CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

050814Orig1s000

OTHER ACTION LETTERS

DEPARTMENT OF HEALTH & HUMAN SERVICES

Public Health Service

Food and Drug Administration
Rockville, MD 20857

NDA 50-814

COMPLETE RESPONSE

Gilead Sciences, Inc.
Attention: Melissa A. Yeager, J.D.
Vice President, Regulatory Affairs
2025 First Avenue, Suite 800
Seattle, Washington 98121

Dear Ms. Yeager:

Please refer to your new drug application (NDA) dated November 16, 2007, received November 16, 2007, submitted pursuant to section 505(b)(2) of the Federal Food, Drug, and Cosmetic Act for aztreonam for inhalation solution (AI).

This application is subject to the exemption provisions of section 125(d)(2) of Title I of the FDA Modernization Act of 1997.

We acknowledge receipt of your amendments dated March 26, April 18, May 2, 9, 16 and 23, June 6 and 27, July 3, 25 and 30, and August 1, 11, 13 and 26, and September 2, 2008.

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

1. CLINICAL/STATISTICAL/CLINICAL PHARMACOLOGY

The clinical evidence is insufficient to establish the efficacy of AI for use in the treatment and improvement of respiratory signs and symptoms and lung functions in cystic fibrosis (CF) patients with chronic *Pseudomonas aeruginosa* infection. The pronounced regimen effect observed in study CP-AI-005, particularly in the placebo BID and TID arms, makes pooling of the placebo groups inappropriate, comparisons with the aztreonam for inhalation arms uninformative because the true placebo effect is unknown, and primary and secondary efficacy results uninterpretable. In fact, subjects in the placebo BID arm fared better than subjects in the AI TID arm. The results of study CP-AI-007, while statistically significant, rely on a primary endpoint of change in the respiratory domain score of the Cystic Fibrosis Questionnaire-Revised (CFQ-R), do not permit conclusions regarding effect of treatment with AI on mortality or irreversible morbidity, and are limited by the use of a 2-week recall period. In addition, the evidence to support the proposed to-be-marketed dose and regimen of 75 mg TID is sparse.

Before the application can be approved, it will be necessary for you to perform an additional adequate and well controlled Phase 3 study which demonstrates:

- A delay in the Time to Need for IV or Inhaled Antibiotics due to Pre-defined Symptoms
- Changes in CFQ-R respiratory domain scores and changes in FEV1 at Day 28 using a sequential testing procedure or other methodologies to control for the overall type-I error rate due to multiple testing.

We strongly recommend the inclusion of a 150 mg BID arm in this study. Sparse sampling of sputum aztreonam concentrations should include additional collection times beyond 10 minutes post-dose (e.g. at 2, 4, and 6 hours post-dose).

2. PRODUCT QUALITY

Our review has identified several deficiencies to be resolved at the two drug manufacturing sites and one diluent manufacturing site, as follows:

a. Drug Product - Gilead Sciences

i. Drug product solution (b) (4)***:*** Provide the efficacy of the (b) (4) in your manufacturing process through post use (b) (4) from three manufactured lots at Gilead.

ii. Sterilization/Depyrogenation of containers, closures, equipment and components:

- (b) (4)
- (b) (4)

- (b) (4)
- (b) (4)

iii. Holding periods: There was no information on the process hold time between the formulation bulk and the final filling step.

- Provide a bioburden data summary to justify the hold time between the formulation bulk and the final filling step.

iv. Media fill procedures and specification: There was no data from a recently performed media fill showing three acceptable process simulation runs.

- Provide a data summary from the three most recent **media fills** conducted to qualify the filling line you propose to use in the manufacture of Aztreonam lysine.
    a. State the acceptance criteria for the media fill simulation in keeping with the Agency's (b) (4) guidance.
    b. Identify the filling line for which this process simulation was conducted.
    c. Identify the dates on which the three consecutive media fills were conducted.
    d. Identify the vial stopper combination used during media fill simulation.
    e. State the number of vials rejected prior to incubation.
    f. State the number of vials actually incubated.
    g. State the number of vials showing growth at the end of 14 day incubation.
    h. Provided a narrative of the process validation through Media Fill simulation study and actions concerning product when media fills fail. List the approved SOP.

i. Provide alert and action levels for the Environmental Monitoring performed in the (b) (4) area. List the approved SOP.

b. Drug Product – (b) (4)

i. Analytical procedures –Endotoxin test: The endotoxin analytical procedures and results provided for Aztreonam Lysine are acceptable provided that there are no OOS results for this product and there are no endotoxin test validation issues.

- For clarification, provide a data summary from the endotoxin test validation report and updated endotoxin test results from the ongoing stability time point studies for Aztreonam Lysine product.

c. Diluent - (b) (4)

(b) (4)

ii. Sterilization/Depyrogenation of containers, closures, equipment and components:

- (b) (4)
- (b) (4)

iii. Holding periods: There was no information on the process hold time between the formulation bulk and the final filling step.

- Provide a bioburden data summary to justify the hold time between the formulation bulk and the final filling step.

iv. Media fill procedures and specification: There was no process simulation data summary from a recently performed media fill showing three acceptable process simulation runs.

- Provide a data summary from the three most recent media fills conducted to qualify the filling line you propose to use in the manufacture of Aztreonam lysine.
    a. State the acceptance criteria for the media fill simulation in keeping with the Agency's (b) (4) guidance.
    b. Identify the filling line for which this process simulation was conducted.
    c. Identify the dates on which the three consecutive media fills were conducted.
    d. State the number of ampoules rejected prior to incubation.
    e. State the number of ampoules actually incubated.
    f. State the number of ampoules showing growth at the end of 14 day incubation.
    g. Provided a narrative of the process validation through Media Fill simulation study and actions concerning product when media fills fail. List the approved SOP.
    h. Provide alert and action levels for the Environmental Monitoring performed in the (b) (4) area. List the approved SOP.

STUDY ENDPOINT RECOMMENDATION

The following recommendations are intended as factors to consider in future studies using the CFQ-R.

- Each of the pediatric subjects age 13 years and under completed two versions of the CFQ-R that differed by method of administration. We recommend inclusion of a side-by-side evaluation of these data by method of administration to determine whether any important differences resulted from the method of administration. For example, demonstrating any important differences observed when the parent/ caregiver administered the questionnaire vs. the investigator/ trial coordinator in children ages 6-11.
- According to the submission, a change of five points represents the minimum change (indicative of either improvement or decline) that can be reliably detected by an individual patient on the respiratory domain scale. This was determined from data obtained from study CP-AI-005. In future studies, it will be helpful in determining clinical relevance, if changes in symptoms as measured by the CFQ-R respiratory domain are linked to improvements in respiratory function and microbiology in individual patients.
- Clarify what the training method/materials are (patient, investigator and other study site personnel) to be used to train personnel in administration of the questionnaire.
- It is important to document the responses to the individual items of the CFQ-R respiratory domain by treatment group to evaluate whether the overall response is driven by single or multiple items.

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/oc/datacouncil/spl.html.

SAFETY UPDATE

When you respond to the above deficiencies, include a safety update as described at 21 CFR 314.50(d)(5)(vi)(*b*). The safety update should include data from all nonclinical and clinical studies/trials of the drug under consideration regardless of indication, dosage form, or dose level.

OTHER

Within one year after the date of this letter, you are required to resubmit or take one of the other actions available under 21 CFR 314.110. If you do not take one of these actions, we will consider your lack of response a request to withdraw the application under 21 CFR 314.65. 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 Guidance for Industry *Formal Meetings With Sponsors and Applicants for PDUFA Products*, February, 2000 (http://www.fda.gov/cder/guidance/2125fnl.htm).

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 Kyong Hyon, Regulatory Project Manager, at (301) 796-0734.

Sincerely,

{See appended electronic signature page}

Katherine Laessig, M.D.
Deputy Director
Division of Anti-Infective and Ophthalmology 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/

Kathrine Laessig
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