CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

201820Orig1s000

OTHER ACTION LETTERS

DEPARTMENT OF HEALTH AND HUMAN SERVICES

Food and Drug Administration
Silver Spring MD 20993

NDA 201820

COMPLETE RESPONSE

Chiesi Pharmaceuticals, Inc.
Attention: Erika Panico, RAC (US)
Vice President and Managing Director
9605 Medical Center Drive, Suite 380
Rockville, MD 20850

Dear Ms Panico:

Please refer to your New Drug Application (NDA) dated October 22, 2010, received October 25, 2010, submitted pursuant to section 505(b)(2) of the Federal Food, Drug, and Cosmetic Act for CHF 1538 (tobramycin 300 mg/4mL inhalation solution).

We acknowledge receipt of your amendments dated October 16 and 26; November 24; December 2, 6, and 20, 2010; January 17, 19, 21 and 28; February 3, 21 and 25; March 18, and 29 (2); April 13, and 28; May 4, 12, 13 (2) and 23; June 10, 16, and 28; July 13 and August 2, and 11, 2011.

We have completed our review of this application as amended, and have determined that we cannot approve this application in its present form. We have described our reasons for this action below and, where possible, our recommendations to address these issues.

CLINICAL

1. You propose labeling the product to be used with either the PARI LC Plus or (b) (4) with the PARI Vios compressor, and this drug device combination is not the same as that evaluated in clinical trials. You have not provided sufficient data to evaluate the change in compressor or the new nebulizer compressor combination. In addition, we note that the osmolality of the test drug used in trials CT-01 and CT-02 was higher than the osmolality of the to-be-marketed product. You should provide comprehensive drug device combination bridging data as recommended in the CLINICAL/DELIVERY DEVICES section below. The data submitted should allow the Agency to make a proper evaluation of the comparability of the various drug-device combinations used in clinical trials and proposed for marketing. If the device data provided are not adequate to bridge the clinical trial and to-be-marketed drug device configurations, then additional clinical trial data will be required. We recommend that you consider conducting a placebo-controlled trial similar in design to trial CT-01 using the to-be-marketed drug device combination. We recommend that you meet with the review division to discuss your plans for providing a complete response.

2. The primary and secondary endpoint results (pulmonary function tests) for the CT-02 trial are not correct as submitted. Pulmonary function test results should be revised for all trial CT-02 individuals at all sites that were affected by inaccurate recording of/loss of source input data including height and age. The primary and secondary outcomes (such as other pulmonary function variables and weight/BMI/height changes over time) that may have been affected by the above issues should also be recalculated and submitted. The methodology and formula for the above recalculations should be submitted. In addition, provide an explanation of exactly what documentation/calculation errors occurred at various sites and how such errors were remedied, as well as a reassessment of trial CT-02 results given the new data.

CLINICAL/DELIVERY DEVICES

1. It appears that a variety of *in vitro* tests have been performed to create a bridge between the to-be-marketed version of the combination product and the product tested in the clinical trials for tobramycin 300 mg/ 4mL inhalation solution (CHF 1538). Please note that *in vitro* data alone may be insufficient to provide a reasonable assurance of safety and efficacy. Specifically, the results of the studies cannot be adequately defined across the range of patients with chronic pulmonary infection due to *Pseudomonas aeruginosa*. Depending on such factors as disease progression, patient age and weight, targeted patients may have a range of breathing patterns. Individual breathing patterns influence particle motion in the airways, affecting deposition of the drug product irrespective of particle size, nebulization time, flow rate etc. Accordingly, *in vitro* tests can only mimic a limited number of representative conditions, and does not account for variability between patients or device usability. For example, a delay between device actuation and inhalation may significantly reduce delivered dose. Please provide a scientific analysis of (1) the effect of variable breathing patterns on drug deposition in the patient airway and (2) the effect or a mistimed inhalation in regards to device actuation.

2. An adequate description of the proposed devices has not been provided for review. Provide a separate device module for the proposed NDA incorporating all descriptive information for all referenced nebulizers and compressors, and all relevant performance data. In addition, identify all models, devices accessories and relevant 510(k) application numbers for each device. Include the following descriptive information in the device module.

a. Provide a tabular summary of all design and specification differences between (1) the Pari LC Plus Nebulizer (b) (4) and (2) (b) (4) and the Vios Compressor. Provide a summary analysis of the effect of each noted design difference on the output specifications for the device.

b. Provide engineering drawings for each proposed device, including descriptions of each device component. Cite the inner dimension of the primary actuator orifice and describe the orientation of the actuator in relation to the patient delivery port.

c. Identify all patient interface accessories (i.e., tee adapter, mouthpiece, mask) and provide engineering drawings which show any breathing holes and/or valves.

d. Illustrate and explain the breathing gas path, including all valves and orifices, during inhalation and exhalation.

e. Provide a list of all device components. Indicate whether each is intended for a single-use (disposable), single-patient reuse or multiple-patient reuse, and ensure that this information appears in the labeling for your device.

f. Provide a shelf-life specification for each of the proposed devices and either cite or provide the corresponding test reports.

g. Provide a summary document detailing the use of the proposed devices with Tobramycin 300 mg/4mL solution (CHF1538). Specifically, describe how the drug is loaded into the device, and provide drug-specific instructions for use in terms of device actuation. In addition, summarize the dosage cycles for the drug (delivered dose per actuation, actuations per treatment, treatments per day, etc.).

3. Provide adequate comparative particle characterization data for review for the proposed to-be-marketed (TBM) combination product and the product tested in the clinical trial (CT). While some relevant data is referenced in the NDA, the overall methodology, procedures used and statistical analyses applied require further clarification. Note that in order to create an *in vitro* bridge between these two device configurations, comparative data must be comprehensive and have a sufficient level of statistical significance. We recommend that you perform a side-by-side particle characterization assessment for the to-be-marketed device and the device configuration used in the clinical trial incorporating the following:

a. Pari LC Plus Nebulizer, TurboBoy S Compressor, CHF 1538 (CT Configuration 1)
b. Pari LC Plus Nebulizer, TurboBoy N Compressor, CHF 1538 (CT Configuration 2)
c. Pari LC Plus Nebulizer, Vios Compressor, CHF 1538 (TBM Configuration 1)
d. [redacted] (b) (4) (TBM Configuration 2)

Please note that if the particle characterization data for TBM Configuration 2 is not substantially equivalent to the two clinical configurations, additional *in vitro* data (e.g. [redacted] (b) (4) Nebulizer [redacted] (b) (4)) may be required to assess the source of the differences. Data collected for the [redacted] (b) (4) are not considered critical information for the bridge between the to-be-marketed device and the devices used in the clinical trials.

We recommend evaluating the equivalent performance of nebulizers via comparative particle characterization data with a cascade impactor consisting of at least six stages (i.e. Next Generation Cascade Impactor). Laser diffraction is currently not accepted as a stand alone method of particle characterization due to concerns regarding reproducibility, specificity, and resolution. Provide particle characterization data for each of the four device configurations cited above with the proposed formulation of tobramycin (CHF 1538) using the drug's labeled concentration, dose volume and salt content. Note that each run should continue until the nebulizer is empty, as indicated by sputtering (i.e., erratic aerosolization). In addition, if the

specified nebulizers operate over a range of flow rates, it is recommended that data be collected at the minimum and maximum flow rate allowable. Test reports should include the following:

a. The original nebulizer dose volume in milliliters of drug.
b. The amount of drug in micrograms recovered on each impactor plate, throat, and outlet filter.
c. The dead volume in micrograms (the amount of drug remaining in the medication cup when sputtering begins and treatment ends).
d. The drug mass recovered in the cascade impactor in the respirable size range (i.e., 0.4 to 4.7 or 0.5 to 5 microns, depending on the type of impactor used) expressed as a percent of the total drug mass in the nebulizer cup.
e. The mass median aerodynamic diameter (MMAD- the diameter above and below which lies 50% of the mass of the particles) of the particles recovered in the impactor.
f. The geometric standard deviation of the MMAD.

We recommend that you collect comparative particle characterization data for TOBI® (tobramycin 300 mg/5 mL solution for inhalation) concurrently with the testing for CHF 1538. This should include the following device configurations:

a. Pari LC Plus Nebulizer, DeVilbiss PulmoAide Compressor, TOBI®
b. Pari LC Plus Nebulizer, TurboBoy N Compressor, TOBI®

We recommend that you collect comparative particle characterization data for CHF 1538 with an osmolality of (b) (4) mOsmoles/kg and (b) (4) mOsmoles/kg.

4. In order to adequately evaluate substantial equivalence, sufficient data must be provided to assess potential sources of variability in terms of particle size, total emitted mass and respirable mass that may be attributable to the device. Please note that an adequate number of device samples should be tested in order to assess potential sources of inter-sample variability (drug batch, nebulizer and compressor batches, and manufacturing site etc.). Also, in order to assess intra-sample variability, provide data demonstrating that a single sample of each of the two to-be-marked configurations can deliver the prescribed dose of the proposed drug in a repeatable manner over the intended number of actuations. For each of the two to-be-marketed device configurations, provide sufficient data to demonstrate that each is able to deliver the prescribed dose in a repeatable manner irrespective of potential sources of inter-sample variability. These data are required to demonstrate that the dosing specifications in your labeling are validated to a specified level of statistical confidence. We recommend that you consider the following recommendations in regards to evaluating potential sources of variability for the proposed combination product:

a. Provide data demonstrating that an individual sample of each of the two proposed device configurations will consistently deliver a specified dose for each medication tested. In doing so, validate dose specifications in terms of particle size, total emitted mass, and respirable mass. These data are intended to demonstrate dose repeatability. In your test report, note the number of runs that were used for each individual device

sample-drug combination, and provide a statistical justification explaining why this number is sufficient to validate the dose specifications in your labeling.

b. Provide data characterizing the potential effect of inter-sample variability on the dose specifications in your labeling. Specify the number of device samples that were used in your performance tests, and provide a statistical analysis explaining why this number of samples is sufficient to demonstrate with an appropriate level of confidence that (l) variability in individual device samples do not noticeably affect the dosing specifications of the proposed device and that (2) develop confidence for particle specifications overall, irrespective of inter-sample variability.

c. In analyzing the results of the tests cited above, justify why the levels of variability shown are appropriate for the use of the devices in delivering the proposed drug formulation.

Additional Comments:

Although the following are not required for submission of a complete response, we request that you respond to these requests for additional information:

1. Provide full audiometric results, if available, for trials CT-01, CT-02, and CT-03. If full audiometric results are not available for all sites, we request that you provide such information for the sites from which the data can be obtained. This would include decibel thresholds recorded at every frequency tested for both ears at every visit for every patient in every trial. This will help to better understand what changes in hearing threshold were occurring during the course of treatment. If such data are unavailable, then any future assessments of ototoxicity (including labeling for ototoxicity) will be based on what has already been provided in the NDA.

2. For trial CT-03, provide tables describing mean and median changes in values over the course of the study, as well as a reference guide to help understand the shift tables provided in the current NDA submission (e.g., what values fall under the parameters of clinically significant, normal, and not clinically significant for each of the laboratory measurements?).

LABELING

We reserve comment on the proposed labeling until the application is otherwise adequate. If you revise labeling, your response must include updated content of labeling [21 CFR 314.50(l)(1)(i)] in structured product labeling (SPL) format as described at http://www.fda.gov/ForIndustry/DataStandards/StructuredProductLabeling/default.htm.

OTHER

Within one year after the date of this letter, you are required to resubmit or take other actions available under 21 CFR 314.110. If you do not take one of these actions, we may consider your

lack of response a request to withdraw the application under 21 CFR 314.65. You may also request an extension of time in which to resubmit the application. A resubmission must fully address all the deficiencies listed. A partial response to this letter will not be processed as a resubmission and will not start a new review cycle.

Under 21 CFR 314.102(d), you may request a meeting or telephone conference with us to discuss what steps you need to take before the application may be approved. If you wish to have such a meeting, submit your meeting request as described in the FDA's "Guidance for Industry - Formal Meetings Between the FDA and Sponsors or Applicants," May 2009 at http://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/UCM153222.pdf.

The drug product may not be legally marketed until you have been notified in writing that this application is approved.

If you have any questions, call Carmen DeBellas, Regulatory Project Manager, at (301) 796-1203.

Sincerely,

{See appended electronic signature page}

John J. Farley, MD, MPH
Acting Division Director
Division of Anti-Infective Products
Office of Antimicrobial Products
Center for Drug Evaluation and Research

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

/s/

JOHN J FARLEY
08/25/2011