DEPARTMENT OF HEALTH AND HUMAN SERVICES

Food and Drug Administration
Silver Spring MD 20993

NDA 022472

NDA APPROVAL

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

Dear Mr. Bedard:

Please refer to your New Drug Application (NDA) dated and received March 16, 2009, submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act (FDCA) for Afrezza (insulin human) Inhalation Powder.

We acknowledge receipt of your amendments dated March 31, April 2 (3), June 4, 15, and 17, July 16, 22, and 30, August 13, 14, and 26, September 1, 11, 18, 25, 28, and 29, October 5, 9, 12, 23, and 30, November 16, December 1 (2), 4(2), 7, 8, 15 (2), and 22 (2), 2009, and January 8, 19 (2), 25, 26 (2), 27, February 19, June 29, July 27, August 6, and 27, September 15, and 24, November 5, 15, and 24 (2), December 14 (2), 2010, and September 29, 2011, October 13, and 17, 2013, and January 31, February 8 (2), 20, 24, 26, 27, and 28, March 4, 11, 14, and 26, April 24, and 30, and June 17, 20, 23, 25, and 27, 2014.

The October 13, 2013, submission constituted a complete response to our January 18, 2011, action letter.

This new drug application provides for the use of Afrezza (insulin human) Inhalation Powder and Inhaler, 4 units per cartridge and 8 units per cartridge, for improved glycemic control in adults with diabetes mellitus.

We have completed our review of this application, as amended. It is approved, effective on the date of this letter, for use as recommended in the enclosed agreed-upon labeling text.

WAIVER OF HIGHLIGHTS SECTION

We are waiving the requirements of 21 CFR 201.57(d)(8) regarding the length of Highlights of prescribing information. This waiver applies to all future supplements containing revised labeling unless we notify you otherwise.

CONTENT OF LABELING

As soon as possible, but no later than 14 days from the date of this letter, submit the content of labeling [21 CFR 314.50(l)] in structured product labeling (SPL) format using the FDA automated drug registration and listing system (eLIST), as described at http://www.fda.gov/ForIndustry/DataStandards/StructuredProductLabeling/default.htm. Content of labeling must be identical to the enclosed labeling. Information on submitting SPL files using eLIST may be found in the guidance for industry *SPL Standard for Content of Labeling Technical Qs and As*, available at http://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/UCM072392.pdf.

The SPL will be accessible via publicly available labeling repositories.

We request that the labeling approved today be available on your website within 10 days of receipt of this letter.

CARTON AND IMMEDIATE CONTAINER LABELS

We acknowledge your June 25, 2014, submission containing final printed carton and container labels.

REQUIRED PEDIATRIC ASSESSMENTS

Under the Pediatric Research Equity Act (PREA) (21 U.S.C. 355c), all applications for new active ingredients, new indications, new dosage forms, new dosing regimens, or new routes of administration are required to contain an assessment of the safety and effectiveness of the product for the claimed indication(s) in pediatric patients unless this requirement is waived, deferred, or inapplicable.

We are waiving the pediatric studies requirement for ages 0 to 3 years (inclusive) because the necessary studies are impossible or highly impracticable. This is because the delivery device for this drug is not appropriate for use in this age range.

We are deferring submission of your pediatric studies for ages 4 to 17 years (inclusive) for this application because this product is ready for approval for use in adults and the pediatric study has not been completed.

Your deferred pediatric study required by section 505B(a) of the FDCA is a required postmarketing study. The status of this postmarketing study must be reported annually according to 21 CFR 314.81 and section 505B(a)(3)(B) of the FDCA. This required study is listed below.

2166-1 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.

The timetable you submitted on June 23, 2014 , states that you will conduct this study according to the following schedule:

Final Protocol Submission:	January 2015
Study Completion:	July 2020
Final Report Submission:	January 2021

Submit the protocol to your IND 061729, with a cross-reference letter to this NDA.

Reports of this required pediatric postmarketing study must be submitted as a new drug application (NDA) or as a supplement to your approved NDA with the proposed labeling changes you believe are warranted based on the data derived from this study. When submitting the reports, please clearly mark your submission "**SUBMISSION OF REQUIRED PEDIATRIC ASSESSMENTS**" in large font, bolded type at the beginning of the cover letter of the submission.

POSTMARKETING REQUIREMENTS UNDER 505(o)

Section 505(o)(3) of the FDCA authorizes FDA to require holders of approved drug and biological product applications to conduct postmarketing studies and clinical trials for certain purposes, if FDA makes certain findings required by the statute.

We have determined that an analysis of spontaneous postmarketing adverse events reported under subsection 505(k)(1) of the FDCA will not be sufficient to assess known serious risks of diabetic ketoacidosis, hypoglycemia, or decline in pulmonary function, to assess a signal of a serious risk of pulmonary malignancy, and to identify an unexpected serious risk of cardiovascular events.

Furthermore, the new pharmacovigilance system that FDA is required to establish under section 505(k)(3) of the FDCA will not be sufficient to assess this serious risk.

Finally, we have determined that only a clinical trial (rather than a nonclinical or observational study) will be sufficient to assess known serious risks of diabetic ketoacidosis, hypoglycemia, or decline in pulmonary function, to assess a signal of a serious risk of pulmonary malignancy, and to identify an unexpected serious risk of cardiovascular events.

Therefore, based on appropriate scientific data, FDA has determined that you are required to conduct the following:

2166-2 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 becomes 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.

The timetable you submitted on June 23, 2014 , states that you will conduct this trial according to the following schedule:

Final Protocol Submission:	January 2015
Trial Completion:	June 2016
Final Report Submission:	March 2017

2166-3 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.

The timetable you submitted on June 23, 2014 , states that you will conduct this trial according to the following schedule:

Final Protocol Submission:	April 2015
Trial Completion:	April 2016
Final Report Submission:	January 2017

2166-4 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-year). The potential for detection bias should be adequately addressed in the trial design. Subjects who discontinue randomized intervention due to lack of efficacy or tolerability 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 or 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.

The timetable you submitted on June 23, 2014 , states that you will conduct this trial according to the following schedule:

Final Protocol Submission:	April 2015
Trial Completion:	April 2023
Final Report Submission:	December 2023

Submit the protocols to your IND 061729, with a cross-reference letter to this NDA. Submit all final reports to your NDA. Prominently identify the submission with the following wording in bold capital letters at the top of the first page of the submission, as appropriate: **"Required Postmarketing Protocol Under 505(o)", "Required Postmarketing Final Report Under 505(o)", "Required Postmarketing Correspondence Under 505(o)"**.

Section 505(o)(3)(E)(ii) of the FDCA requires you to report periodically on the status of any study or clinical trial required under this section. This section also requires you to periodically report to FDA on the status of any study or clinical trial otherwise undertaken to investigate a safety issue. Section 506B of the FDCA, as well as 21 CFR 314.81(b)(2)(vii) requires you to report annually on the status of any postmarketing commitments or required studies or clinical trials.

FDA will consider the submission of your annual report under section 506B and 21 CFR 314.81(b)(2)(vii) to satisfy the periodic reporting requirement under section 505(o)(3)(E)(ii) provided that you include the elements listed in 505(o) and 21 CFR 314.81(b)(2)(vii). We remind you that to comply with 505(o), your annual report must also include a report on the status of any study or clinical trial otherwise undertaken to investigate a safety issue. Failure to submit an annual report for studies or clinical trials required under 505(o) on the date required will be considered a violation of FDCA section 505(o)(3)(E)(ii) and could result in enforcement action.

RISK EVALUATION AND MITIGATION STRATEGY REQUIREMENTS

Section 505-1 of the FDCA authorizes FDA to require the submission of a risk evaluation and mitigation strategy (REMS), if FDA determines that such a strategy is necessary to ensure that the benefits of the drug outweigh the risks [section 505-1(a)]. In accordance with section 505-1 of FDCA, we have determined that a REMS is necessary for Afrezza (insulin human) Inhalation Powder to ensure the benefits of the drug outweigh the risk of acute bronchospasm in patients with chronic lung disease. We have also determined that a communication plan is necessary to support implementation of the REMS.

Your proposed REMS, submitted on June 20, 2014, and appended to this letter, is approved. The REMS consists of a communication plan and a timetable for submission of assessments of the REMS.

Your REMS must be fully operational before you introduce Afrezza (insulin human) Inhalation Powder into interstate commerce.

The REMS assessment plan should include, but is not limited to, the following:

1. REMS communication plan activities:
    a. Number of healthcare providers and professional societies targeted by the REMS.
    b. Number of REMS letters sent to healthcare providers and professional societies via email, standard mail, and facsimile, and the dates the letters were sent. Include the number of letters sent via email because the mailed letter was undeliverable. For letters sent via email, include the number of letters successfully delivered, and the number of email letters opened by the recipients.
    c. Number of REMS Factsheets distributed to healthcare providers by sales representatives and medical liaisons during the reporting period.
    d. Date the REMS website went live and number of total and unique site visits during the assessment period.
    e. Names and dates of all scientific meetings during which REMS materials (REMS letters, REMS Factsheet) were distributed

2. Evaluation of healthcare providers' understanding of:
    a. The risk of acute bronchospasm associated with Afrezza in patients with chronic lung disease
    b. Acute bronchospasm has been observed in patients with asthma and COPD using Afrezza
    c. Afrezza is contraindicated in patients with chronic lung disease
    d. HCPs should evaluate all patients for lung disease (a detailed medical history, physical examination, and spirometry (FEV1) to identify potential lung disease) before starting on Afrezza

3. Afrezza utilization information including, but not limited to, indication for use and type of prescriber (i.e., endocrinologist, general practitioner, internist, etc.)

4. Safety surveillance:
    a. Analysis of serious postmarketing case reports of bronchospasm received during the reporting period. Include in the analysis information on whether or not the patient was evaluated for lung disease before receiving Afrezza, and how the patient was evaluated for chronic lung disease (e.g., baseline FEV1, past medical history, physical examination)
    b. Analysis of postmarketing case reports of serious respiratory adverse events reported for patients with chronic lung disease during the reporting period.

Include in the analysis information on whether or not the patient was evaluated for lung disease before receiving Afrezza, and how the patient was evaluated for chronic lung disease (e.g., baseline FEV1, past medical history, physical examination

The requirements for assessments of an approved REMS under section 505-1(g)(3) include with respect to each goal included in the strategy, an assessment of the extent to which the approved strategy, including each element of the strategy, is meeting the goal or whether 1 or more such goals or such elements should be modified.

We remind you that in addition to the assessments submitted according to the timetable included in the approved REMS, you must submit a REMS assessment and may propose a modification to the approved REMS when you submit a supplemental application for a new indication for use as described in section 505-1(g)(2)(A) of the FDCA.

If the assessment instruments and methodology for your REMS assessments are not included in the REMS supporting document, or if you propose changes to the submitted assessment instruments or methodology, you should update the REMS supporting document to include specific assessment instrument and methodology information at least 90 days before the assessments will be conducted. Updates to the REMS supporting document may be included in a new document that references previous REMS supporting document submission(s) for unchanged portions. Alternatively, updates may be made by modifying the complete previous REMS supporting document, with all changes marked and highlighted. Prominently identify the submission containing the assessment instruments and methodology with the following wording in bold capital letters at the top of the first page of the submission:

NDA 022472 REMS CORRESPONDENCE
(insert concise description of content in bold capital letters, e.g.,
UPDATE TO REMS SUPPORTING DOCUMENT - ASSESSMENT METHODOLOGY)

Prominently identify the submission containing the REMS assessments or proposed modifications with the following wording in bold capital letters at the top of the first page of the submission:

NDA 022472 REMS ASSESSMENT

NEW SUPPLEMENT FOR NDA 022472
PROPOSED REMS MODIFICATION

NEW SUPPLEMENT (NEW INDICATION FOR USE)
FOR NDA 022472
REMS ASSESSMENT
PROPOSED REMS MODIFICATION (if included)

If you do not submit electronically, please send 5 copies of REMS-related submissions.

An authorized generic drug under this NDA must have an approved REMS prior to marketing. Should you decide to market, sell, or distribute an authorized generic drug under this NDA, contact us to discuss what will be required in the authorized generic drug REMS submission.

ADDITIONAL AGREEMENTS

We remind you of your June 20, 2014, agreement to to modify the removable mouthpiece cover to address potential risk of aspiration by January 2016.

PROMOTIONAL MATERIALS

You may request advisory comments on proposed introductory advertising and promotional labeling. To do so, submit, in triplicate, a cover letter requesting advisory comments, the proposed materials in draft or mock-up form with annotated references, and the package insert to:

Food and Drug Administration
Center for Drug Evaluation and Research
Office of Prescription Drug Promotion
5901-B Ammendale Road
Beltsville, MD 20705-1266

As required under 21 CFR 314.81(b)(3)(i), you must submit final promotional materials, and the package insert, at the time of initial dissemination or publication, accompanied by a Form FDA 2253. Form FDA 2253 is available at http://www.fda.gov/downloads/AboutFDA/ReportsManualsForms/Forms/UCM083570.pdf. Information and Instructions for completing the form can be found at http://www.fda.gov/downloads/AboutFDA/ReportsManualsForms/Forms/UCM375154.pdf. For more information about submission of promotional materials to the Office of Prescription Drug Promotion (OPDP), see http://www.fda.gov/AboutFDA/CentersOffices/CDER/ucm090142.htm.

REPORTING REQUIREMENTS

We remind you that you must comply with reporting requirements for an approved NDA (21 CFR 314.80 and 314.81).

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

Sincerely,

{See appended electronic signature page}

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

Enclosures:
- Content of Labeling
- Carton and Container Labeling
- REMS

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

/s/

JEAN-MARC P GUETTIER
06/27/2014