DEPARTMENT OF HEALTH AND HUMAN SERVICES

Food and Drug Administration
Silver Spring MD 20993

NDA 50-814 **NDA APPROVAL**

Gilead Sciences, Inc.
Attention: Jennifer Stephens
Director, Regulatory Affairs
2025 First Avenue, Suite PH
Seattle, Washington 98121

Dear Ms. Stephens:

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 Cayston (aztreonam for inhalation solution) in association with the Altera Nebulizer System which is the subject of 510(k) application K100380.

We acknowledge receipt of your submissions dated August 12, 21 and 26, September 11 and 22, October 15 and 30, and November 10 and 13, 2009, January 18 and 21, February 8, 9, 11 and 12, 2010.

The August 12, 2009, submission constituted a complete response to our September 16, 2008, action letter.

This new drug application provides for the use of Cayston (aztreonam for inhalation solution) to improve respiratory symptoms in cystic fibrosis (CF) patients with *Pseudomonas aeruginosa*.

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.

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.

Because this drug product for this indication has an orphan drug designation, you are exempt from this requirement.

POSTMARKETING REQUIREMENTS UNDER 505(o)

Section 505(o) of the Federal Food, Drug, and Cosmetic Act (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 (section 505(o)(3)(A)).

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 the signal of serious risk of development of aztreonam resistance in *Pseudomonas aeruginosa* from cystic fibrosis (CF) patients.

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

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

1585-001 A prospective study in the United States which includes the five year period of time after introduction of Cayston (aztreonam for inhalation) to the market to determine if decreased susceptibility to aztreonam is increasing in *Pseudomonas aeruginosa* from cystic fibrosis (CF) patients. Provide a detailed protocol to the Agency for review and comment before commencing the study. Interim reports of changes in *P. aeruginosa* susceptibility from CF patients should be submitted annually for five years. After the first year, the report should be cumulative.

The information you submitted on January 18, 2010, states that you will conduct this study according to the following timetable:

Final Protocol Submission: 07/2010
First Interim Report: 01/2013, then annually
Study Completion Date: 04/2017
Final Report Submission: 01/2018

Submit the protocol to your IND 64,402, with a cross-reference letter to this NDA. Submit all interim and 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.

POSTMARKETING COMMITMENTS SUBJECT TO THE REPORTING REQUIREMENTS UNDER SECTION 506B

We remind you of your postmarketing commitments in your submission dated January 18, 2010. These commitment(s) are listed below.

1585-002 Conduct a prospective, randomized trial evaluating the efficacy and safety of Cayston versus TOBI® (tobramycin solution for inhalation) in the treatment of patients with cystic fibrosis. Enrolled patients should receive 75 mg of aztreonam for inhalation three times daily or 300 mg of tobramycin solution for inhalation twice daily in 28-day treatment cycles over a trial period of 24 weeks. The trial should enroll CF patients ≥ 6 years of age with history of *Pseudomonas aeruginosa* on sputum culture.

Final Protocol Submission: April 13, 2009
Trial Completion Date: 05/2010
Final Report Submission: 09/2010

1585-003 Conduct a prospective trial comparing twice daily and three times daily administration of Cayston to evaluate the presence or absence of a regimen effect on efficacy. The trial should enroll CF patients ≥ 6 years of age with history of *Pseudomonas aeruginosa* on sputum culture.

Final Protocol Submission: 07/2010
Trial Completion Date: 04/2013
Final Report Submission: 01/2014

Submit clinical protocols to your IND 64,402 for this product. Submit nonclinical and chemistry, manufacturing, and controls protocols and all final reports to this NDA. In addition, under 21 CFR 314.81(b)(2)(vii) and 314.81(b)(2)(viii), you should include a status summary of

each commitment in your annual report to this NDA. The status summary should include expected summary completion and final report submission dates, any changes in plans since the last annual report, and, for clinical trials, number of patients entered into each trial. Prominently identify all submissions, including supplements, with the following wording in bold capital letters at the top of the first page of the submission, as appropriate:

- **POSTMARKETING COMMITMENT PROTOCOL**
- **POSTMARKETING COMMITMENT FINAL REPORT**
- **POSTMARKETING COMMITMENT CORRESPONDENCE**

CONTENT OF LABELING

As soon as possible, but no later than 14 days from the date of this letter, please submit the content of labeling [21 CFR 314.50(l)] in structured product labeling (SPL) format, as described at http://www.fda.gov/oc/datacouncil/spl.html, that is identical to the enclosed labeling submitted on February 11, 2010. For administrative purposes, please designate this submission, "**SPL for approved NDA 50-814**."

CARTON AND IMMEDIATE CONTAINER LABELS

Submit final printed carton and container labels that are identical to the carton and immediate container labels submitted on October 15, 2009, as soon as they are available, but no more than 30 days after they are printed. Please submit these labels electronically according to the guidance for industry titled *Providing Regulatory Submissions in Electronic Format – Human Pharmaceutical Product Applications and Related Submissions Using the eCTD Specifications (October 2005)*. Alternatively, you may submit 12 paper copies, with 6 of the copies individually mounted on heavy-weight paper or similar material. For administrative purposes, designate this submission "**Final Printed Carton and Container Labels for approved NDA 50-814**." Approval of this submission by FDA is not required before the labeling is used.

Marketing the product with FPL that is not identical to the approved labeling text may render the product misbranded and an unapproved new drug.

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
Division of Drug Marketing, Advertising, and Communications
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. For instruction on completing the Form FDA 2253, see page 2 of the Form. For more information about submission of promotional materials to the Division of Drug Marketing, Advertising, and Communications (DDMAC), 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 Kyong Hyon, Regulatory Project Manager, at (301) 796-0734.

Sincerely,

{See appended electronic signature page}

Katherine A. Laessig, M.D.
Deputy Director
Division of Anti-Infective and Ophthalmology Products
Office of Antimicrobial Products
Center for Drug Evaluation and Research

Enclosure

Application Type/Number	Submission Type/Number	Submitter Name	Product Name
NDA-50814	ORIG-1	GILEAD SCIENCES INC	CAYSTON(AZTREONAM FOR INHALATION SOL)

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

/s/

KATHERINE A LAESSIG
02/22/2010