review of the Sponsor's proposed postmarketing study for Afrezza entitled "A Postmarketing Observational Cohort Study to Evaluate the Long-term Safety of Afrezza in the Treatment of Patients with Diabetes Mellitus" (October 2013 resubmission to the FDA)
Drug Name(s):	Afrezza (Technosphere Insulin Inhalation System)
Application Type/Number:	NDA 022472
Applicant/sponsor:	MannKind
OSE RCM #:	2014-304
TSI #:	Not Applicable

TABLE OF CONTENTS

EXECUTIVE SUMMARY

Afrezza (insulin, human [rDNA] inhalation powder) is an ultra-rapid acting inhaled insulin indicated for improving glycemic control in adults with type 1 and type 2 diabetes.

Following the second Complete Response (CR) of the new drug application in January 2011, the sponsor responded to the FDA's concerns and resubmitted the application to the FDA on October 15, 2013. On October 22, 2013, the Division of Metabolism and Endocrinology Products (DMEP) requested the Division of Epidemiology 1 (DEPI 1) to evaluate the sponsor's proposed postmarketing study for Afrezza entitled "A Postmarketing Observational Cohort Study to Evaluate the Long-term Safety of Afrezza in the Treatment of Patients with Diabetes Mellitus."

The sponsor submission did not include a fully developed postmarketing study protocol, but included a four-page proposal for an observational study. The proposal was for a non-interventional, multicenter, non-comparative, postmarketing study to evaluate the long-term safety profile of Afrezza when prescribed in usual clinical practice for the treatment of diabetes. The main study objective was to determine the incidence of primary pulmonary malignancies in patients taking Afrezza. Secondary objectives were to determine the incidence of the following outcomes: all other malignancies (except non-melanoma skin cancers), serious pulmonary events (besides malignancies), serious allergic events, and hypoglycemic events requiring medical intervention. All treatment decisions would be made at the discretion of the patient's healthcare provider and would not be mandated by the study design or protocol. The study would be conducted in the U.S. with other countries added (contingent upon national approval of Afrezza and the study protocol).

Although the method for site selection was not described, the proposal stated that 200 sites that care for type 1 and type 2 diabetes patients would be identified for study participation (including a heterogeneous sample of family practice, internal medicine, diabetes, and endocrinology practices). The anticipated sample size would be 1,800 participants recruited over approximately two years and followed for at least five years from date of the last patient enrollment. Data collection would take place at usual care visits (with a minimum of every 6 months) and follow-up would take place even if Afrezza is discontinued.

The proposal indicates that the incidence of pulmonary malignancies from the study would be compared to the background rate in the general population based on the National Cancer Institute's Surveillance, Epidemiology, and End Results (SEER) data with 90% power to detect a 3-fold increase in the rate of pulmonary malignancy.

DEPI staff concluded that the registry proposal had insufficient detail. Also, given that pulmonary malignancy risk is heavily confounded by smoking and that Afrezza users may have more thorough or frequent pulmonary assessments than the proposed comparator, the proposed postmarketing approach would be inadequate to evaluate risk of pulmonary malignancies with Afrezza use. In addition, the age-adjusted U.S. incidence rate of lung cancer is a crude comparator. Rather lung cancer incidence rates

adjusted by frequency, duration, and pack-years of cigarette smoking might be a more appropriate comparator. Since frequency and duration of cigarette smoking is the most important risk factor for lung cancer incidence, collection of frequency, duration, and number of pack-years of cigarette smoking would be critical for evaluation of the role of Afrezza in lung cancer incidence and mortality.

DEPI I staff have recommended two alternative post-marketing approaches that might better assess pulmonary malignancy risk with Afrezza use. These approaches are listed at the end of section 4 (Discussion).

Additional recommendations for the sponsor are listed in Section 6 of this review.

1 INTRODUCTION

In March 2010 and January 2011, the FDA issued Complete Responses (CR) for a new drug application (NDA) submission for Afrezza. On October 15, 2013, the sponsor resubmitted the application to the FDA, responding to the FDA's concerns. On October 22, 2013, the Division of Metabolism and Endocrinology Products (DMEP) requested the Office of Surveillance and Epidemiology, Office of Pharmacovigilance and Epidemiology, Division of Epidemiology1 (OSE/OPE/DEPI1) evaluate a sponsor's proposed postmarketing study for Afrezza entitled "A Postmarketing Observational Cohort Study to Evaluate the Long-term Safety of Afrezza in the Treatment of Patients with Diabetes Mellitus."

1.1 BACKGROUND

Brief Drug Description

Afrezza (insulin, human [rDNA] inhalation powder) is an ultra-rapid acting inhaled insulin seeking approval for improving glycemic control in adults with type 1 and type 2 diabetes. The dry powder is administered at the beginning of a meal by a Gen2 inhaler with cartridges containing 10 units or 20 units of drug product.

The sponsor has proposed in the Afrezza labeling that Afrezza be contraindicated in patients with a current diagnosis or history of asthma, chronic obstructive pulmonary disease (COPD) or other chronic lung disease. The sponsor also has proposed labeling under Warnings and Precautions that Afrezza not be recommended for current smokers and those who have smoked in the last 6 months and that prior to initiating therapy with Afrezza, all patients should be clinically evaluated with a detailed medical history, physical examination and spirometry (FEV1) to identify any potential underlying disease.

Safety Concerns

- Lung Cancer

  Exubera

  The FDA approved Exubera, another inhaled insulin, in January 2006, but Exubera was later withdrawn by the sponsor due to lower than expected sales. Prior to official withdrawal, however, the FDA required changes to the Exubera product labeling due to postmarketing pulmonary malignancies. The labeling noted that there were too few cases to determine whether the events were related to Exubera and that all

patients who were diagnosed with lung cancer had a prior history of cigarette smoking.

Since that time, study results from an observational follow-up study of patients previously enrolled in Exubera (FUSE) controlled clinical trials found the following:

- Primary lung cancer mortality--Six cases were reported in 12,605.9 person years in the Exubera group and 2 cases in 11,802.5 person years in the comparator group. The incidence density ratio (IDR) was 2.81 (95% CI: 0.50 - 28.46).
- Primary lung cancer incidence--Twelve cases were reported in 11,180.7 person years in the Exubera group and 3 cases in 10,467.9 person years in the comparator group. The IDR was 3.75 (95% CI: 1.01 - 20.68).

Pulmonary malignancies remain adverse events of special interest for inhaled insulins [1].

Afrezza

During the clinical development program for Afrezza in which Afrezza use was compared primarily with other insulin use[1], two cases of pulmonary malignancies were identified in Afrezza-exposed patients: One was identified after 120 days of treatment in a 62-year-old male subject with a prior history of smoking. The other involved a non-small cell bronchogenic carcinoma in an Afrezza-exposed patient in an uncontrolled trial. The patient was "a 67-year-old male subject with a history of heavy smoking and a family history of lung cancer" [2].

Two additional lung cancers were spontaneously reported at 2.5 and 3.5 years, respectively, after clinical trial discontinuation in a 59-year-old male non-smoker and in a 73-year-old female non-smoker who had been prescribed a high dose of Afrezza [3].

No lung cancer cases were reported in comparator-exposed patients.

- Non-Malignant Pulmonary Adverse Events: Bronchospasms and Pulmonary Function Decline

  The FDA review of pulmonary safety from the original NDA submission found that cough was the most common adverse event, with occasional bronchospasm. This was exacerbated for patients with underlying disease, such as asthma. Although cough rates were similar to those in the Exubera development program, they exceeded frequencies typically found in patients with asthma/chronic obstructive pulmonary disease (COPD) treated with dry powder inhalers [4].

  Patients with type 1 or type 2 diabetes treated with Afrezza also had a non-clinically significant decline in FEV1 (average of 40-50 ml) with a decline of 90-138 ml immediately post inhalation. Declines started during the first three months of treatment and persisted over time. Data were insufficient to evaluate reversal after

[1] The comparators in the trials were generally insulin aspart or insulin lispro with a background basal insulin (typically insulin glargine) as compared to Afrezza with a background basal insulin. Other trials used placebo as a comparator in combination with metformin or two or more oral anti-diabetic agents.

Afrezza discontinuation. In asthmatic patients, FEV1 declined 400 ml at 15 minutes post-inhalation, but recovered over a two-hour period [4].

- Serious Allergic Events and Hypoglycemia
  The 2010 FDA clinical review found that the incidence of hypoglycemia in trial 117 (a randomized open-label study in patients with Type 1 diabetes) was lower for Afrezza than for Humalog, but the difference was not statistically significant. The risk of hypoglycemia was directly proportional to dose [1].

To further assess these safety concerns, the sponsor proposed a non-interventional, post-marketing study to evaluate the long-term safety profile of Afrezza when prescribed in usual clinical practice for the treatment of diabetes. The proposal states that "The study will provide additional quantification and characterization of potential adverse events with low incidence or long latency after exposure to Afrezza. In addition, the study will help identify adverse events that may occur outside of the controlled clinical trial setting." The proposed postmarketing proposal is the basis for this review.

1.2 REGULATORY HISTORY (ABBREVIATED):

- December 22, 2000: IND 061729 submitted to the FDA.
- March 16, 2009: NDA 022472 submitted to the FDA.
- March 12, 2010: The FDA issued a Complete Response letter.
- June 29, 2010: The sponsor sent a class 2 resubmission for NDA 022472.
- January 18, 2011: The FDA issued another Complete Response letter.
- October 15, 2013: The sponsor sent a class 2 resubmission for NDA 022472.
- October 22, 2013: DMEP consulted DEPI1 on the sponsor's submission. The sponsor's proposed postmarketing study is the basis for this review.

1.3 PRODUCT LABELING

Afrezza has not yet been approved and product labeling has not been finalized. However, Mannkind has proposed in the Afrezza labeling that Afrezza be contraindicated in patients with a current diagnosis or history of asthma, chronic obstructive pulmonary disease (COPD) or other chronic lung disease. The sponsor also has proposed labeling under Warnings and Precautions that Afrezza not be recommended for current smokers and those who have smoked in the last 6 months and that prior to initiating therapy with Afrezza, all patients should be clinically evaluated with a detailed medical history, physical examination and spirometry (FEV1) to identify any potential underlying disease.

2 REVIEW METHODS AND MATERIALS

Following the second FDA Complete Response for NDA 022472, the FDA received a third submission for the product on October 15, 2013. On October 22, 2013, DMEP requested that DEPI 1 evaluate the sponsor's proposed postmarketing study for Afrezza entitled "A Postmarketing Observational Cohort Study to Evaluate the Long-term Safety of Afrezza in the Treatment of Patients with Diabetes Mellitus." DEPI staff reviewed this proposal using as a reference "Registries for Evaluating Patient Outcomes: A User's Guide" [5].

3 REVIEW RESULTS

3.1 STUDY OVERVIEW

The sponsor submission did not include a fully developed postmarketing study protocol, but included a four-page proposal for an observational study. This proposal was for a non-interventional, multicenter, non-comparative, postmarketing study to evaluate the long-term safety profile of Afrezza when prescribed in usual clinical practice for the treatment of diabetes. All treatment decisions would be made at the discretion of the patient's healthcare provider and would not be mandated by the study design or protocol. The study would be conducted in the U.S. with other countries added (contingent upon national approval of Afrezza and the study protocol).

Although the method for site selection was not described, the proposal stated that 200 sites that care for type 1 and type 2 diabetes patients would be identified for study participation (including a heterogeneous sample of family practice, internal medicine, diabetes, and endocrinology practices). The anticipated sample size would be 1,800 participants recruited over approximately two years and followed for at least five years from date of the last patient enrollment. Data collection would take place at usual care visits (with a minimum of every 6 months) and follow-up would take place even if Afrezza is discontinued. Study outcomes are listed under the objectives below.

The proposal stated that the investigators will compare the incidence of pulmonary malignancies to the background rate in the general population based on the National Cancer Institute's Surveillance, Epidemiology, and End Results (SEER) data (see the statistical analysis section 3.3.5 below)

3.2 STUDY OBJECTIVES

The primary study objective would be to determine the incidence of primary pulmonary malignancies in patients taking Afrezza. The secondary objectives would be to determine the incidences of:

- All other malignancies (except non-melanoma skin cancers)
- Serious pulmonary events
- Serious allergic events
- Hypoglycemic events requiring medical intervention

3.3 STUDY METHODS

3.3.1 Design & Setting

3.3.1.1 Study Type

The study would be a prospective, observational, follow-up product exposure registry without an internal study comparison group. The study will compare the observed lung cancer incidence rate in the Afrezza registry with the age-adjusted incidence rate of lung cancer in the U.S. population.

3.3.1.2 Time Period

The study population would be recruited over two years until a target of 1,800 patients is reached. Participants would be followed for at least five years from last patient enrollment with the duration of individual patient participation ranging from 5-7 years.

3.3.1.3 Population -- Selection, Inclusion and Exclusion Criteria

Selection:
The proposal stated that 200 sites that care for type 1 and type 2 diabetes patients would be identified for study participation (including a heterogeneous sample of family practice, internal medicine, diabetes, and endocrinology practices). Methods and criteria for site and health care provider selection to participate were not addressed.

Inclusion Criteria:
- Adult patients (age $\geq$ 18 years) who are initiating treatment with Afrezza. The decision to prescribe Afrezza would need to be made prior to study enrollment.
- Patients would need to be able to understand the requirements of the study, and provide written informed consent.

Exclusion Criteria:
- Patients previously enrolled in other studies evaluating inhaled insulin products.
- Patients receiving an investigational agent (any drug or biologic agent that has not received marketing authorization in the Unites States).

3.3.2 Outcome & Exposure

Exposure:
Although Afrezza use is the exposure of interest, the proposal did not address how Afrezza exposure would be determined.

Outcome:
Outcomes of interest in the follow-up study were new (incident) primary pulmonary malignancies, all malignancies (except non-melanoma skin cancers), and serious pulmonary, serious allergic, and hypoglycemic events requiring medical intervention. The proposal did not contain any details on how these outcomes would be defined or validated.

3.3.3 Covariates

Baseline:
The following covariate information would be collected at baseline: age, gender, race/ethnicity, smoking history, height and weight, diabetes treatment (diagnosis, treatment history, complications, history of hypoglycemia), pulmonary history, cancer history, history of allergic conditions, and concomitant medications.

Follow-up:
The following covariate information would be collected at follow-up: weight, current diabetes treatment regimen, changes in concomitant medications, and serious adverse events.

3.3.4 Sample Size/Power

The investigators suggested a sample size of 1,800 participants (calculated using a background rate of 64.6 pulmonary malignancies per 100,000 person-years). The proposal stated that this rate was determined from the SEER database, but the associated years for the rates were not provided. As of Jan 3, 2014, the SEER website reported that the number of new cases of lung and bronchus cancer was 61.4 per 100,000 men and women per year, age-adjusted, based on 2006-2010 cases.

The proposal estimated that if 1,800 patients were enrolled in the study over a two-year period and followed for at least five years after the end of enrollment and assuming a study discontinuation rate of 10%, approximately 8,000 person-years of follow-up would accumulate. The proposal stated that the 8,000 person-years of follow-up would provide 90% power to detect a 3-fold increase in rate of pulmonary malignancy with a two-sided alpha of 0.05.

The calculation appears to rely on the assumption that Afrezza use would have no more than a 10% discontinuation rate throughout the entire study period.

No sample size estimation was provided for estimated ranges of losses to follow-up and for discontinuation rates exceeding 10%.

3.3.5 Statistical Analyses

The proposal stated that "The primary endpoint is the incidence of pulmonary malignancies, with a background rate assumed to be 64.6 events per 100,000 person-years of surveillance. If the lower limit of the 95% confidence interval is above 64.6, then exposure to Afrezza will be deemed to have demonstrated a significant risk for pulmonary malignancies." The proposal further stated that for binomial endpoints, the number of person-years of follow-up and incidence per 100,000 person-years would be calculated with 95% confidence intervals. Exploratory analyses would also be conducted using logistic regression comparing those who experienced the safety outcomes to those who did not. An exploratory analysis would also evaluate Afrezza dose and duration.

4 DISCUSSION

Study Objectives

The objectives appear appropriate, but may need to be revised if the FDA identifies additional safety outcomes of interest through the FDA review process. Such requirements would be specified if the drug receives FDA approval and if a Post-marketing Requirement (PMR) for a safety study is issued to the sponsor.

Study Design

The sponsor proposed a prospective, observational, follow-up product exposure registry without an internal comparator group. Rather, they plan to compare the observed lung cancer incidence rates with the expected rate in the U.S. population. However, since smoking is the major risk factor for lung cancer, lung cancers in Afrezza exposed and comparator groups should be adjusted for, or stratified by, frequency, duration, and pack-years of cigarette smoking to compare risk in the two groups.

Cough is a common side effect in Afrezza exposed patients, and the previous inhaled insulin, Exubera, underwent a labeling change to include information on pulmonary malignancies. Therefore, exposed patients may have more thorough or frequent pulmonary assessments than the general population leading to higher detection rates for pulmonary malignancies (detection bias).

Time Period
The sponsor proposed that the study continue for five years after the last patient enrollment. However, the FDA typically requires observational studies of malignancy to continue for 10 years to allow for sufficient length of follow up given the unknown latency period and to obtain a large enough sample size to evaluate malignancy development and detection.

Selection
The proposal did not clarify how sites will be identified for study participation. If a PMR is issued, we would expect a revised protocol containing greater detail on the methodology for how sites and physicians would be identified and invited to participate.

Inclusions and Exclusions
The proposal stated that inclusion criteria were broad and exclusion criteria were limited so as to include a representative population of patients taking the product in usual clinical practice. We agree with the proposed inclusion and exclusion criteria.

Exposure
The proposal does not address procedures to document Afrezza exposure or adherence beyond collecting data on "current diabetes treatment regimen" at follow-up visits. The proposal should indicate how prescribing information for Afrezza would be documented at enrollment, and how changes in Afrezza exposure would be documented over time (including stopping, starting, changes in dose, and periods of non-adherence). The clinicians should ask and record changes in actual use at each patient visit.

Outcomes
The proposal did not provide details on how the outcomes would be defined and validated (pulmonary malignancies, all malignancies excluding non-melanoma skin cancers, serious pulmonary, serious allergic, and hypoglycemic events requiring medical attention). For malignancies, the protocol should include (as appropriate) plans for documentation of histopathology, stage, invasiveness, tumor size, extension, and lymph node involvement.

We also recommend that the study evaluate the frequency of pulmonary function tests performed at baseline (before Afrezza initiation), lung cancer mortality and all-cause mortality (with cause of death) in study participants as secondary outcomes.

Covariate Data
A detailed smoking history (number of cigarettes smoked per day and duration of smoking) should be collected on all study participants at baseline. In addition to the covariate information mentioned in the proposal, data collection at baseline and as appropriate at each participant visit should include current smoking status and intensity, other tobacco use, personal history of cancer, body mass index (BMI), other

comorbidities, asbestos exposure, radiation exposure, immunosuppressive therapy, family history of cancer, and history of alcohol consumption. Follow-up data collection should address changes in smoking status, tobacco use (and document intensity if applicable), and other variables that may have changed since the previous patient visit.

Follow-up

The proposal did not provide details on procedures to contact and trace participants, but did project 90% participant retention. We encourage the inclusion of more detailed plans to maintain patients' follow-up during the study and a search of the National Death Index (NDI) in the U.S. (and similar databases in other countries) for participants lost to follow-up to ascertain death and causes of death.

Sample Size

The sample size calculated for this study was based on the U.S. age-adjusted incidence rates of pulmonary malignancies per 100,000 person-years (data years not specified). However, since most cases of lung cancer with inhaled insulin have been in previous smokers, we recommend estimating the sample size that would be needed to detect a two-fold increase in the incidence of pulmonary malignancies (with 80% power and 95% confidence) for former smokers in addition to using the U.S. population rates that include both smokers and non-smokers.

Sample size calculations did not account for varying rates of Afrezza loss to follow-up. We suggest that the revised protocol calculate the estimated sample size based on various rates of loss to follow-up and Afrezza discontinuation that exceed 10%.

Analysis

The revised protocol should include a detailed analysis plan and describe how missing data would be addressed.

The investigators should also plan to report registry enrollment to the FDA annually by country.

Alternative study designs:

We suggest two potential postmarketing study approaches to evaluate the relationship between pulmonary malignancies and Afrezza use in addition to the sponsor's proposed study:

- **A registry with methodology to reduce detection bias**
  A study of diabetic patients who are prescribed Afrezza to evaluate the incidence of lung cancer, lung cancer mortality, and all-cause mortality at 3, 5, and 10 years by Afrezza use (lowest quartile for exposure duration as compared to upper two quartiles of exposure duration) adjusting for pack-years of smoking. The study would collect detailed information on smoking history (number of cigarettes smoked per day and duration of smoking) and on other potential risk factors (current smoking status and intensity, other tobacco use, age, gender, race, BMI, diabetes severity, family history of lung cancer, history of cancer and other comorbidities, asbestos exposure, radiation exposure, immunosuppressive therapy, concomitant medications, etc.). After agreement on a targeted sample size with the FDA, the study would continue for 10 years from the date of last patient's enrollment.

By limiting the study to Afrezza users, detection bias could be minimized that might result from Afrezza users undergoing more thorough or frequent pulmonary assessments that might arise due to clinician familiarity with the pulmonary malignancy data associated with Exubera use. Detection bias due to coughing may remain an issue when comparing current users of Afrezza to those who have discontinued.

The total number of events needed to detect the associated hazard ratios (HRs) were calculated by Dr. Mark Levenson of DBVII, and are listed in Table 1 (90% power and a two-sided alpha of 0.05).

Table 1: Numbers of events needed to detect the corresponding HR

Hazard Ratio (HR)	Total Events (lower exposer plus higher exposure)
2	87
3	35
4	22

The secondary outcomes proposed by the sponsor (other malignancies, serious pulmonary events, serious allergic events and hypoglycemic events requiring medical intervention), also could be assessed in this registry.

Or

- **A Large Randomized Controlled Study**
  The FDA may request a large randomized controlled study designed to further assess the long-term pulmonary safety of Afrezza. We recommend that lung cancer, lung cancer mortality, and all-cause mortality be study outcomes. In addition, we recommend that participants also undergo further observational follow-up for lung cancer, lung cancer mortality, and all-cause mortality after trial discontinuation.

  The study would need to collect detailed information on smoking history (number of cigarettes smoked per day, duration of smoking, and pack-years) and on other potential risk factors for pulmonary malignancies (age, gender, race, current smoking status and intensity, other tobacco use, BMI, diabetes severity, personal history of cancer, alcohol use, other comorbidities, asbestos exposure, radiation exposure, immunosuppressive therapy, concomitant medications, etc.). The other outcomes proposed by the sponsor (all malignancies except non-melanoma skin cancers, and serious pulmonary, serious allergic, and hypoglycemic events requiring medical intervention) could also be assessed with this study approach.

5 CONCLUSION

If Afrezza receives FDA approval and if a postmarketing study is required, the sponsor will be obligated to submit to the FDA a formal well-developed study protocol to

evaluate the outcomes identified in the postmarketing requirement. The currently proposed registry has inadequate detail.

Also, given that pulmonary malignancy risk is heavily confounded by smoking and that Afrezza users may have more thorough or frequent pulmonary assessments than a comparator, resulting in possible detection bias, the proposed postmarketing approach would be inadequate to evaluate pulmonary malignancy risk with Afrezza use.

DEPI I staff have recommended two alternative postmarketing approaches that include collecting detailed information on cigarette smoking history and status that might better assess pulmonary malignancy risk with Afrezza use. These approaches are listed above at the end of section 4 (the Discussion).

Additional recommendations for the sponsor concerning this proposal are listed in Section 6 of this review (below).

6 RECOMMENDATIONS TO SPONSOR

If Afrezza receives FDA approval and if a postmarketing study is required, you will have to submit to the FDA a formal well-developed study protocol to evaluate the outcomes identified in the postmarketing requirement. The currently proposed registry includes inadequate detail.

Also, given that pulmonary malignancy risk is heavily confounded by smoking history and that Afrezza users may have more thorough or frequent pulmonary assessments than a comparator (detection bias), the proposed postmarketing approach would be inadequate to evaluate pulmonary malignancy risk with Afrezza use. We suggest that the sponsor discuss with the FDA alternative approaches that may better address the challenges posed in the postmarketing setting.

Our recommendations are listed below about your proposed study. However, the FDA may require an alternative study(ies).

1. The objectives appear appropriate, but you may need to revise them if the FDA identifies additional safety outcomes of interest. Such requirements would be specified if the drug receives FDA approval and if a safety Postmarketing Requirement (PMR) is issued.
2. Evaluate lung cancer mortality and all-cause mortality (with cause of death) in study participants as secondary outcomes.
3. Evaluate the frequency of pulmonary function tests performed at baseline (before Afrezza initiation).
4. Clarify how sites will be identified for study participation. If a PMR is issued, we would expect a revised protocol containing greater detail on the methodology for how sites and physicians will be identified and invited to participate.
5. Describe data collection including standardized forms or instructions to physicians for documenting all information including prescribing information for Afrezza at enrollment, and how changes in Afrezza exposure would be documented over time (including stopping, starting, changes in dose, and periods of non-adherence).

Provide details on how the outcomes will be defined and validated. For malignancies, the protocol should include (as appropriate) plans for documentation of histopathology, stage, invasiveness, tumor size, extension, and lymph node involvement.

6. Collect detailed smoking histories (number of cigarettes smoked per day, duration of smoking, and pack-years) at baseline. In addition to the covariate information mentioned in the proposal, collect current smoking status and intensity, other tobacco use, body mass index (BMI), personal history of cancer, other comorbidities, asbestos exposure, radiation exposure, immunosuppressive therapy, family history of cancer, and history of alcohol consumption. Follow-up data collection should address changes in smoking status or tobacco use (and document intensity) as well as other risk factors that change over time.
7. Analyze the data by age; sex; smoking frequency, duration, and pack years; Afrezza dose and duration; and controlling for covariates.
8. Include procedures to contact and trace participants. We encourage plans to search the National Death Index (NDI) in the U.S. for participants lost to follow-up to ascertain death and causes of death. Obtain vital statistics and cause of death data from countries in which the drug is approved and that participate in the Afrezza registry. Calculate the sample size that would be needed to detect a two-fold increase in the incidence of pulmonary malignancy (with 80% power and 95% confidence) separately for former smokers and for patients with no smoking history. Include sample size projections for differing rates of loss to follow-up and Afrezza discontinuation that exceed 10%.
9. Include a detailed analysis plan and describe how missing data would be addressed.
10. Report registry enrollment to the FDA annually by country.

7 REGULATORY RECOMMENDATIONS TO DMEP

If this drug is approved, DEPI suggests that a PMR obligation be issued to evaluate pulmonary malignancies. We provided recommendations on the proposal submitted by the sponsor. In addition, we also suggested two alternative postmarketing approaches described at the end of the Discussion in Section 4.

8 REFERENCES

[1] Review completed by Lisa Yanoff M.D., Division of Metabolism and Endocrinologic Products (DMEP) of the Office of New Drugs, FDA, dated December 9, 2010.
[2] A postmarketing observational cohort study to evaluate the long-term safety of Afrezza in the treatment of patients with diabetes mellitus. Mannkind, October 2013 resubmission.
[3] Pai-ScherfL. E-mail with additional information on spontaneously reported pulmonary malignancies, Feb 20, 2014.
[4] Review completed by Banu Karimi-Shah M.D., Division of Metabolism and Endocrinologic Products (DMEP) of the Office of New Drugs, FDA, dated December 13, 2010.
[5] Gliklich RE, Dreyer NA, eds. Registries for Evaluating Patient Outcomes: A User's Guide. 2nd ed. (Prepared by Outcome DEcIDE Center [Outcomes Sciences, Inc. d/b/a Outcome] under Contract No.

HHSA29020050035I TO3.) AHRQ Publication No. 10-EHC049. Rockville, MD: Agency for Healthcare Research and Quality. September 2010.

cc: Calloway P/WysowskiD/WangC/DEPI
TossaM/CanidaL/OSE
WhiteheadR/YanoffL/Mohamadi A/BalakrishnanS/ColmanE/GuettierJM/DMEP
SeymourS/DPARP
WeaverJ/LaCavitaC/DRISK
Pai-ScherfL/DOP2/OHOP
XieD/LevensonM/DBVII

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

/s/

PATRICIA L BRIGHT
02/28/2014

DIANE K WYSOWSKI
02/28/2014

CUNLIN WANG
02/28/2014

Department of Health and Human Services
Public Health Service
Food and Drug Administration
Center for Drug Evaluation and Research
Office of Surveillance and Epidemiology
Office of Medication Error Prevention and Risk Management

Human Factors, Label, Labeling and Packaging Review

Date:	January 30, 2014
Reviewer:	Sarah K. Vee, PharmD Division of Medication Error Prevention and Analysis
Team Leader:	Yelena Maslov, PharmD Division of Medication Error Prevention and Analysis
Drug Name and Strength:	Afrezza (insulin human [rDNA origin]) powder for inhalation 3 units and 6 units per cartridge
Application Type/Number:	NDA 22472
Applicant/sponsor:	MannKind Corporation
OSE RCM #:	2013-2341 & 2394

*** This document contains proprietary and confidential information that should not be released to the public.***

Contents

1 INTRODUCTION

This review evaluates the proposed label, carton labeling, instructions for use (IFU), and prescribing information for Afrezza (NDA 22472) for areas of vulnerability that could lead to medication errors.

1.1 REGULATORY HISTORY

Afrezza Inhalation Powder, which is delivered via re-usable, breath-powered, high resistance, dry powder Gen 2 inhaler is a subject of 505 (b)(1) application under NDA 022472 originally submitted to the FDA on March 16, 2009.

Table 1: Regulatory Correspondence Dates

Date	Synopsis
March 16, 2009	NDA 022472 originally submitted
December 28, 2009	DMEPA reviewed the inhaler labels, cartridges, foil pack labels, as well as carton and insert labeling for Afrezza Inhalation Powder that included an earlier inhalation device (Model D) in OSE Review #2009-2440. DMEPA recommended designing the Usability Study by applying the principles of human factors to determine vulnerabilities and potential errors in the device and product design, which could be remedied before the design is finalized.
March 12, 2010	Complete Response (CR)
June 29, 2010	Response to a Complete Response. Applicant included a new inhaler (Gen 2) and a Usability Test applying the principles of human factors regarding the use of Afrezza Inhalation Powder and its associated inhaler.
December 13, 2010	The initial Human Factors Study, Labels and Labeling were reviewed by DMEPA in review RCM 2010-1576 &1577
January 18, 2011	Second complete response
November 18, 2011	Applicant submitted a Human Factors Study Protocol, as well as revised proposed Instructions for Use (IFU)
March 20, 2012	DMEPA provided comments in OSE Review #2011-4385
July 20, 2012	Type C Meeting Request: Human Factors
November 2, 2012	Written Response sent which included DMEPA comments regarding label, labeling and human factors protocol OSE Review #2012-2042
October 11, 2013	Response to second CR

1.2 PRODUCT INFORMATION

The following product information is provided in the October 13, 2013 proprietary name submission.

- Active Ingredient: insulin human [rDNA origin]
- Indication of Use: ultra rapid acting insulin to improve glycemic control in adults with type 1 or type 2 diabetes mellitus
- Route of Administration: oral inhalation
- Dosage Form: powder for inhalation
- Strength: 3 units and 6 units per cartridge
- Dose and Frequency: Individualized dosing taken before a meal (b) (4)
- How Supplied:

> AFREZZA (insulin human [rDNA origin]) Inhalation Powder is available as 3 unit and 6 unit single-use cartridges. Three cartridges are contained in a single cavity of a blister strip. Each card contains 5 blister strips separated by perforations for a total of 15 cartridges. For convenience, the perforation allows users to remove a single strip containing 3 cartridges. Two cards of the same cartridge strength are packaged in a foil laminate overwrap (30 cartridges per foil package).
>
> The cartridges are color-coded, blue for 3 units and green for 6 units. Each cartridge is marked with "*afrezza*" and "3 units" or "6 units".
>
> The AFREZZA Inhaler is individually packaged in a translucent overwrap. The inhaler is fully assembled with a removable mouthpiece cover. The AFREZZA Inhaler can be used for up to 15 days from the date of first use. After 15 days of use, the inhaler must be discarded and replaced with a new inhaler.
>
> AFREZZA is available in the following configurations:
>
> - NDC (<47918-XXX-XX>), AFREZZA (insulin human [rDNA origin]) Inhalation Powder: 60 – 3 unit cartridges and 2 inhalers
> - NDC (<47918-XXX-XX>), AFREZZA (insulin human [rDNA origin]) Inhalation Powder: 90 – 3 unit cartridges and 2 inhalers
> - NDC (<47918-XXX-XX>), AFREZZA (insulin human [rDNA origin]) Inhalation Powder: 90 – 6 unit cartridges and 2 inhalers
> - NDC (<47918-XXX-XX>), AFREZZA (insulin human [rDNA origin]) Inhalation Powder: 90 cartridges; 60 – 3 unit cartridges and 30 – 6 unit cartridges and 2 inhalers
> - NDC (<47918-XXX-XX>), AFREZZA (insulin human [rDNA origin]) Inhalation Powder: 90 cartridges; 30 – 3 unit cartridges and 60 – 6 unit cartridges and 2 inhalers
> - NDC (<47918-XXX-XX>), AFREZZA (insulin human [rDNA origin]) Inhalation Powder: 180 cartridges; 90 - 3 unit cartridges and 90 – 6 unit cartridges and 2 inhalers

- Storage:

Storage

Not in Use: Refrigerated Storage 2-8ºC (36-46ºF)

Sealed (Unopened) Foil Package	May be stored until the Expiration Date*

* If a foil package is not refrigerated, the contents must be used within 10 days.

In Use: Room Temperature Storage 25ºC (77ºF), excursions permitted 15-30 ºC (59-86 ºF)

Sealed (Unopened) Blister Cards + Strips	Must be used within 10 days
Opened Strips	Must be used within 3 days

Inhaler Storage:
Store at 2-25ºC (36-77ºF); excursions permitted. Inhaler may be stored refrigerated, but should be at room temperature before use.

Handling:
Before use, cartridges should be at room temperature for 10 minutes.

- Container and Closure Systems: The to-be-marketed Technosphere® Insulin (TI) Inhalation Powder / Gen2 Inhalation System includes single-use, color coded, pre-metered Cartridges that are manually placed into a re-useable, breath-powered, high resistance dry powder inhaler. Cartridges are packaged in blisters.

2 METHODS AND MATERIALS REVIEWED

2.1 LABELS AND LABELING

Using the principles of human factors and Failure Mode and Effects Analysis,[1] along with post marketing medication error data, the Division of Medication Error Prevention and Analysis (DMEPA) evaluated the following:

- Blister Labels submitted October 11, 2013 (Appendix A)
- Cartridge submitted October 11, 2013 (Appendix B)
- Foil Overwrap submitted October 11, 2013 (Appendix C)
- Carton Labeling submitted October 11, 2013 (Appendix D)
- Inhaler submitted October 11, 2013 (Appendix E)
- Inhaler Overwrap submitted October 11, 2013 (Appendix F)

[1] Institute for Healthcare Improvement (IHI). Failure Modes and Effects Analysis. Boston. IHI:2004.

- Inhaler Carton submitted October 11, 2013 (Appendix G)
- Prescribing Information submitted October 11, 2013
- Instructions for Use submitted October 11, 2013
- Human Factors/Usability Report Summary submitted October 11, 2013

2.2 PREVIOUSLY COMPLETED REVIEWS

DMEPA had previously reviewed Afrezza and we looked at the reviews to ensure all our recommendations were implemented.

DMEPA reviewed the inhaler labels, cartridges, foil pack labels, as well as carton and insert labeling for Afrezza Inhalation Powder that included an earlier inhalation device (Model D) in OSE Review #2009-2440 dated December 28, 2009.

The initial Human Factors Study, Labels and Labeling (Gen 2 Inhaler) were reviewed by DMEPA in review RCM 2010-1576 &1577, dated December 13, 2010.

Written Response sent which included DMEPA comments regarding label, labeling and human factors protocol in OSE Review #2012-2042, dated November 2, 2012.

3 HUMAN FACTORS VALIDATION USABILITY STUDY RESULTS AND EVALUATION

3.1 USABILITY STUDY OBJECTIVE

The study was conducted to determine if any aspects of the inhaler, cartridge, packaging, labeling and instruction for use lead to confusion, failures, high-risk errors, or patient safety risks. Successful validation was to be demonstrated by the absence of any pattern of use failure or difficulty.

3.2 STUDY POPULATION

The study was conducted with a total of 90 participants, with a total of 60 subjects with diabetes, ages 18-75 years old, and 30 Healthcare Providers who work with diabetes patients. All participants were representative of the user population, with three main user groups:

	User Group 1: Diabetes patients currently on Insulin	User Group 2: Diabetes patients currently on oral medication only	User Group 3: HCPs who currently work with diabetes patients	TOTAL
Orientation by CDE	N=15	N=15	N=15	N=45
Untrained	N=15	N=15	N=15	N=45
TOTAL	**N=30**	**N=30**	**N=30**	**N=90**

Group 1: Half of the participants in each of the three user groups (N=45) received a brief "walk-through" orientation from a Certified Diabetes Educator (CDE), that is consistent with the method used by Healthcare Providers (HCP) for currently marketed insulin delivery devices, as reported in MannKind's recent healthcare provider and diabetes

educator research. This orientation consisted of a CDE demonstration of the device, patient demonstration of the device, and a walk through of the IFU.

Group 2: The other half of the participants (N=45) were placed in a worst case scenario where they were untrained and received no training before administering their first assigned dose. However, these participants were free to use the supplied materials to self-educate if desired.

Across user groups 1 and 2, a gender mix known to approximate to gender distribution among diabetes patients was employed. These patients were representative of the patient profile and the study included a representative proportion of individuals with visual impairments, color blindness (or color-blind induced), and neuropathy symptoms affecting the hands.

Factor	Number of Patients
Color-Blind	N= 15 (25%)
Retinopathy	N= 35 (58%)
Neuropathy	N= 21 (35%)

3.3 STUDY DESIGN

All participants completed 3 unaided simulated administrations of three different doses (3, 6, 9, 12, 15, or 18 units). The study used two Dose Sets to assess administration of all 6 dose values. Half of the participants in the study (N=45) were assigned to Dose Set 1 (3, 12, 15 units) and the other half (N=45) were assigned to Dose Set 2 (6, 9, 18 units).

Dose Set 1	Dose Set 2
3 Units – 1 Blue	6 Units – 1 Green
12 Units – 2 Green	9 Units – 1 Blue + 1 Green
15 Units – 2 Green + 1 Blue	18 Units – 3 Green

The study was conducted in two sessions as outlined below:

Study Session 1		Study Session 2 (4-24 Hours After Session 1)	
Orientation by CDE OR Un-Trained (Supplied IFU)	Unaided Simulated Dosing Administration #1	Unaided Simulated Dosing Administration #2	Unaided Simulated Dosing Administration #3
	Context: Cartridges already at room temperature.	**Context:** Cartridges stored in refrigerator.	**Context:** Loose cartridges stored in a blood glucose meter kit.

Dose Conversion Tasks

Based on the FDA's feedback the study design also included two conversion tasks:

1) After the first unaided dose, users were asked to perform a dose conversion from AFREZZA to injected mealtime insulin based on the dose they just performed.

2) After the third unaided dose,u sers were asked to perform a dose conversion from 7 units of injected mealtime insulin to AFREZZA, which was equivalent to 9 units of AFREZZA.

3.4 RESULTS OF THE USABILITY STUDY

A. **Dose 1** occurred during Session 1 and was under the context of the medication already being at room temperature.

1. 99% (89/90) of participants successfully selected the correct type and number of cartridges and performed the inhalation process.
    - One Untrained participant's (P46) session resulted in an overdose. P46 used 3 blue 3-unit cartridges (a total of 9 units) for a 3 unit dose rather than a single cartridge. The participant became self-aware of the error after looking at the dosing chart and realized that one blue cartridge, not a strip of 3 blue cartridges, equaled 3 units. During the failure debriefing, P46 stated that he had misinterpreted that a row of 3 cartridges equaled a dose of 3 units. This participant did not repeat this error in his second and third unaided doses during the comeback session. Additionally, the participant commented they would self-correct for this error by consuming food; a common diabetes management practice.
2. 100% (90/90) of participants interacted with the inhaler in a correct manner and without any actions that would result in a loss of drug, if drug were present, prior to administration (i.e. shaking, dropping, or inverting the inhaler).

B. **Dose 2** took place during Session 2 under the context of the medication being in the refrigerator. This dose was meant to test whether participants knew to wait 10 minutes to let the medication warm to room temperature.

1. 100% (90/90) of participants successfully selected the correct type and number of cartridges for their assigned dose.
2. 100% (90/90) of participants demonstrated the knowledge to wait 10 minutes to let the cartridges warm to room temperature before inhaling their dose.
3. 100% (90/90) of participants interacted with the inhaler in a correct manner and without any actions that would result in a loss of drug, if drug were present, prior to administration (i.e. shaking, dropping, or inverting the inhaler).

- For Dose 2 we observed only one close call; P52 (Untrained Group) came close to not keeping the inhaler level once a cartridge was loaded before inhaling the assigned dose with each cartridge. When debriefed about this the participant attributed it to being left-handed and becoming familiar with the procedure. Note, the participant demonstrated in Dose 3 the ability to hold the inhaler level for her final dosing task.

C. **For Dose 3**, the context was that the participant was out to dinner and had taken loose cartridges with them in a glucose meter bag. The participant had to select the correct cartridges while being exposed to ambient noise mimicking that of a busy restaurant.

1. 98% (88/90) of participants successfully selected the correct type and number of cartridges out of the meter kit for their assigned dose.
   - One Untrained participant's (P2) trial resulted in an under dose. The participant was assigned to take 12 units, but confused the strength and color of the cartridges within the meter kit and did not reference the IFU. This resulted in the participant taking a total of 6 units (2 blue 3-unit cartridges). P2 stated she was overconfident in her knowledge of the color-coding and commented that she could not read the IFU since she forgot her reading glasses (though she had her reading glasses with her during the first session). P2 also stated that she would have never taken the cartridges out of the blister packs.
   - One Trained participant's (P38) trial resulted in an overdose. The participant was assigned 9 units but took 3 of the green 6-unit cartridges (18 units). During debrief, the (P38) stated the assigned dose was 18 units and meant to take 3 of the green 6-unit cartridges. When next prompted to select the correct cartridges for a 9 unit dose, the (P38) correctly selected 3 blue cartridges

D. Dose Conversion

Across all participants, 100% of conversion tasks (180/180) resulted in the successful conversion of either injected mealtime insulin to AFREZZA or AFREZZA to injected mealtime insulin. This demonstrates the effectiveness of the dose conversion tables located on pages 18 and 19 in the IFU. Additionally, no participants stated that they had any difficulty with any of the dose conversion tasks and 100% of participants stated they had no difficulty understanding either dose conversion table.

3.4.1 DMEPA Analysis Study Results

Two types of errors occurred during the validation study. The first type of error occurred when an untrained participant misinterpreted the contents of the blister strip (3 blue cartridges) to equal 3 units. The participant who misinterpreted the blister strip content realized the error after consulting the dosing chart. The results do not discuss whether the patient self-corrected before administering the product but having the information regarding the content of each cartridge in multiple locations in the labeling would help mitigate this type of medication errors from occurring. Blister label was revised (per DMEPA's previous comments to the Applicant) to mitigate misinterpretation errors regarding the contents of the blister strip (i.e. label each well "3 or 6 units per cartridge").

The second type of error occurred during Dose 3 scenario where the participants misinterpreted the strength of the cartridge (i.e. mixed up the color and the associated strength). One untrained participant indicated that the error was mainly due to not having her glasses and being over confident about her knowledge regarding the strength of the cartridges. The second error occurred because the participant thought the assigned dose was 18 units instead of 9 units, in which case the participant correctly selected the number of cartridges (3 green) for the 18 units. These errors occurred due to lapse in the participants' knowledge or misunderstanding of the dose assigned and not necessarily due to the design of the product or labeling.

Human Factors Validation Study results demonstrated that patients were able to safely and effectively use Afrezza in varying use conditions that would be expected in the real use environment. However, since this is a new insulin formulation and design we recommend that training be provided prior to self-administration of this product.

4 CONCLUSIONS

DMEPA concludes that, although Human Factors Validation Study demonstrated that patients are able to safely and effectively use Afrezza, since Afrezza is a new insulin formulation and design we recommend revision of the physician insert regarding training prior to patient self-administration of this product.

5 RECOMMENDATIONS

Based on this review, DMEPA recommends the following be implemented prior to approval of this NDA:

5.1 COMMENTS TO THE DIVISION

Since Afrezza is a new insulin formulation and design, DMEPA recommends revision of the physician insert regarding training prior to patient self-administration of this product.

If you have further questions or need clarifications, please contact Margarita Tossa, project manager, at 301-796-4053.

12 Page(s) of Draft Labeling have 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/

SARAH K VEE
01/30/2014

YELENA L MASLOV
01/30/2014

DGCPC/OSI CONSULT: Request for Clinical Inspections

Date: 1/3/2014

To: Thomas Moreno, Acting Division Director, DGCPC
Kassa Ayalew, M.D., Acting Branch Chief, GCPAB
Janice Pohlman, M.D., M.P.H., Team Leader GCPAB
CDEROCDSIPMOs@fda.hhs.gov
Cynthia Kleppinger, M.D.
Division of Good Clinical Practice Compliance
Office of Scientific Investigations
Office of Compliance/CDER

Through: Lisa Yanoff, M.D.
Medical Reviewer, DMEP
Ali Mohamadi, M.D.
Medical Team Leader, DMEP

From: Richard Whitehead, DMEP

Subject: **Request for Clinical Site Inspections**

I. General Information

Application#: NDA #22472
IND#:61729
Applicant: MannKind Corporation, 61 S. Paramus Road, Paramus, NJ 07652
Phone: 201-983-5143
Regulatory Point of Contact: John Bedard, Sr. Vice President, Regulatory Affairs
Regulatory Point of Contact Phone: (o) 201-983-5143/ (c) (b) (6)
Regulatory Point of Contact Email: jbedard@mannkindcorp.com

Drug Proprietary Name: Affrezza Inhalation Powder and Inhaler
Generic Drug Name: insulin human [rDNA origin]
NME or Original BLA (Yes/No): No
Review Priority (Standard or Priority): 6 month CR resubmission

Study Population includes < 17 years of age (Yes/No): No
Is this for Pediatric Exclusivity (Yes/No): No

Proposed New Indication(s): To improve glycemic control in adults with type 1 or type 2 diabetes mellitus

PDUFA: Tuesday, April 15, 2014

Action Goal Date: Tuesday, April 15, 2014
Inspection Summary Goal Date: March 21, 2014

II. Protocol/Site Identification

Include the Protocol Title or Protocol Number for all protocols to be audited. Complete the following table ***(Note: All items listed are required, to process inspection request. Failure to provide complete information will result in delay of inspection process).***

(Name,Address, Phone number, email, fax#)	Site #	Protocol ID	Number of Subjects	Indication
Franco, Denise Reiz Rua Goias, 193 Higienopolis Sao Paulo, SP 01244-030 BRA Latin America phone:55-112-711-0251 fax:55-112-711-0299 email:d9franco@terra.com.br	483	MKC-TI-175	16	A Phase 3, Multicenter, Double-blind, Placebo-controlled, Randomized Clinical Trial Evaluating the Efficacy and Safety of Technosphere® Insulin Versus Placebo in Insulin Naïve Type 2 Diabetes
Franco, Denise Reiz Rua Goias, 193 Higienopolis Sao Paulo, SP 01244-030 BRA Latin America phone:55-112-711-0298 fax:55-112-711-0299 email:d9franco@terra.com.br	483	MKC-TI-171	23	A Phase 3, Multicenter, Open-label, Randomized Clinical Trial Evaluating the Efficacy and Safety of Technosphere® Insulin Inhalation Powder Versus Insulin Aspart in Type 1 Diabetes
Korpachev, Vadym 69 Vyshgorodska Str. Kiev, UKR 4114 UKR Eastern Europe phone:38-044-431-0284 fax:38-044-430-1036 email:korpacva@yandex.ru	852	MKC-TI-171	32	A Phase 3, Multicenter, Open-label, Randomized Clinical Trial Evaluating the Efficacy and Safety of Technosphere® Insulin Inhalation Powder Versus Insulin Aspart in Type 1 Diabetes
	852	MKC-TI-175	14	A Phase 3, Multicenter, Double-blind, Placebo-controlled, Randomized Clinical Trial Evaluating the Efficacy and Safety of Technosphere® Insulin Versus Placebo in Insulin Naïve Type 2 Diabetes

(Name,Address, Phone number, email, fax#)	Site #	Protocol ID	Number of Subjects	Indication
Marquez, Farid 1490 West 49th Place Suites 205-208 Hialeah, FL 33012 USA United States phone:305-827-3335 fax:305-827-3338 email:fmarquez@psrifl.org	433	MKC-TI-175	3	A Phase 3, Multicenter, Double-blind, Placebo-controlled, Randomized Clinical Trial Evaluating the Efficacy and Safety of Technosphere® Insulin Versus Placebo in Insulin Naïve Type 2 Diabetes

III. Site Selection/Rationale

Site Information

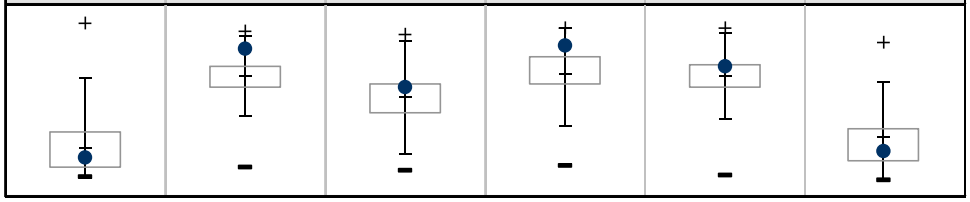
STUDY:	MKC-TI-175	**SITEID:**	433

NAME	Marquez, Farid
LOCATION	1490 West 49th Place Suites 205-208 Hialeah, FL, USA 33012
PHONE/FAX	305-827-3335 / 305-827-3338
EMAIL	fmarquez@psrifl.org

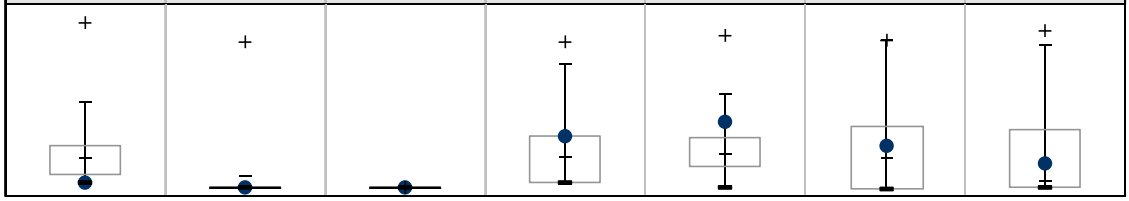
RANK	11	**FINLDISC**	0	**COMPLAINT**	1
SITE RISK	7.2	**OAI**	0	**TSLI**	2

Site Values vs. Overall Study Results

	ENROLL	TRTEFFR	SITEEFFE	EW_TRTEFFR	EW_SITEEFFE	SCREEN
Max	17	0.55	2.15	2.40	4.30	100%
Study Rate	5	-0.62	-0.37	-2.93	-1.09	35%
Min	1	-3.00	-3.30	-13.40	-12.17	5%
Site	3	0.10	0.00	0.30	0.00	25%



	NSAE	SAE	DEATH	DISCONT	PROTVIOL	INDS	EXPERIENCE
Max	8.5	0.7	0%	100%	7.8	7.7	27
Study Rate	1.3	0.0	0%	18%	1.7	1.5	1
Min	0.0	0.0	0%	0%	0.0	0.0	0
Site	0.0	0.0	0%	33%	3.3	2.3	4



Site Memo

(b) (4)

Site Information

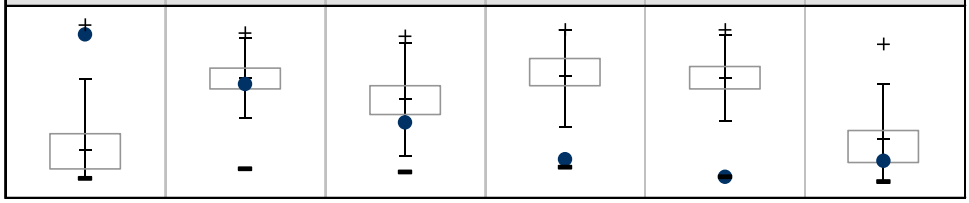
STUDY:	MKC-TI-175	SITEID:	483

NAME	Franco, Denise Reiz
LOCATION	Rua Goias, 193 Higienopolis Sao Paulo, SP, BRA 01244-030
PHONE/FAX	55-112-711-0251 / 55-112-711-0299
EMAIL	d9franco@terra.com.br

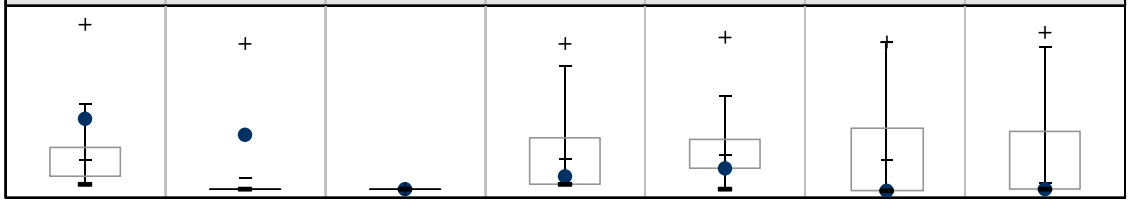
RANK	2	FINLDISC	0	COMPLAINT	0
SITE RISK	13.7	OAI	0	TSLI	3

Site Values vs. Overall Study Results

	ENROLL	TRTEFFR	SITEEFFE	EW_TRTEFFR	EW_SITEEFFE	SCREEN
Max	17	0.55	2.15	2.40	4.30	100%
Study Rate	5	-0.62	-0.37	-2.93	-1.09	35%
Min	1	-3.00	-3.30	-13.40	-12.17	5%
Site	16	-0.78	-1.35	-12.40	-12.17	19%



	NSAE	SAE	DEATH	DISCONT	PROTVIOL	INDS	EXPERIENCE
Max	8.5	0.7	0%	100%	7.8	7.7	27
Study Rate	1.3	0.0	0%	18%	1.7	1.5	1
Min	0.0	0.0	0%	0%	0.0	0.0	0
Site	3.5	0.3	0%	6%	1.1	0.0	0



Site Memo

Reiz. Involved in both studies. Ranked #2 in study 175. (Ranked #8 in study 171). High enroller. Very large weighted site efficacy effect size. High number of adverse events.

Site Information

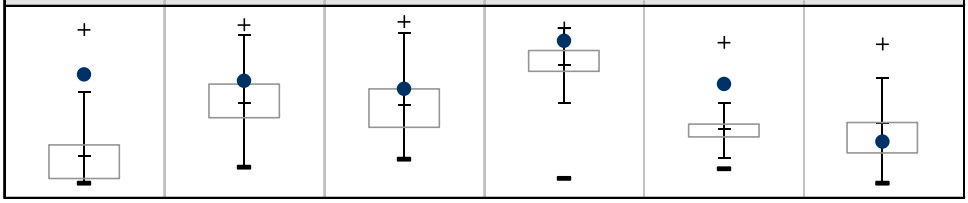
STUDY:	MKC-TI-171	SITEID:	483

NAME	Franco, Denise Reiz
LOCATION	Rua Goias, 193 Higienopolis Sao Paulo, SP, BRA 01244-030
PHONE/FAX	55-112-711-0298 / 55-112-711-0299
EMAIL	d9franco@terra.com.br

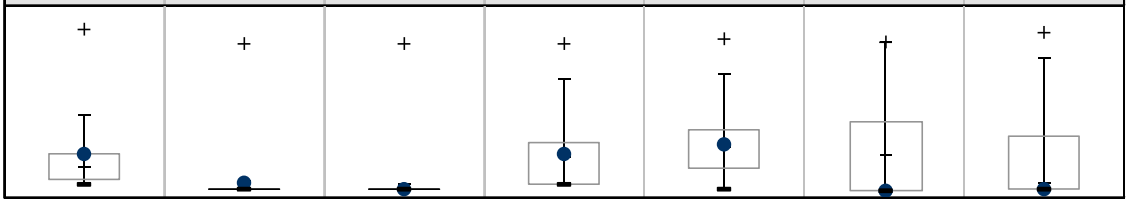
RANK	8	FINLDISC	0	COMPLAINT	0
SITE RISK	10.6	OAI	0	TSLI	3

Site Values vs. Overall Study Results

	ENROLL	TRTEFFR	SITEEFFE	EW_TRTEFFR	EW_SITEEFFE	SCREEN
Max	32	0.85	1.85	2.50	15.28	100%
Study Rate	7	-0.26	0.20	-1.75	0.92	46%
Min	1	-1.20	-0.90	-14.59	-5.73	4%
Site	23	0.05	0.50	1.08	8.44	33%



	NSAE	SAE	DEATH	DISCONT	PROTVIOL	INDS	EXPERIENCE
Max	11.0	1.0	7%	100%	6.0	6.0	27
Study Rate	1.3	0.1	0%	19%	1.6	1.4	1
Min	0.0	0.0	0%	0%	0.0	0.0	0
Site	2.2	0.0	0%	22%	1.7	0.0	0



Site Memo

Reiz. Ranked #8. Involved in both studies and ranked #2 in study 175.

Site Information

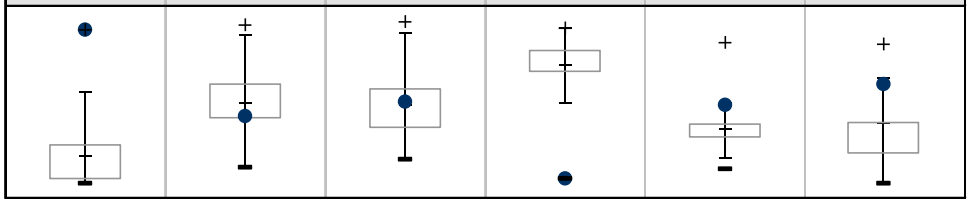
STUDY:	MKC-TI-171	SITEID:	852

NAME	Korpachev, Vadym
LOCATION	69 Vyshgorodska Str. Kiev, UKR, UKR 4114
PHONE/FAX	38-044-431-0284 / 38-044-430-1036
EMAIL	korpacva@yandex.ru

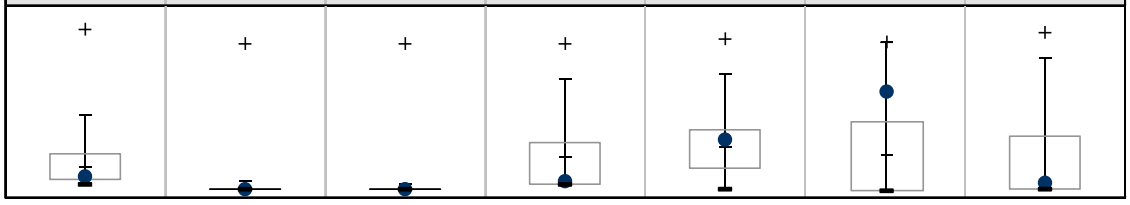
RANK	2	FINLDISC	0	COMPLAINT	0
SITE RISK	13.9	OAI	0	TSLI	3

Site Values vs. Overall Study Results

	ENROLL	TRTEFFR	SITEEFFE	EW_TRTEFFR	EW_SITEEFFE	SCREEN
Max	32	0.85	1.85	2.50	15.28	100%
Study Rate	7	-0.26	0.20	-1.75	0.92	46%
Min	1	-1.20	-0.90	-14.59	-5.73	4%
Site	32	-0.46	0.27	-14.59	4.84	73%



	NSAE	SAE	DEATH	DISCONT	PROTVIOL	INDS	EXPERIENCE
Max	11.0	1.0	7%	100%	6.0	6.0	27
Study Rate	1.3	0.1	0%	19%	1.6	1.4	1
Min	0.0	0.0	0%	0%	0.0	0.0	0
Site	0.6	0.0	0%	3%	2.0	4.0	1



Site Memo

Korpachev. Highest enroller. Ranked #2. Large site specific enrollment weighed efficacy. Ranked #8 in study 171.

Site Information

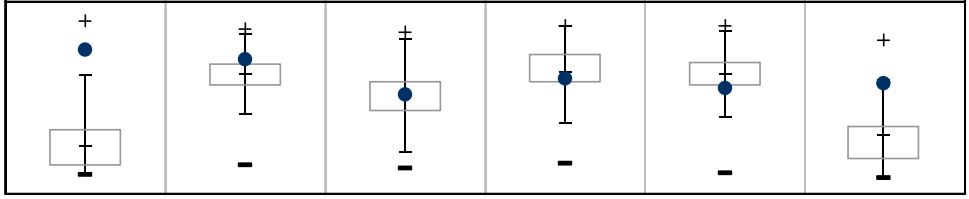
STUDY:	MKC-TI-175	SITEID:	852

NAME	Korpachev, Vadym
LOCATION	69 Vyshgorodska Str. Kiev, UKR, UKR 4114
PHONE/FAX	38-044-431-0284 / 38-044-430-1036
EMAIL	korpacva@yandex.ru

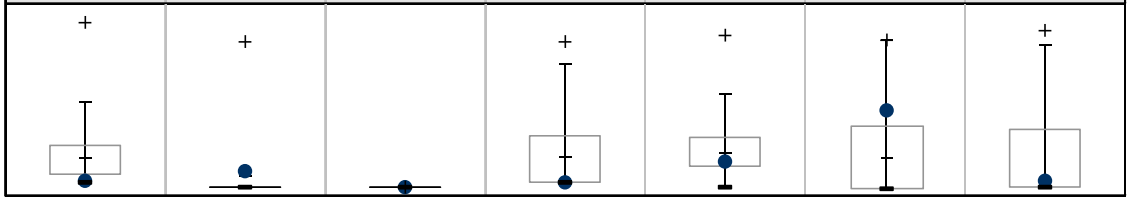
RANK	9	FINLDISC	0	COMPLAINT	0
SITE RISK	7.5	OAI	0	TSLI	3

Site Values vs. Overall Study Results

	ENROLL	TRTEFFR	SITEEFFE	EW_TRTEFFR	EW_SITEEFFE	SCREEN
Max	17	0.55	2.15	2.40	4.30	100%
Study Rate	5	-0.62	-0.37	-2.93	-1.09	35%
Min	1	-3.00	-3.30	-13.40	-12.17	5%
Site	14	-0.26	-0.39	-3.70	-2.70	70%



	NSAE	SAE	DEATH	DISCONT	PROTVIOL	INDS	EXPERIENCE
Max	8.5	0.7	0%	100%	7.8	7.7	27
Study Rate	1.3	0.0	0%	18%	1.7	1.5	1
Min	0.0	0.0	0%	0%	0.0	0.0	0
Site	0.1	0.1	0%	0%	1.3	4.0	1



Site Memo

Korpachev. Ranked #9. Ranked #2 in study 171.

Summarize the reason for requesting OSI consult and then complete the checklist that follows your rationale for site selection. Medical Officers may choose to consider the following in providing their summary for site selection.

Rationale for OSI Audits

- *A specific safety concern at a particular site based on review of AEs, SAEs, deaths, or discontinuations*
- *A specific efficacy concern based on review of site specific efficacy data*
- *Specific concern for scientific misconduct at one or more particular sites based on review of financial disclosures, protocol violations, study discontinuations, safety and efficacy results*

  *See*** at end of consult template for OSI's thoughts on things to consider in your decision making process*

Domestic Inspections:

Reasons for inspections (please check all that apply):

- ✓ Enrollment of large numbers of study subjects
- ✓ High treatment responders (specify): Korpachev and Reiz sites
- ____ Significant primary efficacy results pertinent to decision-making
- ____ There is a serious issue to resolve, e.g., suspicion of fraud, scientific misconduct, significant human subject protection violations or adverse event profiles.
- ____ Other (specify):

International Inspections:

Reasons for inspections (please check all that apply):

- ✓ There are insufficient domestic data
- ____ Only foreign data are submitted to support an application
- ____ Domestic and foreign data show conflicting results pertinent to decision-making
- ____ There is a serious issue to resolve, e.g., suspicion of fraud, scientific misconduct, or significant human subject protection violations.
- ____ Other (specify) (Examples include: Enrollment of large numbers of study subjects and site specific protocol violations. This would be the first approval of this new drug and most of the limited experience with this drug has been at foreign sites, it would be desirable to include one foreign site in the DSI inspections to verify the quality of conduct of the study).

Five or More Inspection Sites *(delete this if it does not apply)*:
We have requested these sites for inspection (international and/or domestic) because of the following reasons: *state reason(s) and prioritize sites*.

Note: International inspection requests or requests for five or more inspections require sign-off by the OND Division Director and forwarding through the Director, DGCPC.

IV. Tables of Specific Data to be Verified (if applicable)

If you have specific data that needs to be verified, please provide a table for data verification, if applicable.

Should you require any additional information, please contact at 301-796- or at 301-796- .

Concurrence: (as needed)

_____ Medical Team Leader
_____ Medical Reviewer

_____ Division Director (for foreign inspection requests or requests for 5 or more sites only)

******Things to consider in decision to submit request for OSI Audit***

- *Evaluate site specific efficacy. Note the sites with the greatest efficacy compared to active or placebo comparator. Are these sites driving the results?*
- *Determine the sites with the largest number of subjects. Is the efficacy being driven by these sites?*
- *Evaluate the financial disclosures. Do sites with investigators holding financial interest in the sponsor's company show superior efficacy compared to other sites?*
- *Are there concerns that the data may be fraudulent or inconsistent?*
    - *Efficacy looks too good to be true, based on knowledge of drug based on previous clinical studies and/or mechanism of action*
    - *Expected commonly reported AEs are not reported in the NDA*
- *Evaluate the protocol violations. Are there a significant number of protocol violations reported at one or more particular sites? Are the types of protocol violations suspicious for clinical trial misconduct?*
- *Is this a new molecular entity or original biological product?*
- *Is the data gathered solely from foreign sites?*
- *Were the NDA studies conducted under an IND?*

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
01/03/2014

DEPARTMENT OF HEALTH AND HUMAN SERVICES **MEMORANDUM**

Food and Drug Administration
Office of Device Evaluation
10903 New Hampshire Avenue
Silver Spring, MD 20993-0002

DATE: **12/13/2010**
FROM: QuynhNhu Nguyen, Biomedical Engineer, DAGID/ARDB 1/23/2012
THROUGH: Ron Kaye, Human Factors and Device Use-Safety Team Leader, DAGID/GHDB
Molly Story, PhD, Human Factors and Accessible Medical Technology Specialist, DAGID 1/23/2012
TO: Lex Schultheis, Branch Chief, DAGID/ARDB
Rachel Hartford, CDER/OND/ODEII/DMEP
SUBJECT: **NDA 022472, Afrezza, MannKindGen2 Insulin Delivery System**
Project Manager: Rachel Hartford
CTS Tracking: CON120445, Human Factors/Usability Review

Review Summary and Recommendation:

Per your request, I have reviewed the Human Factors information provided in the applicant's type C meeting request dated 18 November 2011. The meeting package includes Human Factors Requests (10 – 13) in 18 January 2011 FDA Letter, and supporting documentation for the meeting request, which written response has been granted in place of a face-to-face meeting.

The following pages are organized by the Human Factors questions (10-13). For each question, you will find the original Human Factors question, summary of MannKind's proposed response, MannKind's follow up question(s), and FDA's response to follow up question(s).

Overall, this reviewer disagrees with the 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. The reviewer suggests that the study protocol be modified to address the risk of dosing error. The reviewer also recommends that product labeling including instructions for use (IFU) and extent of training to be provided during the validation study should be representative of actual use. In addition, the reviewer requests that Mannkind provide additional information that addresses two deficiencies identified from the review of the revised protocol.

Review of Afrezza's Response to Human Factors Deficiencies

Human Factors Request in 18 January 2011 FDA Letter– Item # 10
You have proposed changes to the Instructions for Use (IFU) and cartridge strength label based on patient use errors identified in your completed usability study. Perform a new usability study to demonstrate that these changes minimize the previously identified user errors without introducing new risks. We strongly encourage you to submit the protocol for review prior to implementation of the study. This study should test representative device users, with the final design of the Gen2 inhaler and IFU. This study should also 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).

Summary of MannKind's Response to Item # 10:
Modifications to the IFU was made and to evaluate the effectiveness of this mitigation, additional formative studies were conducted. Formative testing indicates that there are no patterns of residual use error and no new risks have been introduced with the updated IFU and cartridge strength labeling. Dosing errors resulting from confusion between the labeled drug content of the cartridges (10 units or 20 units) and the approximate subcutaneous insulin dose (4 or 8 units) have not been observed in the representative device users (including current subcutaneous insulin users) during any of the formative testing.

Additional input was solicited from healthcare providers and patients indicated some concerns that the current labeling may lead to confusion for the health care providers. MannKindstates that they are continue to evaluate alternative labeling (prominently depicting the deliverable insulin dose of 4 and 8 units) to facilitate the safe and effective use of the proposed product.

MannKind's Follow Up Question to FDA – Question 10, Part 1
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's Response to MannKind's Question 10, Part 1:
The Agency agrees 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 right cartridge has to be demonstrated such that the intended users can understand the differences 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 and 20 units of insulin, which match with the amount of insulin that is contained in the 10U and 20U cartridges but not the corresponding subcutaneous insulin dose (4 units and 8 units). The Agency believes that the prescribed dose may be different than the 10U and 20U 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. Therefore, please 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.

MannKind's Follow Up Question to FDA – Question 10, Part 2

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's Response to MannKind's Question 10, Part 2:

Regarding the proposed approach for evaluating alternative labeling, the Agency believes that 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 the health care providers. It is also possible that the labeling may lead to confusion for the patient user group. The Agency recommends that you 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. You should also validate the product labeling to demonstrate that the patient users will be able to successfully understand and follow them 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 on any wording that they found confusing, misleading or incomplete.

Human Factors Request in 18 January 2011 FDA Letter– Item # 11

11. Your usability study did not test whether patients can correctly calculate dosing of insulin when converting from subcutaneous prandial insulin to Afrezza and vice versa. Because patients may need to sometimes switch from Afrezza to subcutaneous insulin (e.g., on sick days) or from subcutaneous insulin to Afrezza (e.g., upon initiating Afrezza, after sick days have resolved), your new usability study should test whether patients can accurately convert between inhaled and subcutaneous insulin doses. If insulin dose conversion charts are needed in product labeling, you should test that patients can adequately use these charts.

Summary of MannKind's Response to Item # 11

MannKind believes that switching insulin formulations is best performed under the supervision of a health care professional. It is MannKind's intent to guide patients to consult with a health care provider if they need to switch insulin formulations and not recommend patients convert insulin formulations on their own. The instruction for use (IFU) has been updated to reflect this guidance and insulin dose conversion charts will be provided in the prescribing information for use only by a health care provider.

MannKind's Follow Up Question to FDA – Question 11

Therefore, 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's Response to MannKind's Question 11

While the dose conversion is performed under the supervision of a healthcare professional, the Agency still has concerns about potential patient confusions 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 provide specific dosing instructions. These patients would be at home, and be using the device for the first time with potential access to both Afrezza inhalation device, and other subcutaneous insulin delivery devices. The Agency is most concerned with patients who are switching from subcutaneous to Afrezza inhalation delivery device, and those that have variable dosing/sliding scale. 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, be able to perform a conversion, and be able to select the correct cartridge(s) for the prescribed dose.

Human Factors Request in 18 January 2011 FDA Letter– Item # 12

12. You state that referring to the IFU will mitigate many of the user errors identified in the completed usability study. However, many of these errors occurred because the users did not recognize or were not aware of the IFU. Therefore, your follow-up usability study should demonstrate that reference to the IFU in its final version is an effective risk mitigation strategy.

Summary of MannKind's Response to Item # 12:

MannKindproposes that the patients undergo an orientation for proper use in the final Human Factors/usability validation study. The orientation provided by the health care provider will include a review of the IFU prior to any dosing with the AFREZZA inhalation system.

MannKind's Follow Up Question to FDA – Question 12

Therefore, the Summative Human Factors Usability Validation study will incorporate patient orientation including reference to the IFU. Does the agency agree?

FDA's Response to MannKind's Question 12

Please note that FDA considers the orientation sessions as part of product training. Please refer to response to Question 13 for product training.

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

Human Factors Request in 18 January 2011 FDA Letter– Item # 13

13. Provide a detailed description of the user training program you propose for your marketed product. Include clarifications with rationale as to whether all patients who are prescribed Afrezza will be trained. If training will not be consistently provided to prescribed users, provide an estimate of the likely proportion of untrained users to the entire user population, and reflect this proportion in your usability study to ensure that your study includes the expected untrained user population.

Summary of MannKind's Response to Item # 13:

MannKind conducted an independent survey of Healthcare Professionals regarding current practices for patients starting insulin. As a result, MannKind expects that all patients starting AFREZZA will receive an orientation to the device and instruction by a health care professional. As with all insulin devices, this instruction will include a demonstration of the device and a review of the IFU.

MannKind's Follow Up Question to FDA – Question 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's Response to MannKind's Question 13

The Agency recommends that the training ("orientation") that will be provided to the test participants is representative of the training that patients will receive in actual use. In addition, you stated that you expect dose conversion is to be performed under the supervision of a healthcare professional. Please revise the protocol to include this step in patient orientation session.

Additional FDA Comments on Revised Human Factors/Usability Validation Study Protocol dated November 2011:

1) **You state that participants will be assigned to receive one of the two doses (10U and 30U). Please address the following:**
    a. **Please include 20U since it is another dose, and it comes in a different cartridge color.**
    b. **Please clarify how your study design addresses situations where participants have sliding scale (variable dosing).**
    c. **Once the participants have been prescribed to either 10U or 20U, it is assumed that those participants have a fixed dose. For this scenario, please 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. **Please provide a copy of the prescription form that the patient will read prior to selecting the cartridge(s).**
    e. **Please discuss how the simulated prescribed dose of 10U and 30U reflect the actual dose, and relate to the subcutaneous insulin amount.**
2) **You state that 6 of the 30 participants will be color-blind or a colorblind-induced condition. The Agency understands that diabetic patients have medical symptoms such as retinopathy and neuropathy, and these symptoms are progressively worsening over time. Therefore, each medical symptom 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 neuropathy.**

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

01/24/2012

On behalf of QuynhNhu Nguyen, Biomedical Engineer
DAGID/ARBD

Food and Drug Administration
10903 New Hampshire Avenue
Document Mail Center - WO66-G609
Silver Spring, MD 20993-0002

ODE Consult Review

Date: January 12, 2011

To: Rachel Hartford, CDER/OND/ODEII/DMEP

From: Chan Lee, M.E, CDRH/ODE/DAGID/ARDB 1/12/2012

Through: Anthony Watson, M.S, MBA, Division Director, DAGID 1/13/12
Kwame Ulmer, M.S, Deputy Director, Science and Policy 1/13/12
Anya Harry, M.D, Deputy Director, Clinical (AH) 1-13-12
Lester Schultheis, M.D, Ph. D, Branch Chief, ARDB 1/12/12

Sponsor: MannKind Corporation
61 South Paramus Rd.
Paramus, NJ 07652

Product Name: Afrezza (insulin human [rDNA origin]) Inhalation Powder and Inhaler

Subject: NDA022472 Gen2C Type C Background Information Package

Summary

The sponsor requested comments on their proposed response to our Complete Response letter dated January 18, 2011. This reviewer believes that the data for vibration testing and mouthpiece retention testing identify risks which may affect drug efficacy. This reviewer recommends that the clinical review team determine whether the data warrants further action.

NDA History

History of NDA submission 022472 by MannKind Corporation is shown in Table 1.

Table 1 - NDA History

Innitiator	*Action*	*Date*	*Notes*
MannKind	Submitted Afrezza NDA 022472	March 16, 2009	Original Application
FDA	Complete Response Letter	March 12, 2010	Additional Information with ARDB deficiencies
MannKind	Requested End-of-Review Meeting	March 26, 2010	
All	EOR #1 Meeting at FDA	June 9, 2010	
MannKind	Complete Response	June 29, 2010	Changed inhaler design from MedTone to Gen2C
FDA	Complete Response Letter	January 18, 2011	Additional Information with ARDB deficiencies
MannKind	Requested EOR Meeting	February 11, 2011	
All	EOR #2 Meeting at FDA	May 4, 2011	ARDB requested human factors and device performance
MannKind	Request for Type C Meeting	October 7, 2011	Clarification on CR dated 1/18/2011
MannKind	Request for Type C Background Information	November 18, 2011	Pre-meeting response

Review of Sponsor's Proposed Response

This reviewer's analysis of sponsor's proposed response to our Complete Response letter dated January 18, 2011 is as follows. Please note that deficiency #6 was not part of ODE comments in previous memo. However, this reviewer believes that the data provided in the sponsor's response package affect device performance.

Deficiency #6: Misuse Conditions Testing

The Agency requested the sponsor to provide emitted dose and aerodynamic particle characterization under misuse conditions. The sponsor provided emitted dose and particle characterization under drop and vibration conditions. For drop testing, the sponsor dropped the device under test (DUT) from 1 meter height. For vibration testing, the sponsor shook the device in all three axes with both vertical and horizontal orientation as shown in Figure 1. The sponsor shook the device two inches at 0.1 second cycle or 10Hz. Test data for 10U and 20U inhaler is shown in Figure 2 and Figure 3, respectively.

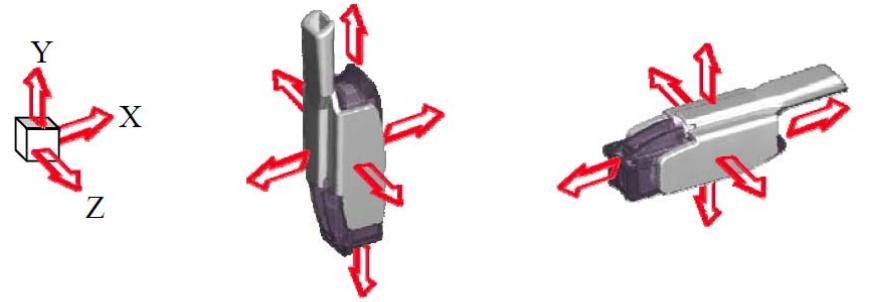


Figure 1 – Shake Testing Configurations

Figure 2 - Emitted Dose for 10U Inhaler after Drop and Shake Testing

Figure 3 - Emitted Dose for 20U Inhaler after Drop and Shake Testing

In both graphs, the sponsor provided target emitted dose of (b) (4) with +/- 25% limits. This reviewer recommends the clinical review team to evaluate whether these values are acceptable according to drug efficacy.

The worst case condition for both 10U and 20U inhaler was for device in vertical orientation and shook along the x-axis. For the 10U inhaler, the device held in both orientation and shook along the z-axis did not meet performance limits.

With the assumption that the target and limits are within drug efficacy, the vibration testing demonstrated that the proposed device may not be adequate. 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 a backpack during walking. The sponsor 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 dropped or shaken. In such conditions, it may be appropriate that the patient be prepared for alternative actions. This includes, but is not limited to: testing for blood glucose level after using the device; and access to other forms of insulin dosing such as insulin injection. This reviewer recommends that the clinical review team determine whether such labeling and precautionary steps are appropriate.

Deficiency #8: Storage Temperature in Labeling

The Agency requested the sponsor to revise labeling with recommended storage temperature from actual testing. The sponsor stated that they revised the labeling to state 2 to 25 degrees Celcius. The actual test condition was 5 to 25 degrees Celcius. The sponsor justified the lower limit of 2 degrees Celcius by citing USP refrigerated storage condition which allows +/-

3 degrees Celcius from actual test condition. This reviewer believes that the sponsor met USP standards and provided adequate labeling.

Deficiency #9: Mouthpiece Retention Testing

The Agency requested the sponsor to provide test data for mouthpiece retention of insulin under shelf-life and simulated use. The sponsor provided data of insulin deposition as shown in Figure 4. Please note that the insulin deposition shown in the y-axis is the total amount for eight 20U inhalers that were tested. The graph shows that the total insulin deposition during the initial days under worst case condition is about (b) (4) units. For a single 20U inhaler at this worst case condition, the mouthpiece can retain about (b) (4) units of insulin. Furthermore, the amount of total insulin deposition dropped noticeably after several days. For example, after 9 days of use, the total insulin deposition is about (b) (4) units. For a single 20U inhaler, this is about (b) (4) units of insulin. The difference between the initial days and at day 9 is about (b) (4) units. This reviewer believes that this drop in insulin deposition may increases the risk of variability in the total emitted dose per each device use.

Please note that the sponsor provided test data for only the 20U inhaler. This reviewer believes that the sponsor should provide test data for the 10U inhaler.

This reviewer recommends that the clinical review team determine whether the amount of insulin deposition during the initial days of use, as well as the noticeable drop in the deposition amount, is within the acceptable limits for drug efficacy.

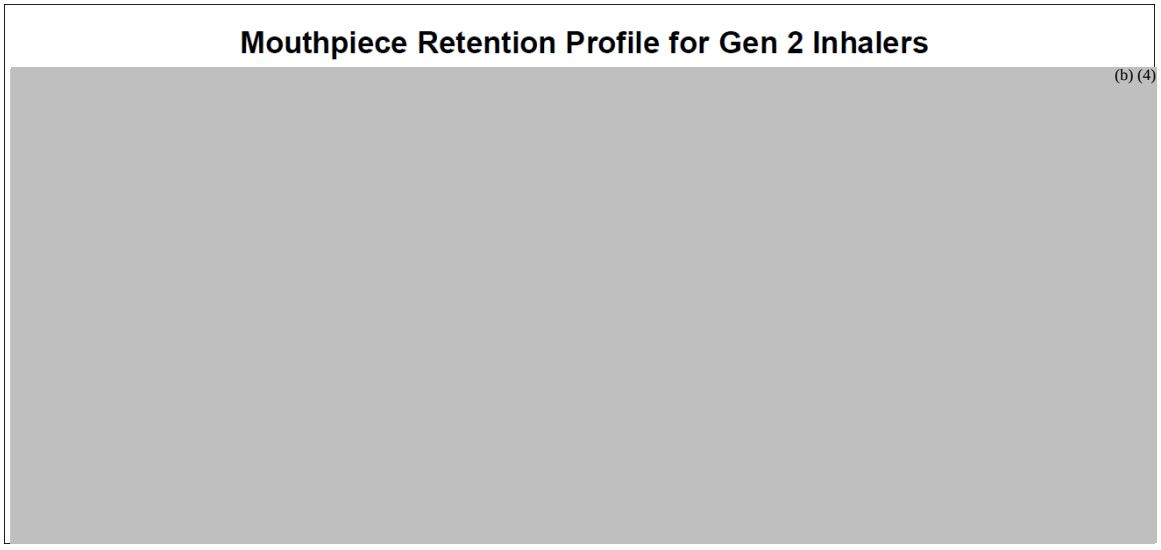


Figure 4 – Mouthpiece Retention for 20U Inhaler

Deficiencies #10 to #13: Human Factors

This reviewer defers these deficiencies to the human factors reviewer for comments.

Deficiency #14: Prescription Use in Labeling

The Agency requested the sponsor to included prescription device statement in the labeling. The sponsor stated that they will include the recommended statement in the labeling. This reviewer believes that the response is adequate.

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

01/24/2012

On behalf of Chan Lee, M.E.
CDRH/ODE/DAGID/ARDB

DEPARTMENT OF HEALTH AND HUMAN SERVICES MEMORANDUM

Food and Drug Administration
10903 New Hampshire Avenue
Document Mail Center - WO66-G609
Silver Spring, MD 20993-0002

ODE Consult Review

Date: April 8, 2011

To: Rachel Hartford, CDER/OND/ODEII/DMEP

From: Chan Lee, M.E, CDRH/ODE/DAGID/ARDB

Through: Anthony Watson, M.S, MBA, Division Director, DAGID 4/8/11
Kwame Ulmer, M.S, Deputy Director, Science and Policy
James Robotham, M.D, Deputy Director, Clinical 04/08/11
Lester Schultheis, M.D, Ph. D, Branch Chief, ARDB 4/8/11

Sponsor: MannKind Corporation
61 South Paramus Rd.
Paramus, NJ 07652

Product Name: Afrezza (insulin human [rDNA origin]) Inhalation Powder and Inhaler

Subject: NDA022472 Gen2C End-of-Review Meeting Package dated March 15, 2011

Summary

On March 23, 2011, CDER consulted CDRH for review of MannKind End-of-Review Meeting Package dated March 15, 2011. In the meeting briefing document, the sponsor proposed two new randomized, controlled phase 3 trials to evaluate efficacy and safety of Technosphere® Insulin (TI) inhalation powder (AFREZZA®) treatment using the Gen2C device compared to treatment with an approved injected short acting insulin. The sponsor provided seven questions with respect to the proposed clinical trials. One question was device related and addressed patient use and device robustness. We agree with the sponsor's proposed evaluation. However, we recommend that the sponsor provide additional information in their report. Furthermore, the sponsor should address all device related deficiencies in our Complete Response letter dated January 18, 2011.

Sponsor Question

In Section 10.4 of the meeting briefing document dated March 15, 2011, the sponsor provided the following question with respect to patient use and device robustness.

> *In the proposed trials (MKC-TI-171 and MKC-TI-172), 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?*

Our response to the sponsor's question is as follows.

- We agree with the proposed evaluation of device robustness if the non-complaint related devices that have been previously evaluated are identical to the Gen2C inhalers that will be distributed in the two proposed clinical trials.
- However, if the sponsor made any modifications to the previously evaluate devices, then the sponsor should provide complete evaluation of the new devices.
- For each complaint and adverse event in the sponsor's full summary report, we recommend that the sponsor provide the following additional information: root cause analysis; Failure Mode and Event Analysis (FMEA); mitigation plan; and verification and validation testing.

Additional CDRH Comments

The sponsor did not comment on the five device related deficiencies in our Complete Response letter dated January 18, 2011. A summary of the deficiencies are as follows.

8. *Storage condition specification in labeling*
9. *Mouth piece retention testing for* (b) (4)
10. *Human factors usability study*
11. *Human factors usability study*
12. *Human factors usability study*
13. *Training program*
14. *Prescription use only statement in labeling*

The sponsor's response to these deficiencies may affect the functionality of the Gen2C inhaler. Specifically, we are concerned with the use errors that were identified in the previous human factors studies. We recommend that the sponsor analyze and evaluate these use errors, implement effective mitigation plan, and re-evaluate the device in additional human factors studies. In addition, we recommend that the sponsor clarify the level of training provided in

the human factor studies and how this training reflects the actual training provided in the clinical trial.

CDRH comments that may be shared directly with the sponsor

1. We agree with your proposed evaluation of device robustness if the non-complaint related devices that have been previously evaluated are identical to the Gen2C inhalers that will be distributed in the two proposed clinical trials. However, if you make any modifications to previously evaluate devices, then you should provide complete evaluation the new devices. Furthermore, for each complaint and adverse event 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.

2. 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.

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

05/24/2011

On behalf of Chan Lee, M.E.
CDRH/ODE/DAGID/ARDB

Department of Health and Human Services
Public Health Service
Food and Drug Administration
Center for Drug Evaluation and Research
Office of Surveillance and Epidemiology

PATIENT LABELING REVIEW

Date:	January 5, 2011
To:	Mary Parks, M.D. Division Director **Division of Metabolism and Endocrinology Products (DMEP)**
Through:	Sharon R. Mills, BSN, RN, CCRP Senior Patient Labeling Reviewer **Division of Risk Management (DRISK)** Barbara Fuller, RN, MSN, CWOCN Patient Labeling Reviewer **Division of Risk Management**
From:	Latonia M. Ford, RN, BSN, MBA Patient Labeling Reviewer **Division of Risk Management**
Subject:	DRISK Review of Patient Labeling (Medication Guide and Instructions for Use)
Drug Name(s):	Afrezza (insulin monomer human [rDNA origin inhalation]) Inhalation Powder) and Afrezza Inhaler
Application Type/Number:	NDA 22472
Applicant/sponsor:	MannKind Corporation
OSE RCM #:	2009-593

The Division of Metabolism and Endocrinology Products requested that the Division of Risk Management (DRISK) review the proposed patient labeling for the New Drug Application (NDA) 22472, submitted by MannKind Corporation on June 28, 2010 for Afrezza (insulin monomer human [rDNA origin inhalation]) Inhalation Powder and Afrezza Inhaler.

This submission will receive a Complete Response (CR) letter and DMEP does not plan to address labeling during this review cycle. This memo serves to close-out the consult request for Afrezza (insulin monomer human [rDNA origin inhalation]) Inhalation Powder) and Afrezza Inhaler NDA 22472.

Please let us know if you have any questions.

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

/s/

LATONIA M FORD
01/05/2011

SHARON R MILLS
01/05/2011

MEMORANDUM

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

DATE: December 27, 2010

TO: Mary H. Parks, M.D.
Director, Division of Metabolism & Endocrinology Products (HFD-510)
Office of New Drugs

FROM: Abhijit Raha, Ph.D., Pharmacologist
Division of Scientific Investigations (HFD-48)

THROUGH: Martin K. Yau, Ph.D. Martin K. Yau 12/27/10
Acting Team Leader - Bioequivalence
GLP & Bioequivalence Branch
Division of Scientific Investigations (HFD-48)

SUBJECT: Review of EIR Covering NDA 22-472, Afrezza™ (insulin human [rDNA origin] inhalation powder) and inhaler, 10 units and 20 units strength, sponsored by MannKind Corporation

At the request of the Division of Metabolism and Endocrinology Products (DMEP), the Division of Scientific Investigations (DSI) audited the clinical portion of the following bioequivalence study.

Study Number: MKC-TI-142

Study Title: "A Phase 1, Open-Label, Randomized, Crossover Clinical Trial in Healthy Normal Volunteers to Evaluate the Bioequivalence of Technosphere® Insulin Inhalation Powder Administered Using the Gen2C Inhaler Compared to a MedTone® Inhaler Model C and Dose Equivalence of Technosphere® Insulin Inhalation Powder of Two 10 U Doses Versus One 20 U Dose Using the Gen2C Inhaler"

Clinical Site: Charles River Clinical Services Northwest, Inc., Tacoma, WA USA

Following the audit of the clinical records at Charles River Clinical Services Northwest, Inc. (Nov 30-Dec 3, Dec 6-10, Dec 14, and Dec 17 of 2010), a one-item Form FDA-483 with three sub-parts **(Attachment 1)** was issued. DSI has not received the firm's response to the 483 observation. DSI will evaluate the response when received. The Form FDA-483 observation **(in bold below)**, and our evaluation of the observation and its three subparts follow.

An investigation was not conducted in accordance with the signed statement of investigator and investigational plan.

a. **There was no documentation that the blister packs containing Gen2C and MedTone cartridges with Technosphere Insulin Inhalation Powder were removed from refrigeration and placed at room temperature for at least 60 minutes before administration of the investigational medicinal product.**

   Specifically, the protocol for study MKC-TI-142 states that blister packs for the Gen2C and MedTone cartridges should be removed from a secured area at the clinical site that is refrigerated at 2°C to 8°C and placed at room temperature for at least one hour prior to administration.

   The biopharmaceutics reviewer should evaluate whether possible non-equilibration to room temperature affected study outcomes.

b. **Blood samples for Pharmacokinetic/Pharmacodynamic evaluation were not collected at protocol-specified collection time points for seven of twenty five subjects reviewed.**

   Pharmacokinetic (PK) samples were not collected according to protocol schedules for the subjects and times listed in **Attachments 1 and 2.** A list of

Randomization numbers applicable to this study is provided in **Attachment 3.**

Because pharmacokinetic calculations were adjusted for the missing PK samples, this observation should not affect study data quality, integrity or bioequivalence outcomes.

c. Blood samples for Pharmacokinetic/Pharmacodynamic evaluation were collected at least one minute after protocol specified time points for 23 out of the 25 subjects reviewed.

Specifically, 71 samples were collected one to eight minutes after the protocol specified time points for the subjects and times listed in **Attachments 1 and 2.**

The OCP Reviewer should determine if pharmacokinetic calculations were adjusted for these deviations by using the actual blood sampling times. This observation should not affect study data quality, integrity or bioequivalence outcomes if actual blood sampling times were used.

Conclusion:

After a review of the inspectional findings, DSI recommends that the data generated at Charles River Clinical Services Northwest, Inc. (Tacoma, WA) for study MKC-TI-142 should be accepted for review.

After you have reviewed this transmittal memo, please append it to the original NDA submission.

Abhijit Raha, Ph.D.

Final Classification:

Charles River Clinical Services Northwest, Inc. - VAI (Clinical Site)

(FEI Number: 3002998793)

cc: DARRTS

CDER DSI PM TRACK
DSI/Ball/Haidar/Yau/Raha/Ead/CF
HFD-510/Mary H. Parks (Division of Metabolism and Endocrinology Products, DMEP)
HFD-510/Rachel Hartford (DMEP)
HFR-PA3540/Maria Kelly-Doggett
HFR-PA350/Carol Gripp (BIMO)
HFR-PA350/Celeste M. Corcoran (DIB)
Draft: AR 12/27/2010
Edit: MFS 12/27/2010; MKY 12/27/2010
DSI: 6147; O:\BE\EIRCover\22472 cha.afr.doc
FACTS: 1236671

Attachments

1: Form FDA-483
2: Blood sampling deviations
3: Randomization of treatments for study MKC-TI-142

13 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/

ABHIJIT RAHA

12/27/2010

Dr. Martin K. Yau, Acting Team Leader, Bioequivalence Group, signed the original paper copy of this document on December 27, 2010.

DEPARTMENT OF HEALTH AND HUMAN SERVICES **MEMORANDUM**

Food and Drug Administration
Office of Device Evaluation
10903 New Hampshire Avenue
Silver Spring, MD 20993-0002

DATE: **12/8/2010**
FROM: QuynhNhu Nguyen, Biomedical Engineer, DAGID/ARDB
THROUGH: Ron Kaye, Human Factors and Device Use-Safety Team Leader, DAGID/GHDB
TO: Melanie Choe, Biomedical Engineer/Scientific Reviewer, DAGID/ARDB
SUBJECT: **Gen2 Insulin Delivery System**
Human Factors/Usability Review

Per your request, I have reviewed information provided in the applicant's response.

Evaluation of Manufacturer Human Factors/Usability Testing Activities – 1st Review

Review Materials

- Summative Usability Test of Gen2 Insulin Delivery System, Final Test Plan
- Instructions for Use
- Risk Assessment, dFMEA

Human Factors Review

The applicant provided in this test plan the following:

- Overall introduction to the usability testing,
- Test methodology including testing materials, environment, set-up, participants, test session, data collection and analysis, reporting
- Risk prioritization and identification
- Appendices A-G contain screening forms, informed consent, directed tasks, post-test interview, user error check list, tentative test schedule, potential distractions, and risk analysis rating scales

Mankind anticipates recruiting a total of 30 participants, and expects that at a minimum 25 participants can complete the testing should they have "no-shows" or cancellations. The applicant plans to use the following tools to simulate deficiencies that might exist in the patient population. These tools include vision blurring glasses to simulate visual impairments, variantor dichromatic spectacles to simulate dichromatic vision color deficiencies, noise-reducing headphones/earplugs to simulate auditory system disorders.

The applicant states that Gen2 is a prescription device that some users might learn to use by working with diabetes nurse educator and/or physician. However, some users might not receive such training, and therefore, the test participants will not receive training before interacting with the device.

For each participant, the test set-up includes a test administrator, who will sit beside the participants while they interact and perform tasks using the Gen2 delivery system. A second staff member will document test data while sitting at a table about 10 feet from the participant, or in an adjacent observation room (if testing in a focus group facility). The applicant also plans to introduce distractions while the participants performing the tasks. Prior to participants performing tasks, the applicant will provide a brief review of the Gen2 delivery system.

The test sessions will be video-taped, and photographed to analyze the precursory activities and consequences of any observed use errors or notable participants interactions. To support validation, the applicant will document task completion, observed use errors, participants' subjective responses, and test observers comments. To support commercial interests, the applicant plans to collect and evaluate data relate to task times, participants comments, ease of use rating, and system strengths and shortcomings.

Appendix C provides a list of directed tasks that the test participants will perform. Appendix D provides a list of questions that will be asked of the participants after the usability testing. Appendix E provides a list of user error checklist.

Human Factors Review Notes

There are several components of the test plan that appear adequate. These components include the number of test participants, test set up and environment, and documents that will be used to support validation. However, there are several components of the test plan for which the applicant will need to provide additional information. These components are noted individually below.

It should be noted that in the introduction section (page 3), the applicant indicates that the testing will focus on high-risk use scenarios and use errors identified during prior analyses. However, in Appendix C, Directed Tasks, the applicant stated that participants will perform all tasks supported by the delivery system and no tasks have been excluded from the usability study. Based on this approach, the applicant concluded that there is need to order the tasks based on their risks-related priority. Furthermore, the applicant provides two high priority use-related risks associated with two user tasks. These tasks are: (1) selecting cartridge(s) of correct dosage; and (2) insert a cartridge into the inhaler.

It should be noted that the high-risk use scenarios are not clearly described in the test plan. Furthermore, while the applicant indicated that all tasks supported by the system, and that there is no need to order the tasks based on their risks-related priority, it should be pointed out that the purpose of prioritizing the tasks is three-fold: (1) to develop conditions/use scenarios for which inadequate performance on these tasks would manifest while users conducting these specific tasks, (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.

The directed tasks list and the instructions for use do not have any information that correlates with a high-use-related risk associated with users selecting cartridge(s) of correct dosage. It is not clear how this user task will be evaluated.

While the applicant indicates that the use error checklist has been developed based on prior analyses, and this approach has some merit in evaluating anticipated use errors, it is not clear how the applicant plans to evaluate unanticipated use errors, or unexpected failures.

Furthermore, the applicant also states that a brief review of the Gen2 delivery system will be provided to the test participants. It is not clear if this represents a realistic approach for devices that will be marketed. In other words, it is not clear if all users of the product will receive a brief review of the system, and it is not clear if this overview will be part of education/training postmarket. It should be noted that the applicant indicates Gen2 is a prescription device that some users might learn to use by working with diabetes nurse educator and/or physician. However, some users might not receive such training, and therefore, the test participants will not receive training before interacting with the device. While this might represent "worse case", the applicant will need to clarify if this represents a realistic approach for the product's usage postmarket. Additionally, it is not clear if diabetes nurse educator and/or physicians are anticipated to use the product.

Regarding data collection and analysis, it is not clear how the applicant defines success and failure of individual tasks, and how they plan to evaluate use errors to support human factors validation. Furthermore, the applicant intends to measure task completion times, and use ease of use rating. While the applicant states that these data will be used to support commercial interests, the applicant should be noted that as part of a human factors validation, subjective data collected from test participants to evaluate and understand how the users committed use errors are necessary to support meaning interpretation of test results. Furthermore, the Agency is not concerned with task performance timing unless it is clinical relevant and it is meaningfully defined prior to testing.

Additionally, it appears that the applicant has not fully addressed CDRH comments regarding:

- detailed description of the intended user population, use environment, user interfaces, and anticipated user interaction with the proposed product
- evaluation of use-related risks and mitigation strategies designed to reduce risks associated with the proposed product

Based on the review of the study design, the applicant will need to address the above concerns.

Human Factors/Usability Recommendation – Request for Additional Information

1. Please provide a complete response to each of the deficiencies, and include any supporting documents as appendices.

2. 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. Additionally, the submission does not indicate how you have systematically evaluated use-related risk and how you would validate user-performance based on performance of 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. Please provide the following additional information for review:

a. Please provide a ***detailed description*** of the intended user population, and use environment; user interfaces, and anticipated user interaction with the proposed device. Please provide a response, and submit a revised test plan including this information.

b. Please provide an evaluation ***use-related hazards and relative risks*** associated with the use of the device have been conducted as part of your human factors study. Please provide an evaluation of use-related risk in the context of overall risk management of the device and mitigation strategies that you may have taken to reduce the risks associated with the proposed device. Please address this concern and submit a revised test plan that includes this evaluation.

c. ***Representative Users*** – You stated that Gen2 is a prescription device that some users might learn to use by working with diabetes nurse educator and/or physicians. It is not clear if you anticipate in addition to the patients, who will be using the products, you also anticipate diabetes nurse educator and/or physicians as part of the intended user populations. In order to successfully review a successful validation, FDA expects to see meaningful evaluation of user performance involving at least 15 representative users of each distinct user groups. Please provide a clarification for review, and submit a revised test plan if appropriate.

d. ***Relative priority of tasks*** - The Agency needs to understand the relative priority of the tasks you selected for testing in terms of the potential results of inadequate performance on these tasks. Indeed, the tasks selected for testing should be selected on this basis. While you stated in the test plan that participants will perform all tasks supported by the delivery system and no tasks have been excluded from the usability study. Based on this approach, you concluded that there is need to order the tasks based on their risks-related priority. However, it should be pointed out that the purpose of prioritizing the tasks is three-fold: (1) to develop conditions/use scenarios for which inadequate performance on these tasks would manifest while users conducting these specific tasks, (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. Please indicate where in the final test plan you have addressed these concerns. Alternatively, please revise your test plan to include the above information.

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

f. The directed tasks list and the instructions for use do not have any information that correlates with a high-use-related risk associated with users selecting cartridge(s) of correct dosage. It is not clear how this user task will be evaluated. Please provide a clarification, and include this information in the revised test plan.

g. ***Data analysis*** - Please direct your analysis of performance and subjective data toward assessment of task failures. The analysis should determine the nature of failures based on subjective and objective data. Please 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 assess 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, please note that study results should be recorded under success or failure of completing a critical task. If failures were found, the applicant should discuss how those failures were evaluated in terms of root cause analysis, clinical impact, and mitigation strategies. If the mitigation strategies involving modifications to user interface, please discuss how those

strategies are reevaluated or validated for safety and effectiveness. The study report should state whether the design is valid (i.e. reasonably safe and meets user's needs) based on a discussion of results of the usability testing and evaluations. Furthermore, please provide a summary of the results in a tabular format that shows the break down of all users, and for each user, include the following information: number of errors per task, error rate per task, number of errors per section, error rate per section, types of error for related tasks, risk evaluation in terms of the errors' clinical impact, root cause, and mitigation strategy, and how mitigation strategy will be evaluated and validated. Please address this concern and provide revised test plan for review.

ii. Pertaining to **subjective data**, please note that user feedback should include descriptions by test participants of difficulties encountered, good and bad aspects of the device user interface characteristics, including the logic of device operation, and suggested changes. Careful collection of subjective assessment of device use can identify problems that were noticed by test participants ("concerns," or "close calls") but did not manifest themselves as errors during use and not identified in objective performance measures. Rating scales (e.g., Likert scales) that assess overall "ease of use" etc. are helpful but do not represent all of the subjective data necessary for an adequate validation test and do not support meaningful interpretation of test results. Please provide subjective data, and a detailed discussion of how you plan to use and incorporate user feedback to the device designs, or potential modifications. Please address this concern and provide revised test plan for review.

h. ***Training.*** You do not describe training of participants prior to the test however it appears that you intend to use "untrained" individuals as a "worst case" condition and interpret your results in this light. Although this kind of information can be useful early in the process of designing your device, its labeling or the training, at the point of a validation test, the Agency expects representative users to be tested. Unless specific training programs are in place with respect to the amount of training a user will receive can serve this purpose. If it is true that your analysis indicates that users will generally not be trained at all then untrained users are appropriate for the study. Although realistic time periods for "training decay" are difficult to build into a testing approach, please allow some period of time to elapse between training and testing (e.g., a minimum time might be a "lunch break.") Please also provide information regarding training regime that will be provided when the device is on the market.

Please 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

Deficiency Sent to the Applicant
From observations based on the investigation of returned inhalers, clinical coordinator reports and a questionnaire regarding the inhaler used in your clinical trials, the Model C inhaler was redesigned to address usability concerns and mechanical robustness (b) (4) However, the usability of the new device (the Model D inhaler) and the corresponding instructions for use that you intend to market have not been validated. It is unclear whether the modifications made to the Model C inhaler and the associated patient labeling mitigate the usability concerns and risks associated with the inhaler. Therefore, you should conduct a Human Factors evaluation (i.e., a systematic evaluation of use-related risks in the context of the overall device risk management) with a full validation study to assess the usability of the final Model D inhaler that you intend to market. For this study, you should provide a detailed description of the intended user population, use environment, user interfaces, and anticipated user interaction with the proposed device. You should also provide an evaluation of use-related risk in the context of overall risk management of the device and mitigation strategies that the user may have taken to reduce the risks associated with the proposed device. The study should address the following specific concerns with the Model D inhaler:

(b) (4)

We recommend that you submit this study protocol for review prior to conducting the study. The study should validate that the final product along with the associated patient labeling has fully met the needs of the intended users and has demonstrated safety and effectiveness in the hands of intended users. During this validation phase, at least 15 representative users should perform real tasks using a device in simulated high-risk use scenarios and in a realistic use environment. During this validation, we recommend you evaluate how the users can utilize the device safely and correctly according to the instructions for use. User performance measures may also include the type and number of errors, time required to do tasks, requests for help, accuracy, success/failure on individual task and overall performance.

For additional guidance on Medical Device Use-Safety and Human Factors, please refer to FDA guidance available at:

http://www.fda.gov/downloads/MedicalDevices/DeviceRegulationandGuidance/GuidanceDocuments/ucm094461.pdf

Evaluation of Manufacturer Human Factors/Usability Testing Activities – 2nd Review

Applicant's Response
A complete Human Factors evaluation of the Gen2 inhalation system was conducted (Module 3.2.P.2.4 Technosphere® Insulin).

Evaluation of Applicant's Response
It should be noted that the deficiency sent to applicant is somewhat different than the itemized deficiency that was generated from the HF reviewer. Nevertheless, the HF review is based on the following materials that were submitted as part of this round of response:

- Appendix I – 3-1-2-p-2 – Human Factors Study Report
- Attachment 3 of Appendix I – Summative Usability Test of AFREZZA Insulin Inhalation System

In Appendix I – Human Factors Report, the applicant provided an overview of the HF effort for the proposed product. It described the intended user profile, description of the system, user interfaces with the system, formative testing research, risk assessment, usability assessment, summary of formal usability testing, resolution/risk mitigation for HF considerations, and conclusions.

The primary focus of this evaluation was based on the formative HF research information, risk and mitigation evaluation, and summative usability test report. The formative research was conducted in August 2008 to obtain input on system design, interface points, and usage for the proposed product. Six small group interviews were conducted with 17 participants with type II diabetes aged 50 years or older. During the interview sessions, subjects were provided inhaler and cartridge samples to evaluate usability. Another formative test were conducted in December 2008 with 45 different subjects aged from 40-70, who are insulin injection users. In this study, participants were presented with 8 inhaler designs, and were asked to select their favorite designs.

The risk assessment section stated that a Failure Mode Effect Analysis (FMEA) method was conducted. A detailed FMEA analysis was provided in Attachment 3 of Appendix I along with the summative report.

The resolutions/risk mitigations for human factors section indicated that the applicant has added labeling on cartridges to identify cartridge strength as a result of observed use errors between dose strength and cartridge color. The applicant also referenced in this section that additional updates to IFU will be made, which will include emphasis on the instruction for Mouthpiece Cover removal and revising front cover image to illustrate proper inhaler orientation during use.

The summative usability test report stated that the purpose was to validate that the proposed product is not vulnerable to dangerous use errors. There were 15 participants, 4 with Type I diabetes, and 11 with Type II diabetes. Of these participants, 6 had prior experience and 9 had no prior experience. The test report described the following scenarios as high risk scenarios:

High Risk Scenarios	Rationale
Use in Low lighting	Dose administrations may occur in environments with low lighting such as in restaurants
Use in environments with distraction	Because of the prandial nature of the therapy, users will utilize the system at a time when many distractions are present. This may include visual (in presence of table clutter), audible (loud music or TV or background noise), physical/tactile, and headache/migraine distraction types.
Use when there is a dexterity reduction or limitation	Peripheral neuropathy, arthritis flare-up, injury to hand/finger may impact usability. In addition, users may dose while traveling in a car or on an airplane where jostling due to motion is expected.
Use during times of high stress, fatigue, or general grogginess	These cognitive impairments are expected. This includes early morning/late night dosings with meals, dosing under general lack of sleep or after repetitive mindless activity (i.e. lunch break syndrome), and/or dosing while performing another task (e.g. eat and read, or eat and drive, or eat and talk on the phone, etc)
Use where Multiple cartridges – new, used and various doses are required	Users may have difficultly distinguishing between new and used Cartridges and Cartridges of various colors
Use when there is a cognitive impairment	Some users may be of advanced age or have mild dementia that impairs their ability to perform assembly tasks

The test report also identified possible use errors, description, and failure modes as follows:

Possible Use Error	Description	Failure
Cartridge advanced manually	A user removes a Cartridge from its secondary package and advances the Cartridge Cup with their thumb or finger	• Powder can spill out leading to a mis-dose and drug exposure • Cartridge may not fit in inhaler
Unable to open device	A user is unable to identify correct Inhaler opening method or is physically unable to open the Inhaler	• User cannot dose
Improperly installed cartridge	A user is unable to identify the correct orientation to install the Cartridge or does not seat the Cartridge fully	• Device will not close • User cannot dose
Unable to install cartridge	A user is unable to install a Cartridge because the device has not been fully opened	• User cannot dose
Improperly closed device	A user fails to close the Inhaler completely or at all	• Potential mis-dose
Dust cover not removed	A user does not or cannot remove the Dust Cover	• User cannot dose
Inhaler mis-orientation	A user fails to keep the Inhaler in the correct orientation prior to, and during use – generally horizontal with Mouthpiece on top	• Potential for powder to spill out and cause a mis-dose
Improper inhalation maneuver	A user inhales too lightly	• Potential mis-dose
Improper Mouthpiece position	A user places Mouthpiece in mouth too deeply, to shallowly, at an oblique angle or with their tongue or teeth in front of the exit or upside down	• Potential for mis-dose
Disposal failure	User cannot open the Inhaler to remove the Cartridge or does not open the Inhaler to discard the used Cartridge or the Inhaler in-use period is exceeded	• Potential to confuse new/used cartridge resulting in a mis-dose
Improper storage	User does not store the Inhaler or Cartridge properly	• Potential for contamination • Potential for mis-dose
Unable to identify correct dose	User unable to distinguish the correct color indicated dosage or the secondary packaging dosage indication	• Potential for mis-dose
Unable to reinstall dust cover	After dose the user must replace the Dust Cover to prevent contamination during storage	• Potential for contamination
Wet inhaler or cartridge	Inhaler and/or Cartridge gets wet prior to use (e.g. the system is used in the rain or user drops the Inhaler/Cartridge in water)	• Potential for mis-dose
Airflow blockage	Inhaler flow path is occluded	• Potential for mis-dose

The following table provides a listing of use errors and descriptions of those errors:

Type of Error	Frequency	Discussion
Delivered wrong insulin dose (used wrong type/number of cartridges)	5	5 participants erroneously delivered wrong insulin dose. The prescription called for 30 units of insulin. 1 participant delivered 2 of the 20 unit (green); 2 participants delivered only a 10 unit (blue); and 2 participants delivered only a 20 unit (green). The report discussed that the test participants did not recognize at first the doses might require multiple cartridges, and that the green and blue have different insulin doses. There were a total of 250 successful dosage delivered. The report also indicated that ultimately, all participants "seemed" to develop an accurate understanding of the dosing scheme after reading the blister pack labels and reviewing the IFU, as indicated by the lack of later dosing errors. (page 16)
Held inhaler upside down during inhalation	12	5 participants held the inhaler with its top facing down. Of these, 3 participants committed the error multiple times. The report indicated that these test participants did this unconsciously rather than purposefully.
Tried to insert an inverted cartridges into inhaler	2	2 participants tried one time to insert a cartridge into the inhaler with the incorrect orientation. The report indicated that the inhaler's design prevented users from fully inserting an inverted cartridge and closing the inhaler's top.
Did not replace the inhaler after 15 days of use	5	5 participants did not switch to a new inhaler after 15 days of use. The report stated that this might be due to the nature of the simulated environment where minutes were used rather than days. However, some participants did indicate that it was Day 16 and did not indicate they would replace the inhaler. Participants indicated that it might be difficult to remember when to replace the inhaler unless the replacement date was written down. Other participants indicated that it might be easier to replace it every 14 days, biweekly.
Did not remove the mouthpiece cover prior to inhalation	2	2 participants did not remove the mouthpiece prior to placing the inhaler in their mouth. The report discussed that the error appeared to be an overlook the pertinent instructions in the IFU, and 1 of the test participant quickly realized the error, and the other participant required test administrator assistance and was directed to review the IFU regarding a proper use.
Mistook used cartridges as new and vice versa	5	5 test participants did not correctly identify the cartridge's status. Of these 2 identified the cartridges as new but they are used; and 3 identified that they are used but they are new. The participants indicated that the IFU's cartridge illustration (page 8) did not draw sufficient attention to the cup position.
Manipulated inhaler in a manner that could cause loss of medication	8	8 participants manipulated inhaler in a manner that could cause loss of medication. Of these, 4 participants committed the error multiple times. The report stated that the common use error of manipulating the inhaler extensively after loading the cartridge and before Inhaling seemed to reflect a lack of awareness of the need to hold the inhaler upright and level prior to an inhalation. Even test participants who appeared to read the IFU instruction to hold the inhaler level prior to inhalation erred.
Held inhaler at the wrong angle during inhalation	9	9 participants held the inhaler at a more severe downward angle (visually estimated to be G 45 degrees) or slightly upward angle during inhalation. Of these, 7 participants committed the use error on multiple occasions. Two test participants occasionally used a "no hands" approach to insulin delivery. The report discussed that the common use error of holding the inhaler at the wrong angle during inhalation seemed to reflect a lack of awareness of the need to tilt the inhaler downward. Even test participants who appeared to read the IFU instruction to hold the inhaler slightly downward during inhalation erred, perhaps because they didn't understand the consequences of failing to hold the inhaler slightly downward. Moreover, some participants seemed to be focused on their breathing, unconscious of the need to hold the inhaler at a slight, downward angle.
Did not breathe	12	12 participants failed to exhale prior to inhalation. Twelve participants committed the use

Type of Error	Frequency	Discussion
out prior to inhalation		error on multiple occasions. The report discussed that the participants did not read the portion of the IFU that directs users to breathe out before using the inhaler, or did not keep the instruction in mind while performing inhalations.
Did not inhale deeply during inhalation	9	9 participants failed to breathe in deeply during inhalation. Nine participants committed the use error on multiple occasions. The report stated that in these cases, the test participants seemed unaware of the need to inhale deeply, usually because they had not read the IFU, at least not thoroughly.
Did not hold breath briefly after inhalation	7	7 participants did not appear to hold their breath after inhalation. Seven participants committed the use error on multiple occasions. The report indicated that test participants who did not hold their breath after an inhalation seemed unaware of the need to do so, despite reviewing the IFU, or forgot to hold their breath despite understanding the need to do so. One participant misinterpreted the term "briefly" and concluded that he should hold his breath for a long time to get the full insulin dose.
Dropped cartridge	5	5 participants dropped a cartridge while preparing the inhaler for use. Of these, 1 participant committed the use error on multiple occasions. The report stated that difficulty maintaining a secure grip on the cartridges when removing them from the blister pack, inserting them into the inhaler, and removing them from the inhaler.
Did not replace mouthpiece cover after inhaler use	2	2 participants did not replace the mouthpiece cover after inhaler use. One participant committed the use error on multiple occasions. The test report indicated that appeared to forget to place the mouthpiece cover on the inhaler after use. Occasionally, the mouthpiece cover fell off the inhaler as the participant placed the inhaler back in its storage bag. In some cases, the cover was more prone to fall off because the test participant incorrectly placed it upside down on the inhaler.

HF Review Discussion

Overall, the applicant has provided better information regarding their human factors evaluation and validation. The applicant has provided detailed description of the user profile, and user interfaces. There is also some information about risk analysis. However, there are still some outstanding concerns regarding the study methodology, and how use errors were addressed. Please see HF recommendation.

Human Factors/Usability Recommendation – Request for Additional Information

Usability Study Methodology

a. While you have provided information about risk analysis and identified simulated use scenarios as well as 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. The Agency expects that the tasks selected are those tasks that that are of highest priority and have potential results of inadequate performance based on use related risk analysis. To fully evaluate the methodology utilized in the study, please provide:
    a. Description of user tasks
    b. Relative priority of user tasks
    c. Rationale for why you selected those tasks
    d. How these tasks are directly related to your risk analysis

Use Errors/ Mitigation

b. The Summative Usability Test of AFREZZA Insulin Inhalation System Report provided detailed discussion of the use errors committed. Please address the following:
    a. It was noted that 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. The other errors did not have a risk table. Please provide a risk table for all of the errors. In these tables, please clearly state the related tasks, and provide an explanation of risk index and risk priority numbers that were selected. Also, for each error type, please include 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. The fact that users have a pattern of similar problems indicates a design flaw (including 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 it is safe and effective in the hands of intended users. Please provide justification as to why all of the use errors detected in your study should be considered acceptable. Alternatively, please submit test results of a usability study that demonstrate acceptable user performance.
    c. Furthermore, on pages 34 – 35 of 3.2 of 3-1-2-p-2 Appendix I, Human Factors Study Report, you discussed some proposed mitigations: 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.
        i. It is not clear how the proposed mitigations can address all of the use errors reported in your study. Please provide a discussion for how the proposed mitigation strategies address all of the use errors.
        ii. Secondly, it is important to note a validation study should be performed to demonstrate the effectiveness of your mitigations derived from use related risk analysis. Your Study Report did not provide any discussion of how you evaluated the effective of the mitigation involving the user interface modifications that include IFU/device labeling you have recommended for the use errors you found. Please perform a validation study and provide the results to enable the Agency to successfully complete its review of your submission.

Evaluation of Manufacturer Human Factors/Usability Testing Activities – 3rd Review

Applicant's Response
Response to FDA Information Request (28 Oct 2010)
Attachment 1 – Failure Modes Effects Analysis (FMEA)
Attachment 2 – Instructions for Use (Proposed Commerical)

Evaluation of Applicant's Response

Usability Study Methodology
FDA Question # 1

9. While you have provided information about risk analysis and identified simulated use scenarios as well as 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. The Agency expects that the tasks selected are those tasks that that are of highest priority and have potential results of inadequate performance based on use related risk analysis. To fully evaluate the methodology utilized in the study, please provide:
    - Description of user tasks
    - Relative priority of user tasks
    - Rationale for why you selected those tasks
    - How these tasks are directly related to your risk analysis

Evaluation of Applicant's Response
Description of the User Tasks (Usability Study Directed Tasks) and Relation to Risk Analysis:
The usability study protocol was designed based on the Failure Mode Effects Analysis (FMEA) and the Instructions-For-Use (IFU) Participants (15) were diabetes patients and representative of the user population. Test participants performed up to 19 tasks by following their intuition and the instructions (IFU). No training was provided. Device use is a sequential three step process detailed in the IFU as Step 1 (Load), Step 2 (Inhale) and Step 3 (Remove).

Relative Priority of User Tasks (Usability Study Directed Tasks): User tasks were not prioritized because 17 of 19 tasks tested the primary failure mode. Furthermore, steps in the IFU are sequential and could not be prioritized.

Rationale for Directed Task Selection (Usability Study Directed Tasks): The applicant stated that they used FMEA to assess use-related risks with the Gen2 Inhalation system. All but two of the risks were in the acceptable range. The two that have the highest priority were 1) failure of the user to identify the correct cartridge strength; and 2) failure of the user to correctly select the right number of cartridges or the cartridge strength for achieving a target dose (e.g. 30 U dose = 10 U cartridge strength + 20 U cartridge strength). Both failures may result in improper dosing and represent the most significant risk and primary failure mode. Thus, all directed tasks performed in the usability study emphasized proper cartridge selection (correct dose strength) and proper dose administration (correct number or combination of cartridges). The usability study was performed with cartridges that were color coded but did not include the numeric identification of strength. This represented a worst case approach. Secondary failure modes were also evaluated during the repetition of the directed tasks.

Review Comments: The applicant has adequately addressed the issues raised in this question. It should be noted that the usability validation study should reflect realistic use of the device when it is marketed. If training is necessary to support safe use, the validation study should evaluate and validate the training and training materials. In addition, the study was performed with cartridges that were only color codes but did not include the numeric identification of strength. The applicant indicated that study was designed to represent worse-case scenario. While this worse case scenario approach has some merit, FDA generally expects that the validation study be conducted using actual training materials, and finalized products to represent actual use. This study should demonstrate that the product can be safely used in the hands of representative users. In this case, the data of the study is potentially skewed towards user confusions and use errors in delivering insulin dose, proper device handling, proper inhalation, etc.

FDA Question # 2

10. The Summative Usability Test of AFREZZA Insulin Inhalation System Report provided detailed discussion of the use errors committed. Please address the following:
    a. It was noted that 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. The other errors did not have a risk table. Please provide a risk table for all of the errors. In these tables, please clearly state the related tasks, and provide an explanation of risk index and risk priority numbers that were selected. Also, for each error type, please include 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. The fact that users have a pattern of similar problems indicates a design flaw (including 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 it is safe and effective in the hands of intended users. Please provide justification as to why all of the use errors detected in your study should be considered acceptable. Alternatively, please submit test results of a usability study that demonstrate acceptable user performance.
    c. Furthermore, on pages 34 – 35 of 3.2 of 3-1-2-p-2 Appendix I, Human Factors Study Report, you discussed some proposed mitigations: 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.
        i. It is not clear how the proposed mitigations can address all of the use errors reported in your study. Please provide a discussion for how the proposed mitigation strategies address all of the use errors.
        ii. Secondly, it is important to note a validation study should be performed to demonstrate the effectiveness of your mitigations derived from use related risk analysis. Your Study Report did not provide any discussion of how you evaluated the effective of the mitigation involving the user interface modifications that include IFU/device labeling you have recommended for the use errors you found. Please perform a validation study and provide the results to enable the Agency to successfully complete its review of your submission.

Evaluation of Applicant's Response

Risk table for all of the errors: The following table provides user task, potential cause, and hazards.

Use Error	User Task	Potential Causes (i.e. use errors)	Potential Hazards
1	Insert a cartridge into the inhaler	Multiple cartridges are needed, but the user does not select the appropriate cartridges that add up to the target dosage	Incorrect dosage amount possibly excessive dose
2	Insert the inhaler in the mouth with correct orientation	User is not aware or does not recognize the content in the IFU	Incorrect dosage amount possible low dose
3	Insert a cartridge into the inhaler	User attempts to insert an inverted cartridge	No dosage device prevents usage when cartridge is not oriented properly
4	Replace inhaler after 15 days of use	User is not aware or does not recognize the content in the IFU	Device becomes unclean
5	Remove Mouthpiece Cover	User does not recognize the Cover must be removed to administer dose	User inhales on the device with the Cover in place possibly inhaling
6	Recognize the cartridge has been use	User can not distinguish the difference between a used and unused cartridge	No dosage an empty cartridge is used
7	Maintain proper device orientation after cartridge is loaded	User is not aware or does not recognize the content in the IFU	Incorrect dosage possible low dose
8	Insert the inhaler in the mouth with correct orientation	User is not aware or does not recognize the content in the IFU	Incorrect dosage possible low dose
9	Breathe out prior to inhaling the powder	User is not aware or does not recognize the content in the IFU	Unknown
10	Inhale deeply through the inhaler to deliver the dose	User is not aware or does not recognize the content in the IFU	Incorrect dosage possible low dose
11	Hold breath briefly after inhalation	User is not aware or does not recognize the content in the IFU	Unknown
12	Hold the cartridge with the Cup side down	User is unable to grasp the cartridge or has difficulty in extraction from secondary packaging	16 for opening package 28 for dropping 112 Cartridge becomes unclean because it is dropped or user is unable to achieve a dose because they cannot load into the inhaler 16 64
13	Replace the Mouthpiece Cover after use	User does not recognize a need to maintain cleanliness	16 112The inner lumen of the Mouthpiece traps foreign debris 10 100

The following provides summary discussion of the use errors:

- Use error #1 occurred when untrained users selected the wrong cartridge or wrong combination of cartridges. Due to the potential for overdose, this error is identified as the most serious error (highest risk index and RPN). This error was observed the first time subjects performed the directed task and was non-recurring. To mitigate this risk, cartridge strength is now molded into the cartridge to supplement the original package labeling (carton, overwrap and blister). Additionally, instructions supplied to users will further reduce the risk. In the clinical trials there were no complaints on cartridge differentiation or dosing as users were able to differentiate and utilize multiple cartridge strengths (note: in these trials, cartridge strength was only differentiated by color and secondary packaging and not yet molded into the cartridge).

- Use error #2 occurred when the device system was used in an inverted position which may deliver a lower dose. In vitro testing shows the inverted orientation results in a lower fine particle dose (b)(4)% lower in cups 3-MOC) however the emitted dose is unaffected. Afrezza® Inhalation Powder is a prandial therapy and intended for use 3 to 4 times daily. Based on this dosing schedule, the potential risk associated with a single low dose is small. Use errors #7-8 may present a similar modest risk. To mitigate this risk, the instruction for use was revised to prominently display proper orientation during use (Attachment 2 - Revised IFU). Coupled with a demonstration by health care professional these mitigations are sufficient.
- Use error #3 occurred when users tried to insert an inverted cartridge, the device, by design, could not be closed. The risk assigned to this error is low because the user is likely to recognize and correct the problem. Tthe usability test showed that subjects independently recognized the mistake and inserted the cartridge properly. The device design thwarted improper use.

- Use error # 4 occurred when users did not replace their inhalers after the simulated 15 day use period. It is important to note that this simulated testing was conducted within a 2 hour period and is not representative of real use. The risk is low because in vitro testing demonstrated acceptable device performance well beyond 15 days. Nevertheless, MannKind will reinforce the proper in-use period with intended market presentations containing a 30 day supply of cartridges and two inhalers. The in-use period will also be prominently displayed on the kit carton, inhaler carton and inhaler overwrap. These mitigations are coupled with modest training and the IFU.

- Use errors #5 and #13 involve the Mouthpiece Cover. Failure to remove the mouthpiece cover (use error #5) is a potential choking hazard. Failure to replace the mouthpiece cover (use error #13) is a potential cleanliness hazard. In error #5, two users did not remove the Cover and attempted to inhale through the device. In both cases, the Cover did not come off during the inhalation attempt. The Cover fits with a retention force sufficient to prevent inadvertent aspiration so the risk of this error is low. Use error # 13 occurred with two users. One user preferred not to replace the mouthpiece cover. The other user forgot to replace the mouthpiece cover. This error is associated with Mouthpiece cleanliness and will be likely noticeable. Modest training with the IFU will reduce these risks.

- Use error # 6 is associated with use error #1 because it involves cartridge selection. Use error #6 is inability, when prompted, to distinguish between used and unused cartridges. The potential hazard is missing a dose. Importantly, during execution of all directed tasks, users never loaded a used cartridge. The cartridge is designed to provide a visual cue to users (Cup location) that it is spent or used and this is shown in the IFU. Modest training with the IFU will reduce these risks. In clinical trials there were no complaints associated with the ability to differentiate used versus unused cartridges.

- Use errors #9-11 represent a minimal risk and were susceptible to subjective evaluation in the summative usability testing. Although these are recommended practices, they are not required to achieve proper dosing.
- Use error # 12 involved cartridge handling including extraction from the package and loading into the inhaler. This hazard is associated with cleanliness because there is risk of dropping the cartridge. During usability testing, users were all able to complete directed tasks. Any observed difficulties in cartridge handling did not prevent proper use.

Justification as to why all of the use errors detected in your study should be considered acceptable
The applicant stated that due to the simplicity of the device, error #1, the primary failure mode, is the only error of concern. This error occurred when untrained users selected the wrong cartridge or wrong combination of cartridges. This error was observed the first time subjects performed the directed task and was non-recurring. To mitigate this risk, cartridge strength is now molded into the cartridge to supplement the original package labeling (carton, overwrap and blister). Additional instruction provided by healthcare practitioners will further reduce the risk.

The applicant noted that in the clinical trials there were no complaints on cartridge differentiation or dosing as users were able to differentiate and utilize multiple cartridges (note: in these trials, cartridge strength was only differentiated by color and secondary packaging and not yet molded into the cartridge).

The applicant stated that to maximize the probability of errors in usability testing, the participants were not given any training, and that this scenario does not represent the intended first time patient experience. In practice, health care providers will interact with patients using demonstration devices in conjunction with the IFU. Testing in the usability study focused on evaluating users that did not receive training and learned to use the product based on their intuition and the IFU. Patients prescribed any type of insulin are expected to receive training in proper dosing. The use errors committed during the testing are a result of unfamiliarity with this system and not a design flaw.

Discussion for how the proposed mitigation strategies address all of the use errors

Use Error	User task	Potential Causes (i.e. use errors)	Potential Hazards	Risk Mitigation
1	Insert a cartridge into the inhaler	Multiple cartridges are needed, but the user does not select the appropriate cartridges that add up to the target dosage	Incorrect dosage amount -possibly excessive dose	Labeling on the cartridges to identify cartridge strength Labeling is readable when the cartridge is placed in the inhaler and provides a redundant level of assistance/messaging to the subjects during dose selection.
2	Insert the inhaler in the mouth with correct orientation	User is not aware or does not recognize the content in the IFU	Incorrect dosage amount -possible low dose	IFU Update: • Revising the front cover image to illustrate proper inhaler orientation during use
3	Insert a cartridge into the inhaler	User attempts to insert an inverted cartridge	No dosage - device prevents usage when cartridge is not oriented properly	Device design prevents usage when cartridge is not oriented properly
4	Replace inhaler after 15 days of use	User is not aware or does not recognize the content in the IFU	Device becomes unclean	Instructions emphasize replacing inhaler after 15 days of use throughout IFU and in the tertiary packaging
5	Remove Mouthpiece Cover	User does not recognize the Cover must be removed to administer dose	User inhales on the device with the Cover in place -possibly inhaling	IFU Update: • Emphasizing the instruction for Mouthpiece Cover removal (and associated cartoon graphic) to promote greater awareness
6	Recognize the cartridge has been use	User can not distinguish the difference between a used and unused cartridge	No dosage -an empty cartridge is used	The IFU provides language and illustration describing used and unused cartridges.
7	Maintain proper device orientation after cartridge is loaded	User is not aware or does not recognize the content in the IFU	Incorrect dosage -possible low dose	The IFU language and illustration reinforce proper orientation for the device: increased prominence with a picture on the front cover.
8	Insert the inhaler in the mouth with correct orientation	User is not aware or does not recognize the content in the IFU	Incorrect dosage -possible low dose	The IFU provides language and illustration on orientation for the device for use including a picture on the front cover.
9	Breathe out prior to inhaling the powder	User is not aware or does not recognize the content in the IFU	Unknown	The graphic in the IFU encourages exhalation prior to dosing. Exhaling is recommended, but not required for dosing.
10	Inhale deeply through the inhaler to deliver the dose	User is not aware or does not recognize the content in the IFU	Incorrect dosage -possible low dose	The inhaler is designed to provide adequate dosing with minimal inhalation effort.
11	Hold breath briefly after inhalation	User is not aware or does not recognize the content in the IFU	Unknown	Text and graphic included in the IFU to encourage holding breath briefly after inhalation. Holding breath is recommended, but not required for dosing.
12	Hold the cartridge with the Cup side down	User is unable to grasp the cartridge or has difficulty in extraction from secondary packaging	Cartridge becomes unclean because it is dropped or user is unable to achieve a dose because they cannot load into the	The cartridge design allows for sufficient area for gripping. For proper orientation, the IFU provides language and illustration for extracting and handling the cartridge.
13	Replace the Mouthpiece Cover after use	User does not recognize a need to maintain cleanliness	The inner lumen of the Mouthpiece traps foreign debris	Text and illustration included in the IFU. Replacing mouthpiece cover may affect cleanliness, but not dosing.

Effectiveness of the Mitigation
The applicant referred to the Human Factors Study that has been conducted. The applicant stated that due to the simplicity of the device, the primary failure mode is failure of the user to properly identify the cartridge strength and select the correct dose. This error occurred in 5 out of 255 tasks involving dose selection, only in untrained users, and was non-recurring. The applicant stated that to mitigate this risk, cartridge strength is now molded into the cartridge to supplement the original package labeling (carton, overwrap and blister). Additional instruction provided by healthcare practitioners will further reduce the risk.

Review Comments: The applicant provided adequate explanation for how the use errors occurred and their associated potential hazards. However, it should be noted that the potential causes for most of the errors were users not aware or does not recognize the content provided in the IFU. This indicates a pattern of use error. It is also important to point out that those risks where their associated mitigation is the IFU or the information contained in the IFU, and users are not aware of the content in the IFU, it is possible to consider that the IFU and its content do not serve as effective mitigation.

In addition, the applicant's justification for the errors detected during the study was that the participants were not given any training. They actually stated that this scenario does not represent the intended first time patient experience. Patients prescribed any type of insulin are expected to receive training in proper dosing. The use errors committed during the testing are a result of unfamiliarity with this system. As previously mentioned, if training is an integral component, the validation study should incorporate training.

It also important to note that the applicant designed the study so that the users are untrained and unfamiliar with the system and they concluded from the study that the errors occurred due to lack of training and unfamiliarity. This does not provide an adequate assurance that that the device is safe in the hands of representative users.

In addition, the applicant identified a number of mitigations focusing on updating the instructions for use, as well as making additional change to the design of the product i.e. cartridge strength is now molded into the cartridge to supplement the original package labeling (carton, overwrap and blister). These modifications being made are results of use errors and use confusions detected during the validation study. FDA requested that the applicant evaluate the effectiveness of these mitigations through another validation study; however, the applicant did not conduct this study. These mitigations require a re-validation study to ensure that the modifications in fact do not introduce new risks. Furthermore, this re-validation study should also demonstrate that the mitigations minimize use errors and improve user comprehension. This validation study should also include representative device users, training, and final device version.

As a result, there are a number of outstanding concerns. Please send the following deficiency to the applicant.

1) **Regarding your response to question 10, Human Factors, you provided an adequate explanation for how the use errors occurred and their associated potential hazards. However, there are some areas of the response that require further information. Please address the following:**

    a. **It should be noted that the potential causes for most of the use errors were users not aware or do not recognize the content provided in the IFU. It is also important to note that specific use-related risks outlined in your FMEA where you stated that their associated mitigation is the information contained in the IFU, and that fact that users are not aware of the content in the IFU, it is possible to consider that the IFU and its content do not serve as effective mitigation. Please comment on how this issue can be addressed.**

    b. **In addition, your justification for the errors detected during the study was that the participants were not given any training. You also stated that this scenario does not represent the intended first time patient experience. Patients prescribed any type of insulin are expected to receive training in proper dosing. It should be noted that the usability validation study should reflect realistic use of the device. If training is necessary to support safe use, the validation study should validate training and training**

materials. Please discuss how you have validated proposed training and training materials. Also, in your response, you indicated that "modest training with the IFU will reduce these risks." It is not clear what "modest" training consists of. Please provide a description of your "modest" training program.

c. **In addition, you identified a number of mitigations focusing on updating the IFU, as well as making additional change to the design of the product i.e. cartridge strength is now molded into the cartridge to supplement the original package labeling (carton, overwrap and blister). These modifications being made are results of use errors and use confusions detected during the validation study. FDA requested that you evaluate the effectiveness of these mitigations through another validation study; however, the response did not provide a report for this study. These mitigations require a re-validation study to ensure that the modifications in fact do not introduce new risks. Furthermore, this re-validation study should also demonstrate that the mitigations are effective in minimizing use errors and improving user comprehension. This validation study should also include representative device users, user training, final IFU (commercial) and final device version. Please provide complete test protocol and report for this validation study.**

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
12/21/2010
On behalf of Melanie Choe and QuynhNhu Nguyen of CDRH

DEPARTMENT OF HEALTH AND HUMAN SERVICES MEMORANDUM

Food and Drug Administration
10903 New Hampshire Avenue
Document Mail Center - WO66-G609
Silver Spring, MD 20993-0002

ODE Consult Review

Date: December 17, 2010

To: Rachel Hartford, OND/ODEII/DMEP

From: Melanie Choe, Ph.D.
Anesthesiology and Respiratory Devices Branch (ARDB)
Division of Anesthesiology, General Hospital, Infection Control, and Dental Devices
Office of Device Evaluation (ODE)
Center for Devices and Radiological Health (CDRH)

Sponsor: MannKind Corporation
61 South Paramus Rd.
Paramus, NJ 07652

Subject: NDA22-472: Gen2 Inhaler System for exclusive use with the Technosphere® Insulin Inhalation Powder Technosphere Insulin filled cartridge

I. SUMMARY

On June 29, 2010, ARDB was requested to review the device within the Complete Response Submission to the original NDA from MannKind (sponsor). The device is a single-patient reusable breath actuated inhaler for specific delivery of Technosphere® Insulin powder contained in predose cartridges. In this submission, the sponsor introduced the next generation Gen2 Inhaler System to achieve optimal user appeal and improved delivery performance and to replace the MedTone Inhaler system, which was the subject of the original NDA. Therefore, the scope of this review is the Gen2 Inhaler system.

After review of the bench test reports, the Gen2 Inhaler system is determined to be equivalent to the MedTone Inhaler system in its technology and intended function to de-agglomerate and deliver respirable particles of Technosphere Insulin. However, due to limitations in bench performance tests, the equivalence of the two systems to effectively deliver insulin with physiological relevance is dependent on clinical studies (e.g., bioequivalence and/or controlled clinical studies). The following highlight the limitations of the bench performance tests:

- According to bench tests, the Gen2 Inhaler system consistently delivered less insulin units in the respirable range by approximately 1 to 4 units (20 U Cartridge), than the MedTone Inhalation system with the equivalent dose. The physiological effect of

variance in delivered insulin dose needs clinical recommendation.

- Inhalation maneuvers for the Gen2 and MedTone devices are different. Gen2 requires one maneuver, while MedTone requires (b) (4) maneuvers for equivalent dosing. The wash and deposit phases after the first second of inhalation in a maneuver are important to the amount of drug particles retained by or effectively delivered to the user. Bench tests for emitted dose (ED) and aerodynamic particle size distribution (APSD) predicts the amount and particle size of the drug delivered to the lung, but it does not measure the effects of differences in inhalation maneuvers and the amount of drug retained by the user.

- In a worst case use test representing 22.5 days of simulated use, APSD in the respirable range generated by Gen2 increased over use time by approximately 1 unit for a 20 unit dose (n=3). While the difference is small, the physiological impact of delivered drug variance, as also noted above, can not be interpreted from bench tests.

While not pivotal to the final recommendation decision for this NDA, the following deficiencies remain and should be addressed by the sponsor as conditions prior to marketing, if the NDA is found approvable:

1. FDA previously requested that you provide a usability study validating the proposed mitigations focusing on updates to the instructions for use (IFU) and additional changes to the cartridge strength label in deficiency number 10, requested on October 28, 2010. In response, you stated that you intend "to confirm the commercial AFREZZA® Inhalation System with the final FDA approved labeling." Provide the complete test protocol and report for this validation study for review.

   FDA notes that such study should demonstrate the proposed mitigation does not introduce new risks, is effective in minimizing user errors and improves user comprehension. In addition, such a study should test the representative device users, user training, final IFU, and final device version intended for the market.

   Also provide an explanation and validation of the following concerns, and in the new study:

   a. It appears that the potential causes for most of the reported use errors were due to the user not being aware of, or recognizing, the content provided in the instructions for use (IFU). However, the mitigation for these errors according to your FMEA, is to refer back to the IFU. Since it appears the user errors were due to lack of user awareness of, or recognizing, the content provided in the IFU, it is unclear how reference to the IFU would be an effective mitigation strategy. Please explain.

   b. You explained that the usability study participants did not receive any training prior to use, which does not represent the intended first time user experience. Patients prescribed any type of insulin are expected to receive training in proper

dosing. Therefore, you justified that the noted use errors were due to lack of training and familiarity of the inhaler system. Again, FDA notes that the usability validation study should reflect the realistic use of the device. Since it appears that training is necessary to support safe use of the subject device, your usability study should also validate the training and its materials. Provide a usability test report that validates your proposed training and its materials. In this response, also provide a description of your modest training program, as you indicated that "modest training with the IFU will reduce these risks".

2. You clarified that the claimed storage condition for the Gen2 Inhaler system will be 2 to 25°C; however, your stability testing is being conducted at 5+/-3°C and 25+/-2°C. The test condition of 5+/-3°C does not mean that the test condition is maintained at 2 or 8°C. These are the tolerance range of the target test temperature of 5°C. Therefore, the claimed storage condition in your labeling should reflect the test condition of 5 to 25°C, exclusive of your test setup temperature tolerance.

3. You clarified that the mouthpiece [redacted] (b) (4) However, you have not provided a rationale or performance test to demonstrate the mouthpiece with the [redacted] (b) (4) will "…prevent [redacted] (b) (4) …" over the claimed shelf-life and simulated use conditions. Therefore, commit to complete a mouthpiece retention testing after shelf-life and simulated use conditions in your stability testings.

4. The prescription use statement for the Gen2 Inhaler could not be found in your labeling. Include in your label the caution statement required by 21 CFR 801.109 for prescription devices: "Caution: Federal law restricts this device to sale by or on the order of a physician."

TABLE OF CONTENTS

II. SUBMISSION AND REVIEW HISTORY

CDRH became involved in the review of the MedTone Inhaler under IND 61,729 when MannKind intended to control incoming inhalers through visual assessment, physical functional testing (including flow resistance), and dimensional measurement (December 2006). Subsequently, MannKind requested a pre-NDA meeting on July 14, 2008 and CDRH was requested to respond to a device related question in the meeting package. MannKind proposed to refine and improve the quality and ruggedness of the Model C inhaler based on feedbacks received during the clinical study to result in the Model D MedTone Inhaler, which they intended to be the subject of the NDA. However, after the review of the original NDA based on the Model D MedTone Inhaler, the sponsor introduced a new inhaler system, Gen2, as the subject of the NDA in response to the Complete Response letter. The following dates outline CDRH review activities:

MedTone Inhaler System Review Phase

March 16, 2009	Date of original NDA submission.
March 30, 2009	The NDA was assigned to CDRH/ODE/ARDB for a consulting review of the MedTone inhaler.
May 19, 2009	CDRH requested additional information (AI) in the filing letter regarding human factors study and stability test reports.
July 22, 2009	AI response to filing letter received in CDER.
August 19, 2009	CDRH received AI response for review.
September 17, 2009	CDRH requested the missing human factors study report.
September 25, 2009	CDRH received the human factors study report.
November 19, 2009	CDRH requested AI on inhaler bench study reports.
December 7, 2009	CDRH received the requested AI from November 19, 2009.
December 17, 2009	CDRH finished original NDA review.
March 12, 2010	Complete Response letter issued by CDER.

Gen2 Inhaler System Review Phase

May 17, 2010	CDRH was assigned to review a Type C meeting request dated May 12, 2010, which introduced the Gen2 Inhaler system.
June 8, 2010	CDRH finalized comments to be included in EOR Preliminary Comments letter on human factors study design and format of bench test reports that should be included in future submission.
June 9, 2010	Melanie Choe and Lex Schultheis, ARDB Chief, attended Type C meeting.
June 29, 2010	CDRH received Complete Response (CR) Submission for review.
October 5, 2010	CDRH completed CR Submission and requested device performance test and human factors related AI.
October 28, 2010	CDER sent CDRH AI request to sponsor.
November 16, 2010	CDRH received response to device performance test related AI requested on October 5, 2010 for review.
November 30, 2010	CDRH received response to human factors related AI requested on October 5, 2010 for review.

III. INTENDED USE

AFREZZA, an ultra rapid acting insulin, is indicated for the treatment of adults with type 1 or type 2 diabetes mellitus for the control of hyperglycemia.

Important limitations:

- For type 1 patients, AFREZZA should be used in regimens that include a long acting insulin.
- AFREZZA should not be used for the treatment of diabetic ketoacidosis.

It is intended for delivery with the Gen2 Inhalation System.

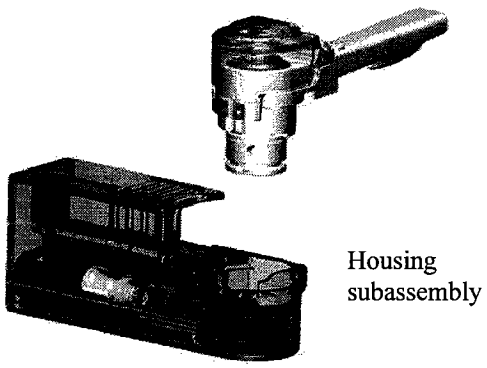
IV. DEVICE DESCRIPTION

The subject device of the original NDA dated March 16, 2009 was the AFRESA Inhaler or the MedTone Inhaler. In subsequent response to the Complete Response letter dated March 12, 2010, the sponsor introduced a new and improved inhaler in their June 28, 2010 submission, the Gen2 Inhaler system, to replace the MedTone Inhaler. The Gen2 Inhaler was developed using the same technological platform as the MedTone Inhaler. Therefore, this section will only briefly describe the MedTone Inhaler and focus on the description of the Gen2 Inhaler. For further device description of the MedTone Inhaler system, please refer to CDRH/ODE memo dated December 14, 2009.

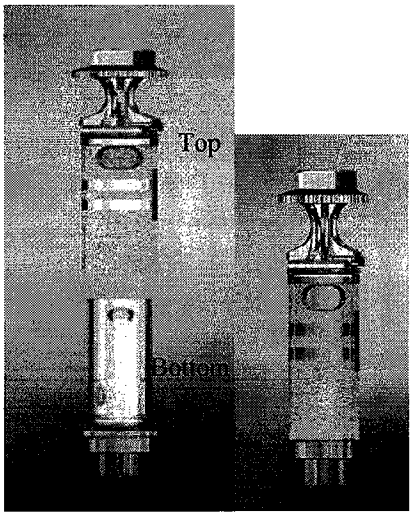
MedTone Inhaler

The Model D MedTone inhaler is a breath-powered device that delivers a pre-dosed dry powder (insulin-absorbed Technosphere) contained in a Cartridge to the airway in the respirable range ((b) (4)). It is a (b) (4) device intended for re-use by a single patient over a 12 month period. The components of the inhaler are arranged within two subassemblies named the Housing and Mouthpiece subassemblies as depicted below.

(b) (4)



MedTone Inhaler



Cartridge

(b) (4)

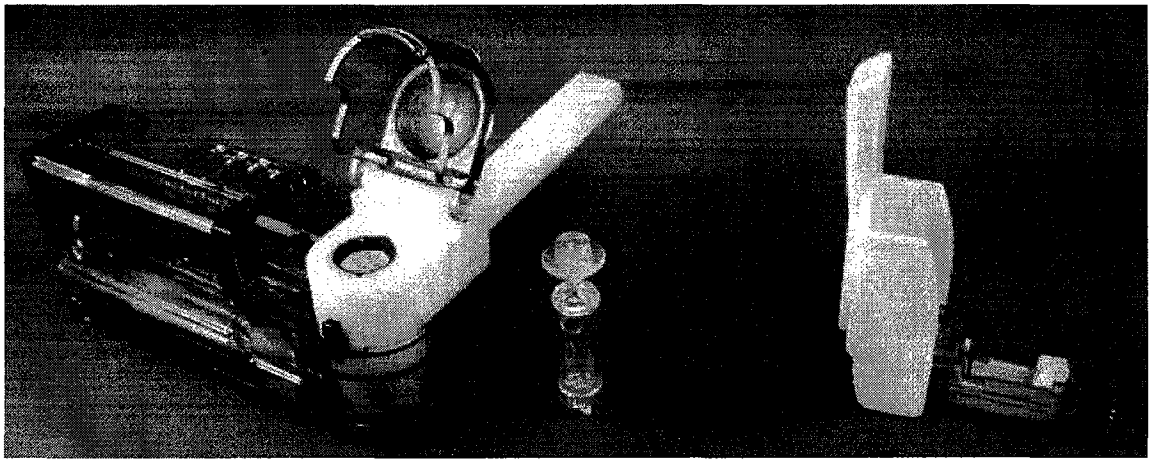
3 Page(s) have been Withheld in Full as B4 (CCI/TS) immediately following this page

Gen2 Inhaler

In the current CR submission, the sponsor introduced their second generation TI delivery device in an effort to achieve optimal user appeal and improved delivery performance to replace the MedTone Inhaler. Gen2 is reportedly based on the MedTone® platform with the following key user attributes in comparison to the MedTone inhaler:

Product Element	MedTone®	Gen2
Cartridge Strengths	15 U (5 mg) 30 U (10 mg)	10 U (3.3 mg) 20 U (6.7 mg) (color coded cartridges)
Resistance	High Resistance ranging from (b) (4) (b) (4) /LPM	High Resistance ranging from (b) (4) (b) (4) LPM
Ease of use	(b) (4)	4 steps 1 inhalation per cartridge
Cleaning	(b) (4)	No cleaning required 15 days (disposable)

Some of these attributes can be seen in a side-by-side comparison picture of the Medtone (Model C) and the Gen2 devices below.

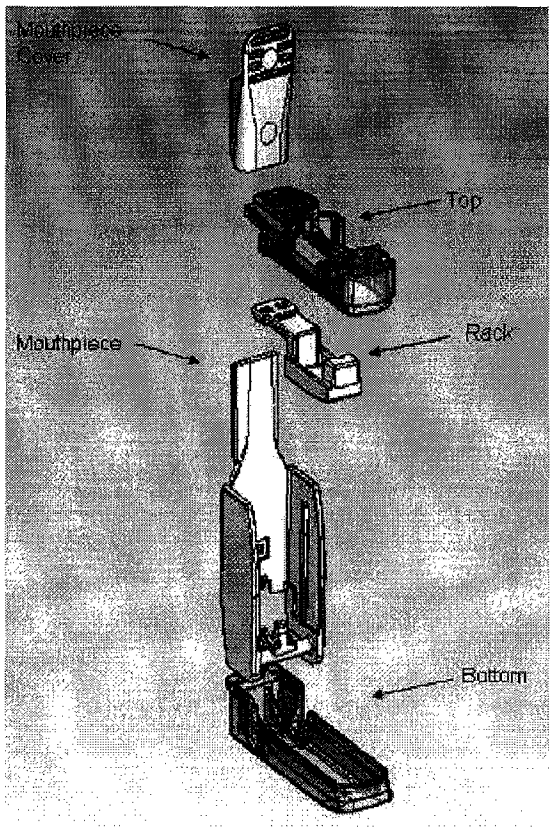


MedTone Inhaler and cartridge on the left and (b) (4) colored cartridge and Gen2 Inhaler on the right.

Gen2 consists of five components shown below. The Top, Rack, Mouthpiece, and Bottom are held together with an ultrasonic weld between the Top and Bottom, which comprise the Housing. The Mouthpiece and Rack are moving pieces and the Mouthpiece is intended to be capped with the Mouthpiece Cover when not in use.

The Mouthpiece is designed to:

- Provide a conduit through which drug will flow into patients
- Provide user grasp surfaces during opening, closing and use
- Move the Rack which configures the Cartridge
- Channel airflow across the top of the Cartridge



The Housing is designed to:

· Provide user grasp surfaces during opening, closing and use

· Provide detents to hold the Mouthpiece closed

· Contain the Mouthpiece & Rack moving parts of the device

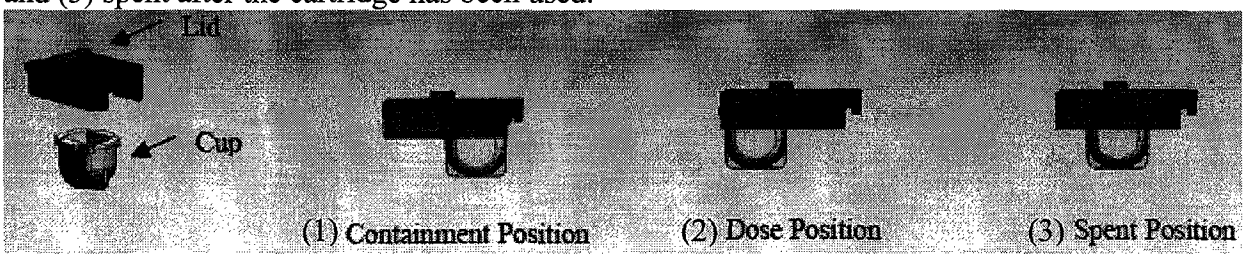
· Receive and hold the Cartridge

· Provide visual indication for proper Cartridge insertion

· Permit airflow to the Cartridge

· Prevent users from blocking air flow into

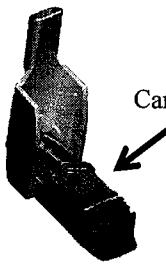
In addition, Gen2 is intended for use with a TI containing cartridge, which is available in fill weights of approximately 3.3 and 6.7 mg for nominal product strengths of 10 and 20U insulin per cartridge, respectively. The Gen2 cartridge consists of two plastic components: a Lid and a Cup shown below. The location of the cup in relation to the lid changes during the various stages of use as depicted below: (1) containment prior to dosing, (2) dosing in the inhaler closed position and (3) spent after the cartridge has been used.



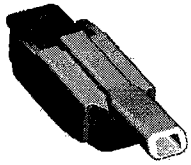
Operating Instructions

The Gen2 system has a simple to use instruction. In the open position, the insulin containing cartridge can be removed from a secondary package and inserted/loaded in the inhaler as depicted below. Then the mouthpiece can be closed in a clam shell-like manner to the closed or dosing position. The inhalation system is then ready for use by simply inhaling deeply to achieve drug delivery. The system resistance works with an end user's inhalation capacity to produce a flow rate that delivers dry powder to the pulmonary tract. The inhaler can then be opened and the spent cartridge can be discarded.

Open/Cartridge Load Position



Close/Dose Position



Operating Principle

Gen2 was developed based on the MedTone® device system, simulating the air flow path and powder de-agglomeration mechanism. Using experience gained from the MedTone® Inhaler development and computer aided flow analysis, the general de-agglomeration mechanism shown below (left) was developed. In this design, (b) (4)

(b) (4)

As in the MedTone inhaler, Gen2 was designed to create a pressure drop during inhalation between the Mouthpiece and Cartridge. The pressure drop results in a flow rate that drives TI dispersion, de-agglomeration and delivery to the patient. This relationship is reported to be the same as the MedTone device with the pressure drop across the inhaler producing flow rates consistent with the Bernoulli principle with the following equation:

(pressure drop)^0.5 = flow rate * resistance

The relation between flow rate and pressure is graphically depicted below for the Gen2 Inhaler. According to these calculations, Gen2 requires less pressure drop to achieve the same flow rates in the linear range, or creates slightly less resistance, than MedTone.

Figure 1. Gen2 Inhalation System Resistance

The sponsor states "[t]he MedTone® device system is characterized with resistance values (b) (4) LPM; the Gen2 device system has a similarly high resistance at (b) (4) LPM. With the MedTone® system, resistance is most linear at flow rates between about (b) (4) sLPM and (b) (4) sLPM and, in Gen2, it is most linear between flow rates of about (b) (4) sLPM and (b) (4) sLPM. The resistance characteristics of both the MedTone® and Gen2 device systems demonstrate reproducibility and consistency. For this reason, resistance remains the preferred control mechanism in assessing inhaler-to-inhaler variation."

Gen2 Versions

Three Gen2 versions were developed with the final version being Gen2C intended for the market.

Version	Highlights	Rationale	Where Used
2A	(b) (4)		MKC-T-140
2B			MKC-TI-141
2C (Final)			MKC-TI-142, MKC-TI-147 (Ongoing), MKC-TI-158,

	(b) (4) [redacted]	MKC-TI-159, MKC-143, Usability Testing for Validation, Verification Testing

V. BENCH PERFORMANCE TESTS

Biocompatibility

The only component of Gen2 in direct mucosal contact with the user is the mouthpiece, which is composed of (b) (4) [redacted]. The sponsor provided the following appropriate test reports for the new mouthpiece in its final form in accordance to ISO 10993-1 for limited duration mucosal contacting device:

- Cytotoxicity testing was conducted in accordance to ISO 10993-5: 2009 with mammalian fibroblast cells and serum supplemented MEM extract (24 hour sample extraction). The new mouthpiece was found not to be reactive with equivalent results to the negative control (b) (4) [redacted]. (Test report 10A0071H-M02G)
- Intracutaneous reactivity testing was conducted in accordance to ISO 10993-10: 2002 on rabbits with samples extracted in sodium chloride and cottonseed oil. Solvents without sample extraction served as controls. After intradermal injection in rabbit backs, no skin irritation was observed up to 72 hours after injection with sample extracted in sodium chloride solvent. While very slight erythema was noted with oil extraction, the test scores for the sample and negative control were identical, and therefore not concerning. (Test report 10A0071H-X04G)
- Maximization for delayed hypersensitivity was conducted in accordance to ISO 10993-12: 2007 and ISO 10993-10:2002 on guinea pigs. Test samples were extracted in sodium chloride and cottonseed oil, and injected intradermally and applied topically on guinea pigs. Skin reaction at the injection and application sites were evaluated and found to have no visible change with discreet or patchy erythema on two animals, one each from test and negative control animals. Therefore, the new mouthpiece was found to have no sensitization potential. (Test report 10A0071H-X03G)

For the mouthpiece cover, the sponsor asserted in response dated November 15, 2010 that it is not in direct contact with the patient mucosa and drug, and therefore does not carry biocompatibility concerns. (b) (4) [redacted]. While the mouthpiece cover can be considered to come in indirect contact with the patient, as it contacts the mouthpiece, the sponsor's rationale appears adequate.

The drug cartridge is in indirect contact with the user; however, as this is part of the drug package, I defer the biocompatibility review of the cartridge to CDER.

Particle Characterization

Comparison of Gen2 to MedTone

The particles generated from Gen2C were compared to that of MedTone. However, the sponsor used Anderson Cascade Impactor (ACI) in the characterization of MedTone and the Next Generation Impactor (NGI) for Gen2. As a result, the sponsor also conducted particle characterization tests for MedTone with NGI to establish equivalence between the MedTone and Gen2 inhalers. The particle characterization tests consisted of assessments of emitted dose (ED) and aerodynamic particle size distribution (APSD). As noted in the table below from sponsor response dated November 15, 2010, the targeted ED criteria is less with Gen2 than MedTone for both dosages; however, the APSD in the respirable range is expected to be similar between the two inhalers and respective dosages.

Table 2. Side-by-side Comparison of Emitted Dose Acceptance Criteria for MedTone and Gen2 Inhalation Systems

MedTone	Gen2	Difference	Rationale
Target Emitted Dose/cartridge: 15 U strength = (b) (4) 30 U strength =	Target Emitted Dose / cartridge 10 U strength: (b) (4) 20U strength:	• Target Emitted Doses	• Different fill contents
Level I, n = 10 cartridges • Mean is within (b) (4)% of target • 9 of 10 determinations are within (b) (4)% of target • All 10 determinations are within (b) (4)% of target	Level I, n = 10 cartridges • Mean is within (b) (4)% of target • 9 of 10 determinations are within (b) (4)% of target • All 10 determinations are within (b) (4)% of target		
If the mean of 10 cartridges is between (b) % and no individual determination is outside of (b) (4)% and not more than 3 individual determinations are outside of (b) (4)%, test an additional 20 cartridges.	If the mean of 10 cartridges is between (b) (4)% and no individual determination is outside of (b) (4)% and not more than 3 individual determinations are outside of (b) (4)%, test an additional 20 cartridges		
Level II, n = 30 cartridges • Mean is within (b) (4)5% of target • 27 of 30 determinations are within (b) (4)% of target • All 30 determinations are within (b) (4)% of target	Level II, n = 30 cartridges • Mean is within (b) (4)% of target • 27 of 30 determinations are within (b) (4)% of target • All 30 determinations are within (b) (4)% of target		

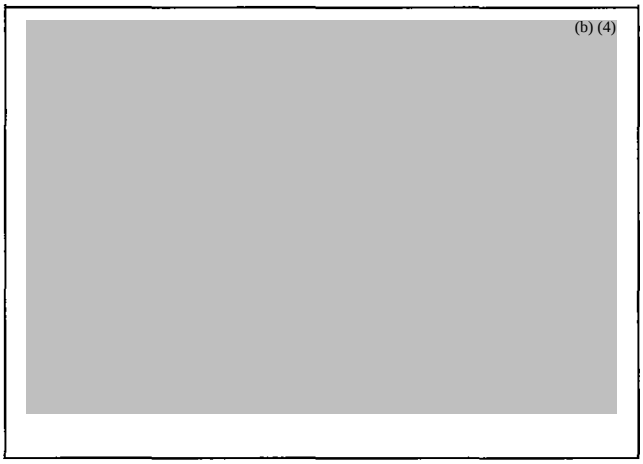
Table 3. Side-by-side Comparison of APSD Acceptance Criteria for MedTone and Gen2 Inhalation Systems

MedTone (ACI)	Gen2 (NGI)	Difference	Rationale
(b) (4)		• Test methods • Number of groupings	• Higher throughput method • Increased number of groupings from 3 to 4 based on comments from the Agency

[a] Evaluated as part of our commitment to the Agency, but not previously submitted.

Comparison of historical ED data from MedTone with Gen2 demonstrated that ED was overall less with Gen2 with smaller variability at flow rates generated at a constant pressure drop of (b) (4). The graphical representation below for the higher dosage unit presented in 3.2.P.2.4 illustrates the range of ED for both devices. The same pattern of variability was observed with the lower dose cartridges.

Figure 28. Emitted Dose Variability Gen2 (20 U) vs. MedTone (30 U)



76 MedTone (30 U Batches) and 13 Gen2 (20 U Batches)

For APSD comparison using NGI, the following averaged data for the low and high dose equivalents for MedTone and Gen2 systems were obtained. The test was conducted at a constant pressure drop of (b) (4) (1 sample from 3 lots with 3 runs for each dose and inhaler system):

	Mean of 3 runs for Cup 3 – MOC (U)		
	Lot 1	Lot 2	Lot 3
Medtone (15U)	(b) (4)		
Gen2 (10U)			

Medtone (30U)	(b) (4)
Gen2 (20U)	

Adapted from Tables 3 to 7presented in Response to FDA Information Request (dated November 15, 2010).
**Based on ACI test setup.*

Insulin units captured only in cups 3 through MOC are presented above, as they generally represent particle sizes in the respirable range. While the Gen2 system consistently delivered less insulin units in this range than compared to the Medtone system (by approximately (b) (4)), the Gen2 results fell within the sponsor specified Gen2 and Medtone systems criteria with the exception of one lot.

To further demonstrate the equivalence of the two systems, the sponsor used a Copley Inhaler Testing Data Analysis Software (CITDAS) to calculate total insulin units for fine particle distribution (FPD) for particle size less than (b) (4) from the APSD test described above. This calculation is meant to correct for the difference in flow rates generated by a pressure drop of (b) (4) in the two inhaler systems. After correction, the data from the APSD test described above is as follows:

	FPD (b) (4) (U)		
	Lot 1	Lot 2	Lot 3
Medtone (15U)	(b) (4)		
Gen2 (10U)			
Medtone (30U)			
Gen2 (20U)			

Adapted from Tables 3 to 7presented in Response to FDA Information Request (dated November 15, 2010).

ED in Gen2

ED test was conducted in accordance to TM5557 methods with the following acceptance criterion: (b) (4)% of strength (10 U: (b) (4) U; 20 U: (b) (4) U). Thirty inhalers were used for the 10 U and 40 inhalers were used for the 20 U test results presented below from 3.2.P.2.4. The results were within set device specifications.

Table 18. Gen2 Emitted Dose Testing Results

	10 U Cartridge Strength (U)[a]	20 U Cartridge Strength (U)[a]
N		(b) (4)
AVG		
STD		
Max		
Min		
[a] each inhaler tested with 1 cartridge		

APSD in Gen2

APSD testing was conducted in accordance to TM5558 methods with the following acceptance criterion for Cups 3-MOC – considered respirable range: (10 U: (b) (4) U,

20 U: (b) (4) U). The APSD results were within set device specifications.

Table 19. APSD Summary for Gen2

	10 U[a]		20 U[b]	
	AVG (U)	STD (U)	AVG (U)	STD (U)
Total Dose (IP - MOC)				(b) (4)
APSD (Cups 3 - MOC)				

[a] each inhaler tested with 3 cartridges
[b] each inhaler tested with 2 cartridges

Varied Flow in Gen2
The effets of flow rate on particle characteristics were also studied and presented in 3.2.P.2.4. Flow rates generated by pressures (b) (4) kPa are evaluated for ED and APSD using TM5557 and TM5558 methods, respectively.

The ED results were all within specified criteria for the entire range of flow studied, as shown below.

Table 20. Gen 2 ED Testing at Varied Flows/Pressures

	10 U	20 U
Pressure (kPa)		(b) (4)
Flow (LPM)		
Inhaler	ED (U)	ED (U)
AVG		(b) (4)
STD		
MAX		
MIN		

Conducted with six (6) inhalers (for each cartridge strength) each discharged with 3 cartridges.

The APSD results were also within the specified criteria for the entire flow rate range studied, as summarized in the next two tables.

Table 22. Gen2 APSD Summary Data at Varied Flows

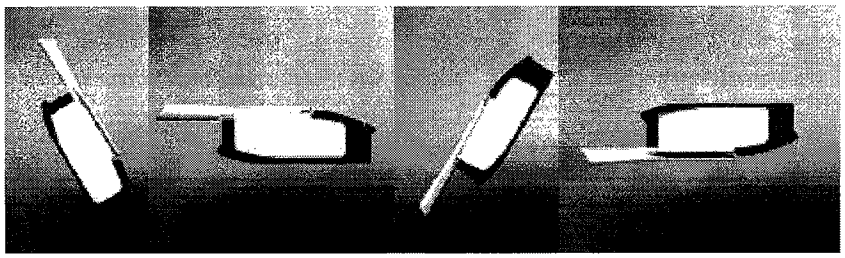
	10 U	20 U
Pressure (kPa)		(b) (4)
Flow (LPM)		
MMAD (µm) (range)		
GSD (range)		
FPD (U) (range)		
FPF, % (range)		

Modified Tables 22 and 24. Gen2 APSD Varied Flow Rate Results

	Mean of 2 or 3 runs for Cup 3 – MOC (U)
	(b) (4)
Gen2 (10U)	
Gen2 (20U)	

Orientation Study

The effects of device orientation (tilt and twist) during inhalation on particle characteristics were also studied. For the following representative device orientations studied, the particle characteristics were unaffected in all studied orientations, except in the far right device orientation:



Pitch -60° Cant 0° | Pitch 0° Cant 0° | Pitch 60° Cant 0° | Pitch 0° Cant 180°

ED was unaffected in all device orientations studied (n=6 for 6 positions). APSD results met set criteria for particles in the respirable range (Cup 3 – MOC) in all studied orientations (the four depicted above), but it did not meet the minimum criteria in the upside down device orientation (Pitch 0°, Cant 180°). An average of (b) (4) was delivered in this orientation with the 20U cartridge, just below the (b) (4) minimum. The sponsor plans to mitigate this issue with better instructions for use as reported in their November 15, 2010 response. In addition, the sponsor indicated that the proposed human factors study on the final approved labeling will be validated once complete, according to their response dated November 24, 2010.

Environmental Conditions

Particle characterization was also evaluated at extreme use conditions of low temperature with low humidity (5°C /25% RH) and high temperature with high humidity (40°C /75% RH) in a controlled chamber. ED and APSD from GEN2 were not affected at these extreme environmental conditions (3.2.P.2.4.5.3).

Reviewer Comment:
As the particles generated by Gen2 is analogous to meter dosed and pressure dosed inhalers, and the sponsor conducted particle characterization studies in accordance to the "1998 FDA Draft Guidance for Industry on Metered Dose Inhaler (MDI) and Dry Powder Inhaler (DPI) Drug Products", I defer the adequacy of particle characterization to CMC/CDER.

Gen2 Design Verification and Stability

The Gen2 design verification studies are planned to verify the visual and mechanical design of Gen2 at baseline and after shelf-life storage conditions. This plan and

preliminary results were presented in 3.2.P.8. Gen2 was found to meet the criteria for all tests discussed below at the initial time period. These tests are also planned to be conducted after real-time storage at 5°C for 24 months and 25°C for 48 months to test the effects of storage conditions. Accelerated storage testing at 50°C for up to 26 weeks is also planned. The tables below depict the planned realtime and accelerated testing schedule.

Storage Condition	T = 0 Months	T = 12 Months	T = 24 Months	T = 48 Months
25°C ±2°C / 60% ± 5%RH	X	X	X	X
5°C ±3°C	N/A	X	X	N/A
15 Inhalers are tested after 15 days of discharge at each test point. N/A = not applicable				

Storage Condition	T = 0 Weeks	T = 6.5 Weeks	T = 13 Weeks	T = 26 Weeks
50°C	N/A	X	X	X
15 Inhalers are tested after 15 days of discharge at each test point. N/A = not applicable				

While not listed in the design verification testing summary below, powder performance, ED and APSD, is also planned using TM5557 and TM5558 methods, respectively. To date, test results at the initial time period and at 13 weeks in the accelerated condition were provided, and all results appear adequate.

Table 3. Gen2 Inhaler Design Verification Testing Summary

Test	Descriptor /Name	Purpose of Test	Acceptance Criteria	Rationale	Test Method
1	Inhaler Visual Inspection	Screen for functionality/ruggedness/integrity	(b) (4)	Visual inspection for defects and evaluation of functionality. Details of inspection provided in the STM.	STM.03-0064
2	Inhaler Resistance Testing	Confirm Flow Mechanics		Range of resistance provides for proper flow rates and flow balance to effectively de-agglomerate powder.	STM.99-0023[a]
3	Inhaler Force To Open	Anticipate end user force required to rotate the mouthpiece relative to the housing		Minimum force of (b) (4) required to remain closed after cartridge assembly is placed in the inhaler. Maximum force (b) (4) set utilizing engineering judgement as the upper threshold a user can comfortably apply.	STM.03-0130
4	Inhaler Force To Close	Anticipate end user force required to rotate the mouthpiece relative to the housing		Minimum force of (b) (4) required to provide tactile feel to user to confirm inhaler is closed. Maximum force (b) (4) set utilizing engineering judgement as the upper threshold a user can comfortably apply.	STM.03-0131
5	Inhaler Ultrasonic Weld strength	Anticipate the failure force (ruggedness) required to break the ultrasonic weld of the mouthpiece to the body		Minimum force of (b) (4) provides for integrity of the inhaler weld. Engineering judgement was utilized to set criteria.	STM.03-0073
6	Device Drop Test, Inhaler (1.0 meter)	Predict the ability (ruggedness) of the inhaler to withstand a drop onto a hard surface without breakage		Confirms integrity of the inhaler if dropped. 1.0 meter chosen to comply with: ISO 20072 Aerosol Drug Delivery Device Design Verification – Requirements and Test Methods	STM.03-0062
7	Force to remove Mouthpiece Cover	Anticipate the end user force required to remove the Mouthpiece Cover		Maximum force (b) (4) set utilizing engineering judgement as the upper threshold a user can comfortably apply.	STM.03-0063

[a] = STM.99-0023 is the laboratory test method which was transferred to (b) (4) as TM5568. The two methods are equivalent.

[b] = As a response to a complaint in a clinical study stating that "the inhaler popped open", we reanalyzed the lower limit for force to open. The specification was increased to (b) (4) in order to maintain integrity during the intended in-use period.

Life-Cycle Verification Test

The sponsor also has plans to test the performance of Gen2 for the simulated-use life after storage in the conditions described above. The sponsor plans to discharge 180 cartridges after storage of Gen2 in the conditions described above. This is to mimic the maximum frequency of possible cartridge discharge over the use life of Gen2, which is 15 days. The sponsor also included a 50% safety factor in calculating discharge times [(8 possible discharge in day + 4 for safety factor) per day x 15 days]. The sponsor plans to conduct test numbers 1 – 4 and 7 above, in addition to ED and APSD using previously described test methods. To date, the sponsor has conducted the tests at baseline (t = 0) and after 6.5 weeks of accelerated storage condition. No degradation in results were reported.

Mouthpiece Powder Buildup

A test was conducted to assess TI powder buildup over the use period. The sponsor again incorporated a 50% safety factor and conducted the test over 22.5 days of simulated use (Note: The 50% safety factor was not included in the possible number of discharges per day. Therefore, the total number of discharge is the same as in the life-cycle test described above.). The powder buildup on the mouthpiece was observed to decrease over time as shown in the table below from 3.2.P.8:

Table 27. Mouthpiece Retention Testing

Days of Use	Number of Cartridges	Total Powder Discharged (mg)	Insulin Deposition (U)	% Deposition
1	8	(b) (4)		
2	15			
6	45			
9	75			
13	105			
15	120			
22.5	180			

Each "Days of Use" time point represents an average of 3 different inhalers tested. A total of 21 inhalers were evaluated.

% Deposition = insulin deposition / (b) (4) * total powder discharge)

However, particle characterization testing showed that APSD in the respirable range slightly increased over simulated use time (see table below from 3.2.P.8), which corroborates with the decreased TI deposition on the mouthpiece over time.

Table 28. Mouthpiece Build-up APSD Testing (U) – 20 U Gen2

(Acceptance Criterion Cups 3-MOC: (b) (4)

	7.5 Days Retention	15 Days Retention	22.5 Days Retention
	AVG	AVG	AVG

DELIVERED DOSE (IP-MOC)	(b) (4)
APSD (Cups 3-MOC)	
Each time point represents an average of 3 inhalers tested. A total of 9 inhalers were evaluated. Each APSD test is conducted with 2-20 U cartridges [a] = Mouthpiece value represents total found in the inhaler mouthpiece following real time discharges. All other values (IP-MOC) represents total units per cartridge	

VI. DEVICE LABELING

Labeling was provided for the Gen2 Inhaler, which included an instruction for use. The appropriate prescription statement as required by 21 CFR 801.109 was not included in the labeling, *and will be requested.*

The inhaler instructions cover identification of the device components, device set up, Cartridge insertion, and proper device orientation for inhalation. The user instructions are described above under the Operating Instructions subsection of the Device Description section.

The device is instructed for disposal after a 15 day use period and requires no cleaning.

VII. HUMAN FACTORS STUDY

The human factors/usability test report submitted for Gen2 was reviewed by Quynh Nguyen in ARDB. A brief summary of the review is presented here. Please refer to her attached memo for further details.

The review of the Gen2 usability study began with the Type C meeting package material from May 2010. After the initial review of the usability test plan for Gen2, a number of comments were generated and included in the EOR Preliminary Comments letter in preparation of the June 9, 2010 meeting with regards to elements to be addressed in a human factors study (e.g., detailed description of intended user, identification of use-related hazards and risks, identification of task priorities, data analysis and presentation, and validation of training material).

Following this review, the sponsor submitted a CR submission on June 29, 2010. This submission included a "Human Factors Study Report" in 3.1.2.P.2, Appendix I and a Summative Usability Test of AFREZZA Insulin Inhalation System Final Report dated April 5, 2010 in Attachment 3 to Appendix I. While some of the comments resulting from the June Type C meeting were addressed in this report, there were remaining issues regarding the usability study methods and validation of proposed use error mitigation. These issues were sent to CDER in an email dated October 5, 2010 for additional information request. The additional information dated on November 24, 2010 was reviewed.

After review of the human factors study report provided to date, the reviewer made the following comments, which are reflected in the recommended deficiencies:

- Overall, the reviewer noted that the study was designed to simulate worst case

conditions without providing complete training materials to user and use of dose color coded cartridges without dosage numbers written on the cartridge. Therefore, the conducted test may have been biased to greater user confusion and use errors.

- The sponsor provided adequate explanation for use error occurrences and associated potential hazards. The most common pattern of use errors were potentially due to user unawareness or ill-recognition of the instructions for use (IFU) content. However, the mitigation for these errors is to refer back to the IFU. This suggests that reference to the IFU may not be an effective mitigation strategy.

- The sponsor explained that the study participants did not receive any training prior to use. Therefore, the noted use errors were due to lack of training and familiarity of the inhaler system. However, this explanation does not address whether these errors would be mitigated with adequate training. As previously noted at the Type C meeting held on June 9, 2010, if training is an integral part of device use, it should be included in the validation study.

- While the sponsor identified a number of mitigation to address the noted use errors by proposing to update the IFU and to include dosage strengths on the cartridge itself, the sponsor has not conducted a validation study to demonstrate these mitigation strategies will minimize use errors and improve user comprehension. Instead, the sponsor has stated that such study will be conducted after the final labeling is approved. The sponsor should be reminded that a validation study of the mitigation strategy is needed, and such a study should include representative device users, training and test the final device version.

VIII. DEFICIENCIES

A. Since the sponsor introduced a new device – Gen2 Inhaler system - in their submission dated June 28, 2010, after the review of the MedTone Inhaler system in the original NDA and FDA's Complete Response letter dated March 12, 2010, the deficiencies discussed below only pertain to the Gen2 Inhaler System. For the review and deficiency communications on the MedTone Inhaler system, please refer to CDRH/ODE memo dated December 14, 2009.

The deficiencies restated in *italics* below were sent to CDER on October 5, 2010 to request additional information from the sponsor for further review. They were sent to the sponsor by CDER on October 28, 2010. ODE received the responses to deficiency numbers 1 to 8 on November 16, 2010 (dated November 15, 2010), and for numbers 9 and 10 on November 30, 2010 (dated November 24, 2010). A summary of the response and FDA comments in normal fonts follows each deficiency. Note: Review of responses to deficiencies 9 and 10 were conducted by Quynh Nguyen and briefly summarized here (see attached memo for further details).

Device Related Issues

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.*

   Response Adequate: The sponsor clarified that all testings reported in section 3.2.P.2.4 was conducted with the Gen2C system with the exception of data presented in Table 14, Table 15, Figure 30, and Figure 31, which were conducted with versions A and B. The sponsor reported that data from tests conducted with versions A and B were applicable to version C, the final version, as the flow resistance was not changed in all three versions.

   In addition, the sponsor provided emitted dose and aerodynamic particle size distribution grouping results for the Gen2C inhaler and cartridge in comparison to Gen2B inhaler with Gen 2C cartridge, the combination with which all tests appeared to have been conducted with. This demonstrated that the particle characterization between inhaler versions B and C may be adequate.

   The sponsor also clarified that all test data presented in 3.2.P.5.6 were presented in Table 2 of Section 3.2.P.5.4, which all appeared to have been conducted with Gen2B and Gen2C models. The data presented in 3.3.P.8 were all reported to be from model Gen2C.

2. *The Gen2C Inhaler mouthpiece now has* (b) (4) *nd 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).*

   Response Adequate: The sponsor clarified that the Gen2C mouthpiece (b) (4) contains an (b) (4) The mouthpiece (b) (4) was tested for biocompatibility, which test results were provided in Section 3.2.P. However, this section was titled "Inhaler – Not Applicable", and therefore, not reviewed until this cycle. It appears the sponsor provided the following appropriate test report for the new mouthpiece in its final form in accordance to ISO 10993-1 for limited duration mucosal contacting device:
   - Cytotoxicity testing was conducted in accordance to ISO 10993-5: 2009 with mammalian fibroblast cells and serum supplemented MEM extract (24 hour sample extraction). The new mouthpiece was found not to be reactive with equivalent results to the negative control (b) (4).
   - Intracutaneous reactivity testing was conducted in accordance to ISO 10993-10: 2002 on rabbits with samples extracted in sodium chloride and cottonseed oil. Solvents without sample extraction served as controls. After intradermal injection in rabbit backs, no skin irritation was observed up to 72 hours after injection with

sample extracted in sodium chloride solvent. While very slight erythema was noted with oil extraction, the test scores for the sample and negative control were identical, and therefore not concerning.

- Maximization for delayed hypersensitivity was conducted in accordance to ISO 10993-12: 2007 and ISO 10993-10:2002 on guinea pigs. Test samples were extracted in sodium chloride and cottonseed oil, and injected intradermally and applied topically on guinea pigs. Skin reaction at the injection and application sites were evaluated and found to have no visible change with discreet or patchy erythema on two animals, one each from test and negative control animals. Therefore, the new mouthpiece was found to have no sensitization potential.

For the mouthpiece cover, the sponsor asserted that it is not in direct contact with the patient mucosa and drug, and therefore does not carry biocompatibility concerns. (b) (4) While the mouthpiece cover can be considered to come in indirect contact with the patient, as it contacts the mouthpiece, the sponsor's rationale appears adequate.

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.*

Response Adequate: The sponsor noted that the AUC and PIP criteria were set to conservative values. Even in the absence of meeting AUC or PIP criterion, as noted above, volumetric median geometric particle diameter criterion can be met.

4. *In 3.2.P.2.4.3.1, Flow Mechanics for the Container Closure System, you theorized that* (b) (4) *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.*

Response Adequate: The sponsor stated that the complaint assessment was incorrect and likely due to patient misuse. The sponsor conducted a bench test in response to demonstrate reverse flow into a drug cartridge loaded Gen2 system resulted in negligible mass loss. An average mass loss of (b) (4) % was noted before and after reverse flow application of (b) (4) drop (using 10 cartridges each with 2 inhalers). The

test results and conclusion appears adequate, and further validates their theory (b) (4) [redacted].

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.*

   Response Adequate: In response to the first part of the deficiency, the sponsor provided the requested tables with clear side-by-side comparison of the MedTone and Gen2 emitted dose (Table 2) and APSD (Table 3) criteria. However, the APSD acceptance criteria comparisons are not analogous, because they were based on two different cascade impactors – MedTone with ACI and Gen2 with NGI. Therefore, to further explain this issue, and address the second part of the above deficiency, the sponsor provided additional APSD data for both the MedTone and Gen2 systems using NGI.

Table 2. Side-by-side Comparison of Emitted Dose Acceptance Criteria for MedTone and Gen2 Inhalation Systems

MedTone	Gen2	Difference	Rationale
Target Emitted Dose/cartridge: 15 U strength = (b) (4) 30 U strength = Level I, n = 10 cartridges • Mean is within (b) (4)% of target • 9 of 10 determinations are within (b) (4)% of target • All 10 determinations are within (b) (4)% of target If the mean of 10 cartridges is between (b) (4)% and no individual determination is outside of (b) (4)% and not more than 3 individual determinations are outside of (b) (4)%, test an additional 20 cartridges. Level II, n = 30 cartridges • Mean is within (b) (4)% of target • 27 of 30 determinations are within (b) (4)% of target • All 30 determinations are within (b) (4)% of target	Target Emitted Dose / cartridge 10 U strength: (b) (4) 20U strength: Level I, n = 10 cartridges • Mean is within (b) (4)% of target • 9 of 10 determinations are within (b) (4)% of target • All 10 determinations are within (b) (4)% of target If the mean of 10 cartridges is between (b) (4)% and no individual determination is outside of (b) (4)% and not more than 3 individual determinations are outside of (b) (4)%, test an additional 20 cartridges Level II, n = 30 cartridges • Mean is within (b) (4)% of target • 27 of 30 determinations are within (b) (4)0% of target • All 30 determinations are within (b) (4)% of target	• Target Emitted Doses	• Different fill contents

Table 3. Side-by-side Comparison of APSD Acceptance Criteria for MedTone and Gen2 Inhalation Systems

MedTone (ACI)	Gen2 (NGI)	Difference	Rationale
(b) (4)		•Test methods •Number of groupings	•Higher throughput method •Increased number of groupings from 3 to 4 based on comments from the Agency

[a] Evaluated as part of our commitment to the Agency, but not previously submitted.

The additional APSD data using NGI resulted in the following averaged data for the low and high dose equivalents for MedTone and Gen2 systems tested at a constant

pressure drop of (b) (4) (1 sample from 3 lots with 3 runs for each dose and inhaler system):

	Mean of 3 runs for Cup 3 – MOC (U)		
	Lot 1	Lot 2	Lot 3
Medtone (15U)	(b) (4)		
Gen2 (10U)			
Medtone (30U)			
Gen2 (20U)			

Adapted from Tables 3 to 7presented in Response to FDA Information Request (dated November 15, 2010).
**Based on ACI test setup.*

Insulin units captured only in cups 3 through MOC are presented above, as they generally represent particle sizes in the respirable range. While the Gen2 system consistently delivered less insulin units in this range than compared to the Medtone system (by approximately (b) (4) units), the Gen2 results fell within the sponsor specified Gen2 and Medtone systems criteria with the exception of one lot.

It is important to note that these results were based on a controlled APSD particle test setup with flow rates created at a constant pressure drop of (b) (4). Therefore, it is unclear how this difference in bench performance results would translate to actual insulin delivered to patient and its physiologic implications in a clinical setting, due to variables such as inhalation pressure drop, exhalation timing after drug inhalation and proper use by patient. This can only be truly be evaluated in a clinical setting.

To further demonstrate the equivalence of the two systems, the sponsor used a Copley Inhaler Testing Data Analysis Software (CITDAS) to calculate total insulin units for fine particle distribution (FPD) for particle size less than (b) (4) from the APSD test described above. This calculation is meant to correct for the difference in flow rates generated by a pressure drop of (b) (4) in the two inhaler systems. After correction, the data from the APSD test described above is as follows:

	FPD (b) (4) (U)		
	Lot 1	Lot 2	Lot 3
Medtone (15U)	(b) (4)		
Gen2 (10U)			
Medtone (30U)			
Gen2 (20U)			

Adapted from Tables 3 to 7presented in Response to FDA Information Request (dated November 15, 2010).

This data correction provides supporting evidence of the equivalence of FPD (b) (4) at a given pressure drop in the two inhaler systems; however, it is unclear if CITDAS is a well validated analysis software. In addition, this analysis highlights the variability and dependence of particle delivery on inhalation flow rate.

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.*

Response Adequate: The sponsor clarified that a minimum discharge volume of (b)(4) L was used in the varied flow parameters studied. Therefore, flow rates of (b)(4) L/min resulted in inhalation duration of (b)(4) seconds, respectively. In each case, the sponsor reported that powder left the mouthpiece within one second regardless of the flow rate in high speed videography analysis. (b)(4) .

The emitted dose and APSD results appear consistent for the Gen2 system over varied flow rates tested in this bench testing. (b)(4) . (b)(4) , it provides limited information on the actual amount of drug retained by the patient, which is highly variable on patient inhalation maneuvers. Since the inhalation maneuvers for the Gen2 and Medtone devices are different, one inhalation for Gen2 and (b)(4) for Medtone, this test does not demonstrate whether the actual amount of drug retained by the patient from the two devices with differing inhalation maneuvers will be the same. These are the limitations of a bench test.

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.*

Response Adequate: The sponsor asserts that there was only a slight decrease in APSD in the upside down orientation, even though the insulin units in the cup 3 – MOC, (b)(4) U, was clearly outside of the accepted APSD criteria of >(b)(4) U. The sponsor intends to mitigate the risk of use in the upside down orientation with clear instructions with graphics on the front cover of the proposed instructions and in the instructional steps. This appears to be an adequate approach that could be addressed by clear instructions. However, as this issue is a usability concern, and is also a subject of evaluation by our human factors (HF) reviewer, I defer the adequacy of the proposed mitigation to the HF reviewer.

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.*

Response Inadequate: The sponsor has clarified that the claimed storage conditions will be 2 to 25°C; however, testing is being conducted at 5+/-3°C and 25+/-2°C. A test condition of 5+/-3°C does not mean that the test condition is maintained at 2 or 8°C. It is only the error limit range of the set temperature. It is unscientific to claim a lower temperature storage limit of 2°C based on this test condition. Therefore, the claimed storage condition should reflect the test condition of 5 to 25°C, exclusive of temperature tolerance of the test setup.

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)

Response Adequate: In addition to accelerated testing, the sponsor plans on continuing the real time stability testing.

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.*

Response Adequate: The sponsor provided an updated Table 3 in 3.2.P.8 with the requested information. It now includes a summary of the verification tests along with the test purpose, acceptance criteria and their rationale and the test method document numbers where the test setup, equipments used and methods information were described. The results for each of the tests are also presented in section 3.2.P.8 and found to all meet test criteria. The sponsor also noted that only the inhaler resistance testing was conducted with the cartridge in place. This appears adequate, as the cartridge would direct impact inhaler resistance, while the remaining tests are not dependent on cartridge performance.

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.*

Response Adequate: The sponsor clarified that the statement in 3.2.P.8.3 was a typographical error. ED tests were conducted at (b) (4) L/min.

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) *over claimed shelf-life and use.*

Response Inadequate: The sponsor clarified that the mouthpiece does not have an (b) (4) This point is understood. However, the sponsor has not provided a rationale or performance test to demonstrate the mouthpiece with the (b) (4) will "…prevent (b) (4) …" over the claimed shelf-life and simulated use conditions. Therefore, the sponsor should be asked to commit to complete a mouthpiece retention testing after shelf-life and simulated use conditions.

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

Response Adequate: The sponsor provided the raw data for the APSD test presented in Table 28 of 3.2.P.8, which consisted of n=3 at 7.5, 15 and 22.5 days of simulated use. The test demonstrated that APSD in the respirable range were within the specified criteria. However, it is important to note that APSD in the respirable range increased over simulated use time (approximately (b) (4) U). Again, as noted in assessments to deficiency number 5 and 6 responses above, the physiological impact of increased drug delivered over simulated use time, while small, can not be concluded from bench tests.

Human Factors Related Issues – These deficiencies were generated and reviewed by a human factors reviewer in CDRH, Quynh Nguyen. Responses dated November 24, 2010 were reviewed and summarized below. Please refer to her attached memo for further details.

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.

Response Adequate: The reviewer noted that the issues raised above were adequately addressed. Overall, the reviewer noted that the study was designed to simulate worse case conditions without complete training materials, and dose color coded cartridges without dosage numbers written on the cartridge. Therefore, the reviewer noted that the conducted test may have skewed towards user confusion and use errors.

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.*

    Response Inadequate (a&b): The sponsor provided adequate explanation for use error occurrences and associated potential hazards. The most common pattern of use errors were potentially due to user unawareness or ill-recognition of the instructions for use (IFU) content. However, the mitigation for these errors is to refer back to the IFU. This suggests that reference to the IFU may not be an effective mitigation strategy.

    In addition, the sponsor explained that the study participants did not receive any training prior to use. Therefore, the noted use errors were due to lack of training and familiarity of the inhaler system. However, this explanation does not address

whether these errors would be mitigated with adequate training. As previously noted at the Type C meeting held on June 9, 2010, if training is an integral part of device use, it should be included in the validation study.

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.*

Response Inadequate: While the sponsor identified a number of mitigation to address the noted use errors by proposing to update the IFU and to include dosage strengths on the cartridge itself, the sponsor has not conducted a validation study to demonstrate these mitigation strategies will minimize use errors and improve user comprehension. Instead, the sponsor has stated that such study will be conducted after the final labeling is approved. The sponsor should be reminded that a validation study of the mitigation strategy is needed, and such a study should include representative device users, training and test the final device version.

B. After review of responses dated November 15 and 24, 2010, the following deficiencies remain:

1. FDA previously requested that you provide a usability study validating the proposed mitigations focusing on updates to the instructions for use (IFU) and additional changes to the cartridge strength label in deficiency number 10, requested on October 28, 2010. In response, you stated that you intend "to confirm the commercial AFREZZA® Inhalation System with the final FDA approved labeling." Provide the complete test protocol and report for this validation study for review.

   FDA notes that such study should demonstrate the proposed mitigation do not introduce new risks, are effective in minimizing user errors and improve user comprehension. In addition, such a study should test the representative device users, user training, final IFU, and final device version intended for the market.

Also provide an explanation and validation of the following concerns, and in the new study:

a. It appears that the potential causes for most of the reported use errors were due to user not being aware of, or recognizing, the content provided in the IFU. However, the mitigation for these errors according to your FMEA, is to refer back to the IFU. Since it appears the user errors were due to lack of user awareness of, or recognizing, the content provided in the IFU, it is unclear how reference to the IFU would be an effective mitigation strategy. Please explain.

b. You explained that the usability study participants did not receive any training prior to use, which does not represent the intended first time user experience. Patients prescribed any type of insulin are expected to receive training in proper dosing. Therefore, you justified that the noted use errors were due to lack of training and familiarity of the inhaler system. Again, FDA notes that the usability validation study should reflect the realistic use of the device. Since it appears that training is necessary to support safe use of the subject device, your usability study should also validate the training and its materials. Provide a usability test report that validates your proposed training and its materials. In this response, also provide a description of your modest training program, as you indicated that "modest training with the IFU will reduce these risks".

2. You clarified that the claimed storage condition for the Gen2 Inhaler system will be 2 to 25°C; however, your stability testing is being conducted at 5+/-3°C and 25+/-2°C. The test condition of 5+/-3°C does not mean that the test condition is maintained at 2 or 8°C. These are the tolerance range of the target test temperature of 5°C. Therefore, the claimed storage condition in your labeling should reflect the test condition of 5 to 25°C, exclusive of your test setup temperature tolerance.

3. You clarified that the mouthpiece (b) (4) However, you have not provided a rationale or performance test to demonstrate the mouthpiece with the (b) (4) will "… (b) (4) …" over the claimed shelf-life and simulated use conditions. Therefore, commit to complete a mouthpiece retention testing after shelf-life and simulated use conditions in your stability testings.

4. The prescription use statement for the Gen2 Inhaler could not be found in your labeling. Include in your label the caution statement required by 21 CFR 801.109 for prescription devices: "Caution: Federal law restricts this device to sale by or on the order of a physician."

Melanie Choe, Ph.D., Reviewer, ARDB

12/21/10
Date

James Robotham, M.D., DAGID Deputy Director

12/21/2010
Date

Department of Health and Human Services
Public Health Service
Food and Drug Administration
Center for Drug Evaluation and Research
Office of Surveillance and Epidemiology

Date:	December 13, 2010
Application Type/Number:	NDA 022472
To:	Mary Parks, MD., Director Division of Metabolism and Endocrine Products
Through:	Zachary Oleszczuk, Pharm.D., Team Leader Denise Toyer, Pharm.D., Deputy Director Carol Holquist, R.Ph., Director
From:	Yelena Maslov, Pharm.D., Safety Evaluator
Subject:	Label and Labeling Review
Drug Name(s):	Afrezza (Insulin human [rDNA origin]) Inhalation Powder
Applicant/sponsor:	MannKind Corporation
OSE RCM #:	2010-1576, 2010-1577

CONTENTS

EXECUTIVE SUMMARY

This review summarizes the Division of Medication Error Prevention and Analysis evaluation of Usability Test as well as labels, labeling, and packaging design of Afrezza Inhalation Powder and its associated inhaler for areas that could lead to medication errors. Our evaluation has determined areas of needed improvement that may help prevent medication errors with the use of this product. We have provided our rationale in Section 4 and we have provided our recommendations in Section 5.

1. BACKGROUND

1.1 INTRODUCTION

This review responds to a request form the Division of Metabolism and Endocrine Products (DMEP) dated July 20, 2010 to evaluate Usability Test as well as inhaler labels, cartridges, foil pack labels, carton and insert labeling, and packaging design for Afrezza Inhalation Powder (NDA 022472) and its associated inhaler for the potential to contribute to medication errors.

1.2 REGULATOY HISTORY

Afrezza Inhalation Powder, which is delivered via re-usable, breath-powered, high resistance, dry powder Gen 2 inhaler is a subject of 505 (b)(1) application under NDA 022472 originally submitted to the FDA on March 16, 2009. DMEPA has previously reviewed the inhaler labels, cartridges, foil pack labels, as well as carton and insert labeling for Afrezza Inhalation Powder that included an earlier inhalation device (Model D) in OSE Review #2009-2440, dated December 28, 2009. In that review, DMEPA recommended designing the Usability Study by applying the principles of human factors to determine vulnerabilities and potential errors in the device and product design, which could be remedied before the design is finalized. On March 12, 2010, The Application recieved a Complete Response.

The Applicant submitted a response to a Complete Response to the FDA on June 29, 2010, in which the Applicant included a new inhaler (Gen 2) and a Usability Test applying the principles of human factors regarding the use of Afrezza Inhalation Powder and its associated inhaler. Additionally, the Applicant submitted a proprietary name review, Afrezza and (b) (4) Inhalation Powder for the product, which DMEPA found unacceptable and this assessment was communicated to the Applicant on August 24, 2010. The Applicant submitted a proprietary name withdrawal request on August 27, 2010. The Applicant resubmitted proprietary name request for the name, Afrezza, on September 24, 2010.

1.3 PRODUCT INFORMATION

Afrezza Inhalation Powder is delivered via re-usable, breath-powered, high resistance, dry powder Gen 2 inhaler. Insulin is intended for the treatment of adults with diabetes mellitus. Afrezza Inhalation Powder is proposed to be marketed in a single dose cartridge of 10 units or 20 units. Each cartridge requires one inhalation to deliver the full dose. The 10 unit cartridge delivers approximately 4 units inhaled insulin and the 20 unit cartridge delivers approximately 8 units inhaled insulin to the patient. Patient specific factors affect the end amount of insulin delivered including health of patient (e.g., FEV1), concomitant health conditions, and user technique.

Insulin naïve patients should start on a 10 unit dose of Insulin (approximately 4 inhaled units) at each meal and titrate to the dose necessary to control blood glucose. For all other patients, the starting dose of Afrezza will be based on the total daily dose of subcutaneous insulin. Patients should replace 50% of the total daily insulin dose with a corresponding dose of Afrezza Inhalation Powder divided between main meals, while the remaining 50% of total dose of subcutaneous insulin will be given as basal long-acting subcutaneous insulin. The prandial dose of Insulin should be adjusted based on blood glucose levels.

Afrezza Inhalation Powder should be stored in the refrigerator (2°C to 8°C) for up to 24 months. However, it can be stored at the temperature of 25°C with excursions between 15° to 30° C permitted for 10 days. Once the blister strip is opened, all 3 cartridges inside of that strip should be used within 72 hours. Inhaler can be stored at the temperature of (b) (4) C with permitted excursions between (b) (4) C.

2. MATERIALS REVIEWED

We use Failure Mode and Effects Analysis (FMEA), lessons learned from post-marketing experience and the principles of human factors to identify potential or actual sources of error with the conducted Afrezza Usability Test as well as the proposed products labels and insert labeling; thereafter, we provide recommendations that aim at reducing the risk of medication errors.

2.1 SUMMATIVE USABILITY TEST OF AFREZZA INSULIN INHALATION SYSTEM

DMEPA reviewed and evaluated the *Summative Usability Test of Afrezza Insulin Inhalation System final report*, dated April 5, 2010, submitted to the FDA on June 29, 2010. The Usability Study was performed in accordance with the FDA guidance document, dated June 18, 2008 titled *Medication Device Safety-Integrating Human Factors Engineering into Risk Management* and *AAMI HE 74:2001 titled Human Factors Design Process for Medical Devices*. (See Appendix A for a brief summary of Usability Test).

Additionally, as a part of the *Summative Usability Test of Afrezza Insulin Inhalation System final report,* DMEPA reviewed the comments the test participants provided regarding the product and inhaler designs as well as instructions for use, inhaler, blister pack, and cartridge labeling.

2.2 LABELS AND LABELING

On June 29, 2010, for this Insulin product, the Applicant submitted blister labels, carton, package insert, and instructions for use labeling (See Appendix A). Additionally, the Applicant submitted samples of cartridges and Gen 2 inhaler for Afrezza Inhalation Powder. Afrezza Inhalation Powder is packaged in kits that contains two Gen 2 inhalers and foil pouches of blister packs that contain insulin cartridges. (b) (4) Each blister pack contains five strips. Each strip contains three insulin cartridges. Insulin kits are available in the following sizes:

(b) (4)

3. RESULTS

The following sections summarize the findings of the usability studies and our medication error review of the labels and labeling.

3.1 SUMMATIVE USABILITY TEST OF AFREZZA INSULIN INHALATION SYSTEM

The Applicant addressed most of the DMEPA's concerns outlined in the Agency's Complete Response Letter dated March 12, 2010 while conducting the Afrezza Usability Test.

The Applicant provided an adequate FMEA that describes the anticipated failures with the use of the device during the usability test. The Applicant recruited the recommended number of participants (n=15) of the intended population, used various test environments to imitate everyday situations such as disruptions, telephone calls, low illumination, and reports of weather and traffic conditions. Moreover, the Applicant created test conditions to imitate certain disease states that may appear in patients with diabetes such as the signs and symptoms of neuropathy (participants were wearing fabric gloves), visual impairment such as glaucoma, macular degeneration, cataracts (participants were wearing vision-blurring glasses), protanopia and deuteranopia (participants were wearing variator dichromatic spectacles), and hearing loss (participants were wearing head phones.

A limitation noted in this study is that the applicant used only the proposed strength of the product, 10 units or 20 units, for the dosing error testing and did not include any reference to the deliverable strength (i.e., 4 units or 8 units).

The study uncovered multiple errors during the use of the Afrezza Inhalation Powder and the Gen2 Inhaler by the participants. The most common errors involved dosing errors and wrong administration technique errors. Overdoses (n=2) and underdoses (n=3) occurred due to miscalculation of the cartridges needed for one dose. Additionally, possible underdoses (n=60) occurred due to holding the inhaler upside down, (12 occasions, 5 different participants) or with excessive tilt (n=17), not breathing out prior to cartridge inhalation (n=12), not inhaling deeply enough (n=9), and not breathing briefly after cartridge inhalation (n=11). Moreover, wrong administration technique errors occurred, in which participants did not remove mouthpiece cover prior to inhalation (n=2), tried to insert inverted cartridge to the inhaler (n=2), did not replace inhaler in fifteen days (n=5), and did not replace mouthpiece cover after inhaler use (n=2).

3.2 LABELS AND LABELING

Our evaluation of the proposed labels, labeling, and product design noted areas where presentation of information can be improved upon to provide better clarity regarding the use of the product to minimize the risk of potential medication errors. Specifically, Afrezza Inhalation Powder will be administered via inhalation device that requires multiple steps of manipulation prior to administration of insulin dose, thus, increasing the potential for medication errors. Additionally, the strength of the product differs from the deliverable dose, which also may contribute to dosing errors associated with the use of Afrezza Inhalation Powder. We attempt to address these limitations through our recommendations for labels, labeling, and inhaler design in Section 4. However, we note that some of our concerns related to the design of the product are best addressed before and during the development process and not after the design is finalized.

4 DISCUSSION

Afrezza Inhalation Powder will be available in a kit containing cartridges of insulin and the inhalation device, Gen2 Inhaler that will be used to inhale a dose of insulin from the cartridge. The Gen 2 product design is still complicated to use despite the revisions made to the device to make it more user friendly than the previous Model D version. The administration of the dose of insulin still requires a multiple step manipulation of the inhaler and the cartridge by a patient, which may lead to medication errors. In order to inhale the dose of Afrezza Inhalation Powder, patients needs to familiarize himself/herself with inhalation device and the cartridge, study the IFU, then load the device, inhaler insulin from the device, and then remove the cartridge from the device. Additionally, the patient may have to reload and inhale another cartridge of insulin if the dose requires the use of more than one cartridge. Also, there are multiple steps involved in loading, inhalation, and removing the cartridge from the inhaler. Moreover, the Gen2 Inhaler may be used for up to 15 days and has to be replaced by a new inhaler. The Usability Study demonstrated that a number of errors occurred with Gen 2 device resulting in wrong technique and wrong doses.

4.1 ERROR IN WRONG TECHNIQUE

Wrong administration technique errors occurred in the Usability Study, some of which could lead to administration of the wrong dose. Participants experienced difficulty removing the cartridge from the blister, did not remove the mouthpiece prior to inhalation, tried to insert the inverted cartridge into the inhaler, did not replace the mouthpiece cover, did not replace the inhaler in 15 days, did not inhale prior to inhalation, did not inhale deeply enough during the inhalation or did not hold their breath after the inhalation.

Although the Applicant tried to address some of the issues by updating the IFU, such as the issue of removing cartridge from the blister by placing the illustration of extraction of cartridge from the blister pack in the IFU, the Applicant did not address all issues that participants made comments on nor did the Applicant conduct follow-up testing to determine if the changes made to correct the failures were successful at preventing the risk.

4.2 DOSING ERRORS

Prior to conducting the usability study, DMEPA was concerned with dosing errors using this product. We determined the design requiring the use of multiple cartridges for a single dose was problematic with respect to calculating the number of cartridges needed for a dose. We were also concerned with dosing confusion based on the deliverable amount of drug versus labeled amount of drug. The Usability Study confirmed our concerns with respect to wrong dose errors resulting from miscalculation of the number of cartridges needed for a dose. Using the labeled amount of

drug, 10 units and 20 units, approximately 1/3 of the study participants calculated an incorrect number of cartridges for a dose.

A major limitation to this study is that participants and practitioners were not tested on their ability to calculate the dose based on the deliverable amount of drug. We are concerned that the product strength (10 units or 20 units) differs from the deliverable inhaled dose (4 units or 8 units) and will increase the confusion already noted with the use of this product. Misunderstanding the labeled versus deliverable dose can contribute to dosing errors during all steps of medication process: prescribing, dispensing, and administering of the Afrezza Inhalation Powder. For example, a written order for 20 units could be misinterpreted as one 20 unit cartridge, which would only deliver 8 units, or could be interpreted as the patient is to receive 20 units of the deliverable dose, which would require two 20 unit cartridges and one 10 unit cartridge. This confusion could result in overdoses or underdoses.

The Applicant attempts to address the dosing calculation errors by including a Table (b) (4) in the instructions for use and carton labeling for inhaler. However, study participants still committed this type of errors. Thus, a specific detachable log sheet may be needed to help patients calculate the number of cartridges used for each dose.

5 CONCLUSIONS AND RECOMMENDATIONS

Based on the outcome of the usability study, we determined that the device requires redesign to minimize the amount of steps required to deliver a dose, and the applicant needs to study how errors in dose calculation with the deliverable amount vs. the labeled amount will affect the safe use of the product. Additionally, all revisions made to the device and IFU need to be reevaluated to ensure the proposed changes mitigate the errors they were intended to address.

Section 5.1 *Comments to the Division* contains our general comments regarding strength expression and recommendations regarding package insert labeling and instructions for use. Section 5.2 *Comments to the Applicant* contains our recommendations for the container labels and the carton labeling. We request the recommendations in Section 5.2 be communicated to the Applicant prior to approval.

We would be willing to meet with the Division for further discussion, if needed. Please copy the Division of Medication Error Prevention and Analysis on any communication to the Applicant with regard to this review. If you have further questions or need clarifications, please contact OSE Regulatory Project Manager Margarita Tossa at 301-796-4053.

5.1 COMMENTS TO THE DIVISION

A. General Comments

Despite the revised design, this product is still too complex to use without error. Our concerns can be summarized as follows:

- The difference between the labeled total drug content (10 units or 20 units) of the cartridges and the deliverable dose (approximately 4 units or 8 units) was not tested. Since we identified this as a potential failure mode that can contribute to dosing errors this risk needs to be evaluated prior to approval. We recommend labeling all cartridges, blister labels, foil labeling, carton, and insert labeling with a deliverable dose only (4 units or 8 units) and revising the Dosage and Administration section of the labeling to reflect the dosing based on the amount delivered per cartridge.
- The use of multiple cartridges to administer a dose larger than 10 units or 20 units strength (approximately 4 units or 8 units of deliverable subcutaneous insulin) resulted in error. The applicant needs to test the proposed revisions to the IFU to demonstrate the changes were effective in minimizing these errors.
- Multiple steps involved in manipulation of the product continue to complicate the use of this device. We recommend the applicant re-design the device to decrease the number of steps required in administration of the drug.

B. Package Insert Labeling

1. Entire Package Insert Labeling

   a. Revise all instances of the abbreviation 'sc' to be replaced with "subcutaneous." 'sc' is a dangerous abbreviation, which appears on the ISMP List of Error-Prone Abbreviations, Symbols, and Dose Designations[1] because abbreviation 'sc' has been misinterpreted as a dangerous abbreviation 'sl' (sublingual).

   On June 14, 2006, the FDA and ISMP launched a campaign to reduce medication errors related to error prone medical abbreviations and dose designations. As part of that campaign, the FDA agreed not to approve labels and labeling that included the use of error prone abbreviations. This abbreviation should be removed throughout all labels and labeling.

   b. Delete the name "(b) (4) from the package insert as the name "Afrezza and (b) (4) Inhaler" was withdrawn by the Applicant on August 27, 2010.

2. *Highlights of Prescribing Information* Section

   a. Revise the *Dosage and Administration* Section to include a prominent statement immediately underneath the heading that explains expressions of strength differences between the cartridge strength and deliverable dose. Additionally, we recommend the Applicant reinforces attention that when prescribing Afrezza, it should be ordered is as a cartridge strength and deliverable dose. We recommend this change to help minimize medication errors that may result due to this difference if our general comments may not be feasible. The following or similar statements may be used: "**Note: 10 unit strength cartridge delivers approximately 4 units of subcutaneous insulin dose and 20 unit strength cartridge delivers approximately 8 units of subcutaneous insulin dose. Prescribers ensure writing both strength and deliverable dose when ordering Afrezza".**

   b. Revise the *Dosage and Administration* Section to include the statements "Each insulin cartridge must be discarded after one inhalation. The (b) (4) Inhaler must be discarded after 15 days of use." in the bullet point format after the third bullet point statement. We recommend this change in order to provide complete dosage and administration instructions and enhance user and prescriber comprehension. Additionally, five participants (n=5) of the Afrezza Usability Study confused the new and used cartridges and five participants (n=5) forgot to replace the inhaler after 15 days.

   c. Revise the phrases "10 unit strength" or "20 unit strength" in the *Dosage Forms and Strength* Section to include the approximate subcutaneous dose of insulin delivered. The revised statements should read, "10 unit strength delivers approximately 4 units of subcutaneous insulin" or "20 unit strength delivers approximately 8 units of subcutaneous insulin." We recommend this change to minimize the risk of medication errors resulting from the difference between the strength and deliverable dose if our general comments regarding the labeling may not be feasible.

3. Full Prescribing Information, Section 2 *Dosage and Administration*

   Revise Subsection 2.1 the *Dosage and Administration* Section to include the statements "Each insulin cartridge must be discarded after one inhalation. The Inhaler can be used for up to 15 days from the date of first use. After 15 days of use, the Inhaler must be discarded and replaced with a new inhaler." We recommend this change in order to provide complete dosage and administration instructions and enhance user and prescriber comprehension. Additionally, five participants (n=5) of the Afrezza Usability Study confused the new and used cartridges and five participants (n=5) forgot to replace the inhaler after 15 days.

[1] Institute for Safe Medication Practices, "List of Error-Prone Abbreviations, Symbols, and Dose Designations. www.ismp.org.

4. Full Prescribing Information, Section 3 *Dosage Forms and Strength*

   a. Revise the first sentence "Afrezza (insulin human [rDNA origin] Inhalation Powder is available as 10 unit and 20 unit single use cartridges to be administered via oral inhalation with Inhaler only" to include the approximate subcutaneous dose of insulin delivered. The revised statement should read, "Insulin human [rDNA origin] Inhalation Powder is available as 10 unit strength, which delivers approximately 4 units of subcutaneous insulin and 20 unit strength, which delivers approximately 8 units of subcutaneous insulin, single use cartridges. Afrezza Inhalation Powder must be administered via oral inhalation with Inhaler only." We recommend this change to help minimize medication errors that may result due to this difference if our general comments may not be feasible.

   b. (b) (4) delete the remainder of the paragraph. We recommend making this change because this sentence refers to dosing instructions and not to the description of the dosage forms and strengths. The remainder of the paragraph duplicates information in Section 2.2.

C. Medication Guide Labeling

Revise the fifth bullet point subheading statement under the Heading titled (b) (4) to include the approximate subcutaneous dose of insulin delivered. The revised statement should read, "Afrezza comes in to strengths, 10 units, which delivers approximately 4 units of subcutaneous insulin, and 20 units, which delivers approximately 8 units of subcutaneous insulin." We recommend this change to help minimize medication errors that may result due to this difference if our general comments regarding labeling with deliverable dose only may not be feasible.

D. Instructions for Use Labeling

1. (b) (4)

   Add this Section to the Instruction for Use (IFU) in a form of a detachable calendar or log sheet to help patients calculate and remember each dose and help to prevent the dosing errors as the doses may change depending on the time of the day and carbohydrate intake. As a result, patients may take multiple different doses per day. Additionally, this Section should contain a reminder regarding the replacement of the inhaler.

   Two participants of the Usability Test commented that they would rather see a log sheet, in which individual doses can be written in and the date of the inhaler replacement printed.

This Section may appear as follows:

(b) (4)

	Day 1		Day 2	…	Day 16: **Replace Inhaler**
	Dose	Cartridges Needed			
Dose 1	50 units	2 of 20 units + 1 of 10 units			
Dose 2					
Dose 3					
*Use this space if additional doses are needed					

2. *KNOW* (b) (4) *YOUR* (b) (4) *INAHLER* Section

   a. (b) (4)

   b. Revise the illustration of the Gen2 Inhaler to depict which part of the inhaler is the top part, which part is the bottom part by using arrows. Additionally, use similar technique for the cartridge by using the arrows to show which part is the 'cup' and which part is the 'lid' of the cartridge. As currently presented, it is not clear which part of the inhaler should be held upward and which part of the cartridge should be first inserted into the inhaler as evidenced by the Usability Test findings, which stated that *on a 12 occasions, 5*

participants held the inhaler with its top facing downwards. Additionally, multiple participants commented that they would like to see a better description regarding which part is the top and which part is the bottom.

c. Revise this Section to add the illustration (b) (4) regarding the cup moving from the side to the center after medication being inhaled to increase the prominence of cartridge appearance when it is new vs. used as five participants of the Usability Test could not identify whether the cartridge was used or new. Additionally, one participant commented that this illustration should be placed to the beginning of the IFU for enhanced comprehension. We agree that moving the illustration to the beginning of the instructions for use labeling may help patients become more familiar with the new and used cartridge.

3. (b) (4)

Revise this Section to add an illustration before the "Remove the Mouthpiece Cover" illustration, which will depict that inhaler held with mouthpiece facing upwards. A sentence should be attached stating "Always hold the inhaler with mouthpiece facing upwards to avoid spilling of the medication". We recommend this change to reduce the chance of underdose errors.

The Usability Test states that on 12 separate occasions, 5 participants turned the inhaler upside-down. Additionally, another eight participants held the inhaler loaded with cartridge the wrong way, which could cause loss of medication.

4. (b) (4)

a. Revise illustration (b) (4) to state the degree of tilt to avoid dosing errors due to severe tilting. *Nine participants held the inhaler with a cartridge at a more severe downward angle or slightly upward angle during inhalation.* Four study participants commented that it would be easier for them to understand the instructions if the degree of tilt would be listed.

b. Revise illustration (b) (4) to state whether the deep inhalation should be slow or fast and forceful, if it is important in order to administer the correct dose.

c. Revise the illustration (b) (4) to state the amount of time for (b) (4) hold of breath" if it is important for administration of the correct insulin dose. Seven study participants stated that they would like a definition of (b) (4) hold your breath."

5. *Care and Storage* Section

Include the storage requirements for insulin from Section 16 from the package insert labeling.

5.2 COMMENTS TO THE APPLICANT

If the device is not revised as recommended, the following labeling changes should be implemented prior to approval to help mitigate the risk of errors resulting from errors in wrong technique and dosing.

A. All Carton, Foil Wrap, and Blister Pack, and Devise Labeling

Delete the name " (b) (4) from all labeling and the device as the name "Afrezza and (b) (4) Inhaler" was withdrawn by the Applicant on August 27, 2010.

B. Cartridge Blister Pack Label

1. Both strengths for Afrezza Inhalation Powder printed on the blister label employ (b) (4) background color; thus, increasing the similarity between the two strengths, which can lead to selection and dosing errors. Thus, revise the background color consistent with other labeling for the product: use the blue color for 10 unit strength and green for the 20 unit strength.

2. The labeled strength does not match the inhaled insulin dose. Thus, we recommend an addition of the statement immediately underneath the strength "delivers approximately X units of subcutaneous insulin."

C. Cartridge Foil Wrap Labeling

1. Revise the phrase [redacted] to state "delivers approximately" As currently presented, the word [redacted]" is misleading. It implies that the [redacted]

2. Revise the statement located on the principle display panel in storage information "Cartridge must be at room temperature before use" to define the amount of time the cartridge must be stored in a room temperature prior to use.

3. Increase the prominence of the statement "Inhale once and then discard cartridge immediately" by increasing the font size and using bold font. We recommend this change to emphasize that the cartridge should discarded immediately after being removed from the inhaler to avoid confusion between the new cartridge and used cartridge as evidenced by the Afrezza Usability Test, during which two participants misidentified a used cartridge as new, and three participants misidentified a new cartridge as used.

4. Decrease the prominence of the statement "Rx Only" as this statement is as prominent the proprietary and established names, and strength.

D. Gen2 Inhaler Packaging Design and Label

1. Revise the label of the mouthpiece to include a statement "this side up" to improve patient comprehension that mouthpiece should always be held in upright position; thus, reducing a potential for dosing errors. Although IFU specifies that inhaler should be held with mouthpiece in upright position after cartridge is loaded, eight participants of the Afrezza Usability Test held inhaler incorrectly that could have caused medication loss. Additionally, on 12 occasions, 5 participants held the inhaler upside down. Moreover, several participants commented that *it is difficult to know which side is the top of the inhaler because it is not labeled.*

2. Revise the label on the inhaler to add a statement "replace Inhaler after 15 days of use" to emphasize that the inhaler needs to be replaced on the 16th day in order to avoid dosing medication errors because this information is easy to forget.

3. Consider using a word "top" on the top part of the mouthpiece cover and using a different color for the ease of use. Three participants commented that they experienced difficulty replacing the mouthpiece cover correctly.

E. Gen2 Inhaler Carton Labeling

1. Decrease the prominence of the phrase "Inhaler" as this phrase is not a part of the proprietary name; and thus, should be in smaller font.

2. Place the established name under the proprietary name in accordance with 21 CFR 201.10 (g)(1)

F. Cartridge and Gen2 Inhaler Carton Labeling

1. See Comments in Section B.1 and D.1, which also apply to this Section

2. Add a prominently displayed, bolded Medication Guide statement to the principle display panel in accordance with 21 CFR 208.24. Include one of the following statements: "Dispense the enclosed Medication Guide to each patient" or "Dispense the accompanying Medication Guide to each patient" on the principle display panel of the container labels and carton labeling. Use the first sentence ("enclosed") if the Medication Guide will be inside the carton/container and the entire carton/container is considered a unit-of-use bottle that is dispensed to a single patient. Use the second sentence ("accompanying") if the Medication Guide is glued to the container/carton, as a tear-off sheet, etc).

3. Include the route of administration "For Oral Inhalation Only" in accordance with 21 CFR 201.100(b)

14 Page(s) of Draft Labeling have 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/

YELENA L MASLOV
12/13/2010

ZACHARY A OLESZCZUK
12/13/2010

CAROL A HOLQUIST
12/14/2010

DSI CONSULT
Request for Biopharmaceutical Inspections

DATE: December 13, 2010

TO: Associate Director for Bioequivalence
Division of Scientific Investigations, HFD-48

FROM: Rachel Hartford**,** Regulatory Project Manager, Division of Metabolism and Endocrinology Products, HFD-510

SUBJECT: **Request for Biopharmaceutical Inspections**
NDA 022472
TRADE NAME: Afrezza (insulin human [rDNA origin]) inhalation powder and inhaler
APPLICANT: MannKind

Study/Site Identification:

As discussed with you, the following studies/sites pivotal to approval (OR, raise question regarding the quality or integrity of the data submitted and) have been identified for inspection:

Study #	Clinical Site (name, address, phone, fax, contact person, if available)	Analytical Site (name, address, phone, fax, contact person, if available)
MKC-TI-142		Analytical laboratory for insulin and C-peptide: (b) (4)

Goal Date for Completion:

We request that the inspections be conducted and the Inspection Summary Results be provided as soon as possible. Please let me know when that would be feasible. Note: a consult for the Clinical Site was submitted 12Nov10.

Should you require any additional information, please contact Rachel Hartford, RPM, 301-796-0331.

EDR Location: \\CDSESUB1\EVSPROD\NDA022472\0045

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
12/13/2010

Date: December 9, 2010
To: Lisa Yanoff, M.D., Medical Officer, DMEP
and Hylton Joffee, M.D., Medical Officer, DMEP
From: Cindy Welsh, M.D., Medical Officer, Good Clinical Practice 1 (GCP1), Division of Scientific Investigations (DSI)
Through: Constance Cullity (formerly Lewin), M.D., M.P.H., Branch Chief, GCP1, DSI
RE: DMEP Consult Request on Media Report regarding Alleged Clinical Trial Misconduct (**NDA 22472)**

DSI received a consult request from DMEP regarding evaluation of an article posted on the pharmalot.com website in which MannKind is charged with allegations of clinical trial "potential fraud and scientific misconduct" (NDA 22472 AFREZZA) by a former executive of the company, John Arditi, Senior Director for Regulatory Affairs. Mr. Arditi filed a lawsuit on September 16, 2010 in New Jersey citing among others, retaliatory termination, in violation of the New Jersey Conscientious Employee Protection Act. In the lawsuit, Mr. Arditi alleges that Good Clinical Practice (GCP) violations occurred at the Russian and Bulgarian clinical investigator sites (Shvarts and Daskalova, respectively) that generated data in support of the current submission of NDA 22472 and that MannKind did not report the information to the Agency despite his recommendation to do so.

The information was also posted in the November 5, 2010 version of the DIA Daily, and The Los Angeles Times Business section.

An information request was sent to the sponsor on November 10, 2010 via the review division asking for information related to the allegations in the lawsuit. The sponsor replied to the information request in a submission to the NDA received November 29, 2010 and submitted the following documents to the NDA:

- Incidence of Treatment-Emergent adverse events for Study MKC-TI-005, site 302, Daskalova, Bulgaria
- Incidence of Treatment-Emergent adverse events for Study MKC-TI-010, site 302, Daskalova, Bulgaria
- Incidence of Treatment-Emergent adverse events for Study MKC-TI-014, site 527, Shvarts, Russia
- (b) (4) Investigation Report
- Memorandum Compliance Investigation Findings of Fact
- PI Subinvestigators for sites 005, 010, and 014
- Response to FDA request for information
- (b) (4) CV

The information submitted by the sponsor to the NDA in response to the information request was reviewed by GCP1. The information submitted appears to refute the allegations made by Mr. Arditi of GCP non-compliance.

CONCLUSION:

No further DSI action on this complaint is warranted at this time considering the following factors:

- Actions taken by the sponsor are appropriate, including conducting their own independent third party audit as well as an internal investigation into the allegations of GCP non-compliance and work place harassment during Mr. Arditi's employment
- Foreign sites – Re-inspection of the Russian site (Shvarts) is not warranted as the PDUFA inspection of this site revealed no regulatory violations, thus not corroborating the allegation that fraudulent data were generated at this site. Additionally, inspection of the Bulgarian site (Daskalova) is not considered of value at this time given that this site contributed approximately 10% of the subjects in the studies in which Dr. Daskalova participated, and neither the Russian nor Bulgarian data were included in the only clinical trial submitted that was supportive of efficacy. Instead, these data were submitted only to the negative/non-supportive trials. Further, we note that the sponsor conducted internal audits at the Bulgarian site.
- No other allegations of GCP violations related to human subject protection or data integrity were found during evaluation of this complaint.

Depending upon the review division's assessment regarding the approvability of the NDA based on the resubmission, DMEP may want to consider asking the sponsor to reanalyze the data with and without the data from the sites of Drs. Shvarts and Daskalova. However, it does appear to be unnecessary as the trials were not supportive of efficacy. Alternatively, the review division may wish to consider additional PDUFA-related inspections of the sponsor and/or clinical investigator sites in the future.

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

/s/

CYNTHIA A WELSH
12/09/2010

CONSTANCE LEWIN
12/09/2010

Department of Health and Human Services
Public Health Service
Food and Drug Administration
Center for Drug Evaluation and Research
Office of Surveillance and Epidemiology

Date:	January 22, 2010
To:	Mary Parks, M.D. Division Director **Division of Metabolic & Endocrine Drug Products**
Through:	Claudia Karwoski, PharmD, Director **Division of Risk Management** LaShawn Griffiths, MSHS-PH, BSN, RN **Patient Labeling Reviewer, Acting Team Leader**
From:	Latonia M. Ford, RN, BSN, MBA Patient Labeling Reviewer Marcia Britt Williams, Ph.D. Health Education Reviewer **Division of Risk Management**
Subject:	DRISK Review of Patient Labeling (Medication Guide, Instruction for Use) & Risk Evaluation Mitigation Strategy (REMS)
Drug Name(s):	Afrezza (insulin monomer human [rDNA origin inhalation]) Inhalation Powder) and Afrezza Inhaler
Application Type/Number:	NDA 22472
Applicant/sponsor:	MannKind Corporation
OSE RCM #:	2009-593

The Division of Metabolic & Endocrine Drug Products(DMEP) requested that the Division of Risk Management (DRISK) review the proposed patient labeling and Risk Evaluation Mitigation Strategy (REMS) for New Drug Application (NDA 22472) submitted by MannKind Corporation for Afrezza (insulin monomer human [rDNA origin inhalation]) Inhalation Powder and Afrezza Inhaler.

DMEP does not plan to address labeling during this review cycle; therefore, we will defer our review of the Medication Guide, Instructions for Use and REMS review until such time as the review division plans to address labeling.

Please send us a new consult request at that time. This memo serves to close-out the consult request for Afrezza (insulin monomer human [rDNA origin inhalation]) Inhalation Powder) and Afrezza Inhaler NDA 22472.

Please let us know if you have any questions.

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/

LATONIA M FORD

01/22/2010

Deferral Memo for DRISK Review of Patient Labeling (Medication Guide, Instruction for Use) & Risk Evaluation Mitigation Strategy (REMS)

CLAUDIA B KARWOSKI

01/22/2010

concur

M E M O R A N D U M

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

DATE: January 4, 2010

TO: Mary H. Parks
Director, Division of Metabolism and Endocrinology Products (HFD-510)

FROM: Sean Y. Kassim, Ph.D.
Pharmacologist
Division of Scientific Investigations (HFD-48)

THROUGH: Martin K. Yau, Ph.D. Martin K. Yau 1/4/2010
Acting Bioequivalence Team Leader
Division of Scientific Investigations (HFD-48)

SUBJECT: Review of EIR Covering NDA 22-472, Technosphere® Recombinant Human Insulin Inhalation Powder Sponsored by MannKind Corporation.

At the request of the Division of Metabolism and Endocrinology, the Division of Scientific Investigations (DSI) audited the clinical and analytical portions of the following bioequivalence studies:

MKC-TI-138: "A Phase 1, Open-Label, Randomized, 2-Way Crossover Clinical Trial to Compare Insulin Pharmacokinetics Following Technosphere® Insulin Inhalation Powder Administration Via 2 MedTone® Inhaler Models in Subjects with Type 1 Diabetes Mellitus"

Following the inspection of the clinical site (December 1 - December 4, 2009), no Form FDA-483 was issued.

Clinical Site: MHI Clinical Hospital for Emergency Care n.a. N.V. Soloviev, Yaroslavl, Russia

Following the inspection of the analytical site (b) (4) , Form FDA-483 was issued (Attachment 1). DSI received the firm's response to the inspectional findings on (b) (4) (Attachment 2). The 483 observations for study MKC-TI-138 and our evaluations follow:

Analytical Site: (b) (4)

12 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/

SEAN Y KASSIM
01/05/2010
Original (scanned) copy was signed by Sean Kassim and Martin Yau

M E M O R A N D U M

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

CLINICAL INSPECTION SUMMARY

DATE: December 28, 2009

TO: Haley Seymour, Regulatory Project Manager
Lisa Yanoff, M.D., Medical Officer
Division of Metabolic and Endocrine Products (DMEP)

FROM: Susan Leibenhaut, M.D.
Good Clinical Practice Branch II
Division of Scientific Investigations

THROUGH: Tejashri Purohit-Sheth, M.D.
Branch Chief
Good Clinical Practice Branch II
Division of Scientific Investigations

SUBJECT: Evaluation of Clinical Inspections

NDA: #22-472

APPLICANT: MannKind Corporation

DRUG: insulin monomer human (rDNA origin) inhalation powder

NME: No

THERAPEUTIC CLASSIFICATION: Standard

INDICATION: Treatment of adults with type 1 or type 2 diabetes mellitus for the control of hyperglycemia

CONSULTATION REQUEST DATE: May 13, 2009

DIVISION ACTION GOAL DATE: January 6, 2010
PDUFA DATE: January 16, 2010

I. BACKGROUND:

MannKind Corporation submitted NDA 22-472 for Afresa (insulin monomer [rDNA origin] inhalation powder), an ultra-rapid acting insulin for the indication of the treatment of adults with type 1 or type 2 diabetes mellitus for the control of hyperglycemia. This was a routine audit request to assess data integrity and human subject protection for clinical trials submitted in support of this application. The efficacy results of the studies are important in making a regulatory decision with regard to drug approval. Selection of sites was based on site enrollment and numbers of INDs in the DSI database. The CRO (b) (4) was inspected because of the analysis of important safety data concerning pulmonary function testing.

The protocols inspected included:

A. Protocol MKC-TI-009 entitled "A Prospective, Multi-Center, Open-Label, Randomized, Controlled Clinical Trial Comparing the Efficacy and Safety in Subjects with Type 1 Diabetes Receiving Subcutaneous Basal Insulin and Prandial Inhalation of Technosphere®/Insulin Versus Subcutaneous Basal and Prandial Insulin Over a 52-Week Treatment Period and a 4-Week Follow-up" and

B. Protocol MKC-TI-102 entitled "A Prospective, Multi-Center, Open-Label, Randomized, Controlled Clinical Trial Comparing the Efficacy and Safety in Subjects with Type 2 Diabetes Receiving Subcutaneous Basal Insulin and Prandial Inhalation of Technosphere®/Insulin Versus Subcutaneous Premixed Insulin Therapy Over a 52-Week Treatment Period and a 4-Week Follow-up" and

C. Protocol MKC-TI-014 entitled, "A Phase 3, Randomized, Open Label, Multi-Center Comparative Study of Technosphere®/Insulin versus Rapid Acting Insulin in Subjects with Type-2 Diabetes Receiving Lantus® as Basal Insulin."

II. RESULTS (by Site):

Name of Clinical Investigator (CI) or Contract Research Organization (CRO) and Location	Protocol #/ # of Subjects	Inspection Dates	Final Classification
CI #1 Jimmie N. Tarro, M.D. 5486 SW Natchez St. Tualatin, OR 97062	MKC-TI-009/ 13 subjects	September 1 to 9, 2009	NAI
CI #2 Sam Miller, M.D. SAM Clinical Research Center 7711 Louis Pasteur Drive, Suite 300 San Antonio, TX 78229	MKC-TI-102/ 14 subjects	August 24 to 28, 2009	VAI
CI #3 Sherwyn L. Schwartz, MD Diabetes and Glandular Disease Research, Inc. 5109 Medical Drive San Antonio, TX 78229	MKC-TI-009/ 13 subjects MKC-TI-102/ 10 subjects	August 31 to September 16, 2009	VAI
CI #4 Prof. Vladimir Yakusevich Yaroslavl Municipal Health Care Institution Clinical Hospital for Emergency Care n.a. N.V. Soloviev 11, Zagorodny Sad str. Yaroslavl, 150003, Russia	Protocol MKC-TI-014/ 32 subjects	November 23 to 26, 2009	Pending (Preliminary classification NAI)
CI #5 Prof. Yury Shavarts State Educational Instiution of High Professional Education Saratov State Medical University Clinical Hospital No. # 137 Bolshaya Sadovaya str. Saratov, 410054, Russia	Protocol MKC-TI-014/ 29 subjects	November 16 to 19, 2009	Pending (Preliminary classification NAI)
CRO (b) (4)	MKC-TI-009/ 26 subjects MKC-TI-102/ 10 subjects	(b) (4)	Pending (Preliminary classification NAI)

Key to Classifications
NAI = No deviation from regulations.
VAI = Deviation(s) from regulations.
OAI = Significant deviations from regulations.

1. Jimmie N. Tarro, M.D.
   5486 SW Natchez St.
   Tualatin, OR 97062

   a. **What was inspected**: For Protocol MKC-TI-009 at this site, 13 subjects were randomized. Five subjects did not complete the study. Subject 1670 did not meet inclusion criteria and was withdrawn. One subject randomized to test article withdrew, and three did not complete the study for other reasons including failure to comply with the study requirements. An audit was conducted of all consent forms, and a comparison of all HgbA1c values contained in source documentation, case report forms (CRFs), and data listings supplied to ORA field office was conducted.

   b. **General observations/commentary:** Dr. Andrew Ahmann was listed in the NDA as the clinical investigator for this site, but the responsibility for the site has been transferred to Dr. Tarro. The primary endpoint data were verifiable, and there was no under-reporting of adverse events. The following items are not considered regulatory violations but are noted for the medical reviewer's information:
      1. Subject 1165 (active) is listed in the NDA as having discontinued because of withdrawn consent, viral bronchitis is listed as an adverse event, and subject is listed in the data listings as having a treatment-emergent cough. The progress note states that the subject withdrew because of inability to attend clinic sessions, and there is a note from the subject in the source documents stating that she stopped the product because of a cough.
      2. Subjects 1088(control), 1222 (control), and 1438 (active) had fasting blood sugars on several occasions recorded on the glucose diary cards in which the trend for fasting plasma glucose was >110 mg and fulfilled criteria in Protocol Section 4.4.2.4 "Basal Insulin Adjustment." According to Dr. Tarro the basal insulin was not increased as specified in the protocol due to concerns regarding the occurrence of hypoglycemia in the subjects.

   c. **Assessment of data integrity:** At this site, the study appears to have been conducted adequately, and the data generated by this site may be used in support of the respective indication.

2. Sam Miller, M.D.
   SAM Clinical Research Center
   7711 Louis Pasteur Drive, Suite 300
   San Antonio, TX 78229

   a. **What was inspected:** For Protocol #MKC-TI-102, 14 subjects were randomized, and 10 completed the study. An audit of all 14 of the randomized subjects' records was conducted.

b. **General observations/commentary**: The primary endpoint data were verifiable, and there was no under-reporting of adverse events. Hypoglycemic events listed in the subject diaries that were not serious were to be recorded on a separate hypoglycemic case report form. This inspection is classified as VAI because the following nonserious hypoglycemic events were recorded in subject diaries but were not included in the hypoglycemia listing:

1. Subject 2188 (active) experienced two hypoglycemic events on May 9, 2008 that were recorded in the subject diary and not reported to the sponsor. No hypoglycemic events were reported to the NDA for this subject.
2. Subject 3061 (active) experienced hypoglycemic events on June 30 and July 2, 2008 that were recorded in the subject diary and not reported to the sponsor. This subject experienced 22 hypoglycemic events that were reported to the sponsor and that are contained in the NDA submission.

For the pulmonary function testing (PFTs), the site completed the PFT request and received a copy of the PFT report from the laboratory. The site determined qualitative data regarding the clinical interpretation of the test. DLco values corrected for hemoglobin were not verifiable at the site because the equation was not provided in the protocol. At this site the following discrepancies concerning the pulmonary function test results were noted:

1. Subject 1344 (control) DLco actual on 10/11/2007 was 16.41 but reported as 16.61 and Total Lung Capacity (TLC) actual was 4.49 but reported as 4.81.
2. Subject 1701 (active) TLC actual on 6/22/2007 was 4.18 but reported as 4.66.

It was the responsibility of (b) (4), the CRO that interpreted the PFTs, to report the results to the sponsor. Please see the discussion concerning (b) (4) below.

c. **Assessment of data integrity:** The study appears to have been conducted adequately, and the data generated by this site may be used in support of the respective indication. However, the review division should consider the impact of the isolated occurrences of underreporting of hypoglycemic episodes to the sponsor in their assessment of the application. The significance of the PFT findings is discussed below in the section on (b) (4)

3. Sherwyn L. Schwartz, MD
Diabetes and Glandular Disease Research, Inc.
5109 Medical Drive, San Antonio, TX 78229

a. **What was inspected:** For Protocol #MKC-TI-009, 13 subjects were enrolled and eight subjects completed the protocol. For Protocol #MKC-TI-102, ten subjects enrolled and six subjects completed the protocol. An audit of all randomized subjects' records was conducted.

b. **General observations/commentary:** The primary endpoint data were verifiable, and there was no under-reporting of adverse events. According to the protocol, only severe hypoglycemic events were to be reported as adverse events. Hypoglycemic events listed in the subject diaries were to be recorded on a separate hypoglycemic case report form. There were some episodes of non-severe hypoglycemia that were not reported to the sponsor. A Form FDA 483 was issued due to violations concerning adherence to the protocol, recordkeeping, drug accountability, and prompt reporting of adverse events to the IRB. These appear to be isolated occurrences and not pervasive throughout the study, and are unlikely to impact data integrity. However, it should be noted that for three subjects in Protocol MKC-TI-009 and one subject in Protocol MKC-TI-102, isolated hypoglycemic episodes were not reported to the sponsor. The following subjects in Protocol #MKC-TI-009 have underreporting of hypoglycemia:

1. Subject 1211 (active) has 8 hypoglycemic events listed in the line listings in the NDA. There were three additional hypoglycemic events that were not reported to the sponsor.
2. Subject 1424 (active) has 18 hypoglycemic events listed in the line listings in the NDA. There were three additional hypoglycemic events that were not reported to the sponsor.
3. Subject 1474 (control) has 12 hypoglycemic events listed in the line listings in the NDA. There was an additional hypoglycemic event that was not reported to the sponsor.

For Protocol #MKC-TI-102 Subject 1759 (control) and Subject 2806 (active) each had one event not listed in the line listings for hypoglycemia.
Dr. Schwartz adequately responded to the inspectional findings in a letter dated October 5, 2009.

c. **Assessment of data integrity:** The study appears to have been conducted adequately, and the data generated by this site may be used in support of the respective indication. However, the review division should consider the impact of the isolated occurrences of underreporting of hypoglycemic episodes to the sponsor in their assessment of the application.

4. Prof. Vladimir Yakusevich
Yaroslavl Municipal Health Care
Institution Clinical Hospital for Emergency Care n.a. N.V. Soloviev
11, Zagorodny Sad str., Yaroslavl, 150003, Russia

Note: Observations noted for this site are based on communications with the FDA investigator, and review of the Form FDA 483. An inspection summary addendum will be generated if conclusions change upon receipt and review of the Establishment Inspection Report (EIR).

a. **What was inspected:** For Protocol #MKC-TI-014, 50 subjects were screened, 30 subjects were randomized, and 25 subjects completed the study. An audit of 30 subjects' records was conducted.

b. **General observations/commentary:** The primary endpoint data were verifiable and there was no under reporting of the adverse events from the clinical site to the sponsor. The following adverse events (AEs) were reported to the sponsor, but were not contained in the line listings submitted in the NDA:
   1. Subject 548(active):hypertension
   2. Subject 152(control): acute pain in lower colon
   3. Subject 580(active): upper respiratory illness.

   This information was communicated to the review division in an e-mail on December 18, 2009.

c. **Assessment of data integrity:** At this site, the study appears to have been conducted adequately, and the data generated by this site may be used in support of the respective indication. It appears that some AEs at the Russian sites were not reported by the sponsor to the NDA. This does not appear to be a systemic issue with respect to under-reporting of AEs by the sponsor. However, the review division may consider an information request to the sponsor concerning their under-reporting of adverse events to the NDA from this site.

5. Prof. Yury Shavarts
   State Educational Instiution of High Professional Education
   Saratov State Medical University Clinical Hospital
   No. # 137 Bolshaya Sadovaya str., Saratov, 410054, Russia

Note: Observations noted for this site are based on communications with the FDA investigator, and review of the Form FDA 483. An inspection summary addendum will be generated if conclusions change upon receipt and review of the EIR.

a. **What was inspected:** For Protocol #MKC-TI-104, 50 subjects were screened, 29 subjects were randomized, and 29 subjects completed the study. An audit of 15 subjects' records was conducted.

b. **General observations/commentary:** There was no under reporting of adverse events by the site to the sponsor and the primary endpoint data were verifiable. The following adverse events were reported to the sponsor, but were not contained in the line listings submitted in the NDA:
   1. Subject 054(control): ischemic event. This event was not listed in the line listings or narrative, but the Case Report Form (CRF) documenting this event was submitted in the NDA.
   2. Subject 409(control): arterial hypertension.

   This information was communicated to the review division in an e-mail on December 18, 2009.

c. **Assessment of data integrity:** At this site, the study appears to have been conducted adequately, and the data generated by this site may be used in support of the respective indication. It appears that some AEs at the Russian sites were not reported by the sponsor to the NDA. This does not appear to be a systemic issue with respect to under-reporting of AEs by the sponsor. The review division may consider an information request to the sponsor concerning their under-reporting of adverse events to the NDA from this site.

5. (b) (4)

Note: Observations noted for this site are based on communications with the FDA investigator, and review of the Form FDA 483. An inspection summary addendum will be generated if conclusions change upon receipt and review of the EIR.

a. **What was inspected:** (b) (4)

b. **General observations/commentary:** (b) (4)

c. **Assessment of data integrity:** (b) (4)

III. OVERALL ASSESSMENT OF FINDINGS AND RECOMMENDATIONS

Five clinical investigator sites and one CRO were inspected in support of this NDA. As discussed above, audits of all the clinical sites were able to validate the primary endpoint. Inspection of (b) (4) the CRO, was able to validate the integrity of the pulmonary function testing system for the protocols in which the (b) (4) system was used. There was some under-reporting of hypoglycemic events at the Miller and Schwartz sites,

and a subject at the Tarro (Ahmann) site had two different reasons for withdrawal documented, only one of which is listed in the case report form. The review division should consider the impact of the isolated occurrences of underreporting of nonsevere hypoglycemic episodes to the sponsor in their assessment of the application.

For both Russian sites, it appears that some AEs and one SAE were not reported by the sponsor to the NDA, but this does not appear to be a systemic error. The review division may consider an information request to the sponsor concerning the under-reporting of adverse events by the sponsor to the NDA.

Although some regulatory violations were noted as per above, these are considered isolated occurrences and are unlikely to importantly impact data integrity. The data are considered reliable in support of the NDA, although the review division should consider the impact, if any, of the infrequent occurrences of under-reporting of adverse events of hypoglycemia, in some cases by the CI and in some cases by the sponsor, in their evaluation.

Note: The final classifications for the inspections of Drs. Yakusevich and Shavarts and of (b) (4) are pending. An addendum to this clinical inspection summary will be forwarded to the review division if additional observations of clinical and regulatory significance are discovered after reviewing the EIRs for these inspections.

{See appended electronic signature page}

Susan Leibenhaut, M. D.
Good Clinical Practice Branch II
Division of Scientific Investigations

CONCURRENCE:

{See appended electronic signature page}

Tejashri Purohit-Sheth, M.D.
Branch Chief
Good Clinical Practice Branch II
Division of Scientific Investigations

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/

SUSAN LEIBENHAUT
12/29/2009

TEJASHRI S PUROHIT-SHETH
12/29/2009

Department of Health and Human Services
Public Health Service
Food and Drug Administration
Center for Drug Evaluation and Research
Office of Surveillance and Epidemiology

Date:	December 28, 2009
To:	Mary Parks, M.D., Director Division of Metabolism and Endocrine Products
Through:	Kellie Taylor, PharmD, MPH, Associate Director Denise Toyer, PharmD, Deputy Director Carol Holquist, RPh, Director Division of Medication Error Prevention and Analysis
From:	Laura Pincock, RPh, PharmD, Acting Team Leader Division of Medication Error Prevention and Analysis, HFD-420
Subject:	Label and Labeling Review
Drug Name(s):	**Afrezza (Insulin Inhalation Powder)** 15 unit and 30 unit cartridges
Application Type/Number:	NDA 022472
Applicant/sponsor:	MannKind Corporation
OSE RCM #:	2009-2440

1 INTRODUCTION

This review was written in response to a request from the Division of Metabolism and Endocrine Products (DMEP) to evaluate the Afrezza inhaler label, cartridges, foil pack labels, carton, and insert labeling (NDA 022472), for areas that could lead to medication errors.

2 BACKGROUND

2.1 INTRODUCTION

The previous proposed proprietary name, Afresa, was found unacceptable in a previous review (OSE # 2007-2449, dated June 30, 2009) because our evaluation determined it was vulnerable to confusion with the currently marketed product Apidra. The subsequent proposed proprietary name, Afrezza, was found acceptable in DMEPA's review dated December 8, 2009 (OSE RCM # 2009-1741.

2.2 PRODUCT INFORMATION

Afrezza is the proposed proprietary name for insulin inhalation powder delivered via a re-usable, breath-powered, high resistance, dry powder delivery device. Afrezza is intended for the treatment of adults with diabetes mellitus. Afrezza is proposed to be marketed in single dose cartridges of 15 units or 30 units. (b) (4)
Per CMC (b) (4)
Other patient specific factors affect the end amount of insulin delivered including particle size, health of the patient (e.g., FEV1) and technique of the inhaler, thus the amount of insulin delivered (b) (4) is variable per patient.

(b) (4)

Insulin naïve patients should start on a dose of approximately 4 inhaled units at each meal. For all other patients, the starting dose of Afrezza will be based on the total daily dose of subcutaneous insulin. Subjects will replace 50% of the total daily subcutaneous insulin dose with a corresponding dose of Afrezza divided between main meals, while the remaining 50% of total dose of subcutaneous insulin will be given as basal long-acting subcutaneous insulin. The prandial dose of Afrezza should be adjusted based on blood glucose levels.

Afrezza should be stored in the refrigerator (2-8 °C). Once dispensed, it can be stored at room temperature for up to (b) (4), with excursions permitted. The Afrezza inhaler can be used for up to one year from date of first use.

3 METHODS AND MATERIALS

3.1 ADVERSE EVENTS REPORTING SYSTEM (AERS) DATABASE

Another inhaled insulin recombinant human product (Exubera) was approved on January 27, 2006 as NDA 021868. Although Exubera's manufacturer stopped marketing Exubera in 2007, DMEPA conducted a search of the Adverse Events Reporting System (AERS) on November 30, 2009, to determine if any medication errors issues have been reported for Exubera that might also

be useful in our evaluation of this similar product. We searched using the tradename "Exub%", the verbatim term "Exub%" and the MedDRA reaction terms "Medication Errors" (HLGT), "Product Quality Issue" (PT) and "Product Label Issue" (PT).

3.2 LABELS AND LABELING

The Division of Medication Error Prevention and Analysis used Failure Mode and Effects Analysis (FMEA)[1] in our evaluation of the Afrezza inhaler label, cartridges, foil pack labels, carton, and insert labeling that were received October 2, 2009 (dated September 28, 2009) and November 16, 2009 (dated October 28, 2009) [see Appendices A through G].

4 RESULTS

4.1 ADVERSE EVENTS REPORTING SYSTEM (AERS) DATABASE

Our search strategy did not produce any cases (n=0) that were pertinent to this Afrezza review. Fifteen cases were retrieved for Exubera but they specifically reported malfunction of the Exubera device, confusion between the two blister strengths of Exubera, concerns about the Exubera dose designation in milligrams, adverse drug events, product sample quality issues, lack of effect, missed or late doses, and running out of the Exubera medication.

4.2 LABELS AND LABELING

4.2.1 Product Design May Contribute to Errors

The dose of Afrezza will be administered using a cartridge with the Afrezza (Model D) inhaler. (b) (4) Therefore the prescriber or patient will need to calculate how many cartridges are needed to administer the prescribed dose, and the dose is titrated due to patient response. Because of the differences between the labeled strength and the approximated inhaled insulin dose, confusion can result when prescribing, dispensing, or administering the Afrezza cartridges as patients and their providers are used to ordering subcutaneous insulin in units.

(b) (4) . Repetitive and multiple steps in the preparation process for a total dose which may include several cartridges is problematic, because they may lead to confusion or errors during the process if a patient loses track during the administration process which can result in an overdose or underdose of insulin.

Therefore overall, the device is cumbersome and not easy to use because of the multiple steps involved. The numerous repetitive steps can lead to confusion and short cuts by a patient when administering a dose, (b) (4) . Addressing these issues in the labels and labeling for Afrezza cannot completely mitigate the risk of medication errors.

[1] Institute for Healthcare Improvement (IHI). Failure Modes and Effects Analysis. Boston. IHI:2004.

4.2.2 Afrezza Cartridge

(b) (4)

4.2.3 Foil Pouch Labels and Carton Labeling

(b) (4)

4.2.4 Package Insert

A review of the package insert noted a few areas that could be revised to provide clarity and decrease the risk for misinterpretation. Per DMEP request, we have placed our revisions and comments onto the tracked version of the insert labeling in the e-room for discussion during labeling negotiations.

5 DISCUSSION

Our evaluation of the proposed labels and labeling identified potential failure modes through our FMEA of the following sources for potential medication errors.

5.1.1 Product Design

The Model D Inhaler used for Afrezza has design issues that can lead to confusion and medication errors during prescribing, preparation, and administration. Our concerns can be summarized as follows:

(b) (4)

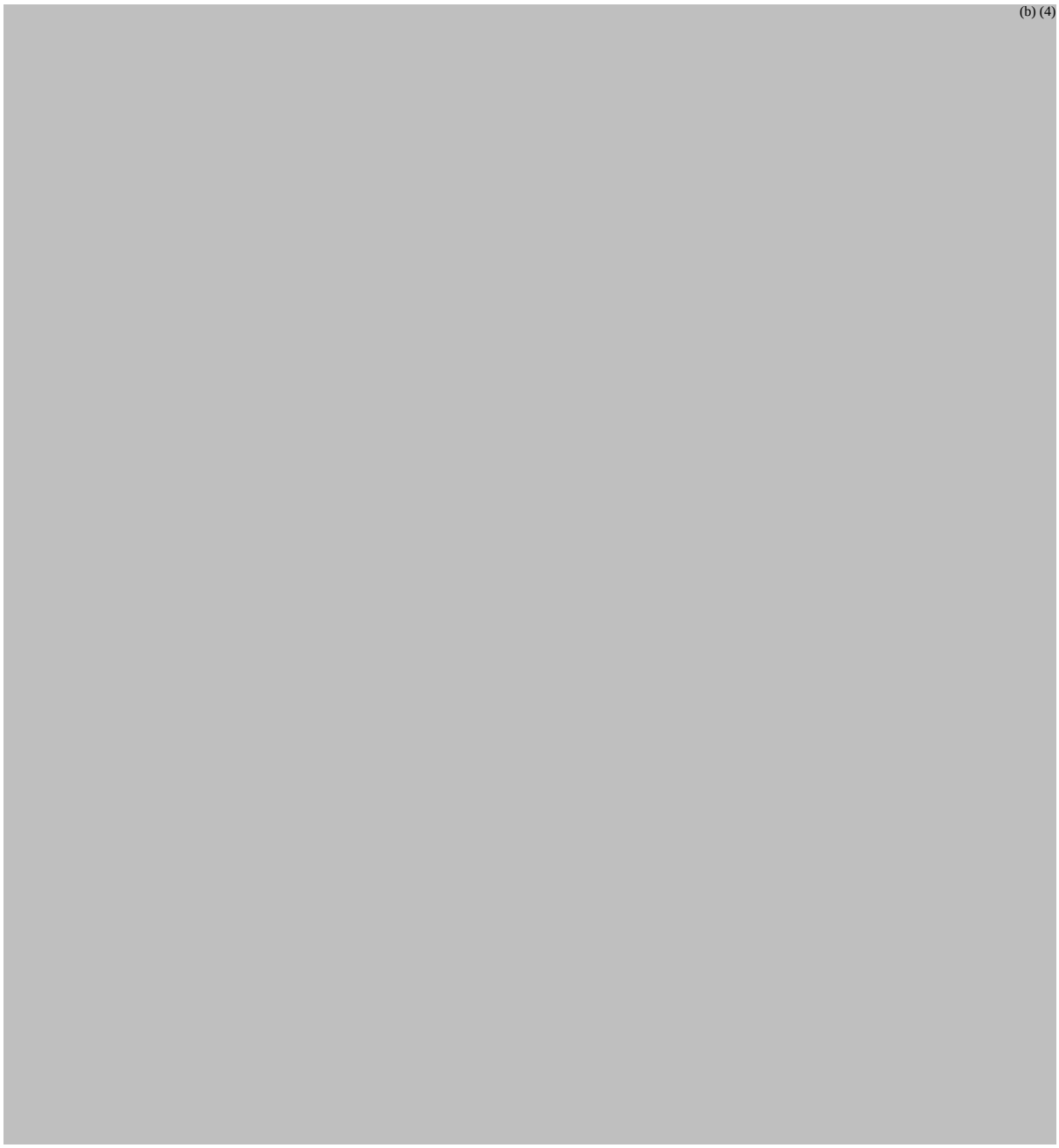
We will attempt to address these limitations to the current Model D Inhaler through clarification and communication in the labels and labeling for Afrezza. However we note that these concerns related to the design of the device are best addressed before and during the device design process and not after the design is finalized. Since the device design is finalized, the only strategy available to address our concerns is labeling. Given these limitations, we do not think we can

mitigate all the risks of medication error without redesigning this cumbersome device. DMEPA has discussed all of these concerns with the review team during meetings.

DMEPA notes that it is anticipated that a second generation inhaler will be submitted by the Applicant at a future date, but we have no knowledge of this specific product, other than that it does not use the same cartridges as the current inhaler. DMEPA would appreciate notice when this new inhaler is submitted or discussions regarding its design begin. We can offer guidance in advance of product design, and recommend usability studies applying the principles of human factors to determine vulnerabilities and potential errors in the device and product design which can remedy potential safety issues before the design is finalized.

5.1.2 Afrezza cartridge

(b) (4)



5.1.3 Foil Pouch Labels and Carton Labeling

(b) (4)

5.1.4 Package Insert

Review of the package insert noted a few areas that could be revised to provide clarity and decrease risk for misinterpretation. Per DMEP request, we have placed our revisions and comments onto the tracked changes version of the insert labeling in the e-room for discussion during labeling negotiations with the Applicant.

6 CONCLUSIONS AND RECOMMENDATIONS

The Label and Labeling Risk Assessment findings indicate that the presentation of information and design of the proposed carton and container labels introduces vulnerability to confusion that could lead to medication errors. DMEPA provides recommendations in the following sections that aim at reducing the risk of medication errors.

We would be willing to meet with the Division for further discussion, if needed. Please forward the comments provided in Section 5.2 to the Applicant and copy the Division of Medication Error Prevention and Analysis on any communication to the Applicant with regard to this review.

If you have further questions or need clarifications, please contact Margarita Tossa, project manager, at 301-796-4053.

6.1 COMMENTS TO THE DIVISION

A. Product Design

The Model D inhaler and cartridges used for Afrezza have design issues that can lead to confusion and medication errors during prescribing, preparation, and administration. Our concerns can be summarized as follows:

(b) (4)

We will attempt to address these limitations to the current Model D Inhaler through clarification and communication in the labels and labeling for Afrezza. However, we note that these concerns related to the design of the device are best addressed before and during the device design process

and not after the design is finalized. Since the device design is finalized, the only strategy available to address our concerns is labeling. Given these limitations, we do not think we can mitigate all the risks of medication error without redesigning this cumbersome device. DMEPA has discussed all of these concerns with the review team during meetings.

DMEPA notes that it is anticipated that a second generation inhaler will be submitted by the Applicant at a future date, but we have no knowledge of this specific product, other than that it does not use the same cartridges as the current inhaler. DMEPA would appreciate notice when this new inhaler is submitted or discussions regarding its design begin. We can offer guidance in advance of product design, and recommend usability studies applying the principles of human factors to determine vulnerabilities and potential errors in the device and product design which can remedy potential safety issues before the design is finalized.

B. Package Insert

Refer to Appendix G for our comments and edits as tracked changes on the Afrezza insert labeling for discussion during labeling negotiations with the Applicant

6.2 COMMENTS TO THE APPLICANT

A. General Comments

(b) (4)

B. Afrezza cartridge

(b) (4)

C. Foil Pouch Labels

(b) (4)

(b) (4)

D. Carton Labeling

(b) (4)

41 Page(s) has 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/

LAURA L PINCOCK
12/28/2009

DENISE P TOYER on behalf of KELLIE A TAYLOR
12/28/2009

DENISE P TOYER
12/28/2009

DENISE P TOYER on behalf of CAROL A HOLQUIST
12/28/2009

Interdisciplinary Review Team for QT Studies Consultation: Thorough QT Study Review

NDA	22-472
Brand Name	Technosphere® Particles
Generic Name	Fumaryl diketopiperazine (FDKP)
Sponsor	MannKind
Indication	Treatment of Diabetes Mellitus
Dosage Form	Inhalation Powder
Drug Class	Excipient
Therapeutic Dosing Regimen	Anticipated maximum therapeutic dose of TI Inhalation Powder in humans is 90 U of insulin, which would contain approximately (b) (4) mg of FDKP
Duration of Therapeutic Use	Chronic
Maximum Tolerated Dose	40 mg FDKP
Submission Number and Date	SDN 001, 11/16/2009
Review Division	DMEP / HFD 510

1 SUMMARY

1.1 OVERALL SUMMARY OF FINDINGS

Only the excipient, Technosphere® Particles containing fumaryl diketopiperazine (FDKP), was evaluated in the TQT study.

No significant QT prolongation effect of FDKP (20 mg and 40 mg) was detected in this TQT study. The largest upper bounds of the 2-sided 90% CI for the mean difference between FDKP (20 mg and 40 mg) and placebo were below 10 ms, the threshold for regulatory concern as described in ICH E14 guidelines. The largest lower bound of the two-sided 90% CI for the ΔΔQTcI for moxifloxacin was greater than 5 ms, and the moxifloxacin profile over time is adequately demonstrated in Figure 5, indicating that assay sensitivity was established.

In this randomized, double-blind, double-dummy, placebo-and active-controlled four-period crossover study, 48 healthy subjects received FDKP 20 mg, FDKP 40 mg, placebo, and a single oral dose of moxifloxacin 400 mg. Overall summary of findings is presented in Table 1.

Table 1: The Point Estimates and the 90% CIs Corresponding to the Largest Upper Bounds for FDKP (20 mg and 40 mg) and the Largest Lower Bound for Moxifloxacin (FDA Analysis)

Treatment	Time (hour)	ΔΔQTcI (ms)	90% CI (ms)
FDKP 20 mg	8	0.7	(-1.0, 2.5)
FDKP 40 mg	8	0.8	(-0.9, 2.6)
Moxifloxacin 400 mg*	4	10.2	(9.0, 11.4)

* Multiple endpoint adjustment was not applied. The largest lower bound after Bonferroni adjustment for 4 timepoints is also above 5 ms.

The supratherapeutic dose (40 mg) produces mean C_{max} values of 2.2-fold higher than the mean C_{max} for the therapeutic dose (20 mg). These concentrations are above those for the predicted worst case scenario (co-administration of salbutamol in asthmatic patients) and show that at these concentrations there are no detectable prolongations of the QT-interval. It is expected from drug interaction studies that co-administration of salbutamol in asthmatic patients can elevate FDKP's mean C_{max} as much as 1.3-fold higher. Type 2 subjects with mild and moderate diabetic nephropathy have 1.3-fold higher and 0.9-fold lower mean C_{max} values compared to Type 2 subjects with normal renal function. Subjects with mild and moderate hepatic impairment have 1.1-fold higher mean C_{max} values compared to normal subjects. Co-administration of inhaled albuterol and fluticason resulted in a 1.2-fold and 1.1-fold increase in mean C_{max} in healthy subjects.

2 PROPOSED LABEL

The sponsor did not propose labeling language about the effects of FDKP on the QTc interval. In our opinion, this is reasonable because only the excipient was evaluated.

3 BACKGROUND

3.1 PRODUCT INFORMATION

AFRESA® (previously referred to as Technosphere® Insulin [TI]) is an ultra-rapid-acting prandial insulin for the treatment of type 1 and type 2 diabetes mellitus in adults.

AFRESA consists of Technosphere® Insulin Inhalation Powder, pre-metered into unit-dose cartridges and the MedTone® Inhaler. TI is comprised primarily of insulin and an excipient, fumaryl diketopiperazine in a dry powder formulation.

3.2 MARKET APPROVAL STATUS

Technosphere® insulin is not approved for marketing in any country.

3.3 PRECLINICAL INFORMATION

Source Pharmacology Written Summary, eCTD 2.6.2

> "TI and Technosphere particle solutions were tested at concentrations up to 100 uM in HB-PS+0.3% DMSO. The hERG currents were evaluated at physiological temperature in HEK293 cells stably expressing the hERG channel. At concentrations of 1, 10, 30 and 100 μM, TI inhibited the hERG currents (mean ±

SEM, n = 3) by 1.3 ± 0.2%, 12.9 ± 0.9%, 27.4 ± 3.8% and 61.2 ± 2.8%, respectively. Based on these data, the calculated TI IC50 for hERG currents was 67.4 μM. Technosphere particle solution (FDKP) inhibited hERG currents by 14.0 ± 3.1% (mean ± SEM; n = 3) at 100 μM. Since the mean current inhibition at this concentration did not exceed 20%, the lower concentrations identified in the study protocol were not evaluated, and an IC50 was not determined. The control vehicle (HB-PS + 0.3% DMSO) that was used to prepare the TI and Technosphere particle solutions tested in this study minimally inhibited hERG currents by -0.2 ± 0.4% (n = 3). Under identical conditions, the positive control, terfenadine, a potent hERG channel blocker, inhibited hERG potassium current at 60 nM concentration by 82.0 ± 2.1% (mean ± SD; n = 2). For TI and Technosphere particles, calculated hERG current inhibitions occur at concentrations that are approximately 65- and >96-fold greater, respectively, than the maximum serum clinical concentrations of serum FDKP at the maximum anticipated clinical dose (105 mg per day TI or 315 U of insulin, approximately (b) (4) ng/mL or (b) (4) μM FDKP).

"There was no evidence of cardiac adverse effects in telemeterized, conscious dogs in a single dose CV safety pharmacology study or in a 39-week inhalation toxicology study in dogs. There were no effects on electrocardiograms (ECGs) or QTc intervals. Hemodynamic changes were observed in dogs receiving Technosphere particles containing polysorbate 80, a component of TI powder. However, these changes were not observed with polysorbate-free Technosphere particles and were considered to be species-specific."

3.4 PREVIOUS CLINICAL EXPERIENCE

Source: Summary of Clinical Safety eCTD 2.7.4

"A total of 2409 Technosphere Insulin Inhalation Powder (TI) -treated and 1944 Comparator treated subjects with type 1 or type 2 diabetes mellitus (the Combined Population) were included in the safety population for the pooled Phase 2/3 trials.

"Of the 14 subjects who died in the pooled phase 2/3 controlled trials, 9 (0.3%) received TI and 5 (0.3%) received Comparator. None of the deaths were considered related to the study drugs by the investigators. In both treatment groups, the majority of deaths were due to cardiovascular and cerebrovascular events, primarily myocardial ischemia and stroke. The incidence of ischemic and cerebrovascular events was similar in the two treatment groups.

"An analysis of overall cardiovascular risk showed that for subjects in the Combined Population the relative risk of having a Cardiovascular TEAE if treated with TI was 1.01 compared with treatment with Comparator (Table 35). The Confidence Intervals for this analysis are 0.84 to 1.20. This meets the criteria cited in the Guidance that the upper bound of the two-sided 95 % CI (confidence interval) for the estimated increased risk (i.e., risk ratio) be less than <1.8.

Table 35. Relative Risk of Cardiovascular Adverse Events With TI Type 1 or Type 2 Subjects Safety Population – Pooled Controlled Phase 2/3 Trials				
	Method	Relative Risk with TI	95% CI Lower Bound	95% CI Upper Bound
Type 1 and 2 Subjects Controlled Pooled Phase 2/3 Trials	Mantel Haenszel	1.01	0.84	1.20
Type 1 Subjects Controlled Pooled Phase 2/3 Trials	Mantel Haenszel	0.85	0.55	1.30
Type 2 Subjects Controlled Pooled Phase 2/3 Trials	Mantel Haenszel	1.02	0.84	1.24

CI= confidence interval; TI = Technosphere® Insulin
Data source: Table G.3.14.3

"A total of 1483 TI subjects and 1491 Comparator subjects had both Baseline and on-therapy ECG assessments In the TI group, 9.8% of the subjects who began the study with a normal ECG developed clinically nonsignificant abnormal findings and 0.3% developed clinically significant abnormal findings. Findings were similar for the Comparator group; 11.3% developed clinically non-significant abnormal findings and 0.5% developed clinically significant abnormal findings. A small fraction of the subjects who began the study with a clinically nonsignificant abnormal finding developed a clinically significant finding [0.4% in the TI group, 0.4% in the Comparator, and 1.1% in the Technosphere powder (TP) group)] These findings show no difference between TI and Comparator in the percentage of subjects who develop new ECG findings that were either not clinically significant or clinically significant.

"In the Combined Population, and in the type 1 and type 2 populations, no risk of QT prolongation was found in shifts from baseline in QTc intervals, in the percent of subjects who had increases in QTc interval of > 30 or > 60 ms, or in subjects who had an increase in QTc interval to > 500 msec."

Reviewer's Comments: In patients taking Technosphere insulin inhalation powder (TI), there are no reports of sudden death, TdP or significant ventricular arrhythmias. There was one cardiac arrest in the TI group secondary to acute MI and two events in the comparator group. The number of seizures were also balanced between groups and reported as due to hypoglycemia and epilepsy.

3.5 CLINICAL PHARMACOLOGY

Appendix 6.1 summarizes the key features of FDKP's clinical pharmacology.

4 SPONSOR'S SUBMISSION

4.1 OVERVIEW

The QT-IRT reviewed the protocol prior to conducting this study under IND 61,729. The sponsor submitted the study report *mkc-t-131-csr.pdf* for the study drug, FDKP, including electronic datasets and waveforms to the ECG warehouse.

4.2 TQT STUDY

4.2.1 Title

A Phase 1, Randomized, Double-Blind, Cross-Over, Placebo- and Active-Controlled Cardiac Safety Study of Therapeutic and Supratherapeutic Doses of Fumaryl Diketopiperazine Administered as Technosphere® Inhalation Powder in Healthy Subjects

4.2.2 Protocol Number

MKC-T-131

4.2.3 Study Dates

27 May 2008 to 09 Aug 2008

4.2.4 Objectives

Primary:

The primary objective of this study was to determine if the supra-therapeutic dose of T Inhalation Powder would prolong the mean QT/QTc interval. This was measured by the maximum change in time-matched, placebo-subtracted, individualized QT interval corrected (QTcI) for the supra-therapeutic dose of T Inhalation Powder, where the upper bound of the 95% 1-sided confidence interval (CI) on the day of treatment for the supra-therapeutic dose versus placebo was not to exceed 10 ms.

Secondary:

- To determine if the therapeutic dose of T Inhalation Powder would prolong the mean QT/QTc interval. This was measured by the maximum change in time-matched, placebo subtracted, QTcI for the therapeutic dose of T Inhalation Powder, where the upper bound of the 95% 1-sided CI on the day of treatment for the therapeutic dose versus placebo was not to exceed 10 ms
- To determine if the supra-therapeutic and therapeutic doses of T Inhalation Powder would prolong the mean QT/QTc interval as measured by the maximum change in time matched, placebo-subtracted QTc (corrected by the Fridericia formula QTcF] and the Bazett formula [QTcB]), where the upper bound of the 95% 1-sided CI on the day of treatment for the therapeutic dose versus placebo was not to exceed 10 ms
- To evaluate the pharmacokinetics of FDKP for the therapeutic and supra-therapeutic doses to determine possible relationships between FDKP plasma concentrations and QTc interval duration, if prolonged
- To evaluate the safety of therapeutic and supra-therapeutic doses of T Inhalation Powder in healthy subjects

To evaluate other ECG results (heart rate [HR], RR interval, PR interval, QRS interval, uncorrected QT interval, and any change in morphology)

4.2.5 Study Description

4.2.5.1 Design

This was a Phase 1, randomized, 4-period cross-over, double-blind, double-dummy, placebo and active-controlled cardiac safety study of FDKP administered as T Inhalation Powder in 48 healthy subjects.

Subjects were confined to the clinical study unit as inpatients for the entire study (11 nights and 12 days). A washout period of at least 3 days (72 hours) followed each study treatment dosing in a treatment sequence.

4.2.5.2 Controls

The Sponsor used both placebo and positive (moxifloxacin) controls.

4.2.5.3 Blinding

All treatment arms were administered blinded using a double dummy approach. The moxifloxacin pills and placebo "dummy" capsules were not identical. They were masked as much as possible by making them similar in weight and placing them in opaque, screw-cap containers. Moreover, regardless of masking at the site, the ECG reader was masked to subject treatment.

4.2.6 Treatment Regimen

4.2.6.1 Treatment Arms

Each subject was assigned to receive a single dose of T Inhalation Powder 40 mg (supratherapeutic dose), T Inhalation Powder 20 mg (therapeutic dose), placebo (empty cartridge and empty capsule), and an oral dose of moxifloxacin 400 mg (active control) in a randomized sequence of 4 periods.

Table 2: Study Design and Treatment Sequences

Treatment Sequence	Period 1	Period 2	Period 3	Period 4
1 (n = 12)	20 mg T Inhalation Powder	40 mg T Inhalation Powder	Placebo	Moxifloxacin
2 (n = 12)	40 mg T Inhalation Powder	Moxifloxacin	20 mg T Inhalation Powder	Placebo
3 (n = 12)	Placebo	20 mg T Inhalation Powder	Moxifloxacin	40 mg T Inhalation Powder
4 (n = 12)	Moxifloxacin	Placebo	40 mg T Inhalation Powder	20 mg T Inhalation Powder

4.2.6.2 Sponsor's Justification for Doses

"The supratherapeutic dose of T Inhalation Powder for this study (40 mg given as 4 cartridges and 8 inhalations) was based on several important considerations. The anticipated maximum therapeutic dose of TI Inhalation Powder in humans is 90 U of insulin, which would contain approximately (b) (4) mg of FDKP. Each cartridge of T Inhalation Powder contains 10 mg. Therefore, a supratherapeutic dose that was 5 times that amount (or 150 mg) would have required each subject to inhale 15 cartridges and perform 30 inhalations (b) (4) This would be extremely difficult for subjects to accomplish and would have caused the time to C_{max} (T_{max}) to vary considerably. It might also have posed a safety risk, since the safety of inhaling large amounts of dry powder at one time has not been established."

Reviewer's Comment: The typical doses of T Inhalation (TI) Powder ranged from 15U to 90U and the FDKP amount ranged from about (b) (4) in 15-U TI to (b) (4) in 90-U TI. Therefore, the FDKP therapeutic dose of 20 mg seems reasonable. The sponsor used 40 mg as the supra-therapeutic dose which is acceptable because a 2.2-fold higher value of C_{max} was observed at the supra-therapeutic dose compared to the therapeutic dose. This exceeded the increase in C_{max} of 1.3-fold for the predicted worst case scenario of co-administration of salbutamol in asthmatic patients. Type 2 subjects with mild and moderate diabetic nephropathy have 1.3-fold higher and 0.9-fold lower mean C_{max} values compared to Type 2 subjects with normal renal function. Subjects with mild and moderate hepatic impairment have 1.1-fold higher mean C_{max} values compared to normal subjects. Co-administration of inhaled albuterol and fluticason resulted in a 1.2-fold and 1.1-fold increase in mean C_{max} in healthy subjects.

4.2.6.3 Instructions with Regard to Meals

Doses should be administered at the beginning of a meal. In some patients, the total dose per meal may be split before and after the meal when using more than one cartridge.

Reviewer's Comment: This is a product for inhalation; therefore, food effects are not anticipated.

4.2.6.4 ECG and PK Assessments

ECG Assessment

Six 12-lead ECGs (providing 6 replicate ECGs for each time point) were collected on Days 1, 4, 7, and 10 for each treatment arm at the following time points: 45, 30, and 15 minutes before dosing; approximately 5, 10, 15, 20, and 30 minutes after dosing; and approximately 1, 2, 3, 4, 8, 12, and 23 hours after dosing.

PK Assessment

Blood samples for the determination of plasma concentrations of FDKP were collected 45 minutes before dosing and 5, 10, 15, 20, 30 minutes after dosing as well as at 1, 2, 3, 4, 8, 12, and 23 hours after dosing. To assess the plasma concentrations of moxifloxacin,

blood samples were collected 45 minutes before dosing and 1, 2, 3, 4 and 23 hours after dosing.

Reviewer's Comment: ECG measurements were collected frequently enough to monitor the effects of FDKP over a 24-hour interval. The first ECG sample after dosing was collected at 5 minutes which is reasonable because this is a product of inhalation and it is expected that earlier time points would reflect the maximum concentrations observed in the heart.

4.2.6.5 Baseline

The baseline used for the time-matched analyses was the arithmetic mean of the 3 ECG at 45, 30, 15 minutes before dosing on the same day.

4.2.7 ECG Collection

Electrocardiograms were obtained digitally using a Mortara Instrument (Milwaukee, WI) H-12+ ECG continuous 12-lead digital recorder. The ECGs were obtained starting on Days 1, 4, 7, and 10 while subjects were in a supine resting state. These ECGs were not available for review until the card was received by the central ECG laboratory and analyzed. ECGs to be used in the thorough ECG analysis were selected at predetermined time points as detailed below and were read centrally using a high-resolution, manual, on-screen caliper, semiautomatic method with annotations.

Six 12-lead ECGs were downloaded from the H-12+ flash card (providing 6 ECGs for each time point) on Days 1, 4, 7, and 10 of each treatment sequence at the time points specified above.

The thorough ECG analysis was conducted using data from lead II and, when not analyzable, data from lead V5 or the most appropriate other lead.

The central ECG readers were blinded to subject identifiers, treatment, and visit. A single reader reviewed and measured all ECGs for a given subject. Inter- and intra-observer variability was evaluated by (b) (4) and the results presented in quality assurance reports to the Sponsor.

4.2.8 Sponsor's Results

4.2.8.1 Study Subjects

Overall, 48 healthy subjects, 18–45 years of age, with a normal baseline ECG and BMI between 19 and ≤ 30 kg/m² were enrolled in this study.

A total of 47 randomized subjects (97.9%) completed the study. Subject 0205 withdrew informed consent, possibly because the subject experienced AEs of nausea and vomiting after taking moxifloxacin.

4.2.8.2 Statistical Analyses

4.2.8.2.1 Primary Analysis

The primary ECG analysis was the largest time-matched baseline-adjusted least squares (LS) mean difference in QTcI between FDKP and placebo at post-dose ECG collection time points.

The time-matched analysis of baseline versus on-treatment ECGs for each day of treatment was based on the placebo-adjusted change from baseline in QTc interval – the delta-delta approach. One-sided 95% CIs were calculated using the Intersection Union test (although raw mean difference data were also provided), thus making multiple endpoint adjustment unnecessary. The corresponding baseline value of ECG as a covariate was calculated for each on-treatment time point, where the ECGs around each time point at baseline and at steady state were first averaged to provide the value for that time point and then the on-treatment time point value (calculated in the same manner) was subtracted from the baseline value to produce the change from baseline value. Then, this value was placebo adjusted from data obtained at the same time point in the subjects receiving placebo. Sponsor's results are presented in Table 3 and Figure 1.

Table 3: Time-Matched Placebo-Corrected QTcI Mean Change from Baseline - Estimates from Mixed-Effects Model Analysis of Variance: ECG Population

Time	Treatment Group					
	Therapeutic (n = 47)		Supratherapeutic (n = 48)		Moxifloxacin 400 mg (n = 47)	
	Estimate[a]	Upper Bound[b]	Estimate[a]	Upper Bound[b]	Estimate[a]	Upper Bound[b]
5 min	-1.1	0.9	-0.4	1.5	-0.8	2.4
10 min	-2.3	-0.3	-1.6	0.4	-0.5	2.7
15 min	-0.4	1.6	0.5	2.4	2.8	6.1
20 min	0.5	2.4	0.6	2.6	4.5	7.7
30 min	-1.0	1.0	-2.0	-0.0	4.5	7.7
1 hour	0.2	2.2	-1.6	0.4	6.8	10.0
2 hours	-0.2	1.8	-0.6	1.4	10.3	13.5
3 hours	-1.7	0.3	-0.7	1.3	8.6	11.8
4 hours	-1.7	0.3	-1.0	1.0	10.2	13.4
8 hours	0.6	2.6	0.9	2.9	9.7	12.9
12 hours	-0.3	1.7	-0.5	1.5	6.4	9.7
23 hours	-0.0	1.9	1.7	3.7	5.7	8.9

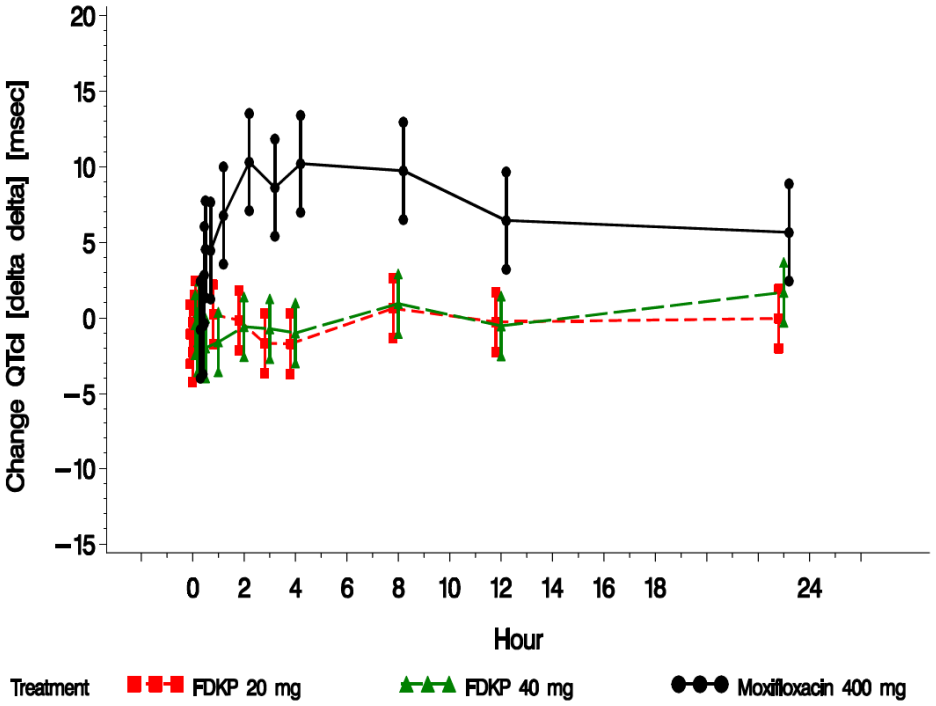
a Estimates are from a mixed-effects general linear model that was fit for placebo-adjusted baseline-corrected and includes terms for treatment, time, gender, time-by-treatment and gender-by-treatment interactions, and baseline value.

b Upper bound = upper one-sided 95% ANOVA model-based confidence limit.

ANOVA = analysis of variance; ECG = electrocardiogram; QTcI = individualized QT interval corrected.

Source: Sponsor's CSR Table 7 on Page 54.

Figure 1: Time-Matched Placebo-Corrected QTcI Mean Change from Baseline — Estimates from Mixed Model Analysis of Variance: ECG Population



FDKP = fumaryl diketopiperazine; QTcI = individualized QT interval corrected.
Data Source: Appendix 16.5.1, Figure 3.1.

Source: Sponsor's CSR Figure 1 on Page 55.

Reviewer's Comments: We agree with the sponsor's conclusions of lack of QTc prolongation for the study treatment. The results of our independent analyses are presented in section 5.2.

4.2.8.2.2 Assay Sensitivity

Assay sensitivity was established in that the QTcI placebo-corrected mean change from baseline for moxifloxacin 400 mg was 5.5 ms (expected, 5 ms to 10 ms) (Appendix 16.5.1).

Reviewer's Comments: For assay sensitivity, the 90% lower bound instead of the upper bound of delta-delta should be evaluated. Our independent analyses results are presented in section 5.2. We agree with the sponsor's conclusion of the establishment of assay sensitivity.

4.2.8.2.3 Categorical Analysis

Results of the outlier analysis of ECG parameter data are summarized in Table 4. Outlier analysis of changes in QTcI revealed that no subjects experienced a new QTcI > 500 ms or > 480 ms. A 30 ms to 60 ms increase in QTcI from baseline was observed in 1 subject in the moxifloxacin treatment group. No subjects experienced a > 60 ms increase in QTcI from baseline.

Table 4: Time-Averaged Analysis of ECG Outliers: ECG Population

Parameter	Treatment Group			
	Therapeutic (n = 47)	Supratherapeutic (n = 48)	Moxifloxacin 400 mg (n = 48)	Placebo (n = 47)
Heart rate				
Tachycardia, n (%)	1 (2%)	0	0	1 (2%)
Bradycardia, n (%)	0	0	0	0
PR outliers, n (%)	0	0	0	0
QRS outliers, n (%)	0	0	0	0
QT new > 500 ms, n (%)	0	0	0	0
QTcI				
New > 500 ms, n (%)	0	0	0	0
New > 480 ms, n (%)	0	0	0	0
30-60 ms increase from Baseline, n (%)	0	0	1 (2%)	0
> 60 ms increase from Baseline, n (%)	0	0	0	0
QTcF				
New > 500 ms, n (%)	0	0	0	0
New > 480 ms, n (%)	0	0	0	0
30-60 ms increase from Baseline, n (%)	0	0	1 (2%)	0
> 60 ms increase from Baseline, n (%)	0	0	0	0
QTcB				
New > 500 ms, n (%)	0	0	0	0
New > 480 ms, n (%)	0	0	0	0
30-60 ms increase from Baseline, n (%)	0	0	4 (8%)	2 (4%)
> 60 ms increase from Baseline, n (%)	0	0	0	0

ECG = electrocardiogram; ms = milliseconds; QTcI = individualized QT interval corrected; QTcB = QT interval corrected by the Bazett formula; QTcF = QT interval corrected by the Fridericia formula.

Data Source: Appendix 16.5.1, Tables 1 through 7.

4.2.8.3 Safety Analysis

There were no deaths or SAEs in this study. One subject discontinued due to an AE.

Two AEs of vasovagal syncope were recorded (1 of mild severity in Subject 0039 after treatment with placebo and 1 of moderate severity in Subject 0189 after treatment with the therapeutic [20 mg] dose of T Inhalation Powder); both events were considered to be not related to study treatment and resolved within 1 day. According to the study site, both syncope events were related to phlebotomy. Subjects were monitored with ECGs, both subjects had normal vital signs at the time the events occurred, and neither subject was withdrawn from the study.

4.2.8.4 Clinical Pharmacology

4.2.8.4.1 Pharmacokinetic Analysis

The PK results for FDKP are presented in Table 5. C_{max} and AUC values in the thorough QT study were 2.2-fold and 2.0-fold higher following administration of the supra-therapeutic dose (40 mg) compared with the therapeutic dose (20 mg). The mean FDKP concentration profiles at the therapeutic and supra-therapeutic dose are shown in Figure 2.

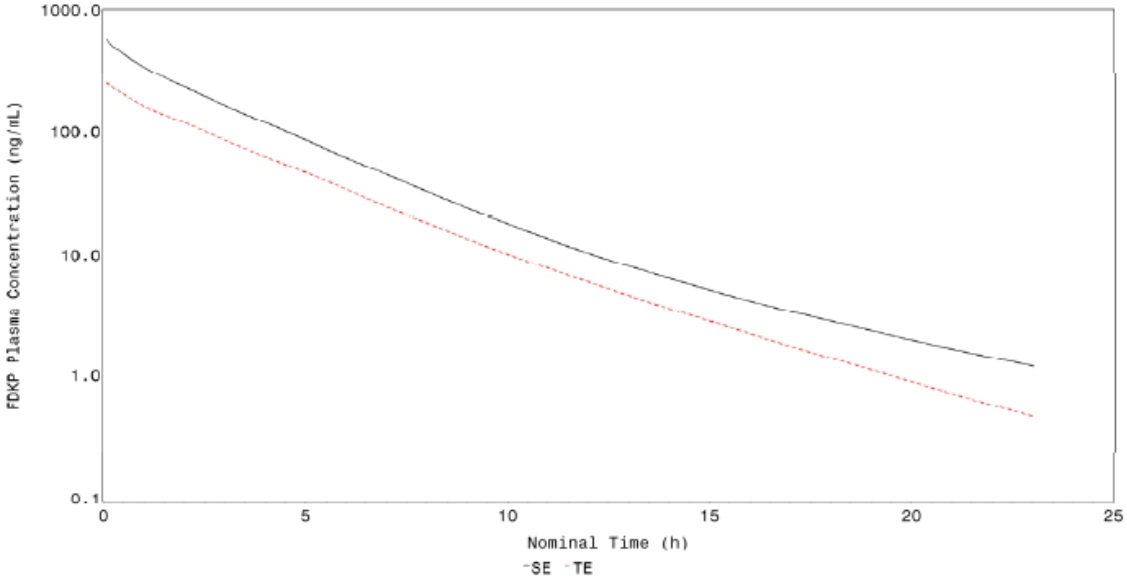
Table 5: Sponsor's Mean PK Parameters for FDKP

Treatment	Statistic	Cmax (ng/mL)	Tmax (h)	AUClast (ng*h/mL)	t1/2 (h)
TE	N	47	47	47	47
	Mean	268.37	0.19	799.95	2.53
	SD	107.88	0.11	176.73	0.71
	%CV	40.20	58.10	22.09	28.00
	Minimum	94.24	0.10	378.62	1.75
	Median	268.40	0.12	772.21	2.34
	Maximum	561.84	0.55	1232.94	6.10
	Geometric Mean	246.75		780.61	
SE	N	47	47	47	47
	Mean	598.70	0.16	1631.16	2.73
	SD	225.61	0.07	445.62	0.80
	%CV	37.68	43.47	27.32	29.29
	Minimum	250.60	0.12	893.85	1.69
	Median	556.73	0.12	1526.53	2.49
	Maximum	1284.68	0.37	2686.44	5.35
	Geometric Mean	560.61		1575.25	

TE = Therapeutic dosing of T Inhalation powder (20 mg)
SE = Supratherapeutic dosing of T Inhalation powder (40 mg)

(Source: Table 14.2.2 from MKC-T-131-tfls report)

Figure 2: Sponsor's Mean FDKP concentration-time profiles for 20 mg (red line) and 40 mg FDKP (black line)

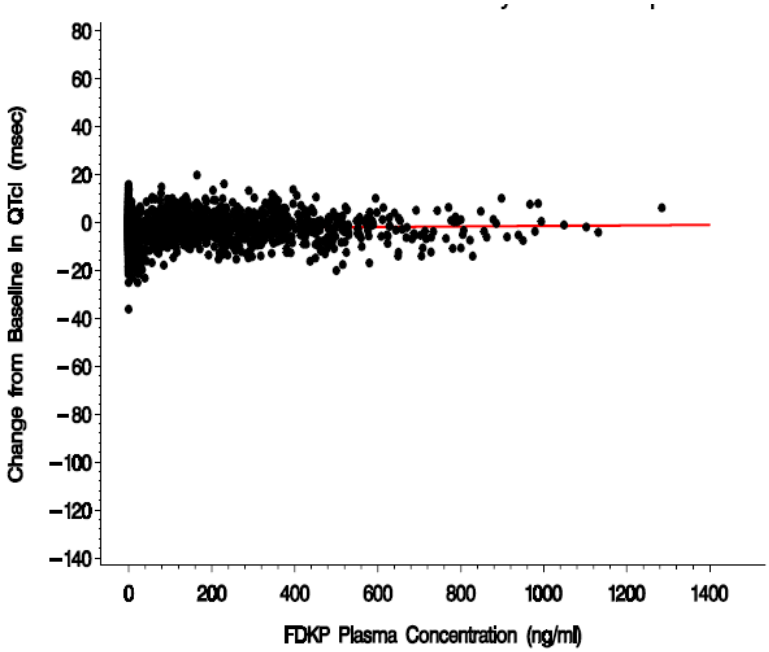


(Source: Figure 1 from MKC-T-131 report)

4.2.8.4.2 Exposure-Response Analysis

Sponsor's ΔΔQTcI vs. FDKP plasma concentrations is shown in Figure 3. Across the studied concentration range, there appeared to be no increase in QTcI duration.

Figure 3: Sponsor's ΔΔQTcI vs. FDKP Plasma Concentration



(Source: Figure 2 from MKC-T-131 report)

Reviewer's Analysis: We agree with the sponsor's exposure-response analysis that shows no increase in QTcI duration with increasing FDKP concentration. Since both QTcF and QTcI correction methods were similar, for completeness, a plot of ΔΔQTcF vs. FDKP plasma concentrations is also presented in Figure 6. Consistent with the sponsor's conclusion, there appeared to be no increase in QTcF with increasing FDKP concentrations.

5 REVIEWERS' ASSESSMENT

5.1 EVALUATION OF THE QT/RR CORRECTION METHOD

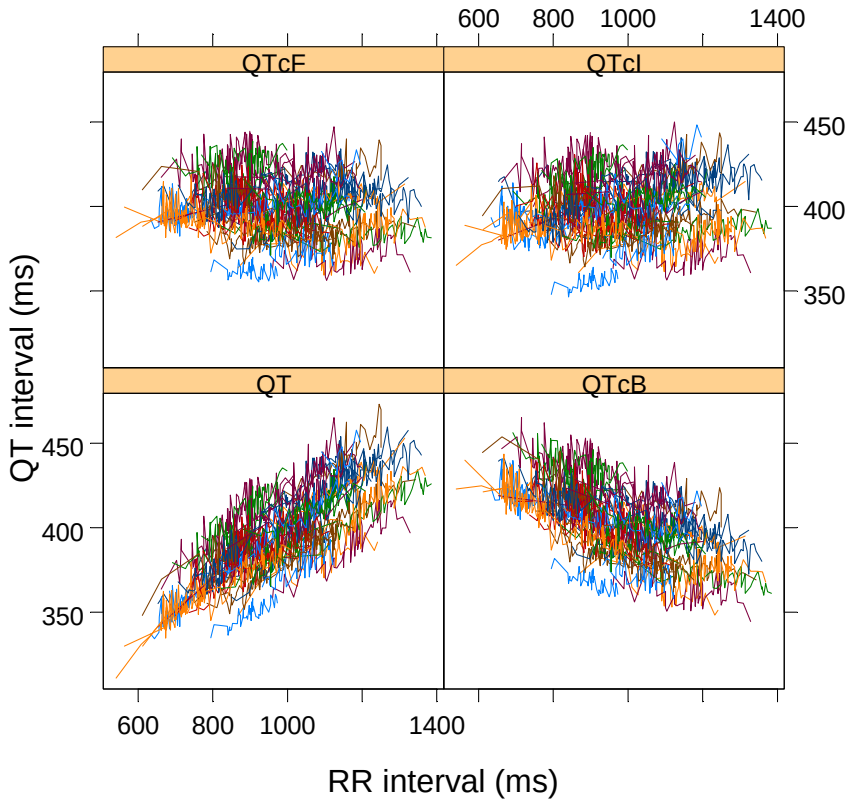
The QT-RR interval relationship is presented in Figure 4 together with the Bazett's (QTcB), Fridericia (QTcF), and individual correction (QTcI).

We also evaluated the linear relationships between different correction methods (QTcB, QTcF, QTcI) and RR. We used the average sum of squared slopes as the criterion. The smaller this value is, the better the correction. Based on the results listed in the following table, it appears that both QTcF and QTcI are similar. Therefore, this statistical reviewer used QTcI for the primary statistical analysis. This is also consistent with the sponsor's primary endpoint.

Table 6: Average of Sum of Squared Slopes for Different QT-RR Correction Methods

	Correction Method					
	QTcB		QTcF		QTcI	
	N	MSSS	N	MSSS	N	MSSS
FDKP 20 mg	47	0.0065	47	0.0021	47	0.0032
FDKP 40 mg	47	0.0060	47	0.0020	47	0.0033
Moxifloxacin	48	0.0100	48	0.0026	48	0.0027
Placebo	47	0.0069	47	0.0015	47	0.0020
All	48	0.0051	48	0.0016	48	0.0028

Figure 4: QT, QTcB, QTcF, and QTcI vs. RR (Each Subject's Data Points are Connected with a Line)



5.2 STATISTICAL ASSESSMENTS

5.2.1 QTc Analysis

5.2.1.1 The Primary Analysis for FDKP and Assay Sensitivity

The statistical reviewer used a mixed model to analyze the ΔQTcI effect at each of the time points. The model included TIME, SEQUENCE, and PERIOD as fixed effects and SUBJECT as a random effect. The model also included the time-matched baseline and gender as covariates. The analysis results are presented in Table 7. The largest upper bound of the two-sided 90% CI for the mean difference between FDKP 40 mg and placebo was 2.6 ms.

For the moxifloxacin group, the largest lower bound of the unadjusted 90% confidence interval is 9.0 ms. By considering Bonferroni multiple endpoint adjustment, the largest lower bound also exceeds 5 ms, which indicates that an at least 5-ms QTcI effect due to moxifloxacin can be detected from the study.

Table 7: Analysis Results of ΔQTcI and ΔΔQTcI

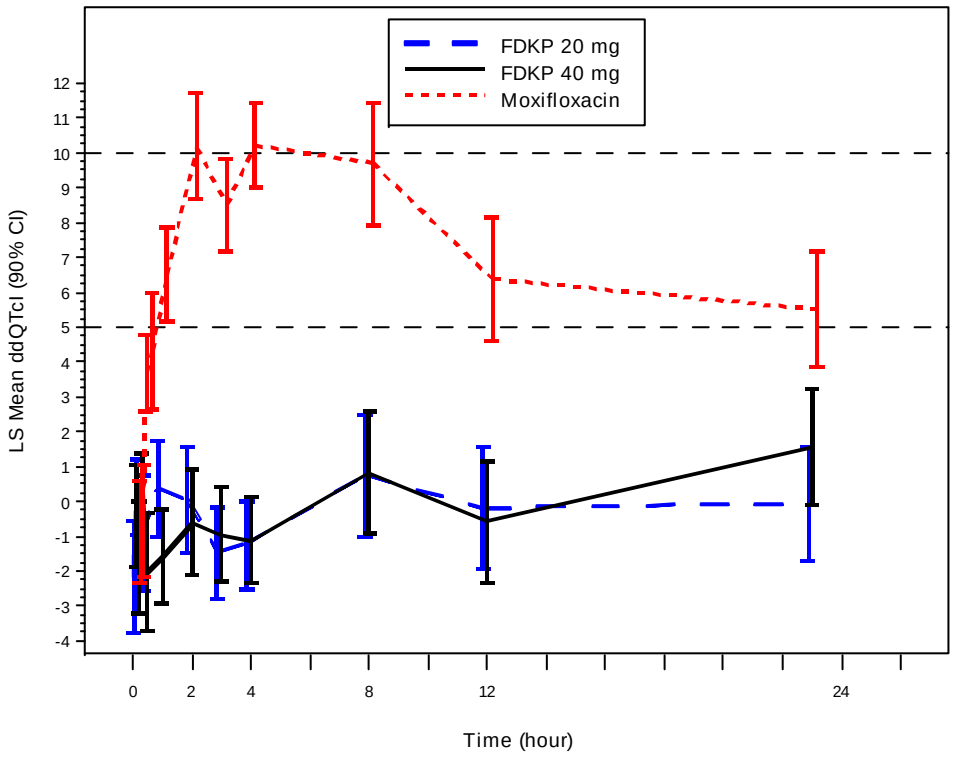
	Placebo	FDKP 20 mg			FDKP 40 mg			Moxifloxacin		
	ΔQTcI	ΔQTcI	ΔΔQTcI		ΔQTcI	ΔΔQTcI		ΔQTcI	ΔΔQTcI	
Time (hrs)	LS Mean	LS Mean	Diff LS Mean	90% CI	LS Mean	Diff LS Mean	90% CI	LS Mean	Diff LS Mean	90% CI*
0.1	-0.4	-1.4	-1.0	(-2.5, 0.5)	-0.8	-0.4	(-1.9, 1.0)	-1.2	-0.9	(-2.3, 0.6)
0.2	-0.6	-2.7	-2.2	(-3.8, -0.6)	-2.2	-1.6	(-3.2, 0.0)	-1.2	-0.6	(-2.2, 1.0)
0.3	-4.0	-3.9	0.1	(-0.9, 1.2)	-3.7	0.3	(-0.8, 1.4)	-0.3	3.7	(2.6, 4.7)
0.5	-0.4	-1.3	-0.9	(-2.6, 0.7)	-2.4	-2.0	(-3.7, -0.4)	3.9	4.3	(2.7, 6.0)
1.0	0.9	1.2	0.4	(-1.0, 1.7)	-0.7	-1.6	(-2.9, -0.2)	7.4	6.5	(5.1, 7.9)
2.0	0.1	0.2	0.0	(-1.5, 1.6)	-0.5	-0.6	(-2.1, 0.9)	10.3	10.2	(8.6, 11.7)
3.0	0.9	-0.6	-1.5	(-2.8, -0.2)	-0.0	-0.9	(-2.3, 0.4)	9.4	8.5	(7.2, 9.8)
4.0	0.2	-1.1	-1.2	(-2.5, 0.0)	-0.9	-1.1	(-2.4, 0.1)	10.4	10.2	(9.0, 11.4)
8.0	-9.4	-8.7	0.7	(-1.0, 2.5)	-8.6	0.8	(-0.9, 2.6)	0.3	9.7	(7.9, 11.4)
12.0	-6.1	-6.4	-0.2	(-2.0, 1.5)	-6.7	-0.6	(-2.4, 1.2)	0.2	6.4	(4.6, 8.1)
23.0	-1.3	-1.4	-0.1	(-1.7, 1.6)	0.3	1.6	(-0.1, 3.2)	4.2	5.5	(3.9, 7.2)

*The largest lower bound of the 90% CI is 8.5 ms at 4 hours after Bonferroni adjustment for 4 time points.

5.2.1.2 Graph of ΔΔQTcI Over Time

The following figure displays the time profile of ΔΔQTcI for different treatment groups.

Figure 5: Mean and 90% CI ΔΔQTcI Timecourse



5.2.1.3 Categorical Analysis

There were no subjects with QTcI above 450 ms. Nor were there any subjects with ΔQTcI above 60 ms. Table 8 presents the categorical analysis results for the ΔQTcI.

Table 8: Categorical Analysis of ΔQTcI

	N	Value<=30 ms	30 ms<Value<=60 ms
Treatment Group			
FDKP 20 mg	47	47 (100%)	0 (0.0%)
FDKP 40 mg	47	47 (100%)	0 (0.0%)
Moxifloxacin	48	47 (97.9%)	1 (2.1%)
Placebo	47	47 (100%)	0 (0.0%)

5.2.2 PR Analysis

The same statistical analysis used for the QTc intervals was performed based on PR intervals. The point estimates and the 90% confidence intervals are presented in Table 9. The largest upper limits of 90% CI for the PR mean differences between FDKP 40 mg and placebo was 4.2 ms. The outlier analysis results for PR are presented in Table 10.

Table 9: Analysis Results of ΔPR and ΔΔPR

	Placebo	FDKP 20 mg			FDKP 40 mg		
	ΔPR	ΔPR	ΔΔPR		ΔPR	ΔΔPR	
Time (hrs)	LS Mean	LS Mean	Diff LS Mean	90% CI	LS Mean	Diff LS Mean	90% CI
0.1	-2.1	-2.4	-0.2	(-1.9, 1.4)	-0.4	1.7	(0.0, 3.4)
0.2	-1.2	-0.2	0.9	(-0.7, 2.6)	0.3	1.5	(-0.1, 3.2)
0.3	-1.7	-0.7	1.0	(-0.3, 2.2)	0.4	2.2	(0.9, 3.4)
0.5	-0.4	0.7	1.2	(-0.8, 3.2)	0.5	0.9	(-1.0, 2.9)
1.0	-2.6	-1.2	1.5	(-0.2, 3.1)	-0.6	2.0	(0.4, 3.6)
2.0	-1.8	-2.2	-0.4	(-2.0, 1.2)	-2.5	-0.7	(-2.3, 0.9)
3.0	-2.2	-3.0	-0.8	(-2.3, 0.8)	-1.3	1.0	(-0.6, 2.6)
4.0	-3.3	-3.0	0.3	(-1.1, 1.7)	-2.0	1.3	(-0.1, 2.8)
8.0	-8.2	-8.6	-0.4	(-2.2, 1.4)	-6.6	1.6	(-0.2, 3.5)
12.0	-6.6	-7.3	-0.6	(-2.4, 1.2)	-7.1	-0.4	(-2.3, 1.4)
23.0	-1.9	-2.6	-0.7	(-2.8, 1.4)	0.2	2.1	(-0.1, 4.2)

Table 10: Categorical Analysis for PR

Treatment Group	N	PR < 200 ms	PR >=200 ms
FDKP 20 mg	47	45 (95.7%)	2 (4.3%)
FDKP 40 mg	47	45 (95.7%)	2 (4.3%)
Moxifloxacin	48	44 (91.7%)	4 (8.3%)
Placebo	47	45 (95.7%)	2 (4.3%)

5.2.3 QRS Analysis

The same statistical analysis used for the QTc intervals was performed based on QRS intervals. The point estimates and the 90% confidence intervals are presented in Table 11. The largest upper limits of 90% CI for the QRS mean differences between FDKP 40 mg was 0.9 ms. There are no subjects who experienced absolute QRS interval greater than 120 ms in the FDKP 40 mg group.

Table 11: Analysis Results of ΔQRS and ΔΔQRS

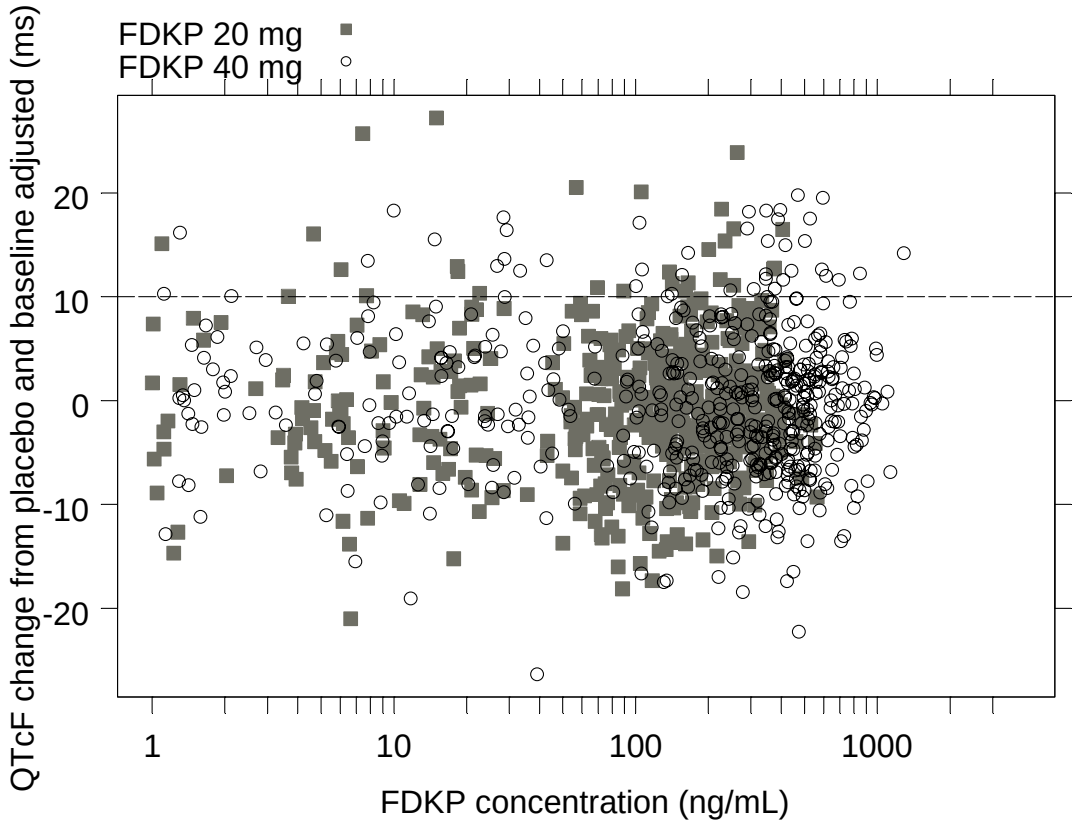
	Placebo	FDKP 20 mg			FDKP 40 mg		
	ΔQRS	ΔQRS	ΔΔQRS		ΔQRS	ΔΔQRS	
Time (hrs)	LS Mean	LS Mean	Diff LS Mean	90% CI	LS Mean	Diff LS Mean	90% CI
0.1	0.5	0.1	-0.4	(-1.0, 0.1)	-0.4	-0.9	(-1.5, -0.4)
0.2	0.4	0.2	-0.2	(-0.7, 0.4)	-0.1	-0.4	(-1.0, 0.1)
0.3	-0.2	-0.0	0.2	(-0.2, 0.6)	-0.1	0.2	(-0.2, 0.6)
0.5	-0.0	0.1	0.1	(-0.6, 0.8)	0.2	0.2	(-0.5, 0.8)
1.0	0.2	-0.3	-0.5	(-1.1, 0.1)	-0.1	-0.3	(-0.9, 0.3)
2.0	0.1	-0.3	-0.4	(-1.1, 0.3)	-0.6	-0.7	(-1.4, -0.1)
3.0	-0.3	-0.4	-0.0	(-0.7, 0.6)	-0.1	0.2	(-0.5, 0.8)
4.0	-0.8	-0.6	0.2	(-0.5, 0.9)	-0.8	-0.1	(-0.7, 0.6)
8.0	-1.1	-0.9	0.2	(-0.5, 0.9)	-1.0	0.1	(-0.6, 0.9)
12.0	-0.4	-0.1	0.3	(-0.3, 1.0)	-0.3	0.1	(-0.6, 0.8)
23.0	0.1	0.1	-0.0	(-0.7, 0.6)	0.1	-0.1	(-0.7, 0.6)

5.3 CLINICAL PHARMACOLOGY ASSESSMENTS

The mean FDKP concentration-time profile is illustrated in Figure 2 in section 4.2.8.4.1.

The relationship between ΔΔQTcF and FDKP concentrations is visualized in Figure 6 with no evident exposure-response relationship which is consistent with sponsor's exposure-response analysis utilizing QTcI.

Figure 6: ΔΔQTcF vs. FDKP Concentration



5.4 CLINICAL ASSESSMENTS

5.4.1 Safety assessments

One subject developed syncope reported as vaso-vagal after receiving FDKP 20 mg. This was not associated with any ECG changes.

5.4.2 ECG assessments

Waveforms from the ECG warehouse were reviewed. According to ECG warehouse statistics over 86% of the ECGs were annotated in the primary lead (II) with V5 being the usual back up lead on review of subsets of the waveforms. Less than 0.1% of the ECGs had any significant QT bias, according to the automated algorithm. ECG acquisition and interpretation in this trial appears acceptable.

5.4.3 PR and QRS Interval

There were no clinically relevant effects on the PR and QRS intervals.

6 APPENDIX

6.1 HIGHLIGHTS OF CLINICAL PHARMACOLOGY

5.1 Highlights of Clinical Pharmacology

Therapeutic dose	(b) (4) (3 X 90U + 1 X 45U TI (b) (4)	
Maximum tolerated dose	Unknown clinically; highest clinical dose (90 U TI three times daily + 45 U once daily) is well tolerated from ongoing clinical trial data.	
Principal adverse events	FDKP adverse events are unknown clinically;	
Maximum dose administered	Single Dose	(b) (4) FDKP (from a 100 U TI dose at (b) (4) – study PDC-INS-0002)
	Multiple Dose	up to (b) (4) daily ((b) (4) mg before meals and (b) (4) mg before evening snack from 315 U maximum daily TI dose, 105 mg at (b) (4)
Exposures Achieved at Maximum Dose Administered	Single Dose	Mean (%CV) Cmax and AUC - unknown
	Multiple Dose	Mean (%CV) Cmax and AUC - unknown
Tested Dose[a]	Single Dose – (b) (4) (60 U TI dose at (b) (4)	
	Multiple Dose - NA	
Exposures Achieved at Tested Dose[a]	Single Dose – Cmax = 171 ± 103 ng/mL; Tmax = 7.5 ± 5.3 min	
	Multiple Dose - NA	
Range of linear PK	(b) (4) mg (from 30 U and 60 U TI dosing) – $AUC_{8.9mg}$ = 15200 ± 7100 ng/mL/min, $Cmax_{8.9mg}$ = 145 ± 81 ng/mL; $AUC_{17.7mg}$ = 23700 ± 8400 ng/mL/min, $Cmax_{17.7mg}$ = 171 ± 103 ng/mL. [Note that the Cmax in the higher dose group is muted due to the time necessary to inhale from two cartridges.]	
Accumulation at steady state	Mean (%CV); specify dosing regimen – TI administered three times daily (additional dose allowed at night if necessary) > 6 mos; FDKP plasma concentrations taken in the morning before the first dose of the day indicated that in the vast majority of samples the FDKP concentration was consistently below 40 ng/mL (and usually below the quantitation limit [1 ng/mL]). A few subjects had samples with concentrations > 40 ng/mL, but were not consistent over the course of the sampling.	
Metabolites	None identified (multiple in vitro and preclinical in vivo studies; definitive human metabolism study [MKC-T-123] is currently underway].	
Absorption	Absolute/Relative Bioavailability	Mean (%CV) – unknown (gamma scintigraphic study utilizing ^{99m}Tc-labeled microparticles showed that ca. 30% of amount in cartridge reaches the lungs; assuming all material absorbed the bioavailability of FDKP would be 30%)
	Tmax	• Median (range) for parent - 6.2 ± 5.2 min for (b) (4) mg dose, 7.5 ± 5.3 min for (b) (4) mg. Overall median Tmax – 6.5 minutes. • Median (range) for metabolites - NA
Distribution	Vd/F or Vd	Mean (%CV)
	% bound	< 10%

Elimination	Route	• Pulmonary - Absorbed dose is eliminated unchanged in the urine. The material swallowed from deposition in the nasopharynx is eliminated in the feces. • No other intended routes
	Terminal t½	• Mean (%CV): from 30 U TI dose ([b) (4)] FDKP) – 143 min (CV% 26)(median – 137 min); 60 U TI dose ([b) (4)] FDKP) – 161 min (CV% 27)(median – 153 min)
	CL/F[b] or CL	Mean (%CV): estimate from 30 U TI dose ([b) (4)] mg FDKP) – 530 mL/min; estimate from 60 U TI dose ([b) (4)] mg FDKP) – 560 mL/min.
Intrinsic Factors	Age	unknown
	Sex	no difference upon post-hoc assessment of limited data
	Race	unknown
	Hepatic & Renal Impairment	Preliminary data indicates no significant difference (MKC-T-017 and MKC-T-111 trials)
Extrinsic Factors	Drug interactions	None known (interaction with pulmonary products [β-agonist, inhaled steroid] ongoing)
	Food Effects	NA (Inhalation product)
Expected High Clinical Exposure Scenario	15 U TI equals [b) (4)] mg FDKP on a w/w basis. The maximum daily amount of FDKP on a w/w basis administered to subjects using 90 U TI three times a day plus 45 U TI for evening snack is [b) (4)] mg.	

[a]Tested dose = dose of FDKP where FDKP concentrations were measured

[b]estimate from Dose/AUC = CL/F, where dose is the cartridge fill amount.

Submitted to Protocol Review

Study	Population	C_{max} (ng/mL)	Dose (Units)
MKC-TI-003B2	Type 2	160[a]	48
MKC-TI-015	Healthy	93	30
	COPD	95	30
MKC-TI-016	Type 2, nonsmokers	75	30
	Smokers	72	30

MKC-T-017	Type 2, normal renal function	147	60[a]
	Type 2, mild diabetic nephropathy	184	60[a]
	Type 2, moderate diabetic nephropathy	126	60[a]
MKC-TI-025	Type 1, Prototype A	95	30
	Type 1, Prototype B	95	30
MKC-TI-027	Type 2, nonasthmatic, single dose	74	30
	Type 2, nonasthmatic, subchronic dose	94	30
MKC-TI-110	Type 1	131[b]	30
		171[b]	60
MKC-T-111	Healthy	143[c]	60[a]
	Mild Hepatic Impairment	162[c]	60[a]
	Moderate Hepatic Impairment	157[c]	60[a]
MKC-TI-112	Type 1 and 2 during and after a URI	NA	Varied doses
MKC-TI-113	Healthy, TI alone	283	45
	Healthy, TI plus salbutamol	265	45
	Asthmatic, TI alone	197	45
	Asthmatic, TI plus salbutamol	258	45
	Asthmatic, MCT plus TI	258	45
MKC-TI-114	Healthy, TI alone	191	45
	Healthy, TI plus albuterol	233	45
	Healthy, TI plus fluticasone	203	45
MKC-TI-116	Type 1	118	2 × 15 U
		131	1 × 30 U
MKC-TI-122	Healthy	268	60
MKC-T-131	Healthy	247[c]	60[c]
		781[d]	120[d]

COPD = chronic obstructive pulmonary disease; URI = upper respiratory infection; MCT = methacholine challenge test; TI = Technosphere® Insulin Inhalation Powder.

6.2 TABLE OF STUDY ASSESSMENTS

Table 3. Schedule of Events

Visit	Visit 1 (Screening)	Visit 2[a] (Admission)	Baseline ECG, Inpatient Care, Treatment and Evaluation Phase[a]			
			Visit 3 (Period 1)	Visit 4 (Period 2)	Visit 5 (Period 3)	Visit 6 (Period 4)
Day	−28 to −2	−1	1 to 3	4 to 6	7 to 9	10 to 11
Informed consent	X					
Eligibility criteria	X	X				
Review of pulmonary and smoking status	X	X				
Demographic data and medical history	X					
Concomitant medications	X	X	X	X	X	X
Adverse events	X	X	X	X	X	X
HIV serology	X					
Hepatitis serology	X					
Clinical chemistry	X	X[b]	X[b]	X[b]	X[b]	X[b]
Serum pregnancy test (β-hCG)	X	X				X
Hematology	X	X[b]	X[b]	X[b]	X[b]	X[b]
Urine cotinine	X	X				
Urinalysis	X	X	X[b]	X[b]	X[b]	X[b]
Urine drug screening	X	X				
Supine 12-lead ECG	X	X	X[c]	X[c]	X[c]	X[c]
Physical examination	X	X[d]				X
Vital signs	X	X	X[e]	X[e]	X[e]	X[e]
Chest x-ray	X					
Pulmonary function test	X[f]					
Study treatment[g]			X	X	X	X
12-lead telemetry[h]		X	X	X	X	X
Holter continuous ECG[i]			X	X	X	X
PK sampling[j]			X	X	X	X
Study exit						X

a	Study subjects remained at the clinical site for the entire 12 days and 11 nights of the study. Each study period consisted of Baseline treatment (45, 30, and 15 minute ECGs before treatment, a predose [−45 minute] PK sample, and safety assessment), after-treatment ECGs, PK samples and safety assessments up to 24 hours, and a washout period between treatments.
b	Clinical chemistry, hematology, and urinalysis were performed before treatment. At Visit 6 the same tests were also performed after all procedures (after the 23-hour ECG).
c	Safety ECGs were performed before dosing and approximately 15 minutes, 2 hours, and 23 hours after dosing.
d	An abbreviated physical examination was conducted before treatment. The abbreviated examination included general appearance, respiratory and cardiovascular systems, and any other evaluations deemed appropriate by the PI.
e	At Visits 3 through 6, vital signs were assessed before dosing, approximately 15, 30, and 45 minutes after dosing, approximately 1, 1.5, 2, 3, 4, 5, and 6 hours after dosing; and after the 23-hour ECG.
f	PFT testing at Screening (Visit 1) consisted of DL_{co}, TLC, and spirometry before and after bronchodilator administration. A blood sample for hemoglobin was obtained within 14 days of DL_{co} testing.
g	Study treatment was carried out according to randomization schedule (outlined in Section 9.1, Table 1).
h	12-Lead telemetry equipment was attached on the evening of admission (to allow for at least 10 hours of telemetry before enrollment decision) and before and throughout the Holter monitoring days.
i	24-Hour, continuous, Holter ECG monitoring data with downloads were collected approximately 45, 30 and 15 minutes before treatment and at proposed PK sampling times after dosing. Six consecutive ECGs were taken at each time point.
j	Plasma FDKP samples were taken 45 minutes before dosing, approximately 5, 10, 15, 20, and 30 minutes after dosing, and approximately 1, 2, 3, 4, 8, 12, and 23 hours after dosing. Moxifloxacin samples were taken before dosing and approximately 1, 2, 3, 4 and 23 hours after dosing.

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/

CHRISTINE E GARNETT

12/23/2009

Members of review team were Anshu Marathe (clinical pharmacology), Jinglin Zhong (statistics), and Suchitra Balakrishnan (clinical).

NORMAN L STOCKBRIDGE

12/23/2009

DEPARTMENT OF HEALTH AND HUMAN SERVICES MEMORANDUM

Food and Drug Administration
10903 New Hampshire Avenue
Document Mail Center - WO66-G609
Silver Spring, MD 20993-0002

ODE Consult Review

Date: December 14, 2009

To: Rachel Hartford, OND/ODEII/DMEP

Cc: Lester Schultheis, M.D., Ph.D., CDRH/ODE/DAGID/ARDB
Kwame Ulmer, M.S., CDRH/ODE/DAGID
Alan Schroeder, Ph.D., CDER/OPS/ONDQA/DPA I
Laura L. Pincock, R.Ph., Pharm.D. CDER/OSE/DMEPA
Lisa Yanoff, M.D., OND/ODEII/DMEP
Suong, Tran, Ph.D., OPS/ONDQA/DPA I

From: Melanie Choe, Ph.D., CDRH/ODE/DAGID/ARDB

Sponsor: MannKind Corporation
61 South Paramus Rd.
Paramus, NJ 07652

Product Name: Technosphere® Insulin Inhalation Powder and MedTone Inhaler

Subject: NDA22-472 – Model D MedTone Inhaler for exclusive use with the Technosphere Insulin filled cartridge

I. SUMMARY

CDRH was requested to review the MedTone Inhaler. My review encompassed the engineering validation of the inhaler only. The sponsor has provided adequate validation to demonstrate the equivalence of the improved Model D inhaler to the Model C inhaler in performance. However, I recommend the following three conditions for the Model D inhaler, if approved:

(b) (4)

[redacted]

44 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/

RACHEL E HARTFORD
12/17/2009
on behalf of CDRH

NDA REGULATORY FILING REVIEW
(Including Memo of Filing Meeting)

NDA # 22-472 Supplement # Efficacy Supplement Type SE-

Proprietary Name: Afresa (insulin human [rDNA origin]) Inhalation Powder) and Afresa inhaler
Established Name:
Strengths: 15 unit and 30 unit/cartridge
Applicant: MannKind Corporation
Agent for Applicant (if applicable): N/A
Date of Application: March 16, 2009
Date of Receipt: March 16, 2009
Date clock started after UN:
Date of Filing Meeting: May 1, 2009
Filing Date: May 15, 2009
Action Goal Date (optional): January 6, 2010 User Fee Goal Date: January 16, 2010
Indication(s) requested: treatment of adults with type I or type II diabetes mellitus for the control of hyperglycemia.

Type of Original NDA: (b)(1) ☒ (b)(2) ☐
AND (if applicable)
Type of Supplement: (b)(1) ☐ (b)(2) ☐

NOTE:
(1) If you have questions about whether the application is a 505(b)(1) or 505(b)(2) application, see Appendix A. A supplement can be either a (b)(1) or a (b)(2) regardless of whether the original NDA was a (b)(1) or a (b)(2). If the application or efficacy supplement is a (b)(2), complete Appendix B.

Review Classification: S ☒ P ☐
Resubmission after withdrawal? ☐ Resubmission after refuse to file? ☐
Chemical Classification: (1,2,3 etc.) 5 (New dosage form)
Other (orphan, OTC, etc.)

Form 3397 (User Fee Cover Sheet) submitted: YES ☒ NO ☐

User Fee Status: Paid ☒ Exempt (orphan, government) ☐
Waived (e.g., small business, public health) ☐

User fee payment ID number: PD 3008968 paid $1,247,200.00 on 3/11/09

NOTE: *If the NDA is a 505(b)(2) application, and the applicant did not pay a fee in reliance on the 505(b)(2) exemption (see box 7 on the User Fee Cover Sheet), confirm that a user fee is not required by contacting the User Fee staff in the Office of Regulatory Policy. The applicant is required to pay a user fee if: (1) the product described in the 505(b)(2) application is a new molecular entity or (2) the applicant claims a new indication for a use that that has not been approved under section 505(b). Examples of a new indication for a use include a new indication, a new dosing regime, a new patient population, and an Rx-to-OTC switch. The best way to determine if the applicant is claiming a new indication for a use is to compare the applicant's proposed labeling to labeling that has already been approved for the product described in the application. Highlight the differences between the proposed and approved labeling. If you need assistance in determining if the applicant is claiming a new indication for a use, please contact the User Fee staff.*

- Is there any 5-year or 3-year exclusivity on this active moiety in any approved (b)(1) or (b)(2) application? YES ☐ NO ☒
  If yes, explain:

Note: If the drug under review is a 505(b)(2), this issue will be addressed in detail in appendix B.

- Does another drug have orphan drug exclusivity for the same indication? YES ☐ NO ☒

- If yes, is the drug considered to be the same drug according to the orphan drug definition of sameness [21 CFR 316.3(b)(13)]? N/A
  YES ☐ NO ☐

  If yes, consult the Director, Division of Regulatory Policy II, Office of Regulatory Policy (HFD-007).

- Is the application affected by the Application Integrity Policy (AIP)? YES ☐ NO ☒
  If yes, explain:

- If yes, has OC/DMPQ been notified of the submission? YES ☐ NO ☒

- Does the submission contain an accurate comprehensive index? YES ☒ NO ☐
  If no, explain:

- Was form 356h included with an authorized signature? YES ☒ NO ☐
  If foreign applicant, both the applicant and the U.S. agent must sign.

- Submission complete as required under 21 CFR 314.50? YES ☒ NO ☐
  If no, explain:

- Answer 1, 2, or 3 below (do not include electronic content of labeling as an partial electronic submission).

1. This application is a paper NDA YES ☐

2. This application is an eNDA or combined paper + eNDA YES ☐
   This application is: All electronic ☐ Combined paper + eNDA ☐
   This application is in: NDA format ☐ CTD format ☐
   Combined NDA and CTD formats ☐

   Does the eNDA, follow the guidance? N/A
   (http://www.fda.gov/cder/guidance/2353fnl.pdf) YES ☐ NO ☐

   If an eNDA, all forms and certifications must be in paper and require a signature.

   If combined paper + eNDA, which parts of the application were submitted in electronic format?

   Additional comments:

3. This application is an eCTD NDA. YES ☒
   If an eCTD NDA, all forms and certifications must either be in paper and signed or be electronically signed.

Additional comments:

- Patent information submitted on form FDA 3542a? YES ☒ NO ☐

- Exclusivity requested? YES, 3 years Years NO ☐

NOTE: *An applicant can receive exclusivity without requesting it; therefore, requesting exclusivity is not required.*

- Correctly worded Debarment Certification included with authorized signature? YES ☒ NO ☐
If foreign applicant, both the applicant and the U.S. Agent must sign the certification.

NOTE: *Debarment Certification should use wording in FD&C Act section 306(k)(1) i.e., "[Name of applicant] hereby certifies that it did not and will not use in any capacity the services of any person debarred under section 306 of the Federal Food, Drug, and Cosmetic Act in connection with this application." Applicant may not use wording such as "To the best of my knowledge . . . ."*

- Are the required pediatric assessment studies and/or deferral/partial waiver/full waiver of pediatric studies (or request for deferral/partial waiver/full waiver of pediatric studies) included?
Deferral and partial waiver requested.
YES ☒ NO ☐

- If the submission contains a request for deferral, partial waiver, or full waiver of studies, does the application contain the certification required under FD&C Act sections 505B(a)(3)(B) and (4)(A) and (B)? YES ☐ NO ☐

- Is this submission a partial or complete response to a pediatric Written Request? YES ☐ NO ☒

If yes, contact PMHT in the OND-IO

- Financial Disclosure forms included with authorized signature? YES ☒ NO ☐
(Forms 3454 and/or 3455 must be included and must be signed by the APPLICANT, not an agent.)
NOTE: *Financial disclosure is required for bioequivalence studies that are the basis for approval.*

- Field Copy Certification (that it is a true copy of the CMC technical section) YES ☒ NO ☐

- PDUFA and Action Goal dates correct in tracking system? YES ☒ NO ☐
If not, have the document room staff correct them immediately. These are the dates EES uses for calculating inspection dates.

- Drug name and applicant name correct in COMIS? If not, have the Document Room make the corrections. Ask the Doc Rm to add the established name to COMIS for the supporting IND if it is not already entered.

- List referenced IND numbers:

- Are the trade, established/proper, and applicant names correct in COMIS? YES ☒ NO ☐
If no, have the Document Room make the corrections.

- End-of-Phase 2 Meeting(s)? Date(s) October 12, 2004 NO ☐
If yes, distribute minutes before filing meeting.

- Pre-NDA Meeting(s)? Date(s) July 14, 2008 (IND 61,729 Technosphere Insulin) NO ☐
  If yes, distribute minutes before filing meeting.

- Any SPA agreements? Date(s) _____ NO ☒
  If yes, distribute letter and/or relevant minutes before filing meeting.

Project Management

- If Rx, was electronic Content of Labeling submitted in SPL format? YES ☒ NO ☐
  If no, request in 74-day letter.

- If Rx, for all new NDAs/efficacy supplements submitted on or after 6/30/06:
  Was the PI submitted in PLR format? YES ☐ NO ☐

  If no, explain. Was a waiver or deferral requested before the application was received or in the submission? If before, what is the status of the request:

- If Rx, all labeling (PI, PPI, MedGuide, carton and immediate container labels) has been consulted to DDMAC? YES ☒ NO ☐

- If Rx, trade name (and all labeling) consulted to OSE? YES ☒ NO ☐

- If Rx, MedGuide and/or PPI (plus PI) consulted to ODE/DSRCS?
  REMS consulted 3/31/09 ☐ YES ☐ NO ☐

- Risk Management Plan consulted to OSE/IO? N/A ☐ YES ☐ NO ☐

- If a drug with abuse potential, was an Abuse Liability Assessment, including a proposal for scheduling submitted? NA ☐ YES ☐ NO ☒

If Rx-to-OTC Switch or OTC application: not applicable

- Proprietary name, all OTC labeling/packaging, and current approved PI consulted to OSE/DMETS? YES ☐ NO ☐

- If the application was received by a clinical review division, has DNPCE been notified of the OTC switch application? Or, if received by DNPCE, has the clinical review division been notified? YES ☐ NO ☐

Clinical

(Not applicable)

- If a controlled substance, has a consult been sent to the Controlled Substance Staff?
  YES ☐ NO ☐

Chemistry

- Did applicant request categorical exclusion for environmental assessment? YES ☒ NO ☐
  If no, did applicant submit a complete environmental assessment? YES ☐ NO ☐
  If EA submitted, consulted to EA officer, OPS? YES ☐ NO ☐

- Establishment Evaluation Request (EER) submitted to DMPQ? YES ☒ NO ☐
- If a parenteral product, consulted to Microbiology Team? YES ☒ NO ☐ (March 23, 2009)

ATTACHMENT

MEMO OF FILING MEETING

DATE: May 1, 2009

NDA #: 22-472

DRUG NAMES: Afresa (insulin human [rDNA origin]) Inhalation Powder and Afresa Inhaler

APPLICANT: MannKind Corporation

BACKGROUND:

NDA 22-472 was submitted by MannKind Corporation on March 16, 2009. The application provides for the indication for the treatment of adults with type 1 or type 2 diabetes mellitus for the control of hyperglycemia. The application is a drug-device combination product and consists of the AFRESA Inhalation powder pre metered into single unit dose cartridges and the AFRESA Inhaler as the delivery device for oral inhalation.

PerC meeting is scheduled for October 28, 2009.

Review Team:

Mary Parks, M.D.	Division Director, DMEP
Lisa Yanoff, M.D.	Medical Officer, DMEP
Hylton Joffe, M.D.	Team Leader, DMEP
Miyun Tsai-Turton, Ph.D.	Pharmo/Tox reviewer, DMEP
Karen Davis-Bruno, Ph.D.	Team Leader, DMEP
Suong Tran, Ph.D.	PAL, Chemistry
Theodore Carver	CMC reviewer (not present)
Alan Schroeder	CMC reviewer
Sang Chung, Ph.D.	Clinical Pharmacology Reviewer
Denise Miller, Ph.D.	Microbiologist
Joy Mele, MS	Statistician (safety review) (not present)
Todd Sahlroot, Ph.D.	Team Leader, Statistics
Cynthia Liu, MS	Statistician (efficacy review)
Melanie Choe	CDRH Reviewer (via teleconference)
Banu Karimi-Shah, MD.	Pulmonary Reviewer
Susan Leibenhaut, M.D.	DSI (not present)
Mildred Wright	Project Manager, OSE (not present)
Cheryl Campbell	Project Manager, OSE (via teleconference)
Adeolu Abolade	Project Manager, OSE
Laura Pincock	Project Manager, DMEPA (via teleconference)
Robin Duer	Project Manager, DRISK (not present)
Mary Dempsey	(not present)
Jodi Duckhorm	(not present)
Laura Pincock	(not present)
Sam Skariah	Project Manager, DDMAC (not present)
Kendra Jones	Project Manager, DDMAC
Enid Galliers	Chief Project Management Staff, DMEP (via teleconference)

Lina AlJuburi Chief Project Management Staff, DMEP
Haley Seymour Project Manager, DMEP

ASSIGNED REVIEWERS (including those not present at filing meeting):

Discipline/Organization	**Reviewer**
Medical:	Lisa Yanoff, M.D.
Secondary Medical:	Hylton Joffe, M.D. (Team Leader)
Statistical:	Joy Mele, MS
	Cynthia Liu, Ph.D.
	Todd Sahlroot, Ph.D. (Team Leader)
Pharm/Tox:	Miyun Tsai-Turton, Ph.D.
	Karen Davis-Bruno, Ph.D. (Team Leader)
Statistical Pharmacology:	
Chemistry:	Theodore Carver, Ph.D.
	Alan Schroeder, Ph.D.
Chemistry (PAL):	Su Tran, Ph.D.
Environmental Assessment (if needed):	
Biopharmaceutical:	Sang Chung, Ph.D.
Microbiology, sterility:	Denise Miller, Ph.D.
Microbiology, clinical (for antimicrobial products only):	
DSI:	Susan Leibenhath, M.D.
	Inspection request made 5/11,13/09
OPS:	
OSE:	Mildred Wright, Project Manager
	Laura Pincock, DMEPA
	Robin Duer, DRISK
	Sam Skariah, DDMAC
	Kendra Jones, DDMAC
Regulatory Project Management:	Haley Seymour
	Enid Galliers
Other Consults: Pulmonary (3/27/09)	Banu Karimi-Shah, M.D.
Statistical review of carci study (4/20/09)	Min Min, Ph.D., reassigned on 5/18/09 to Mohamed Nagem.

Per reviewers, are all parts in English or English translation? YES ☒ NO ☐
If no, explain:

CLINICAL FILE ☐ REFUSE TO FILE ☐

- Clinical site audit(s) needed? Request made on 5/13/09 ☒ NO ☐
  YES
  If no, explain:
- Advisory Committee Meeting needed? Not known YES, NO ☐
  date if known _____

- If the application is affected by the AIP, has the division made a recommendation regarding whether or not an exception to the AIP should be granted to permit review based on medical necessity or public health significance?
  N/A ☒ YES ☐ NO ☐

CLINICAL MICROBIOLOGY N/A ☐ FILE ☐ REFUSE TO FILE ☐

STATISTICS N/A ☐ FILE ☐ REFUSE TO FILE ☐

BIOPHARMACEUTICS FILE ☐ REFUSE TO FILE ☐

- Biopharm. study site audits(s) needed? Consult send on 5/11/09 YES ☒ NO ☐

PHARMACOLOGY/TOX N/A ☐ FILE ☐ REFUSE TO FILE ☐

- GLP audit needed? YES ☐ NO ☒

CHEMISTRY FILE ☐ REFUSE TO FILE ☐

- Establishment(s) ready for inspection? YES ☐ NO ☐
- Sterile product? YES ☐ NO ☐
  If yes, was microbiology consulted for validation of sterilization? YES ☒ NO ☐

ELECTRONIC SUBMISSION:
Any comments:

REGULATORY CONCLUSIONS/DEFICIENCIES:
(Refer to 21 CFR 314.101(d) for filing requirements.)

☐ The application is unsuitable for filing. Explain why:

☒ The application, on its face, appears to be well-organized and indexed. The application appears to be suitable for filing.

☐ No filing issues have been identified.

☒ Filing issues to be communicated by Day 74. List (optional):

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 (b) (4) 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., (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 (b) (4) µm and greater than (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 (b) (4) present in the product.

17. (b) (4)

18. Justify the lack of testing for particulates larger than (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 "(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.

21. Regarding the Aerodynamic Particle Size Distribution test by the cascade impactor, provide data to show the amounts of insulin deposited on each stage, (b) (4). 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 (b) (4) FDKP and packaged in the commercial Model D cartridges), and Batches PPT2008.27, PPT2008.28, PPT2008.29, and PPT2008.30 (formulated with the commercial (b) (4) FDKP but packaged in the non-commercial Model C cartridges). The additional data should be received by FDA prior to Month 5 of the review cycle in order to be included in the determination of the expiration dating periods (long term and in-use) for your product.

23. Provide information (or the location of this information in the NDA) to support (b) (4)

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.

ACTION ITEMS:

1. ☒ Ensure that the review and chemical classification codes, as well as any other pertinent classification codes (e.g., orphan, OTC) are correctly entered into COMIS.

2. ☐ If RTF, notify everybody who already received a consult request of RTF action. Cancel the EER.

3. ☐ If filed and the application is under the AIP, prepare a letter either granting (for signature by Center Director) or denying (for signature by ODE Director) an exception for review.

4. ☒ If filed, complete the Pediatric Page at this time. (If paper version, enter into DFS.)

5. ☒ Convey document filing issues/no filing issues to applicant by Day 74.

Haley Seymour
Regulatory Project Manager

*****This NDA is a (b)(1), therefore, the remaining pages were not filled out.

Appendix A to NDA Regulatory Filing Review

NOTE: The term "original application" or "original NDA" as used in this appendix denotes the NDA submitted. It does not refer to the reference drug product or "reference listed drug."

An original application is likely to be a 505(b)(2) application if:

(1) it relies on published literature to meet any of the approval requirements, and the applicant does not have a written right of reference to the underlying data. If published literature is cited in the NDA but is not necessary for approval, the inclusion of such literature will not, in itself, make the application a 505(b)(2) application,
(2) it relies for approval on the Agency's previous findings of safety and efficacy for a listed drug product and the applicant does not own or have right to reference the data supporting that approval, or
(3) it relies on what is "generally known" or "scientifically accepted" about a class of products to support the safety or effectiveness of the particular drug for which the applicant is seeking approval. (Note, however, that this does not mean *any* reference to general information or knowledge (e.g., about disease etiology, support for particular endpoints, methods of analysis) causes the application to be a 505(b)(2) application.)

Types of products for which 505(b)(2) applications are likely to be submitted include: fixed-dose combination drug products (e.g., heart drug and diuretic (hydrochlorothiazide) combinations); OTC monograph deviations(see 21 CFR 330.11); new dosage forms; new indications; and, new salts.

An efficacy supplement can be either a (b)(1) or a (b)(2) regardless of whether the original NDA was a (b)(1) or a (b)(2).

An efficacy supplement is a 505(b)(1) supplement if the supplement contains all of the information needed to support the approval of the change proposed in the supplement. For example, if the supplemental application is for a new indication, the supplement is a 505(b)(1) if:

(1) The applicant has conducted its own studies to support the new indication (or otherwise owns or has right of reference to the data/studies),

(2) No additional information beyond what is included in the supplement or was embodied in the finding of safety and effectiveness for the original application or previously approved supplements is needed to support the change. For example, this would likely be the case with respect to safety considerations if the dose(s) was/were the same as (or lower than) the original application, and.

(3) All other “criteria” are met (e.g., the applicant owns or has right of reference to the data relied upon for approval of the supplement, the application does not rely for approval on published literature based on data to which the applicant does not have a right of reference).

An efficacy supplement is a 505(b)(2) supplement if:

(1) Approval of the change proposed in the supplemental application would require data beyond that needed to support our previous finding of safety and efficacy in the approval of the

original application (or earlier supplement), and the applicant has not conducted all of its own studies for approval of the change, or obtained a right to reference studies it does not own. For example, if the change were for a new indication AND a higher dose, we would likely require clinical efficacy data and preclinical safety data to approve the higher dose. If the applicant provided the effectiveness data, but had to rely on a different listed drug, or a new aspect of a previously cited listed drug, to support the safety of the new dose, the supplement would be a 505(b)(2),

(2) The applicant relies for approval of the supplement on published literature that is based on data that the applicant does not own or have a right to reference. If published literature is cited in the supplement but is not necessary for approval, the inclusion of such literature will not, in itself, make the supplement a 505(b)(2) supplement, or

(3) The applicant is relying upon any data they do not own or to which they do not have right of reference.

If you have questions about whether an application is a 505(b)(1) or 505(b)(2) application, consult with your ODE's Office of Regulatory Policy representative.

Appendix B to NDA Regulatory Filing Review
Questions for 505(b)(2) Applications

1. Does the application reference a listed drug (approved drug)? YES ☐ NO ☐

*If "**No**," skip to question 3.*

2. Name of listed drug(s) referenced by the applicant (if any) and NDA/ANDA #(s):

3. Is this application for a drug that is an "old" antibiotic (as described in the draft guidance implementing the 1997 FDAMA provisions? (Certain antibiotics are not entitled to Hatch-Waxman patent listing and exclusivity benefits.)

YES ☐ NO ☐

*If "**Yes**," skip to question 7.*

4. Is this application for a recombinant or biologically-derived product?

YES ☐ NO ☐

*If "**Yes** "contact your ODE's Office of Regulatory Policy representative.*

5. The purpose of the questions below (questions 5 to 6) is to determine if there is an approved drug product that is equivalent or very similar to the product proposed for approval that should be referenced as a listed drug in the pending application.

   (a) Is there a pharmaceutical equivalent(s) to the product proposed in the 505(b)(2) application that is already approved?

   YES ☐ NO ☐

   (***Pharmaceutical equivalents*** are drug products in identical dosage forms that: **(1)** contain identical amounts of the identical active drug ingredient, i.e., the same salt or ester of the same therapeutic moiety, or, in the case of modified release dosage forms that require a reservoir or overage or such forms as prefilled syringes where residual volume may vary, that deliver identical amounts of the active drug ingredient over the identical dosing period; **(2)** do not necessarily contain the same inactive ingredients; **and** **(3)** meet the identical compendial or other applicable standard of identity, strength, quality, and purity, including potency and, where applicable, content uniformity, disintegration times, and/or dissolution rates. (21 CFR 320.1(c))

*If "**No**," to (a) skip to question 6. Otherwise, answer part (b and (c)).*

   (b) Is the pharmaceutical equivalent approved for the same indication for which the 505(b)(2) application is seeking approval? YES ☐ NO ☐

   (c) Is the approved pharmaceutical equivalent(s) cited as the listed drug(s)? YES ☐ NO ☐

*If "**Yes**," (c), list the pharmaceutical equivalent(s) and proceed to question 6.*

*If "**No**," to (c) list the pharmaceutical equivalent and contact your ODE's Office of Regulatory Policy representative.*
Pharmaceutical equivalent(s):

6. (a) Is there a pharmaceutical alternative(s) already approved? YES ☐ NO ☐

(***Pharmaceutical alternatives*** are drug products that contain the identical therapeutic moiety, or its precursor, but not necessarily in the same amount or dosage form or as the same salt or ester. Each such drug product individually meets either the identical or its own respective compendial or other applicable standard of identity, strength, quality, and purity, including potency and, where applicable, content uniformity, disintegration times and/or dissolution rates. (21 CFR 320.1(d)) Different dosage forms and strengths within a product line by a single manufacturer are thus pharmaceutical alternatives, as are extended-release products when compared with immediate- or standard-release formulations of the same active ingredient.)

*If "**No**," to (a) skip to question 7. Otherwise, answer part (b and (c)).*

(b) Is the pharmaceutical alternative approved for the same indication for which the 505(b)(2) application is seeking approval? YES ☐ NO ☐

(c) Is the approved pharmaceutical alternative(s) cited as the listed drug(s)? YES ☐ NO ☐

*If "**Yes**," to (c), proceed to question 7.*

NOTE: *If there is more than one pharmaceutical alternative approved, consult your ODE's Office of Regulatory Policy representative to determine if the appropriate pharmaceutical alternatives are referenced.*

*If "**No**," to (c), list the pharmaceutical alternative(s) and contact your ODE's Office of Regulatory Policy representative. Proceed to question 7.*

Pharmaceutical alternative(s):

7. (a) Does the application rely on published literature necessary to support the proposed approval of the drug product (i.e. is the published literature necessary for the approval)? YES ☐ NO ☐

*If "**No**," skip to question 8. Otherwise, answer part (b).*

(b) Does any of the published literature cited reference a specific (e.g. brand name) product? Note that if yes, the applicant will be required to submit patent certification for the product, see question 12.

8. Describe the change from the listed drug(s) provided for in this (b)(2) application (for example, "This application provides for a new indication, otitis media" or "This application provides for a change in dosage form, from capsules to solution").

9. Is the application for a duplicate of a listed drug and eligible for approval under section 505(j) as an ANDA? (Normally, FDA may refuse-to-file such NDAs (see 21 CFR 314.101(d)(9)). YES ☐ NO ☐

10. Is the application for a duplicate of a listed drug whose only difference is that the extent to which the active ingredient(s) is absorbed or otherwise made available to the site of action less than that of the reference listed drug (RLD)? (See 314.54(b)(1)). If yes, the application may be refused for filing under 21 CFR 314.101(d)(9)). YES ☐ NO ☐

11. Is the application for a duplicate of a listed drug whose only difference is YES ☐ NO ☐

that the rate at which the product's active ingredient(s) is absorbed or made available to the site of action is unintentionally less than that of the RLD (see 21 CFR 314.54(b)(2))? If yes, the application may be refused for filing under 21 CFR 314.101(d)(9).

12. Are there certifications for each of the patents listed in the Orange Book for the listed drug(s) referenced by the applicant (see question #2)? (This is different from the patent declaration submitted on form FDA 3542 and 3542a.) YES ☐ NO ☐

13. Which of the following patent certifications does the application contain? (Check all that apply and identify the patents to which each type of certification was made, as appropriate.)

☐ Not applicable (e.g., solely based on published literature. See question # 7

☐ 21 CFR 314.50(i)(1)(i)(A)(1): The patent information has not been submitted to FDA. (Paragraph I certification)
Patent number(s):

☐ 21 CFR 314.50(i)(1)(i)(A)(2): The patent has expired. (Paragraph II certification)
Patent number(s):

☐ 21 CFR 314.50(i)(1)(i)(A)(3): The date on which the patent will expire. (Paragraph III certification)
Patent number(s):

☐ 21 CFR 314.50(i)(1)(i)(A)(4): The patent is invalid, unenforceable, or will not be infringed by the manufacture, use, or sale of the drug product for which the application is submitted. (Paragraph IV certification)
Patent number(s):

NOTE: *IF FILED, and if the applicant made a "Paragraph IV" certification [21 CFR 314.50(i)(1)(i)(A)(4)], the applicant must **subsequently** submit a signed certification stating that the NDA holder and patent owner(s) were notified the NDA was filed [21 CFR 314.52(b)]. The applicant must also submit documentation showing that the NDA holder and patent owner(s) received the notification [21 CFR 314.52(e)]. OND will contact you to verify that this documentation was received.*

☐ 21 CFR 314.50(i)(3): Statement that applicant has a licensing agreement with the patent owner (must also submit certification under 21 CFR 314.50(i)(1)(i)(A)(4) above).
Patent number(s):

☐ Written statement from patent owner that it consents to an immediate effective date upon approval of the application.
Patent number(s):

☐ 21 CFR 314.50(i)(1)(ii): No relevant patents.

☐ 21 CFR 314.50(i)(1)(iii): The patent on the listed drug is a method of use patent and the labeling for the drug product for which the applicant is seeking approval does not include any indications that are covered by the use patent as described in the corresponding use code in the Orange Book. Applicant must provide a statement that the method of use patent does not claim any of the proposed indications. (Section viii statement)
Patent number(s):

14. Did the applicant:

- Identify which parts of the application rely on the finding of safety and effectiveness for a listed drug or published literature describing a listed drug or both? For example, pharm/tox section of application relies on finding of preclinical safety for a listed drug.

  YES ☐ NO ☐

  *If "**Yes**," what is the listed drug product(s) and which sections of the 505(b)(2) application rely on the finding of safety and effectiveness or on published literature about that listed drug*
  Was this listed drug product(s) referenced by the applicant? (see question # 2)

  YES ☐ NO ☐

- Submit a bioavailability/bioequivalence (BA/BE) study comparing the proposed product to the listed drug(s)?

  N/A ☐ YES ☐ NO ☐

15. (a) Is there unexpired exclusivity on this listed drug (for example, 5 year, 3 year, orphan or pediatric exclusivity)? Note: this information is available in the Orange Book.

YES ☐ NO ☐

If "**Yes**," please list:

Application No.	Product No.	Exclusivity Code	Exclusivity Expiration

---

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
5/22/2009 09:35:09 AM
CSO