CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

050814Orig1s000

ADMINISTRATIVE and CORRESPONDENCE DOCUMENTS

Department of Health and Human Services
Food and Drug Administration

Form Approved: OMB No. 0910-0513
Expiration Date: 7/31/10
See OMB Statement on Page 3.

PATENT INFORMATION SUBMITTED UPON AND AFTER APPROVAL OF AN NDA OR SUPPLEMENT

For Each Patent That Claims a Drug Substance (Active Ingredient), Drug Product (Formulation or Composition) and/or Method of Use

NDA NUMBER: 050814

NAME OF APPLICANT/NDA HOLDER: Gilead Sciences, Inc.

The following is provided in accordance with Section 505(b) and (c) of the Federal Food, Drug, and Cosmetic Act.

TRADE NAME: CAYSTON®

ACTIVE INGREDIENT(S)	STRENGTH(S)
Aztreonam	75 mg/mL

DOSAGE FORM	APPROVAL DATE OF NDA OR SUPPLEMENT
Lyophylized aztreonam (75 mg/vial) Diluent (0.17% sodium chloride): 1 mL/ampule	22 February 2010

This patent declaration form is required to be submitted to the Food and Drug Administration (FDA) within thirty (30) days after approval of an NDA or supplement or within thirty (30) days of issuance of a patent as required by 21 CFR 314.53(c)(2)(ii) at the address provided in 21 CFR 314.53(d)(4). To expedite review of this patent declaration form, you may submit an additional copy of this declaration form to the Center for Drug Evaluation and Research "Orange Book" staff.

For hand-written or typewriter versions of this report: If additional space is required for any narrative answer (i.e., one that does not require a "Yes" or "No" response), please attach an additional page referencing the question number.

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For each patent submitted for the approved NDA or supplement referenced above, you must submit all the information described below. If you are not submitting any patents for this NDA or supplement, complete above section and sections 5 and 6.

1. GENERAL

a. United States Patent Number	b. Issue Date of Patent	c. Expiration Date of Patent
7208141	24 April 2007	20 December 2021

d. Name of Patent Owner	Address *(of Patent Owner)*	
Gilead Sciences, Inc. (Corus Pharma, Inc., former patent owner, was merged into Gilead Sciences, Inc.)	Attn: Frank P. Grassler, 333 Lakeside Drive	
	City/State: Foster City, CA	
	ZIP Code: 94404	FAX Number *(if available)*: 650 522-5575
	Telephone Number: 650 522-1597	E-Mail Address *(if available)*: frank.grassler@gilead.com

e. Name of agent or representative who resides or maintains a place of business within the United States authorized to receive notice of patent certification under section 505(b)(3) and (j)(2)(B) of the Federal Food, Drug, and Cosmetic Act and 21 CFR 314.52 and 314.95 (if patent owner or NDA applicant/holder does not reside or have a place of business within the United States)	Address *(of agent or representative named in 1.e.)*	
	City/State	
	ZIP Code	FAX Number *(if available)*
	Telephone Number	E-Mail Address *(if available)*

f. Is the patent referenced above a patent that has been submitted previously for the approved NDA or supplement referenced above? ☐ Yes ☒ No

g. If the patent referenced above has been submitted previously for listing, is the expiration date a new expiration date? ☐ Yes ☒ No

PSC Graphics (301) 443-1090 EF

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2. Drug Substance (Active Ingredient)

2.1 Does the patent claim the drug substance that is the active ingredient in the drug product described in the approved NDA or supplement?	☐ Yes	☒ No
2.2 Does the patent claim a drug substance that is a different polymorph of the active ingredient described in the NDA?	☐ Yes	☒ No
2.3 If the answer to question **2.2** is "Yes," do you certify that, as of the date of this declaration, you have test data demonstrating that a drug product containing the polymorph will perform the same as the drug product described in the NDA? The type of test data required is described at 21 CFR 314.53(b).	☐ Yes	☐ No
2.4 Specify the polymorphic form(s) claimed by the patent for which you have the test results described in **2.3**.		
2.5 Does the patent claim only a metabolite of the approved active ingredient? (Complete the information in section 4 below if the patent claims an approved method of using the approved drug product to administer the metabolite.)	☐ Yes	☒ No
2.6 Does the patent claim only an intermediate?	☐ Yes	☒ No
2.7 If the patent referenced in **2.1** is a product-by-process patent, is the product claimed in the patent novel? (An answer is required only if the patent is a product-by-process patent.)	☐ Yes	☐ No

FDA will not list the patent in the Orange Book as claiming the drug substance if:

- **the answers to 2.1 and 2.2 are "No," or,**
- **the answer to 2.2 is "Yes" and the answer to 2.3 is "No," or,**
- **the answer to 2.3 is "Yes" and there is no response to 2.4, or,**
- **the answer to 2.5 or 2.6 is "Yes."**
- **the answer to 2.7 is "No."**

3. Drug Product (Composition/Formulation)

3.1 Does the patent claim the approved drug product as defined in 21 CFR 314.3?	☒ Yes	☐ No
3.2 Does the patent claim only an intermediate?	☐ Yes	☒ No
3.3 If the patent referenced in **3.1** is a product-by-process patent, is the product claimed in the patent novel? (An answer is required only if the patent is a product-by-process patent.)	☐ Yes	☐ No

FDA will not list the patent in the Orange Book as claiming the drug product if:

- **the answer to question 3.1 is "No," or,**
- **the answer to question 3.2 is "Yes," or,**
- **the answer to question 3.3 is "No."**

4. Method of Use

Sponsors must submit the information in section 4 for each approved method of using the approved drug product claimed by the patent. For each approved method of use claimed by the patent, provide the following information:

4.1 Does the patent claim one or more approved methods of using the approved drug product?	☒ Yes	☐ No

4.2 Patent Claim Number(s) *(as listed in the patent)*	Does (Do) the patent claim(s) referenced in **4.2** claim an approved method of use of the approved drug product?		
11-21, 22, 30		☒ Yes	☐ No

4.2a If the answer to **4.2** is "Yes," identify the use with specific reference to the approved labeling for the drug product.	Use: *(Submit indication or method of use information as identified specifically in the approved labeling.)* CAYSTON® is indicated to improve respiratory symptoms in cystic fibrosis (CF) patients with Pseudomonas aeruginosa.

4.2b If the answer to 4.2 is "Yes," also provide the information on the indication or method of use for the Orange Book "Use Code" description.	Use: *(Submit the description of the approved indication or method of use that you propose FDA include as the "Use Code" in the Orange Book, using no more than 240 total characters including spaces.)* CAYSTON® is indicated to improve respiratory symptoms in cystic fibrosis (CF) patients with Pseudomonas aeruginosa.

FDA will not list the patent in the Orange Book as claiming the method of use if:

- **the answer to question 4.1 or 4.2 is "No," or**
- **if the answer to 4.2 is "Yes" and the information requested in 4.2a and 4.2b is not provided in full.**

5. No Relevant Patents

For this NDA or supplement, there are no relevant patents that claim the approved drug substance (active ingredient) or the approved drug product (formulation or composition) or approved method(s) of use with respect to which a claim of patent infringement could reasonably be asserted if a person not licensed by the owner of the patent engaged in the manufacture, use, or sale of the drug product. ☐ Yes

6. Declaration Certification

6.1 ***The undersigned declares that this is an accurate and complete submission of patent information for the NDA or supplement approved under section 505 of the Federal Food, Drug, and Cosmetic Act. This time-sensitive patent information is submitted pursuant to 21 CFR 314.53. I attest that I am familiar with 21 CFR 314.53 and this submission complies with the requirements of the regulation. I verify under penalty of perjury that the foregoing is true and correct.***

Warning: A willfully and knowingly false statement is a criminal offense under 18 U.S.C. 1001.

6.2 Authorized Signature of NDA Applicant/Holder or Patent Owner *(Attorney, Agent, Representative or other Authorized Official) (Provide Information below)*	Date Signed
Frank Grassler	2/25/10

NOTE: Only an NDA applicant/holder may submit this declaration directly to the FDA. A patent owner who is not the NDA applicant/ holder is authorized to sign the declaration but may not submit it directly to FDA. 21 CFR 314.53(c)(4) and (d)(4).

Check applicable box and provide information below.

☐ NDA Applicant/Holder	☒ NDA Applicant's/Holder's Attorney, Agent (Representative) or other Authorized Official
☐ Patent Owner	☐ Patent Owner's Attorney, Agent (Representative) or Other Authorized Official

Name Frank P. Grassler	
Address Gilead Sciences, Inc. 333 Lakeside Drive	City/State Foster City, CA
ZIP Code 94404	Telephone Number 650 522-1597
FAX Number *(if available)* 650 522-5575	E-Mail Address *(if available)* frank.grassler@gilead.com

Department of Health and Human Services
Food and Drug Administration

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Form Approved: OMB No. 0910-0513
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NDA NUMBER
050814

NAME OF APPLICANT/NDA HOLDER
Gilead Sciences, Inc.

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TRADE NAME
CAYSTON®

ACTIVE INGREDIENT(S)	STRENGTH(S)
Aztreonam	75 mg/mL
DOSAGE FORM	APPROVAL DATE OF NDA OR SUPPLEMENT
Lyophylized aztreonam (75 mg/vial) Diluent (0.17% sodium chloride): 1 mL/ampule	22 February 2010

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1. GENERAL

a. United States Patent Number	b. Issue Date of Patent	c. Expiration Date of Patent
7214364	8 May 2007	20 December 2021

d. Name of Patent Owner	Address *(of Patent Owner)*	
Gilead Sciences, Inc. (Corus Pharma, Inc., former patent owner, was merged into Gilead Sciences, Inc.)	Attn: Frank P. Grassler, 333 Lakeside Drive	
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e. Name of agent or representative who resides or maintains a place of business within the United States authorized to receive notice of patent certification under section 505(b)(3) and (j)(2)(B) of the Federal Food, Drug, and Cosmetic Act and 21 CFR 314.52 and 314.95 (if patent owner or NDA applicant/holder does not reside or have a place of business within the United States)	Address *(of agent or representative named in 1.e.)*	
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2. Drug Substance (Active Ingredient)

2.1 Does the patent claim the drug substance that is the active ingredient in the drug product described in the approved NDA or supplement?	☐ Yes	☒ No
2.2 Does the patent claim a drug substance that is a different polymorph of the active ingredient described in the NDA?	☐ Yes	☒ No
2.3 If the answer to question **2.2** is "Yes," do you certify that, as of the date of this declaration, you have test data demonstrating that a drug product containing the polymorph will perform the same as the drug product described in the NDA? The type of test data required is described at 21 CFR 314.53(b).	☐ Yes	☐ No
2.4 Specify the polymorphic form(s) claimed by the patent for which you have the test results described in **2.3**.		
2.5 Does the patent claim only a metabolite of the approved active ingredient? (Complete the information in section 4 below if the patent claims an approved method of using the approved drug product to administer the metabolite.)	☐ Yes	☒ No
2.6 Does the patent claim only an intermediate?	☐ Yes	☒ No
2.7 If the patent referenced in **2.1** is a product-by-process patent, is the product claimed in the patent novel? (An answer is required only if the patent is a product-by-process patent.)	☐ Yes	☐ No

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3. Drug Product (Composition/Formulation)

3.1 Does the patent claim the approved drug product as defined in 21 CFR 314.3?	☒ Yes	☐ No
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4.2 Patent Claim Number(s) *(as listed in the patent)*	Does (Do) the patent claim(s) referenced in **4.2** claim an approved method of use of the approved drug product?	☐ Yes	☐ No
4.2a If the answer to **4.2** is "Yes," identify the use with specific reference to the approved labeling for the drug product.	Use: *(Submit indication or method of use information as identified specifically in the approved labeling.)*		

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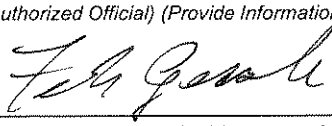	2/25/10

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☐ NDA Applicant/Holder	☒ NDA Applicant's/Holder's Attorney, Agent (Representative) or other Authorized Official
☐ Patent Owner	☐ Patent Owner's Attorney, Agent (Representative) or Other Authorized Official

Name Frank P. Grassler	
Address Gilead Sciences, Inc. 333 Lakeside Drive	City/State Foster City, CA
ZIP Code 94404	Telephone Number 650 522-1597
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ACTIVE INGREDIENT(S)	STRENGTH(S)
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a. United States Patent Number	b. Issue Date of Patent	c. Expiration Date of Patent
7427633	23 September 2008	20 December 2021

d. Name of Patent Owner	Address *(of Patent Owner)*	
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f. Is the patent referenced above a patent that has been submitted previously for the approved NDA or supplement referenced above? ☐ Yes ☒ No

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2. Drug Substance (Active Ingredient)

2.1 Does the patent claim the drug substance that is the active ingredient in the drug product described in the approved NDA or supplement?	☐ Yes	☒ No
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3. Drug Product (Composition/Formulation)

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3.2 Does the patent claim only an intermediate?	☐ Yes	☒ No
3.3 If the patent referenced in **3.1** is a product-by-process patent, is the product claimed in the patent novel? (An answer is required only if the patent is a product-by-process patent.)	☐ Yes	☐ No

FDA will not list the patent in the Orange Book as claiming the drug product if:

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- **the answer to question 3.2 is "Yes," or,**
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4. Method of Use

Sponsors must submit the information in section 4 for each approved method of using the approved drug product claimed by the patent. For each approved method of use claimed by the patent, provide the following information:

4.1 Does the patent claim one or more approved methods of using the approved drug product?	☒ Yes	☐ No
4.2 Patent Claim Number(s) *(as listed in the patent)* 14-28, 31-36	Does (Do) the patent claim(s) referenced in **4.2** claim an approved method of use of the approved drug product? ☒ Yes	☐ No
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Frank Grassler	2/25/10

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ZIP Code 94404	Telephone Number 650 522-1597
FAX Number *(if available)* 650 522-5575	E-Mail Address *(if available)* frank.grassler@gilead.com

ACTION PACKAGE CHECKLIST

APPLICATION INFORMATION[1]

NDA # 50-814 BLA #	NDA Supplement # BLA STN #	If NDA, Efficacy Supplement Type:
Proprietary Name: Cayston Established/Proper Name: aztreonam for inhalation solution Dosage Form: For Inhalation Solution (Diluent provided)		Applicant: Gilead Sciences, Inc. Agent for Applicant (if applicable):
RPM: Kyong Hyon		Division: Anti-Infective and Ophthalmology Products

NDAs:
NDA Application Type: ☐ 505(b)(1) ☒ 505(b)(2)
Efficacy Supplement: ☐ 505(b)(1) ☐ 505(b)(2)

(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). Consult page 1 of the NDA Regulatory Filing Review for this application or Appendix A to this Action Package Checklist.)

505(b)(2) Original NDAs and 505(b)(2) NDA supplements:
Listed drug(s) referred to in 505(b)(2) application (include NDA/ANDA #(s) and drug name(s)):

Azactam (NDA 50-580)

Provide a brief explanation of how this product is different from the listed drug.

This proposed product is an inhalation formulation and the Reference Listed Drug is intravenous formulation (injection)

☐ If no listed drug, check here and explain:

Prior to approval, review and confirm the information previously provided in Appendix B to the Regulatory Filing Review by re-checking the Orange Book for any new patents and pediatric exclusivity. If there are any changes in patents or exclusivity, notify the OND ADRA immediately and complete a new Appendix B of the Regulatory Filing Review.

☒ No changes ☐ Updated
Date of check: 02/22/2010

If pediatric exclusivity has been granted or the pediatric information in the labeling of the listed drug changed, determine whether pediatric information needs to be added to or deleted from the labeling of this drug.

On the day of approval, check the Orange Book again for any new patents or pediatric exclusivity.

❖ Actions	
• Proposed action • User Fee Goal Date is 02-13-10 which was extended to 02-22-10 due to emergency closure of Federal Government	☒ AP ☐ TA ☐ CR
• Previous actions *(specify type and date for each action taken)*	☐ None CR 09-16-08

[1] The **Application Information** section is (only) a checklist. The **Contents of Action Package** section (beginning on page 5) lists the documents to be included in the Action Package.

❖ If accelerated approval, were promotional materials received? Note: For accelerated approval (21 CFR 314.510/601.41), promotional materials to be used within 120 days after approval must have been submitted (for exceptions, see http://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/ucm069965.pdf). If not submitted, explain _____	☐ Received
❖ Application Characteristics [2]	

Review priority: ☒ Standard ☐ Priority
Chemical classification (new NDAs only):

☒ Fast Track
☒ Rolling Review
☒ Orphan drug designation
☐ Rx-to-OTC full switch
☐ Rx-to-OTC partial switch
☐ Direct-to-OTC

NDAs: Subpart H
- ☐ Accelerated approval (21 CFR 314.510)
- ☐ Restricted distribution (21 CFR 314.520)

Subpart I
- ☐ Approval based on animal studies

BLAs: Subpart E
- ☐ Accelerated approval (21 CFR 601.41)
- ☐ Restricted distribution (21 CFR 601.42)

Subpart H
- ☐ Approval based on animal studies

☐ Submitted in response to a PMR
☐ Submitted in response to a PMC
☐ Submitted in response to a Pediatric Written Request

Comments:

❖ BLAs only: *RMS-BLA Product Information Sheet for TBP* has been completed and forwarded to OBPS/DRM *(approvals only)*	☐ Yes, date N/A
❖ BLAs only: is the product subject to official FDA lot release per 21 CFR 610.2 *(approvals only)*	☐ Yes ☐ No
❖ Public communications *(approvals only)*	
• Office of Executive Programs (OEP) liaison has been notified of action	☒ Yes ☐ No
• Press Office notified of action (by OEP)	☒ Yes ☐ No
• Indicate what types (if any) of information dissemination are anticipated	☐ None ☐ HHS Press Release ☐ FDA Talk Paper ☐ CDER Q&As ☐ Other

[2] Answer all questions in all sections in relation to the pending application, i.e., if the pending application is an NDA or BLA supplement, then the questions should be answered in relation to that supplement, not in relation to the original NDA or BLA. For example, if the application is a pending BLA supplement, then a new *RMS-BLA Product Information Sheet for TBP* must be completed.

❖ Exclusivity	
• Is approval of this application blocked by any type of exclusivity?	☒ No ☐ Yes
• NDAs and BLAs: Is there existing orphan drug exclusivity for the "same" drug or biologic for the proposed indication(s)? *Refer to 21 CFR 316.3(b)(13) for the definition of "same drug" for an orphan drug (i.e., active moiety). This definition is NOT the same as that used for NDA chemical classification.*	☒ No ☐ Yes If, yes, NDA/BLA # and date exclusivity expires:
• (b)(2) NDAs only: Is there remaining 5-year exclusivity that would bar effective approval of a 505(b)(2) application)? *(Note that, even if exclusivity remains, the application may be tentatively approved if it is otherwise ready for approval.)*	☒ No ☐ Yes If yes, NDA # and date exclusivity expires:
• (b)(2) NDAs only: Is there remaining 3-year exclusivity that would bar effective approval of a 505(b)(2) application? *(Note that, even if exclusivity remains, the application may be tentatively approved if it is otherwise ready for approval.)*	☒ No ☐ Yes If yes, NDA # and date exclusivity expires:
• (b)(2) NDAs only: Is there remaining 6-month pediatric exclusivity that would bar effective approval of a 505(b)(2) application? *(Note that, even if exclusivity remains, the application may be tentatively approved if it is otherwise ready for approval.)*	☒ No ☐ Yes If yes, NDA # and date exclusivity expires:
• NDAs only: Is this a single enantiomer that falls under the 10-year approval limitation of 505(u)? *(Note that, even if the 10-year approval limitation period has not expired, the application may be tentatively approved if it is otherwise ready for approval.)*	☒ No ☐ Yes If yes, NDA # and date 10-year limitation expires:
❖ Patent Information (NDAs only)	
• Patent Information: Verify that form FDA-3542a was submitted for patents that claim the drug for which approval is sought. If the drug is an old antibiotic, skip the Patent Certification questions.	☐ Verified ☒ Not applicable because drug is an old antibiotic.
• Patent Certification [505(b)(2) applications]: Verify that a certification was submitted for each patent for the listed drug(s) in the Orange Book and identify the type of certification submitted for each patent.	21 CFR 314.50(i)(1)(*i*)(A) ☐ Verified 21 CFR 314.50(i)(1) ☐ (ii) ☐ **(**iii)
• [505(b)(2) applications] If the application includes a **paragraph III** certification, it cannot be approved until the date that the patent to which the certification pertains expires (but may be tentatively approved if it is otherwise ready for approval).	☐ No paragraph III certification Date patent will expire
• [505(b)(2) applications] For **each paragraph IV** certification, verify that the applicant notified the NDA holder and patent owner(s) of its certification that the patent(s) is invalid, unenforceable, or will not be infringed (review documentation of notification by applicant and documentation of receipt of notice by patent owner and NDA holder). *(If the application does not include any paragraph IV certifications, mark "N/A" and skip to the next section below (*Summary Reviews*)).*	☐ N/A (no paragraph IV certification) ☐ Verified

- [505(b)(2) applications] For **each paragraph IV** certification, based on the questions below, determine whether a 30-month stay of approval is in effect due to patent infringement litigation.

  Answer the following questions for **each** paragraph IV certification:

  (1) Have 45 days passed since the patent owner's receipt of the applicant's notice of certification? ☐ Yes ☐ No

  (Note: The date that the patent owner received the applicant's notice of certification can be determined by checking the application. The applicant is required to amend its 505(b)(2) application to include documentation of this date (e.g., copy of return receipt or letter from recipient acknowledging its receipt of the notice) (see 21 CFR 314.52(e))).

  *If "**Yes**," skip to question (4) below. If "**No**," continue with question (2).*

  (2) Has the patent owner (or NDA holder, if it is an exclusive patent licensee) submitted a written waiver of its right to file a legal action for patent infringement after receiving the applicant's notice of certification, as provided for by 21 CFR 314.107(f)(3)? ☐ Yes ☐ No

  *If "**Yes,**" there is no stay of approval based on this certification. Analyze the next paragraph IV certification in the application, if any. If there are no other paragraph IV certifications, skip the rest of the patent questions.*

  *If "**No**," continue with question (3).*

  (3) Has the patent owner, its representative, or the exclusive patent licensee filed a lawsuit for patent infringement against the applicant? ☐ Yes ☐ No

  (Note: This can be determined by confirming whether the Division has received a written notice from the (b)(2) applicant (or the patent owner or its representative) stating that a legal action was filed within 45 days of receipt of its notice of certification. The applicant is required to notify the Division in writing whenever an action has been filed within this 45-day period (see 21 CFR 314.107(f)(2))).

  *If "**No**," the patent owner (or NDA holder, if it is an exclusive patent licensee) has until the expiration of the 45-day period described in question (1) to waive its right to bring a patent infringement action or to bring such an action. After the 45-day period expires, continue with question (4) below.*

  (4) Did the patent owner (or NDA holder, if it is an exclusive patent licensee) submit a written waiver of its right to file a legal action for patent infringement within the 45-day period described in question (1), as provided for by 21 CFR 314.107(f)(3)? ☐ Yes ☐ No

  *If "**Yes,**" there is no stay of approval based on this certification. Analyze the next paragraph IV certification in the application, if any. If there are no other paragraph IV certifications, skip to the next section below (*Summary Reviews*).*

  *If "**No**," continue with question (5).*

(5) Did the patent owner, its representative, or the exclusive patent licensee bring suit against the (b)(2) applicant for patent infringement within 45 days of the patent owner's receipt of the applicant's notice of certification? (Note: This can be determined by confirming whether the Division has received a written notice from the (b)(2) applicant (or the patent owner or its representative) stating that a legal action was filed within 45 days of receipt of its notice of certification. The applicant is required to notify the Division in writing whenever an action has been filed within this 45-day period (see 21 CFR 314.107(f)(2)). If no written notice appears in the NDA file, confirm with the applicant whether a lawsuit was commenced within the 45-day period). *If "**No**," there is no stay of approval based on this certification. Analyze the next paragraph IV certification in the application, if any. If there are no other paragraph IV certifications, skip to the next section below (*Summary Reviews*).* *If "**Yes**," a stay of approval may be in effect. To determine if a 30-month stay is in effect, consult with the OND ADRA and attach a summary of the response.*	☐ Yes ☐ No
CONTENTS OF ACTION PACKAGE	
❖ Copy of this Action Package Checklist[3]	included
Officer/Employee List	
❖ List of officers/employees who participated in the decision to approve this application and consented to be identified on this list *(approvals only)*	☒ Included
Documentation of consent/non-consent by officers/employees	☒ Included
Action Letters	
❖ Copies of all action letters *(including approval letter with final labeling)*	Action(s) and date(s) 09-16-08 (CR) and 02-22-10 (AP)
Labeling	
❖ Package Insert *(write submission/communication date at upper right of first page of PI)*	
• Most recent draft labeling. If it is division-proposed labeling, it should be in track-changes format.	02-10-10
• Original applicant-proposed labeling	08-21-09 and November 16, 2007
• Example of class labeling, if applicable	N/A

[3] Fill in blanks with dates of reviews, letters, etc.

❖ Medication Guide/Patient Package Insert/Instructions for Use *(write submission/communication date at upper right of first page of each piece)*	☐ Medication Guide ☐ Patient Package Insert ☐ Instructions for Use ☒ None
• Most-recent draft labeling. If it is division-proposed labeling, it should be in ttrack-changes format.	
• Original applicant-proposed labeling	
• Example of class labeling, if applicable	
❖ Labels (**full color** carton and immediate-container labels) *(write submission/communication date on upper right of first page of each submission)*	
• Most-recent draft labeling	01-21-10
❖ Proprietary Name • Acceptability/non-acceptability letter(s) *(indicate date(s))* • Review(s) *(indicate date(s))*	01-08-10 and 05-12-08
❖ Labeling reviews *(indicate dates of reviews and meetings)*	☒ RPM 09-10-08 ☒ DMEDP 12-07-09 ☒ DRISK 02-05-10 ☒ DDMAC 02-04-10 ☐ CSS ☐ Other reviews
Administrative / Regulatory Documents	
❖ Administrative Reviews *(e.g., RPM Filing Review[4]/Memo of Filing Meeting) (indicate date of each review)*	08-25-09 (Regulatory Filling Review): 02-22-10 and 09-16-08 (505(b)(2) assessments); Does not need Exclusivity Summary because the drug is an old antibiotic.
❖ NDAs only: Exclusivity Summary *(signed by Division Director)*	☐ Included
❖ Application Integrity Policy (AIP) Status and Related Documents http://www.fda.gov/ICECI/EnforcementActions/ApplicationIntegrityPolicy/default.htm	
• Applicant in on the AIP	☐ Yes ☒ No
• This application is on the AIP o If yes, Center Director's Exception for Review memo *(indicate date)* o If yes, OC clearance for approval *(indicate date of clearance communication)*	☐ Yes ☒ No ☐ Not an AP action
❖ Pediatrics *(approvals only)* • Date reviewed by PeRC _____ If PeRC review not necessary, explain: _____ • Pediatric Page *(approvals only, must be reviewed by PERC before finalized)*	☐ Included
❖ Debarment certification (original applications only): verified that qualifying language was not used in certification and that certifications from foreign applicants are cosigned by U.S. agent *(include certification)*	☒ Verified, statement is acceptable
❖ Outgoing communications *(letters (except action letters), emails, faxes, telecons)*	

[4] Filing reviews for scientific disciplines should be filed behind the respective discipline tab.

❖ Internal memoranda, telecons, etc.	
❖ Minutes of Meetings	
• Pre-Approval Safety Conference *(indicate date of mtg; approvals only)*	Not applicable
• Regulatory Briefing *(indicate date of mtg)*	☒ No mtg
• If not the first review cycle, any end-of-review meeting *(indicate date of mtg)*	☐ N/A or no mtg 10-02-09
• Pre-NDA/BLA meeting *(indicate date of mtg)*	☐ No mtg 02-14-07
• EOP2 meeting *(indicate date of mtg)*	☐ No mtg 11-23-04
• Other milestone meetings (e.g., EOP2a, CMC pilot programs) *(indicates dates)*	05-30-07: CMC Pre-NDA meeting
❖ Advisory Committee Meeting(s)	☐ No AC meeting
• Date(s) of Meeting(s)	12-10-09
• 48-hour alert or minutes, if available *(do not include transcript)*	
Decisional and Summary Memos	
❖ Office Director Decisional Memo *(indicate date for each review)*	☒ None
Division Director Summary Review *(indicate date for each review)*	☐ None 02-22-10, 02-12-10 and 09-16-08
Cross-Discipline Team Leader Review *(indicate date for each review)*	☐ None 02-12-10, 02-10-10, and 09-15-08
PMR/PMC Development Templates *(indicate total number)*	☐ None 09-15-08 (3)
Clinical Information[5]	
❖ Clinical Reviews	
• Clinical Team Leader Review(s) *(indicate date for each review)*	02-12-10, 02-10-10, and 09-15-08
• Clinical review(s) *(indicate date for each review)*	Medical Officer Reviews: 02-09-10 and 09-05-08 Study End Point Review by SEALD Team: 02-01-10 and 06-12-08
• Social scientist review(s) (if OTC drug) *(indicate date for each review)*	☐ None N/A
❖ Financial Disclosure reviews(s) or location/date if addressed in another review OR If no financial disclosure information was required, check here ☐ and include a review/memo explaining why not *(indicate date of review/memo)*	See 09-05-08 Medical Review, P9
❖ Clinical reviews from immunology and other clinical areas/divisions/Centers *(indicate date of each review)*	☒ None
❖ Controlled Substance Staff review(s) and Scheduling Recommendation *(indicate date of each review)*	☒ Not applicable
❖ Risk Management • REMS Document and Supporting Statement *(indicate date(s) of submission(s))* • REMS Memo *(indicate date)* • Risk management review(s) and recommendations (including those by OSE and CSS) *(indicate date of each review and indicate location/date if incorporated into another review)*	☒ None

[5] Filing reviews should be filed with the discipline reviews.

❖ DSI Clinical Inspection Review Summary(ies) *(include copies of DSI letters to investigators)*	☐ None requested 07-14-08 (4 reviews) and 06-19-08
Clinical Microbiology ☐ None	
❖ Clinical Microbiology Team Leader Review(s) *(indicate date for each review)*	☒ None
Clinical Microbiology Review(s) *(indicate date for each review)*	☐ None 01-14-10, 05-28-09, and 08-04-08
Biostatistics ☐ None	
❖ Statistical Division Director Review(s) *(indicate date for each review)*	☒ None
Statistical Team Leader Review(s) *(indicate date for each review)*	☒ None
Statistical Review(s) *(indicate date for each review)*	☐ None 01-27-10 and 07-22-08
Clinical Pharmacology ☐ None	
❖ Clinical Pharmacology Division Director Review(s) *(indicate date for each review)*	☒ None
Clinical Pharmacology Team Leader Review(s) *(indicate date for each review)*	☒ None
Clinical Pharmacology review(s) *(indicate date for each review)*	☐ None 01-22-10 and 06-27-08
❖ DSI Clinical Pharmacology Inspection Review Summary *(include copies of DSI letters)*	☒ None
Nonclinical ☐ None	
❖ Pharmacology/Toxicology Discipline Reviews	
• ADP/T Review(s) *(indicate date for each review)*	☒ None
• Supervisory Review(s) *(indicate date for each review)*	☒ None
• Pharm/tox review(s), including referenced IND reviews *(indicate date for each review)*	☐ None 12-09-09 and 07-18-08
❖ Review(s) by other disciplines/divisions/Centers requested by P/T reviewer *(indicate date for each review)*	☒ None
❖ Statistical review(s) of carcinogenicity studies *(indicate date for each review)*	☐ No carc 10-14-08
❖ ECAC/CAC report/memo of meeting	☐ None 06-11-08 Included in P/T review, page
❖ DSI Nonclinical Inspection Review Summary *(include copies of DSI letters)*	☒ None requested
Product Quality ☐ None	
❖ Product Quality Discipline Reviews	
• ONDQA/OBP Division Director Review(s) *(indicate date for each review)*	☒ None
• Branch Chief/Team Leader Review(s) *(indicate date for each review)*	☐ None 01-18-08
• Product quality review(s) including ONDQA biopharmaceutics reviews *(indicate date for each review)*	☐ None 02-12-10 and 08-27-08
❖ Microbiology Reviews ☒ NDAs: Microbiology reviews (sterility & pyrogenicity) (OPS/NDMS) *(indicate date of each review)* ☐ BLAs: Sterility assurance, microbiology, facilities reviews (DMPQ/MAPCB/BMT) *(indicate date of each review)*	☐ Not needed 11-09-09 and 08-27-08
❖ Reviews by other disciplines/divisions/Centers requested by CMC/quality reviewer *(indicate date of each review)*	☒ None

❖ Environmental Assessment (check one) (original and supplemental applications)	
☐ Categorical Exclusion *(indicate review date)(all original applications and all efficacy supplements that could increase the patient population)*	See 02-12-10 CMC review See 08-27-08 CMC review
☐ Review & FONSI *(indicate date of review)*	
☐ Review & Environmental Impact Statement *(indicate date of each review)*	
❖ Facilities Review/Inspection	
☐ NDAs: Facilities inspections (include EER printout) *(date completed must be within **2 years** of action date)*	Date completed: 02-02-10 and 07-02-08 ☒ Acceptable ☐ Withhold recommendation
☐ BLAs: TB-EER *(date of most recent TB-EER must be within **30 days** of action date)*	Date completed: ☐ Acceptable ☐ Withhold recommendation
❖ NDAs: Methods Validation *(check box only, do not include documents)*	☐ Completed ☐ Requested ☒ Not yet requested ☐ Not needed

Appendix A to Action Package Checklist

An NDA or NDA supplemental 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) **Or** 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.
(3) **Or** 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) **And** 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.
(3) **And** 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) **Or** 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.
(3) **Or** 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 ADRA.

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

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/s/

KYONG M HYON
02/25/2010

Frances V LESANE
03/01/2010

DEPARTMENT OF HEALTH AND HUMAN SERVICES

Food and Drug Administration
Silver Spring, MD 20993

NDA 50-814

DISCIPLINE REVIEW LETTER

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) submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act for aztreonam for inhalation.

We are providing these comments to you before we complete our review of the entire application to give you preliminary notice of issues that we have identified. In conformance with the prescription drug user fee reauthorization agreements, these comments do not reflect a final decision on the information reviewed and should not be construed to do so. These comments are preliminary and subject to change as we finalize our review of your application. In addition, we may identify other information that must be provided before we can approve this application. If you respond to these issues during this review cycle, depending on the timing of your response, and in conformance with the user fee reauthorization agreements, we may not be able to consider your response before we take an action on your application during this review cycle.

We also refer to your submission dated November 10, 2009 which contains the vial label with two options to be considered.

We acknowledge the changes you have made to the labels and labeling based on our previous recommendations, dated June 18 and September 14, 2008 for improvement. However, we have the following additional recommendation to minimize vulnerability to medication errors:

A. Diluent Label

1. Revise the second line to read: DILUENT for Cayston.
2. Revise the presentation of Gilead Sciences so that it is not in all capital letters. The current presentation makes it appear as the most prominent information on the label.

B. Container Label

- We prefer option 1, which includes the route of administration and single-use vial on the principle display panel.

C. Carton Labeling (14 day and 28 day)

- Increase the size of the product strength as in its current presentation it appears small.

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

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

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/s/

KATHERINE A LAESSIG
12/17/2009

DEPARTMENT OF HEALTH AND HUMAN SERVICES

Food and Drug Administration
Silver Spring, MD 20993

NDA 50-814

ACKNOWLEDGE CLASS 2 RESPONSE

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

Dear Ms. Stephens:

We acknowledge receipt on August 13, 2009 of your August 11, 2009 resubmission to your new drug application for aztreonam for inhalation solution (AI).

We consider this a complete, class 2 response to our September 16, 2008 action letter. Therefore, the user fee goal date is February 13, 2010.

If you have any questions, call Kyong Hyon, Regulatory Project Manager, at (301) 796-0734.

Sincerely,

{See appended electronic signature page}

Frances V. LeSane
Chief, Project Management Staff
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/

JOSEPH C DAVI
08/26/2009

DEPARTMENT OF HEALTH & HUMAN SERVICES

Public Health Service

Food and Drug Administration
Rockville, MD 20857

NDA 50-814

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) submitted under section 505(b)(2) of the Federal Food, Drug, and Cosmetic Act for aztreonam for inhalation solution.

We also refer to the meeting between representatives of your firm and the FDA on April 24, 2009.

The official minutes of that meeting are enclosed. You are responsible for notifying us of any significant differences in understanding regarding the meeting outcomes.

If you have any questions, call Amy Bertha, Regulatory Project Manager, at (301) 796-1647.

Sincerely,

{See appended electronic signature page}

RADM Sandra L. Kweder, M.D.
United States Public Health Service
Deputy Director
Office of New Drugs
Center for Drug Evaluation and Research

Enclosure

MEMORANDUM OF MEETING MINUTES

MEETING DATE:	April 24, 2009
TIME:	1:00 pm – 2:30pm
LOCATION:	White Oak Campus, Building 22, Room 1419
APPLICATION:	NDA 50-814
DRUG NAME:	Aztreonam for inhalation solution
TYPE OF MEETING:	Formal Dispute Resolution
MEETING CHAIR:	Sandra Kweder
MEETING RECORDER:	Amy Bertha

FDA ATTENDEES:

Sandra Kweder	Deputy Director, Office of New Drugs
Edward Cox	Director, Office of Antimicrobial Products
Robert ONeill	Director, Office of Biostatistics
John Farley	Deputy Director, Office Antimicrobial Products
Wiley Chambers	Acting Director, Division of Anti-Infective Ophthalmology Products
John Alexander	Medical Team Leader, Division of Anti-Infective Ophthalmology Products
Menfo Imoisili	Medical Reviewer, Division of Anti-Infective Ophthalmology Products
Thamban Valapil	Statistical Team Leader, Division of Biostatistics IV
Christopher Kadoorie	Statistical Reviewer, Division of Biostatistics IV
Kim Quaintance	Associate Director of Regulatory Affairs, Office of New Drugs
Amy Bertha	Senior Regulatory Health Project Manager, Office of New Drugs
Kyong Hyon	Senior Regulatory Health Project Manager, Division of Anti-Infective Ophthalmology Products

EXTERNAL CONSTITUENT ATTENDEES:

A. Bruce Montgomery	Senior Vice President, Respiratory Therapeutics, Gilead
Melissa A. Yeager	Vice President, Regulatory Affairs, Gilead
Michael Wulfsohn	Vice President, Biometrics

(b) (4)

BACKGROUND:

Gilead submitted a formal dispute resolution request to the Office of Antimicrobial Products on November 24, 2008. Edward Cox, Director of the Office of Antimicrobial Products was the deciding authority. Gilead requested a reconsideration of DAIOP's September 16, 2008, complete response (CR) action to their NDA 50-814 (aztreonam for inhalation solution). The appeal was denied on February 18, 2009. Gilead submitted a second formal dispute resolution request to the Office of New Drugs on March 13, 2009. Sandra Kweder, Deputy Director Office of New Drugs is the deciding authority of the second request. FDA requested a meeting with Gilead and provided specific questions to discuss at the meeting in a letter dated April 10, 2009. On April 22, 2009 Gilead submitted a meeting package.

MEETING OBJECTIVES:

The objective of this meeting was to discuss the questions provided in FDA's April 10, 2009 letter to Gilead (questions below).

1. Based on the data in Study CP-AI-005, explain how the results can be meaningfully interpreted despite having a strong treatment regimen effect. Specifically, explain how a pooled analysis can be justified in light of the treatment regimen effect.

2. You have proposed that the indication for inhaled aztreonam would be three-times-a-day dosing for acute treatment of patients with cystic fibrosis (CF), and the outcome data from Study CP-AI-007 support this. However, it is widely known that most use of inhaled antibiotics in patients with CF is for multiple cycles. Given this expected treatment strategy in the medical practice community and the observed regimen effect in study CP-AI-005, it is unclear whether and how to advise utilization beyond a single one-month course. Specifically, if one were to accept the results of CP-AI-005, the twice daily dosing regimen would be the preferred treatment strategy.

3. Please provide information about your discussions with the EMEA about this application and your plans to address the concerns raised.

DISCUSSION:

Gilead presented slides that addressed the questions FDA outlined in the April 10, 2009 letter. FDA and Gilead discussed the questions.

DECISIONS (AGREEMENTS) REACHED:

This meeting was not conducted with the expectation that decisions would be made or agreements reached at the meeting. The issues discussed will be taken into consideration when reaching a decision about the formal dispute resolution which will be made in 30 days.

ATTACHMENTS/HANDOUTS:

Slides from Gilead's meeting presentation

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/s/

Sandra L. Kweder

6/17/2009 04:06:01 PM

DEPARTMENT OF HEALTH & HUMAN SERVICES

Public Health Service

Food and Drug Administration
Rockville, MD 20857

NDA 50-814

Gilead Sciences, Inc.
ATTENTION: Melissa Yeager, JD
Vice President, Regulatory Affairs
2025 1st Avenue, Suite PH
Seattle, WA 98121

Dear Ms. Yeager:

We refer to your New Drug Application (NDA) submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act for Cayston (aztreonam for inhalation solution).

We also refer to your November 24, 2008, formal dispute resolution request (FDRR) to the Office of Antimicrobial Products. The appeal concerned the decision by the Division of Anti-Infective and Ophthalmology Products (DAIOP) to issue a Complete Response (CR) letter on September 16, 2008, specifically, whether you have demonstrated substantial evidence of effectiveness of aztreonam in treating patients with Cystic Fybrosis (CF) as submitted in NDA 50-814. The appeal was denied on February 18, 2009. We also refer to your March 13, 2009, request for formal dispute resolution to the Office of New Drugs. I have carefully reviewed this appeal and your submission of additional information on April 8, 2009 and April 22, 2009. I have also considered our discussion at the April 24, 2009 meeting. We acknowledge receipt on your May 22, 2009 submission, but given our review of the material from April 8 and 22, 2009, decided that it constituted new data and analyses and thus we would not review it in detail.

I have focused on the fundamental Clinical/Statistical/Clinical Pharmacology issue leading to your application not being approved, the results for study CP-AI-005 including evaluation of the primary outcome for each of the dosing regimens. The CR letter also raised concerns about the use of the Cystic Fibrosis Questionnaire-Revised (CFQ-R) as an instrument in measuring efficacy in study CP-AI-007 I believe that the issues with study CP-AI-005 warrant more concern on their face and are magnified by any uncertainties posed by the CFQ-R in study CP-AI-007. Specifically, while the statistical plan for study CP-AI-005's analysis called for pooling of the twice daily (BID) and three times daily (TID) treatment arms and placebo arms, the presence of a treatment regimen effect in the study outcomes on its face precludes this being a valid strategy. When the four study arm results are compared, there is substantial inconsistency of the findings, including:

- The placebo arms, when compared, have a statistically significant difference in outcome ($p=0.0043$)
- The placebo BID arm appears to outperform the aztreonam TID arm

In light of these findings, I agree with those who have reviewed this application that it is problematic to accept the pooled analysis, because such an approach presumes there is no regimen effect.

In the NDA itself and throughout the FDRR process you have provided explanations as to why you chose to study both the TID and BID treatment regimens. However, despite these explanations the observed results from study CP-AI-005 when looking at treatment regimen lead to uncertainty about the efficacy of AZLI in study CP-AI-005. Regardless of the reason for choosing to include both a BID and TID regimen in study CP-AI-005, having now studied both dose regimens, the results of the trial call into question whether you have identified the effective dose AZLI. After going through this FDRR process I am encouraged that some of the work you have done to address these issues, as described in your submission dated April 22, 2009, (in response to my letter dated April 10, 2009) may help get to the heart of what was occurring in the study and why the results turned out the way they did.

First, I asked you to explain how your pooled efficacy analysis of study CP-AI-005 can be justified in light of the treatment regimen effect. Your response did not specifically address the issue of pooling, but rather focused on your perspective that a regimen effect is biologically implausible and most likely a false finding. You did point out a number of factors that contributed to your conclusions, including that there was no treatment regimen effect for endpoints other than the primary endpoint; Cox models for the regimen effect indicated that there was no interaction between the treatment and regimen, and that the comparison of AZLI TID to placebo TID showed a significant benefit to AZLI.

Your response also pointed out that the primary endpoint for study CP-AI-005, "time to need for treatment," has, "A built in bias which results in an effective regimen appearing to be less effective than it really is." This is an interesting approach to analyzing the results of study CP-AI-005 in order to explore why the observed behavior of the BID and TID AZLI groups. I found your analyses and our discussion of them in our meeting on April 24, 2009, thought-provoking and indicate that you have undertaken an extensive amount of work to better characterize the properties of this endpoint in cystic fibrosis since your original submission of NDA 50-814. As new information, I believe that they warrant a more careful assessment by our review staff. As you are aware, the Guidance for Industry Formal Dispute Resolution: Appeals Above the Division Level, specifically states that no new information should be submitted as part of the appeal.

My second question to you in my letter of April 10, 2009 can be summarized as asking how, given the findings in study CP-AI-005, you have confidence in recommending a dosing strategy of three times a day (especially when the twice daily regimen outperformed it) and that recurrent treatment courses are likely to be part of how AZLI is used. Your rationale refers back to your response to my first question, although the likely close in time recurrent nature of the treatment over years that could be expected to be used for cystic fibrosis patients is not fully addressed.

My third question to you was to ask for some clarification on the nature of your interactions with the EMEA Scientific Advice Working Group, which I thank you for providing.

As I stated in our meeting on April 24, 2009, I find the decision about whether you have demonstrated the safety and efficacy of AZLI for the treatment of patients with pulmonary exacerbations of cystic fibrosis due to pseudomonas infections to be a difficult one. Your development strategy of looking at the activity of the drug in two different study methodologies was sound, and despite some weaknesses of the methods in study CP-A1-007, its findings are interesting and help frame the efficacy of the drug over a short period of time. Your further exploration of the study CP-AI-005 design, nature of the

primary endpoint and effect of prior treatment success does provide interesting insight to how the results could have come about. What remains at issue is whether that exploratory work is robust enough to stand on its own as an explanation for the treatment regimen effect or it should simply be considered hypothesis generating. The decision can only be made on the basis of a full review of these new data analyses.

Cystic Fibrosis (CF) is a serious disease with few treatments available. There is a clear need for more and better options to manage CF. Like my colleagues in the Office of Antimicrobial Products, I am firmly committed to ensuring that we keep an open mind about what constitutes clinically meaningful benefit as we review data for CF treatments. I am also concerned that we not accept a lesser standard of evidence demonstrating the safety and efficacy for a product for CF simply because existing treatments are few. Data collected and analyzed with scientific rigor must form the underpinnings of any new drug review and this one is no exception. On the other hand, the interpretation and application of scientific data requires judgment, and in the case of this NDA I believe that this interface is critical.

As noted above, the FDRR Guidance specifically proscribes new data from consideration by the deciding official. Your new work to address and understand the results of study CP-AI-005 constitute new data. Therefore, while I am denying your appeal, I recommend the following actions.

1. You should submit, in response to the September 16, 2008 CR letter, your new analyses of data relevant to NDA 50-814. I recommend that before that submission you meet with the Division of Anti-Infective and Ophthalmology Drug Products and their statistical experts to discuss what it will include in order to ensure that specific issues of concern to review staff will be addressed.
2. As part of their review of your response to the CR letter for NDA 50-814, the Division of Anti-Infective and Ophthalmology Products should present the full application to the Anti-Infectives Advisory Committee. That Advisory Committee should include participation by experts in the field of cystic fibrosis.

If you wish to appeal this decision to the next level, your appeal should be directed to Douglas C. Throckmorton, M.D., Deputy Director, Center for Drug Evaluation and Research. The appeal should be sent through the Center's Dispute Resolution Project Manager, Amy Bertha. Any questions concerning your appeal should be addressed via Ms. Bertha at (301) 796-1647.

Sincerely,

{See appended electronic signature page}

RADM Sandra L. Kweder, M.D.
United States Public Health Service
Deputy Director
Office of New Drugs
Center for Drug Evaluation and Research

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/s/

Sandra L. Kweder

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DEPARTMENT OF HEALTH & HUMAN SERVICES

Public Health Service

Food and Drug Administration
Rockville, MD 20857

NDA 50-814

Gilead Sciences, Inc.
ATTENTION: Melissa Yeager, JD
Vice President, Regulatory Affairs
2025 1st Avenue, Suite PH
Seattle, WA 98121

Dear Ms. Yeager:

We refer to your New Drug Application (NDA) submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act for Cayston (aztreonam for inhalation solution.)

We refer also to your March 13, 2009, request for formal dispute resolution received on March 13, 2009. The appeal concerned the decision by the Division of Anti-Infective and Ophthalmology Products (DAIOP) to issue a Complete Response letter on September 16, 2008. The September 16, 2008, complete response (CR) letter from DAIOP enumerates deficiencies in two categories, Clinical/Statistical/Clinical Pharmacology and Product Quality.

As per the conversation between Ms. Jennifer Stevens, Gilead Sciences, Inc., and Ms. Kim Quaintance, Office of New Drugs, we have reviewed your appeal and conclude that additional input is needed to reach a decision. Therefore, we would like to schedule a meeting with you to discuss the following issues:

1. Based on the data in Study CP-AI-005, explain how the results can be meaningfully interpreted despite having a strong treatment regimen effect. Specifically, explain how a pooled analysis can be justified in light of the treatment regimen effect.

2. You have proposed that the indication for inhaled aztreonam would be three-times-a-day dosing for acute treatment of patients with cystic fibrosis (CF), and the outcome data from Study CP-AI-007 support this. However, it is widely known that most use of inhaled antibiotics in patients with CF is for multiple cycles. Given this expected treatment strategy in the medical practice community and the observed regimen effect in study CP-AI-005, it is unclear whether and how to advise utilization beyond a single one-month course. Specifically, if one were to accept the results of CP-AI-005, the twice daily dosing regimen would be the preferred treatment strategy.

3. Please provide information about your discussions with the EMEA about this application and your plans to address the concerns raised.

We will respond to the appeal within 30 days after the meeting.

Please contact Amy Bertha, Formal Dispute Resolution Project Manager, at (301) 796-0700 to schedule the meeting.

Sincerely,

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RADM Sandra L. Kweder, M.D.
United States Public Health Service
Deputy Director
Office of New Drugs
Center for Drug Evaluation and Research

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Sandra L. Kweder

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DEPARTMENT OF HEALTH & HUMAN SERVICES

Public Health Service

Food and Drug Administration
Rockville, MD 20857

NDA 50-814

Gilead Sciences, Inc.
ATTENTION: Melissa A. Yeager, J.D.
2025 1st Avenue, Suite PH
Seattle, WA 98121

Dear Ms. Yeager:

We refer to your New Drug Application (NDA) submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act for aztreonam for inhalation solution.

We acknowledge receipt on November 24, 2008, of your November 21, 2008, request for formal dispute resolution concerning the Agency's September 16, 2008, Complete Response letter to NDA 50-814 (aztreonam for inhalation solution). You dispute the opinions expressed by DAIOP in the CLINICAL/STATISTICAL/CLINICAL PHARMACOLOGY section of the Complete Response letter.

Pursuant to the CDER/CBER draft Guidance to Industry "Formal Dispute Resolution: Appeals Above the Division Level," we have thirty (30) calendar days from the receipt date of the formal request to respond to the appeal. Therefore, our response to this FDRR is due on or before December 24, 2008.

This FDRR has been forwarded for review to Dr. Edward Cox, Director, Office of Antimicrobial Products, Center for Drug Evaluation and Research. We will contact you should we have any questions or require additional information.

If you have any questions, please call me at (301) 796-0799.

Sincerely,

{See appended electronic signature page}

David Roeder
Associate Director for Regulatory Affairs
Office of Antimicrobial Products
Center for Drug Evaluation and Research

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/s/

David Roeder

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DEPARTMENT OF HEALTH & HUMAN SERVICES

Public Health Service

Food and Drug Administration
Rockville, MD 20857

NDA 50-814

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) submitted under section 505(b)(2) of the Federal Food, Drug, and Cosmetic Act for aztreonam for inhalation solution.

We also refer to your submission dated October 6, 2008 which contains one question and request Division's response.

We have reviewed the referenced material and have the following comments and recommendations. The original question is reproduced in bold below, followed by the Division's response.

Sponsor Question 1. Does the Division agree that Gilead can use the previously produced container labels and packaging cartons at the time of commercial launch and subsequently use updated labels and cartons produced in line with the changes requested by the Division?

Division Response: No. The labels and labeling that have already been produced in anticipation of commercial launch would not be acceptable as they do not reflect revisions contained in the FDA Discipline Review Letter, dated September 14, 2008.

We also note that labeling can not be considered to be approved until a final approval action is taken on the product. You take the risk that any carton/container labeling you generate now may not be acceptable when we take action on the product.

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

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/s/

Kathrine Laessig

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DEPARTMENT OF HEALTH & HUMAN SERVICES

Public Health Service

Food and Drug Administration
Rockville, MD 20857

NDA 50-814

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) submitted under section 505(b)(2) of the Federal Food, Drug, and Cosmetic Act for aztreonam for inhalation solution.

We also refer to the meeting between representatives of your firm and the FDA on August 28, 2008. The purpose of the meeting was to discuss the status of the application.

The official minutes of that meeting are enclosed. You are responsible for notifying us of any significant differences in understanding regarding the meeting outcomes.

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

Enclosure

MEMORANDUM OF MEETING MINUTES

MEETING DATE: August 28, 2008
TIME: 10:00 AM – 11:00AM (EST)
LOCATION: White Oak Building 22, Room 1309
APPLICATION: NDA 50-814
DRUG NAME: Aztreonam for Inhalation Solution
TYPE OF MEETING: Type A

MEETING CHAIR: Wiley A. Chambers, M.D.

MEETING RECORDER: Kyong Hyon

FDA ATTENDEES: (FDA)
Division of Anti-Infective and Ophthalmology Products, DAIOP:

Wiley A. Chambers, MD, Acting Director
Katherine Laessig, MD, Deputy Director
John Alexander, MD, MPH, Clinical Team Leader
Menfo Imoisili, MD, MPH, Clinical Reviewer
Frederic Marsik, PhD, Clinical Microbiology Team Leader
Peter Coderre, PhD, Clinical Microbiology Reviewer
Mark Seggel, PhD, Chemistry Reviewer
Charles Bonapace, PharmD, Clinical Pharmacology Team Leader
Sarah Robertson, PharmD, Clinical Pharmacology Reviewer
Scott Komo, PhD, Acting Statistical Team Leader
Christopher Kadoorie, PhD, Statistical Reviewer
Kyong Hyon, Regulatory Project Manager

EXTERNAL CONSTITUENT ATTENDEES: (Sponsor)
Gilead Sciences, Inc.:

Norbert Bischofberger, PhD, Executive Vice President, Research and Development, Chief Scientific Officer
Bruce Montgomery, MD, Senior Vice President, Respiratory Therapeutics
David Pizzuti, MD, Vice President, Regulatory Affairs
Melissa Yeager, JD, Vice President, Regulatory Affairs
Michael Wulfson, MD, PhD, Vice President, Biometrics
James Whitmore, PhD, Sr. Director, Biometrics

(b) (4)

BACKGROUND: On August 21, 2008, the Sponsor requested a face-to-face meeting with the Division to discuss further the review status of their application. The face-to-face meeting was granted on August 22, 2008 and scheduled to occur on August 28, 2008.

DISCUSSION POINTS: The meeting started with the introduction of the attendees followed by the Sponsor's presentation of an overview of the clinical development program, the relevant FDA guidance, and Phase 3 study results (see attached slides). The discussion then focused on the results of CP-AI-005 study.

- The Division stated that the review was still on-going and that no final decision had been made. Nevertheless, the preliminary conclusion was that enough information had been gathered from the NDA to make a determination that it would not be worthwhile spending time and effort on a labeling review as previously discussed in the July 25, 2008 teleconference meeting. The Division agreed to this face-to-face meeting because the Sponsor requested a meeting to present study result analyses from their perspective.
- The Sponsor asked where the Division stood on the issue of one pivotal study as the basis for approval. The Division explained that more than one study is the usual standard and that situations allowing claims based on one study are rare. The Division expressed that there was already another drug product approved and available for use in the same indication. Therefore, in this case, more than one study would be expected.
- A study investigator present at the meeting (at the request of Gilead) provided reasons for needing an additional inhalational therapeutic agent for CF patients and stated that AI ought to be approved for the following reasons:
    - The median age at death for cystic fibrosis (CF) patients is 26 years and this has remained unchanged for the last 10 years.
    - As many as 50% of CF patients die before they are 26 years old.
    - Most of these deaths were in patients with *Pseudomonas aeruginosa* infection.
    - Clinically, the magnitude and consistency of lung function improvements seen with AI treatment were not seen in tobramycin inhalation solution (TOBI).
    - In the AI Expanded Access program, the experience of the 30 CF patients with severe CF disease was indicative of the benefits of AI. In this regard, the use of CFQ-R tool in patient assessments has demonstrated improved CFQ-R score, i.e. better or improved lung function for these patients.
    - Many CF centers (about 50%) in the US have now used AI. The clinicians want to use AI because of persuasive improvements in lung function they have seeen in clinical cases.
- The Sponsor further noted that TOBI is only approved in a 28-day on/off cycles. They argued that AI could complement TOBI use by patients during the off months. In this respect, AI would fill this unmet medical need, knowing that there has been no other approved option to TOBI. Of note, in study CP-AI-005, the receipt of AI versus placebo treatment by study patients was preceded by a 28-day course of TOBI.
- The Division stated that a different approach is needed during the off–month study periods.
- The Sponsor asked about the acceptability of study CP-AI-007 as a single study upon which the approval of the NDA could be based. The Division stated that study 007 also had a few design issues, including the following:
    - The pre-planned interim analysis involving sample size re-estimation (SSR) might

have unblinded the Sponsor and may have resulted in over power and over-enrollment. The Sponsor responded that Sponsor blinding was maintained by using an unblinded independent third party based on variability of CFQ-R results. The decision to increase the sample size was due to a higher than expected variance.

- There were differences in the results by age and geographic study site locations which favored treatment drug. The Sponsor showed slides of two subgroup results for CFQ-R and FEV_1 and explained that the younger age group showed more improvement because they represented a subpopulation with less chronicity of CF disease and probably with less lung compromise; this meant better lung compliance, better lung response, and therefore made the benefit to the patient more apparent. However, the overall study results were not driven by children alone because the adult populations (over 18 years old) represent 80% of the study population. In addition, the Sponsor explained further that a difference in regional effect may be due to seasonal differences at locations where patients received treament at the time of study, which was also seen in the TOBI registration trials. A similar phenomenon would be expected in CP-AI-006 trial.
- There was some concern over the validation and adequacy of the CFQ-R tool due to potential recall bias in measuring the primary endpoint in CP-AI-007 trial. The Sponsor responded that the validation of the tool was discussed with FDA.

- The Sponsor stated that they had not conducted a head-to-head trial of AI against TOBI because most CF patients in the US had been exposed to TOBI. It was difficult to find patients who were naïve to TOBI for comparison to AI. However, the Sponsor added that they had initiated a head-to-head trial in Europe, using two patient cohorts - one that was TOBI- experienced and the other that was TOBI-naïve.
- The Division stated that the CP-AI-006 trial cannot be viewed as a separate trial because it used patients from the other trials, i.e. studies CP-AI-005 and CP-AI-007.
- The issue of the placebo differences was raised for study CP-AI-005. The Division stated that the long period of time (28 days) between randomization (visit 2), rather than at baseline (visit 3), may have contributed to study results obtained. Although all patients received a course of TOBI between visit 2 and 3, it appears that there were differences in response. Therefore, the treatment groups were no longer similar at baseline (the beginning of AI/placebo treatment). The Sponsor responded that the randomization does not guarantee that there would be no imbalances, but they examined analyses that adjusted for baseline prognostic factors for the primary endpoint, and these revealed that the comparison for pooled AI versus pooled placebo and AI TID versus placebo TID remained statistically significant when adjusting for Day 0 or Day -28 FEV_1 and CFQ-R.
- The Division stated that as a general rule, cross-study comparisons, especially p-values, may not necessarily be accurate or appropriate. There were multiple differences between the two trials and furthermore, there were issues about the AI regimen effect (BID vs. TID dosing) and duration of the therapy. The Sponsor responded that the lack of distinction between the BID and TID groups for the primary endpoint in study CP-AI-005 is likely related to the lack of assay sensitivity for the endpoint with highly effective treatments. Given the unexpected magnitude of treatment effect experienced following TOBI, one could have anticipated intervention with IV or inhaled antibiotic rescue therapy in these patients given that the protocol mandated this be done in the presence of symptoms of exacerbations that could have occurred as patients lost the treatment effect following completion of the 28-day course.

After an improvement in the CFQ-R respiratory domain, a subsequent decline during an off-period could have given a physician the signal to treat with IV or inhaled antibiotics. The Sponsor believed this was a likely explanation why TID AI had more events than BID during the off-period.

- The Division stated that they would continue with the review and would make a determination regarding the action. This would be communicated to the Sponsor via an action letter on or before the PDUFA goal date. The Sponsor asked about a possible extension of the PDUFA goal date to continue further discussion of the analysis of the study results. The Division responded that they would make the determination and communicate with the Sponsor via an action letter.

DECISIONS (AGREEMENTS) REACHED:
The Division would continue with the review as planned and an action letter would be sent to the Sponsor by the PUDUFA goal date of September 16, 2008.

ATTACHMENTS/HANDOUTS:
Slides presentation

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/s/

Kathrine Laessig

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DEPARTMENT OF HEALTH & HUMAN SERVICES

Public Health Service

Food and Drug Administration
Rockville, MD 20857

NDA 50-814

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) submitted under section 505(b)(2) of the Federal Food, Drug, and Cosmetic Act for aztreonam for inhalation solution.

We also refer to the meeting between representatives of your firm and the FDA on October 2, 2008. The purpose of the meeting was to discuss the Complete Response letter issued to you on September 16, 2008.

The official minutes of that meeting are enclosed. You are responsible for notifying us of any significant differences in understanding regarding the meeting outcomes.

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

Enclosure

MEMORANDUM OF MEETING MINUTES

MEETING DATE: October 2, 2008
TIME: 10:00 AM – 11:00AM (EST)
LOCATION: White Oak Building 22, Room 1315
APPLICATION: NDA 50-814
DRUG NAME: Aztreonam for Inhalation Solution
TYPE OF MEETING: Type A

MEETING RECORDER: Kyong Hyon

FDA ATTENDEES: (FDA)
Division of Anti-Infective and Ophthalmology Products, DAIOP:

Wiley A. Chambers, MD, Acting Director
Katherine Laessig, MD, Deputy Director
John Alexander, MD, MPH, Clinical Team Leader
Menfo Imoisili, MD, MPH, Clinical Reviewer
Frederic Marsik, PhD, Clinical Microbiology Team Leader
Peter Coderre, PhD, Clinical Microbiology Reviewer
Mark Seggel, PhD, Chemistry Reviewer
Charles Bonapace, PharmD, Clinical Pharmacology Team Leader
Thamban Valappil, PhD, Statistical Team Leader
Christopher Kadoorie, PhD, Statistical Reviewer
Vinayak Pawar, PhD, Micorbiology Sterility Reviewer
Kyong Hyon, Regulatory Project Manager

EXTERNAL CONSTITUENT ATTENDEES: (Sponsor)
Gilead Sciences, Inc.:

Norbert Bischofberger, PhD, Executive Vice President, Research and Development and Chief Scientific Officer
Gregg Alton, JD, Senior Vice President and General Counsel
Mike Wulfsohn, MD, PhD, Vice President Biometrics
(b) (4)

BACKGROUND: On September 19, 2008, the Sponsor requested a face-to-face meeting with the Division to discuss the complete response (CR) letter, dated September 16, 2008 and the steps the Sponsor needs to take before the Aztreonam for Inhalation (AI) application can be approved. The face-to-face meeting was granted on September 22, 2008 and scheduled to occur on October 2, 2008.

DISCUSSION POINTS: The meeting started with the introduction of the attendees followed by the Sponsor's few remarks regarding what they wished to accomplish from this meeting and why. The Sponsor stated that the Microbiology Sterility deficiencies listed in the CR letter were straightforward and clear and therefore they wanted to focus on the clinical aspects in this meeting.

- The Sponsor requested further elaboration on the Division's interpretation of the imbalance between the AI treatment arms and placebo arms of study CP-AI-005 results. The Division responded that the primary endpoint results were analyzed by the Sponsor such that pooled AI regimens were compared to pooled placebo subgroup results. But there was a strong regimen effect in the study. For example, placebo BID arm performed better than the AI TID arm. Since the placebo groups performed differently, it would be inappropriate to pool the data as was done.
- The Sponsor stated that they reviewed a previously submitted SPA for study 005 where each treatment arm (AI BID or AI TID) was to be compared to the pooled placebo group. The hypothesis was, however, different from what was actually demonstrated due to the results seen in the placebo arms. The Sponsor stated that they believed it was problematic not to follow the protocol and statistical analysis plan. The Division responded that sometimes it may not be appropriate to follow the statistical analysis plan, such as in this situation.
- The Sponsor stated that, as they understood the rule, if the study achieved its pre-defined primary endpoint, then, it should have been considered a successful study. In addition, they believed that in the same study (005), all secondary measures showed quantifiable and solid results that were statistically strong. Among these secondary endpoints, they believed that FEV_1 outcomes showed strong evidence of effect. The Division responded that FEV_1 data on their own would not be clinically meaningful unless they were in association with other clinical benefits that were meaningful to the patient. The Sponsor suggested that FEV_1 as an endpoint should be reconsidered as an outcome that is clear and meaningful and should serve as confirmative evidence of effect in study 005. The Division did not agree. The Sponsor then asked if the data derived from the use of a patient reported outcome (PRO) tool (i.e., CFQ-R) used for patient assessment in one of the secondary endpoints in study 005 could not serve to provide clinically meaningful evidence to support FEV_1 results in the same study. The Division responded that unless the primary endpoint was met, any consideration of secondary endpoint data to support FEV_1 results would not be appropriate or meaningful. The Division reiterated that the issue of study 005 is the imbalance of results between placebo and treatment groups and this trial alone could not answer the reason for this imbalance. There was larger difference among the placebo groups (placebo BID and placebo TID) than the difference among the treatment groups, AI BID and AI TID. Therefore, there is need for another study.
- The Phase 2 study 003 evaluated changes in FEV_1 as a primary endpoint, but was not able to demonstrate a statistically significant treatment difference between the AI (75 mg or 225 mg) and the placebo groups. The follow-on study, CP-AI-006 was a roll over study using patients from studies 005 and 007. Therefore, conclusive statements on the regimen effect or efficacy could not be made. The Division further pointed out that the issues of study 005 might be: 1) the issue of timing of randomization relative to the actual start of the AI/placebo dosing of study patients. There might have been a post-randomization effect both on the primary and secondary endpoints, and which therefore rendered the data uninterpretable; 2) in terms of regimen effect, the BID regimen demonstrated better response than the TID. This was clinically counterintuitive. The Sponsor stated that the third possibility might be that the primary endpoint might not have been a good choice for this study.
- The Sponsor queried the Division's statistical concerns over study CP-AI-007 results. The Sponsor expressed that the study demonstrated a statistically significant difference in FEV_1 results. The Division stated that they had reservations about the robustness of the results although the study met the primary endpoint. The Division's other concern was the reliance of the study on a primary endpoint change in the respiratory domain score of the CFQ-R which limited the results due to biases resulting from the 14-day recall period. It was felt that it would be hard for patients to remember what happened 14 days earlier. The current PRO

guidance emphasizes capturing a patient's current state, rather than asking them to compare their current state to an earlier period or recalling an earlier period.

- The Sponsor queried also if the reason for the inadequacy of study 007 would be due to its inability to show clinical efficacy. The Division responded that the overall results were acceptable, but could not be considered robust. The Sponsor asked if the Division's concern was about the characterization of the study data as robust or with the use of the CFQ-R for primary endpoint assessment of study patients. The Division's stated that the reservation had to do with basing a claim on one study alone, particularly when the primary endpoint evidence provided from the study was derived from the use of this less than adequate PRO tool.
- The Division believed that studies 005 and 007 should have been complimentary to one another with respect to the endpoints such that the results of study 005 would corroborate those of study 007 and vice versa since the primary endpoint of each study was evaluated as a secondary endpoint in the other study.
- The Sponsor asked what the next study should be. The Division recommended one option that study 005 could be repeated using a revised design to correct the problems with randomization and to employ a PRO tool that uses the recent draft Guidance on PRO tools as reference. Furthermore, a 150 mg BID dosing regimen should be evaluated given the previous result indicating that BID dosing regimen was better than TID regimen and no clear evidence of a dose response from previous studies.

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/s/

Kathrine Laessig
10/16/2008 05:14:23 PM

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/s/

Tejashri Purohit-Sheth

7/14/2008 08:55:41 AM

DEPARTMENT OF HEALTH & HUMAN SERVICES

Public Health Service

Food and Drug Administration
Rockville, MD 20857

NDA 50-814

DISCIPLINE REVIEW LETTER

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

We are providing these comments to you before we complete our review of the entire application to give you preliminary notice of issues that we have identified. In conformance with the prescription drug user fee reauthorization agreements, these comments do not reflect a final decision on the information reviewed and should not be construed to do so. These comments are preliminary and subject to change as we finalize our review of your application. In addition, we may identify other information that must be provided before we can approve this application. If you respond to these issues during this review cycle, depending on the timing of your response, and in conformance with the user fee reauthorization agreements, we may not be able to consider your response before we take an action on your application during this review cycle.

We also refer to your submission dated May 23, 2008 which contains a new proposed labeling text for the diluent ampules for your product.

The Division finds the Mock-up B, in which the trade name Cayston is used on the diluent labeling, acceptable. However, we suggest that the remaining wordings read as follows:

Sodium Chloride 0.17%
Cayston – 1mL Diluent
Inhalation use only
Gilead Sciences

The suggested arrangement attempts to distinguish your company name (Gilead Sciences) from the rest of the content by italicizing it. However, you may wish to highlight the name some other way preferable to you.

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

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/s/

Kathrine Laessig
6/18/2008 10:56:29 AM

DEPARTMENT OF HEALTH & HUMAN SERVICES

Public Health Service

Food and Drug Administration
Rockville, MD 20857

NDA 50-814

DISCIPLINE REVIEW LETTER

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

We are providing these comments to you before we complete our review of the entire application to give you preliminary notice of issues that we have identified. In conformance with the prescription drug user fee reauthorization agreements, these comments do not reflect a final decision on the information reviewed and should not be construed to do so. These comments are preliminary and subject to change as we finalize our review of your application. In addition, we may identify other information that must be provided before we can approve this application. If you respond to these issues during this review cycle, depending on the timing of your response, and in conformance with the user fee reauthorization agreements, we may not be able to consider your response before we take an action on your application during this review cycle.

We also refer to your submission dated July 18, 2007 to your IND which contains a trade name appeal.

The Division of Medication Error Prevention (DMEP) is reversing its previous objection to the name Cayston. Cayston will only be distributed by specialty pharmacies thereby decreasing the likelihood that the drug would be dispensed for Capoten. Therefore, we have no objections to the use of the proprietary name Cayston for this product. If any of the proposed product characteristics are altered prior to approval of the product, the Division of Medication Error Prevention will rescind this Risk Assessment finding, and recommend that the name be resubmitted for review. Please note that the DMEP will re-evaluate your proposed proprietary name just prior to the approval of your NDA.

In addition, please note that the established name should be 'aztreonam for inhalation solution'.

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

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/s/

Kathrine Laessig
5/21/2008 10:28:03 AM

DEPARTMENT OF HEALTH & HUMAN SERVICES

Public Health Service

Food and Drug Administration
Rockville, MD 20857

NDA 50-814 **DISCIPLINE REVIEW LETTER**

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

We are providing these comments to you before we complete our review of the entire application to give you preliminary notice of issues that we have identified. In conformance with the prescription drug user fee reauthorization agreements, these comments do not reflect a final decision on the information reviewed and should not be construed to do so. These comments are preliminary and subject to change as we finalize our review of your application. In addition, we may identify other information that must be provided before we can approve this application. If you respond to these issues during this review cycle, depending on the timing of your response, and in conformance with the user fee reauthorization agreements, we may not be able to consider your response before we take an action on your application during this review cycle.

We also refer to your submission dated April 18, 2008 which contains two questions for the Division. The original questions are reproduced in bold below, followed by Division's response.

Question 1: Gilead requests that the Division reconsider the use of "lysine" in the established name of the drug product. Gilead proposes an established name of 'aztreonam lysine for inhalation solution'. *Does the Division concur?*

Division Response: No, the Division does not concur. It is our current understanding that the basis for your request to keep "lysine" in the established name of aztreonam for inhalation is to distinguish it from the IV formulation of aztreonam which contains arginine as a buffer. Our disagreement is based on the following:

- We consider the evidence in the literature you cited to support your proposal (or request) inadequate.
- The drug label is a reasonable alternative place in which, by proper wording, the concern can be highlighted. That way, the issue can be brought to the attention of healthcare providers, patients, or the general public, should the product be approved.
- The proposal to use "lysine" in the established name of the drug product would be inconsistent with traditional nomenclature of such products. Also, keep in mind that the form of the drug substance in the established name and the declared strength must match. In this case, the strength of the drug product is expressed as 75mg aztreonam, not as a lysine salt or salts of aztreonam. In addition, as formulated, the product consists of lysine and aztreonam in a ratio of (b) (4) The identities of the resulting salts are not defined and product strength cannot be adequately expressed in terms of these salts.

Question 2: (b) (4)

Division Response: No, we do not recommend (b) (4). We recommend the following:

- "Sodium Chloride 0.17%, 1 mL" and "Diluent for Aztreonam for Inhalation" appear on the same side of the ampule.
- "Sodium Chloride 0.17%, 1 mL" should be the most prominent information on the ampule.
- If feasible, the phrase "Diluent for" should be more prominent than the phrase “Aztreonam for Inhalation” (see example above with "Aztreonam for Inhalation" in a smaller font size than "Diluent for").
- Your company’s name should appear on the ampule as well. However, it should not appear opposite of any other embossing because this will make the embossing difficult to read.

Additional Information Request:

Please send samples of the drug product vial with closure and tear-off seal and the diluent ampule.

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

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/s/

Kathrine Laessig
5/14/2008 09:02:16 AM

DEPARTMENT OF HEALTH & HUMAN SERVICES

Public Health Service

Food and Drug Administration
Rockville, MD 20857

NDA 50-814

DISCIPLINE REVIEW LETTER

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

We are providing these comments to you before we complete our review of the entire application to give you preliminary notice of issues that we have identified. In conformance with the prescription drug user fee reauthorization agreements, these comments do not reflect a final decision on the information reviewed and should not be construed to do so. These comments are preliminary and subject to change as we finalize our review of your application. In addition, we may identify other information that must be provided before we can approve this application. If you respond to these issues during this review cycle, depending on the timing of your response, and in conformance with the user fee reauthorization agreements, we may not be able to consider your response before we take an action on your application during this review cycle.

CHEMISTRY:

1. Drug product accelerated stability studies were done at 25 °C and not at 25 °C/60% RH. If this is not a typographical error, explain why humidity was not included and discuss the potential impact of humidity on the stability outcome.
2. The NDA contains two separate 3.2.P sections for diluent made at (b) (4) and diluent made at (b) (4) Please submit a summary table outlining the differences between the two submissions. If the two diluent submissions are identical, please state that they are identical.
3. The Pharmaceutical Development section in Module 3 (page 45) states that the 510(k) license number and additional characterization data will be included in the NDA for aztreonam lysine for inhalation prior to the final NDA. We did not locate this information. Please indicate where this information is located or resubmit this information.
4. Please indicate if PARI had filed a 510(k) application with CDRH for the eFlow Device Modification. If the device has received 510(k) clearance, please provide the 510(k) number and the date of the clearance letter. If clearance has not been received, please provide the number and the date of submission.
5. Please note that the correct established name for the drug product is 'aztreonam for inhalation solution'.
6. Before we can determine the appropriate nomenclature for the diluent, please indicate if the diluent complies with the USP monograph for Sodium Chloride Inhalation Solution.

PROPOSED LABELING:

Highlights

- Refer to http://www.fda.gov/cder/regulatory/physLabel/default htm for fictitious examples of labeling in the new format.
    - After Initial US Approval, delete 2008 and replace with 1986. Initial U.S. Approval is the four-digit year in which the FDA initially approved a new molecular entity or new combination of active ingredients. [See 21 CFR 201.57(a)(3)]

- Type size for all labeling information, headings, and subheadings must be a minimum of 8 points, except for trade labeling. This also applies to Contents and the FPI. [See 21 CFR 201.57(d)(6) and Implementation Guidance]
- The Highlights must be limited in length to one-half page, in 8 point type, two-column format. [See 21 CFR 201.57 (d)(8)]
- Insert one line of white space between each major heading in Highlights.
- The following statement regarding antibiotic resistance should follow after the initial US approval date. [See 21 CFR 201.24]: "To reduce the development of drug-resistant bacteria and maintain the effectiveness of TRADENAME and other antibacterial drugs, TRADENAME should be used only to treat or prevent infections that are proven or strongly suspected to be caused by bacteria".
- All text of new paragraphs should consistently be either left justified or indented throughout the labeling.
- After "See 17 for PATIENT COUNSELING INFORMATION", delete "and FDA approved patient labeling". [See 21 CFR 201.57(a)(14)]

Full Prescribing Information: Contents

- The Contents subsection headings must be indented. [See 21 CFR 201.57(b)]
- Create subsection headings that identify the content. Avoid using the word General, Other, or Miscellaneous as the title for a subsection heading.

Full Prescribing Information

- Other than the required bolding [See 21 CFR 201.57(d)(1), d)(5), and (d)(10)], use bold print sparingly. Use another method for emphasis such as italics or underline.
- Regarding references, are these references necessary? Include only references that are important to the prescriber. [See 21 CFR 201.57(c)(16)]
- Refer to the Institute of Safe Medication Practices' website (http://www.ismp.org/Tools/abbreviationslist.pdf) for a list of error-prone abbreviations, symbols, and dose designations.

If you have any questions, call Kyong Hyon, Regulatory Project Manager, at 301-796-0734.

Sincerely,

{See appended electronic signature page}

Wiley A. Chambers, M.D.
Acting Director
Division of Anti-Infective and Ophthalmology Products
Office of Antimicrobial Products
Center for Drug Evaluation and Research

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/s/

Wiley Chambers

3/27/2008 11:54:18 AM

DEPARTMENT OF HEALTH & HUMAN SERVICES

Public Health Service

Food and Drug Administration
Rockville, MD 20857

NDA 50-814

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) submitted pursuant to section 505(b)(2) of the Federal Food, Drug, and Cosmetic Act, for Cayston (aztreonam for inhalation solution).

We also refer to the teleconference between representatives of your firm and the FDA on February 15, 2008. The purpose of the meeting was to discuss the Division's decision of standard review classification for NDA 50-814.

The official minutes of that discussion are enclosed. You are responsible for notifying us of any significant differences in understanding regarding the teleconference outcomes.

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

Enclosure

MEMORANDUM OF TELECON

DATE: February 15, 2008

APPLICATION NUMBER: NDA 50-814

DRUG: Cayston (aztreonam lysine for inhalation)

BETWEEN:

Name: Representatives from Gilead Sciences, Inc

Bruce Montgomery, MD – Senior Vice President, Respiratory Therapeutics
Melissa Yeager, JD – Vice President, Regulatory Affairs
Marissa Braff, PhD – Research Scientist, Microbiology
Jennifer Stephens – Director, Regulatory Affairs
Lauren Cutler – Senior Regulatory Affairs Associate
Marissa Braff, PhD, Clinical Research Scientist, Microbiology
Jim Whitmore, PhD, Senior Director, Biometrics

Phone: 1-866-417-8608, Pass code: *4645783*

AND

Name: Representatives from Division of Anti-Infective and Ophthalmology Products (DAIOP) HFD-520

Wiley A, Chambers, MD, Acting Director
Katherine Laessig, MD, Deputy Director
John Alexander, MD, MPH, Clinical Team Leader
Menfo Imoisili, MD, MPH, Clinical Reviewer
Norman Schmuff, PhD, Branch Chief, ONDQA, DPA II
Mark Seggle, PhD, Chemistry Reviewer, ONDQA, DPA II
Kyong Hyon, Regulatory Project Manager

BACKGROUND: This teleconference was requested by the Sponsor on January 17, 2008 to dispute Division's decision of granting a standard review classification for this NDA on January 10, 2008.

MEETING OBJECTIVES: The overall objective of the requested teleconference was to discuss the rationale for standard review classification.

DISCUSSION POINTS: The following is a summary of the minutes of the teleconference held on February 15, 2008. The Sponsor submitted their rationale for a priority review classification for this NDA and a list of discussion items in their meeting request. The Sponsor's discussion items are in bold followed by the points discussed during the teleconference. The meeting started with a round of individual attendee self-introduction. After everyone introduced themselves, the meeting proceeded. The Sponsor requested not to present the rationale for their request for reclassification because it was included in the meeting request. The Division agreed that the written rationale was thorough and well understood. Then the meeting continued as follows:

Discussion Item 1:

Please provide the rationale for the determination that AI is not eligible for priority review.

Discussion at the February 15, 2008 teleconference: The Division stated that they granted a standard review for this NDA per policy and procedure MAPP. The rationale for a standard review classification can be explained more clearly after discussion item 2.

Discussion Item 2:

Please delineate the difference in criteria for fast track versus priority review.

Discussion at the February 15, 2008 teleconference: The Division explained that while the fast track designation is for products that are intended to treat serious or life-threatening diseases and that have the potential to address unmet medical needs, the priority reviews are granted based on results from a clinical study or studies that demonstrate how the product actually fulfills an unmet medical need. The Division stated that since the Sponsor's study did not provide a head-to head comparison that demonstrated superiority of AI in either efficacy or safety over the existing product. The Sponsor failed to provide data from a head to head statistically valid comparison with the existing product, a priority review was not warranted. The Division also stated that the argument in the meeting request regarding a potential long term effect of toxicity of tobramycin and on multiple antibiotic-resistant *Pseudomonas aeruginosa* was a theoretically based argument and therefore, could not serve as a basis for granting a priority review classification. The Sponsor acknowledged that they did not have a head-to head comparison study. They also agreed that a standard review classification was applicable and appropriate in this case. The remaining meeting time was spent with the questions that the Sponsor had regarding other review issues as listed below:

Additional Questions and Discussions:

1. The Sponsor asked what they should expect from now till the PDUFA goal date of September 16, 2008 in terms of review process and the questions from the Division.

Discussion: The Division responded that the review is ongoing at this time and will contact the Sponsor as questions arise.

2. The Sponsor asked when the review of a tradename appeal would be ready.

Discussion: The Division stated that they will check with DMETS regarding review status and will provide it to the Sponsor. The Division recommended that the Sponsor have an alternate name ready because history suggested that DMETS usually does not overturn their decision of the initial review of trade name request.

Post meeting Note: The Division contacted DMETS and was informed that the tradename review is still ongoing and they will provide their recommendation as soon as possible.

3. The Sponsor stated that the contract manufacturer, (b) (4) for AI production was issued a warning letter concerning compliance issues and asked how this will impact review process. They asked if providing another facility with three months of stability data would delay the review process.

Discussion: The Division encouraged the Sponsor to submit the information on alternate site with at least 3 months stability data, facility details, including CFN number as soon as possible formally to the NDA. However, the Division could not guarantee that they would be able to review this information during this cycle. The Division also informed the Sponsor that an alternate site would be a subject to inspection and it would be the responsibility of the Sponsor to have this new site ready for an inspection. The Sponsor responded that the new site would be in the jurisdictional region of the Los Angeles District Office. The Sponsor noted that this facility manufactured (b) (4)® and that they were experienced with FDA inspection process. The Division stated that the new site should be immediately ready for an inspection for AI. The Sponsor responded that the site will be ready for an inspection within a week.

4. The Sponsor asked if this NDA would be considered for an advisory committee (AC) meeting.

Discussion: The Division stated that under FDAAA, New Molecular Entities(NMEs) usually go to AC meetings; however AI is not a NME. With regards to the current NDA, a need to seek input from an AC meeting would depend on the Division's findings during the review process and if the Division believes that such outside assistance might be helpful in reaching a final decision about the product.

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/s/

Kathrine Laessig
3/13/2008 05:08:50 PM

DEPARTMENT OF HEALTH & HUMAN SERVICES

Public Health Service

Food and Drug Administration
Rockville, MD 20857

FILING COMMUNICATION

NDA 50-814

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 Cayston (aztreonam lysine for inhalation).

We also refer to your submissions dated July 14, 2006, August 9, 2007, and September 13, 2007.

We have completed our filing review and have determined that your application is sufficiently complete to permit a substantive review. Therefore, this application is considered filed 60 days after the date we received your application in accordance with 21 CFR 314.101(a). The review classification for this application is standard. Therefore, the user fee goal date is September 16, 2008.

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

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/s/

Kathrine Laessig

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DEPARTMENT OF HEALTH & HUMAN SERVICES

Public Health Service

Food and Drug Administration
Rockville, MD 20857

NDA 50-814

NDA ACKNOWLEDGMENT

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

Dear Ms. Yeager:

We have received your new drug application (NDA) submitted pursuant to section 505(b)(2) of the Federal Food, Drug, and Cosmetic Act for the following:

Name of Drug Product: Cayston (aztreonam lysine for inhalation)

Date of Application: November 16, 2007

Date of Receipt: November 16, 2007

Our Reference Number: NDA 50-814

Unless we notify you within 60 days of the receipt date that the application is not sufficiently complete to permit a substantive review, we will file the application on January 15, 2008 in accordance with 21 CFR 314.101(a).

If you have not already done so, promptly submit the 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. Failure to submit the content of labeling in SPL format may result in a refusal-to-file action under 21 CFR 314.101(d)(3). The content of labeling must be in the Prescribing Information (physician labeling rule) format.

The NDA number provided above be cited at the top of the first page of all submissions to this application. Send all submissions, electronic or paper, including those sent by overnight mail or courier, to the following address:

Food and Drug Administration
Center for Drug Evaluation and Research
Division of Anti-Infective and Ophthalmology Products
5901-B Ammendale Road
Beltsville, MD 20705-1266

All regulatory documents submitted in paper should be three-hole punched on the left side of the page and bound. The left margin should be at least three-fourths of an inch to assure text is not obscured in the fastened area. Standard paper size (8-1/2 by 11 inches) should be used; however, it may occasionally be necessary to use individual pages larger than standard paper size. Non-standard, large pages should be folded and mounted to allow the page to be opened for review without disassembling the jacket and refolded without damage when the volume is shelved. Shipping unbound documents may result in the loss of portions of the submission or an unnecessary delay in processing which could have an adverse impact on the review of the submission. For additional information, please see http:www.fda.gov/cder/ddms/binders.htm.

If you have any questions, call Kyong Hyon, Regulatory Project Manager, at (301) 796-0734.

Sincerely,

{See appended electronic signature page}

Frances V. LeSane
Chief, Project Management Staff
Division of Anti-Infective and Ophthalmology Products
Office of Antimicrobial Products
Center for Drug Evaluation and Research

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/s/

Frances LeSane

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