CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

050814Orig1s000

CHEMISTRY REVIEW(S)

NDA 50-814

CAYSTON™
(aztreonam for inhalation solution)

Gilead Sciences, Inc.

Mark R. Seggel
ONDQA
Division of Pre-Marketing Assessment II

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Chemistry Review Data Sheet

1. NDA 50-814

2. REVIEW #: 2

3. REVIEW DATE: 05-FEB-2010

4. REVIEWER: Mark R. Seggel

5. PREVIOUS DOCUMENTS:

Previous Documents Reviewed	Document Date	e-CTD Sequence
Original (Quality)	13-SEP-2007	0002
Original (Final portion plus additional CMC)	16-NOV-2007	0003
Amendment (add San Dimas product facility)	14-MAR-2008	0006
Amendment (Response to IQA comments; Nomenclature)	18-APR-2008	0008
Amendment (CMC update)	09-MAY-2008	0010
Amendment (CMC update; San Dimas stab.)	06-JUN-2008	0013
Amendment (Response)	03-JUL-2008	0015
Amendment (Response)	25-JUL-2008	0016
Amendment (Response)	30-JUL-2008	0017
Amendment (Revised documentation per 0017)	11-AUG-2008	0019
Amendment (Gilead request)	13-AUG-2008	0020

6. SUBMISSION(S) BEING REVIEWED:

Submissions Reviewed (Labeling)	Document Date	e-CTD Sequence
Amendment	16-NOV-2007	0003
Amendment	14-MAR-2008	0006
Amendment	06-JUN-2008	0013
Amendment	27-JUN-2008	0014
Amendment	26-AUG-2008	0022
Amendment	06-OCT-2008	0028
Amendment	12-NOV-2008	0030
Resubmission	11-AUG-2009	0040
Amendment	10-NOV-2009	0047
Amendment	21-JAN-2010	0050

Submissions Reviewed (CMC)	Document Date	e-CTD Sequence
Amendment (Updated list of facilities and contacts)	26-AUG-2009	0042
Amendment (New responsibility for facility; update of device status in Section P.2.)	10-NOV-2009	0047
Amendment (Changes in Section P.2 highlighted)	13-NOV-2009	0048

Chemistry Review Data Sheet

7. NAME & ADDRESS OF APPLICANT:

Name:	Gilead Sciences, Inc.
Address:	2025 1st Avenue, Suite 800 Seattle, WA 98121
Representative(s):	Melissa A. Yeager, J.D. Vice President, Regulatory Affairs
Telephone:	206-792-3015

8. DRUG PRODUCT NAME/CODE/TYPE:
   a) Proprietary Name: Cayston™
   b) Non-Proprietary Name (USAN): Aztreonam
   c) Code Name/#: GS-9268
   d) CAS Registry Number: 827611-49-4
   e) Chem. Type/Submission Priority:
      i. Chem. Type: 3
      ii. Submission Priority: S

9. LEGAL BASIS FOR SUBMISSION: 505(b)(2) (RLD: NDA 50-580, Azactam, BMS)

10. PHARMACOL. CATEGORY: Synthetic, monocyclic beta-lactam antibacterial.

11. DOSAGE FORM: For Inhalation Solution (Diluent provided)

12. STRENGTH/POTENCY: 75 mg Aztreonam / Vial; diluted with 1 mL sodium chloride, 0.17% w/v Diluent.

13. ROUTE OF ADMINISTRATION: Oral Inhalation

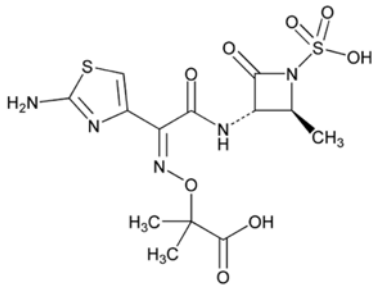
14. Rx/OTC DISPENSED: _X_Rx ___OTC

15. SPOTS (SPECIAL PRODUCTS ON-LINE TRACKING SYSTEM)
    _____SPOTS product – Form Completed
    ___X__Not a SPOTS product

16. CHEMICAL NAME, STRUCTURAL FORMULA, MOLECULAR FORMULA, MOLECULAR WEIGHT

Aztreonam: USAN [1983] (and USP)
CAS: 78110-38-0
$C_{13}H_{17}N_5O_8S_2$ 435.43

(1) Propanoic acid, 2-[[[1-(2-amino-4-thiazolyl)-2-[(2-methyl-4-oxo-1-sulfo-3-azetidinyl)amino]-2-oxoethylidene]amino]oxy]-2-methyl-, [2S-[2α,3β(Z)]]-;
(2) (Z)-2-[[[(2-Amino-4-thiazolyl)[(2S,3S)-2-methyl-4-oxo-1-sulfo-3-azetidinyl]carbamoyl]-methylene]amino]oxy]-2-methylpropionic acid.



17. RELATED/SUPPORTING DOCUMENTS

A. DMFs:

DMF #	TYPE	HOLDER	ITEM REFERENCED	CODE[1]	STATUS[2]	DATE REVIEW COMPLETED	COMMENTS
[redacted]			(b) (4)	3	Adequate	11-APR-2008	
				3	Adequate	13-OCT-2006 06-APR-2006 30-JAN-2003 24-MAY-1999	
							for PQM review
				4	N/A		See Review Section P.4.1
				3	Adequate	01-FEB-2000	
				4	N/A		
				1	Adequate	07-AUG-2008	

[1] Action codes for DMF Table:
1 – DMF Reviewed.
Other codes indicate why the DMF was not reviewed, as follows:
2 –Type 1 DMF
3 – Reviewed previously and no revision since last review
4 – Sufficient information in application
5 – Authority to reference not granted
6 – DMF not available
7 – Other (explain under "Comments")

[2] Adequate, Inadequate, or N/A (There is enough data in the application, therefore the DMF did not need to be reviewed)

B. Other Documents:

APPLICATION NUMBER	DESCRIPTION
IND 64,402	Commercial IND for 'Aztreonam for inhalation', 16-APR-2003 Salus Pharma / Corus Pharma / Gilead

18. STATUS

CONSULTS/ CMC RELATED REVIEWS	RECOMMENDATION	DATE	REVIEWER
Biometrics	-		
EES	Acceptable Acceptable	02-JUL-2008 02-FEB-2010	HFD-322
Pharm/Tox	Impurity qualification study conduct adequate (but interpretation somewhat inaccurate)	16-JUL-2008	A. Ellis, HFD-520
Biopharm	-		
LNC	Informal discussions	Various	Various
Methods Validation	-		
DMEPA	Proprietary name, Cayston, acceptable Revised container/carton and package insert	08-JAN-2010 *Pending*	D. Hamilton-Stokes
EA	Categorical exclusion acceptable	15-JUL-2008	M. Seggel
Microbiology	Approval recommendation	09-NOV-2009	V. Pawar
CDRH	*Final CDRH action on PARI eFlow device pending action on NDA*	-	
ONDQA Pulmonary	Informal discussions	Various	P. Peri, ONDQA

The Chemistry Review for NDA 50-814

The Executive Summary

I. Recommendations

A. Recommendation and Conclusion on Approvability

This New Drug Application for 'Aztreonam for Inhalation Solution', as amended, is recommended for approval from the chemist's perspective of the chemistry, manufacturing and controls.

B. Recommendation on Phase 4 (Post-Marketing) Commitments, Agreements, and/or Risk Management Steps, if Approvable

None

II. Summary of Chemistry Assessments

A. Description of the Drug Product(s) and Drug Substance(s)

Cayston® (aztreonam for inhalation solution) is a sterile, lyophilized powder containing 75 mg of aztreonam, a synthetic, monocyclic beta-lactam (monobactam) antibacterial with activity against *Pseudomonas aeruginosa*. Aztreonam is the active ingredient in Bristol-Myers-Squibb's Azactam®, an intravenous product available since 1986 (NDA 50-580).

Each vial of 'aztreonam for inhalation solution' contains a solid mixture of aztreonam (75 mg) and L-lysine, (b) (4), respectively. L-Lysine, a basic amino acid, (b) (4) No other excipients are present. Note that Azactam contains arginine, which is reportedly less well tolerated in the lung. Reconstitution of the drug product with 1-mL of sodium chloride 0.17% w/v results in an inhalation solution with an osmolality not exceeding 550 mOsm/kg and a pH of 4.5-6.0.

The manufacturing process is relatively straightforward - (b) (4) Finished product quality is further assured by tests for assay, content uniformity, solution pH, moisture content, impurities, sterility and endotoxins. Known degradants include (b) (4) and two (b) (4) The formation of impurities is controlled by protection from light and storage at 2-8°C. The container closure system consists of a 2-mL USP Type I amber glass vial with a (b) (4) rubber stopper and an aluminum overseal cap.

Diluent for 'aztreonam for inhalation solution' consists of 1-mL sterile sodium chloride 0.17% w/v packaged in low density polyethylene [redacted] (b) (4) ampules. Shelf-life is limited by moisture loss.

Aztreonam, the active ingredient in 'aztreonam for inhalation solution', has been well characterized and is described in 'Analytical Profiles of Drug Substances'. It is also the subject of a USP monograph. The drug substance used in the manufacture of 'aztreonam for inhalation solution' is supplied by [redacted] (b) (4) and is described in DMF [redacted] (b) (4) It differs from the material described in the current USP monograph in that it contains [redacted] (b) (4) water ([redacted] (b) (4)

The aqueous solubility of aztreonam increases as the solution pH increases due to ionization of the sulfonyl and carboxyl groups. At pH values above 4.2, solubility exceeds 75 mg/mL. It has a partition coefficient (logP) -0.66.

B. Description of How the Drug Product is Intended to be Used

The drug product is indicated for the treatment of cystic fibrosis patients (CF) with *Pseudomonas aeruginosa*. One dose (75 mg aztreonam diluted with 1 mL sodium chloride, 0.17% w/v diluent) is to be administered three times a day for 28 days. The inhalation solution must be administered with the PARI eFlow nebulizer configuration specified for Cayston [Altera Nebulizer System; most recently 510(k) K093316 (a new 510(k) apparently will need to be issued by CDRH)].

The drug product is supplied in a carton containing a 28-day supply of vials of lyophilized aztreonam for inhalation (84 vials) and an equal number of ampules of the saline diluent, plus four extras in case of spillage (88 ampules). The carton is further broken down into two 14-day carton inserts. For long-term storage, aztreonam for inhalation solution should refrigerated (2-8°C). However, once dispensed to patients, the product may be stored at 25°C for up to 28 days. A 24-month expiration dating period has been established for aztreonam vials.

[redacted] (b) (4)

C. Basis for Approvability or Not-Approval Recommendation

From the chemistry, manufacturing and controls perspective the relevant requirements of 21 CFR 314.50 and, specifically, paragraphs 314.50(d)(1)(i), (ii) and (iii) are

satisfied by Gilead in this amended new drug application. Evidence for sterility assurance was evaluated by OPS/NDMS and found adequate.

The manufacture of the drug substance, as documented in (b) (4) DMF (b) (4) (as amended), is adequately controlled. The specification necessary to ensure the identity, strength, quality, and purity of the drug substance and the bioavailability of the drug product made from the substance is adequate.

Likewise, the manufacture of the aztreonam drug product and diluent are adequately controlled. The specifications necessary to ensure the identity, strength, quality, purity, potency, and bioavailability of the drug product and diluent are, as amended, adequate. While there is limited manufacturing history (and consequently limited release data), the proposed acceptance criteria for impurities and degradation products in aztreonam for inhalation solution appeared to be rather 'loose'. In addition, the applicant's original analysis of impurity qualification data was based on an assumed exposure ten times that generally used by CDER pharm/tox reviewers in calculating total deposited dose. (It appears that the applicant's analysis was based on total systemic exposure rather than dose deposited in lung.) The applicant has recalculated the qualified levels, and has reduced the limit for the (b) (4) Gilead has proposed re-evaluating the release and shelf-life limits for individual impurities and total impurities after data from twenty additional commercial batches are obtained. Revisions will be submitted via an Annual Report. Based on the toxicity data and the absence of any special concerns about the impurities (e.g., no structural alerts; identity as metabolite), the revised specification and commitment to re-evaluate the impurity limits are acceptable. The stability of the drug product has been adequately characterized. Post-approval stability studies will provide additional assurance that the drug product and diluent continue to meet the established specification, and support the established expiration dating periods.

The compatibility of the drug product with the eFlow nebulizer and its performance characteristics (emitted dose, particle size distribution, plume geometry) were thoroughly evaluated.

Verification of the analytical procedures by one or more FDA laboratories is not considered necessary at this time given the relatively straightforward methodology employed (e.g., HPLC).

All drug substance and drug product manufacturing and test facilities were found to have acceptable cGMP status based on inspection or profile. An overall Acceptable recommendation was made by the Office of Compliance on 02-FEB-2010 (see EES).

A categorical exclusion from the requirement for the preparation of an environmental assessment (EA) is claimed in accordance with 21 CFR 25.15(d) and 21 CFR 25.31(b), and is acceptable based on the EIC (<1 ppb).

Throughout the original application the drug product was referred to as 'aztreonam lysine for inhalation' ('AI' or 'AZLI'). However, the dosage form is more correctly a lyophilized powder "for inhalation solution". Furthermore, the USAN name 'aztreonam lysine' refers specifically to the 1:1 salt. The current drug product, with a 1:1.9 ratio of aztreonam to lysine, would appear to contain a mixture of undefined salts. Finally, the strength of the product, 75 mg, is expressed in terms of the free acid. The established name has been revised accordingly.

Cayston®, the proposed proprietary name, has been found acceptable by the Division of Medication Error Prevention (DMEP). They have also made other recommendations regarding the container labels, carton labeling, and package and patient inserts. From the CMC perspective, the revised package insert, container labels and cartons accurately reflect the information documented in the NDA.

III. Administrative

A. Reviewer's Signature

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B. Endorsement Block

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C. CC Block

{see darrts}

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

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

/s/

MARK R SEGGEL
02/12/2010

STEPHEN P MILLER
02/12/2010

NDA 50-814

CAYSTON™
(aztreonam for inhalation solution)

Gilead Sciences, Inc.

Mark R. Seggel
ONDQA
Division of Pre-Marketing Assessment II

Table of Contents

Chemistry Review Data Sheet

1. NDA 50-814

2. REVIEW #: 1

3. REVIEW DATE: 18-AUG-2008

4. REVIEWER: Mark R. Seggel

5. PREVIOUS DOCUMENTS:

Previous Documents	Document Date
Not applicable	

6. SUBMISSION(S) BEING REVIEWED:

Note: This application was submitted as a rolling submission. The final portion was submitted November 16, 2007. The PDUFA goal is September 16, 2008. It is in the e-CTD format.

Submission(s) Reviewed	Document Date	e-CTD Sequence
Original (Quality)	13-SEP-2007	0002
Original (Final portion plus additional CMC)	16-NOV-2007	0003
Amendment (add San Dimas product facility)	14-MAR-2008	0006
Amendment (Response to IQA comments; Nomenclature)	18-APR-2008	0008
Amendment (CMC update)	09-MAY-2008	0010
Amendment (CMC update; San Dimas stab.)	06-JUN-2008	0013
Amendment (Response)	03-JUL-2008	0015
Amendment (Response)	25-JUL-2008	0016
Amendment (Response)	30-JUL-2008	0017
Amendment (Revised documentation per 0017)	11-AUG-2008	0019
Amendment (Gilead request)	13-AUG-2008	0020

7. NAME & ADDRESS OF APPLICANT:

Name:	Gilead Sciences, Inc.
Address:	2025 1st Avenue, Suite 800 Seattle, WA 98121
Representative(s):	Melissa A. Yeager, J.D. Vice President, Regulatory Affairs
Telephone:	206-792-3015

8. DRUG PRODUCT NAME/CODE/TYPE:
   a) Proprietary Name: Cayston™
   b) Non-Proprietary Name (USAN): Aztreonam
   c) Code Name/#: GS-9268
   d) CAS Registry Number: 827611-49-4
   e) Chem. Type/Submission Priority:
      i. Chem. Type: 3
      ii. Submission Priority: S

9. LEGAL BASIS FOR SUBMISSION: 505(b)(2) (RLD: NDA 50-580, Azactam, BMS)

10. PHARMACOL. CATEGORY: Synthetic, monocyclic beta-lactam antibacterial.

11. DOSAGE FORM: For Inhalation Solution (Diluent provided)

12. STRENGTH/POTENCY: 75 mg Aztreonam / Vial; diluted with 1 mL sodium chloride, 0.17% w/v Diluent.

13. ROUTE OF ADMINISTRATION: Oral Inhalation

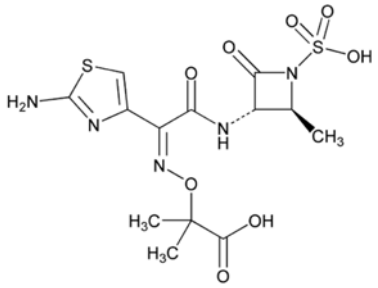
14. Rx/OTC DISPENSED: _X_Rx ___OTC

15. SPOTS (SPECIAL PRODUCTS ON-LINE TRACKING SYSTEM)
    _____SPOTS product – Form Completed
    __X__Not a SPOTS product

16. CHEMICAL NAME, STRUCTURAL FORMULA, MOLECULAR FORMULA, MOLECULAR WEIGHT

Aztreonam: USAN [1983] (and USP)
CAS: 78110-38-0
$C_{13}H_{17}N_5O_8S_2$ 435.43

(1) Propanoic acid, 2-[[[1-(2-amino-4-thiazolyl)-2-[(2-methyl-4-oxo-1-sulfo-3-azetidinyl)amino]-2-oxoethylidene]amino]oxy]-2-methyl-, [2S-[2α,3β(Z)]]-;
(2) (Z)-2-[[[(2-Amino-4-thiazolyl)[[(2S,3S)-2-methyl-4-oxo-1-sulfo-3-azetidinyl]carbamoyl]-methylene]amino]oxy]-2-methylpropionic acid.



17. RELATED/SUPPORTING DOCUMENTS

A. DMFs:

DMF #	TYPE	HOLDER	ITEM REFERENCED	CODE[1]	STATUS[2]	DATE REVIEW COMPLETED	COMMENTS
[redacted]			(b) (4)	3	Adequate	11-APR-2008	
				3	Adequate	13-OCT-2006 06-APR-2006 30-JAN-2003 24-MAY-1999	
							for PQM review
				4	N/A		See Review Section P.4.1
				3	Adequate	01-FEB-2000	
				4	N/A		
				1	Adequate	07-AUG-2008	

[1] Action codes for DMF Table:
1 – DMF Reviewed.
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4 – Sufficient information in application
5 – Authority to reference not granted
6 – DMF not available
7 – Other (explain under "Comments")

[2] Adequate, Inadequate, or N/A (There is enough data in the application, therefore the DMF did not need to be reviewed)

B. Other Documents:

APPLICATION NUMBER	DESCRIPTION
IND 64,402	Commercial IND for 'Aztreonam for inhalation', 16-APR-2003 Salus Pharma / Corus Pharma / Gilead

18. STATUS

CONSULTS/ CMC RELATED REVIEWS	RECOMMENDATION	DATE	REVIEWER
Biometrics	-		
EES	Acceptable	02-JUL-2008	S. Ferguson, HFD-322
Pharm/Tox	Impurity qualification study conduct adequate (but interpretation somewhat inaccurate)	16-JUL-2008	A. Ellis, HFD-520
Biopharm	-		
LNC	Informal discussions	Various	Various
Methods Validation	-		
DMEP	Proprietary name, Cayston, acceptable; other label/labeling recommendations made	13-MAY-2008 29-MAY-2008	D. Hamilton-Stokes
EA	Categorical exclusion acceptable	15-JUL-2008	M. Seggel
Microbiology	*Pending*		
CDRH	Final recommendation re: PARI eFlow device pending		
ONDQA Pulmonary	Informal discussions	Various	P. Peri, ONDQA

The Chemistry Review for NDA 50-814

The Executive Summary

I. Recommendations

A. Recommendation and Conclusion on Approvability

This New Drug Application for 'Aztreonam for Inhalation Solution', as amended, is recommended for approval from the chemist's perspective of the chemistry, manufacturing and controls. However, the Product Quality Microbiology review is still pending.

B. Recommendation on Phase 4 (Post-Marketing) Commitments, Agreements, and/or Risk Management Steps, if Approvable

None

II. Summary of Chemistry Assessments

A. Description of the Drug Product(s) and Drug Substance(s)

Cayston® (aztreonam for inhalation solution) is a sterile, lyophilized powder containing 75 mg of aztreonam, a synthetic, monocyclic beta-lactam (monobactam) antibacterial with activity against *Pseudomonas aeruginosa*. Aztreonam is the active ingredient in Bristol-Myers-Squibb's Azactam®, an intravenous product available since 1986 (NDA 50-580).

Each vial of 'aztreonam for inhalation solution' contains a solid mixture of aztreonam (75 mg) and L-lysine, (b) (4) respectively. L-Lysine, a basic amino acid, (b) (4) No other excipients are present. Note that Azactam contains arginine, which is reportedly less well tolerated in the lung. Reconstitution of the drug product with 1-mL of sodium chloride 0.17% w/v results in an inhalation solution with an osmolality not exceeding 550 mOsm/kg and a pH of 4.5-6.0.

The manufacturing process is relatively straightforward - (b) (4) Finished product quality is further assured by tests for assay, content uniformity, solution pH, moisture content, impurities, sterility and endotoxins. Known degradants include (b) (4) and two (b) (4) The formation of impurities is controlled by protection from light and storage at 2-8°C. The container closure system consists of a 2-mL USP Type I amber glass vial with a (b) (4) rubber stopper and an aluminum overseal cap.

Diluent for 'aztreonam for inhalation solution' consists of 1-mL sterile sodium chloride 0.17% w/v packaged in low density polyethylene (b) (4) ampules. Shelf-life is limited by moisture loss.

Aztreonam, the active ingredient in 'aztreonam for inhalation solution', has been well characterized and is described in 'Analytical Profiles of Drug Substances'. It is also the subject of a USP monograph. The drug substance used in the manufacture of 'aztreonam for inhalation solution' is supplied by (b) (4) and is described in DMF (b) (4). It differs from the material described in the current USP monograph in that it contains (b) (4) water (b) (4)

The aqueous solubility of aztreonam increases as the solution pH increases due to ionization of the sulfonyl and carboxyl groups. At pH values above 4.2, solubility exceeds 75 mg/mL. It has a partition coefficient (logP) -0.66.

B. Description of How the Drug Product is Intended to be Used

The drug product is indicated for the treatment of cystic fibrosis patients (CF) with *Pseudomonas aeruginosa*. One dose (75 mg aztreonam diluted with 1 mL sodium chloride, 0.17% w/v diluent) is to be administered three times a day for 28 days. The inhalation solution must be administered with the PARI eFlow nebulizer configuration specified for Cayston [510(k) K080237].

The drug product is supplied in a carton containing a 28-day supply of vials of lyophilized aztreonam for inhalation (84 vials) and an equal number of ampules of the saline diluent, plus four extras in case of spillage (88 ampules). The carton is further broken down into two 14-day carton inserts. For long-term storage, aztreonam for inhalation solution should refrigerated (2-8°C). However, once dispensed to patients, the product may be stored at 25°C for up to 28 days. A 24-month expiration dating period has been established for aztreonam vials.

(b) (4)

C. Basis for Approvability or Not-Approval Recommendation

From the chemistry, manufacturing and controls perspective the relevant requirements of 21 CFR 314.50 and, specifically, paragraphs 314.50(d)(1)(i), (ii) and (iii) are satisfied by Gilead in this amended new drug application. Evidence for sterility assurance is under review in OPS/NDMS.

The manufacture of the drug substance, as documented in (b) (4) DMF (b) (4) (as amended), is adequately controlled. The specification necessary to ensure the identity, strength, quality, and purity of the drug substance and the bioavailability of the drug product made from the substance is adequate.

Likewise, the manufacture of the aztreonam drug product and diluent are adequately controlled. The specifications necessary to ensure the identity, strength, quality, purity, potency, and bioavailability of the drug product and diluent are, as amended, adequate. While there is limited manufacturing history (and consequently limited release data), the proposed acceptance criteria for impurities and degradation products in aztreonam for inhalation solution appeared to be rather 'loose'. In addition, the applicant's original analysis of impurity qualification data was based on an assumed exposure ten times that generally used by CDER pharm/tox reviewers in calculating total deposited dose. (It appears that the applicant's analysis was based on total systemic exposure rather than dose deposited in lung.) The applicant has recalculated the qualified levels, and has reduced the limit for the (b) (4) Gilead has proposed re-evaluating the release and shelf-life limits for individual impurities and total impurities after data from twenty additional commercial batches are obtained. Revisions will be submitted via an Annual Report. Based on the toxicity data and the absence of any special concerns about the impurities (e.g., no structural alerts; identity as metabolite), the revised specification and commitment to re-evaluate the impurity limits are acceptable. The stability of the drug product has been adequately characterized. Post-approval stability studies will provide additional assurance that the drug product and diluent continue to meet the established specification, and support the established expiration dating periods.

The compatibility of the drug product with the eFlow nebulizer and its performance characteristics (emitted dose, particle size distribution, plume geometry) were thoroughly evaluated.

Verification of the analytical procedures by one or more FDA laboratories is not considered necessary at this time given the relatively straightforward methodology employed (e.g., HPLC).

Upon receipt of the NDA, a request for evaluation of the manufacturing and test facilities was submitted through EES. At the time, (b) (4) had been placed under OAI status, although it was not known whether or not the issues behind the OAI would directly impact the manufacture of aztreonam vials. In early 2008, following discussions with FDA, Gilead decided to add a second drug product manufacturing site, Gilead - San Dimas, in the event that the problems at (b) (4) were not resolved in time for the action on this NDA (Amendment 14-MAR-2008, Sequence 0006). All drug substance and drug product manufacturing and test facilities were found to have acceptable cGMP status based on inspection or profile. An overall Acceptable recommendation was made by the Office of Compliance on July 2, 2008 (see EES).

Product quality microbiology issues remain to be resolved by OPS/NDMS. (b) (4) sterility controls are documented in DMF (b) (4). However, the corresponding information to support sterility assurance at Gilead - San Dimas (e.g., building and facilities, equipment qualification, (b) (4) environmental monitoring) does not appear to have been submitted to the NDA or a DMF. Sterility assurance at diluent manufacturer (b) (4) also remains to be evaluated from the Product Quality Microbiology perspective. Because diluent manufacturing by (b) (4) was withdrawn by the applicant, no further evaluation of sterility assurance at that facility is necessary. In addition to assessment of manufacturing sterility assurance, suitable of the proposed endotoxin acceptance criteria (add at our request) for both aztreonam and diluent must be evaluated. Finally, the need for additional annual sterility or container/closure integrity testing of the lyophilized aztreonam product and the diluent must be evaluated.

A categorical exclusion from the requirement for the preparation of an environmental assessment (EA) is claimed in accordance with 21 CFR 25.15(d) and 21 CFR 25.31(b), and is acceptable based on the EIC (<1 ppb).

Throughout the application the drug product is referred to as 'aztreonam lysine for inhalation' ('AI' or 'AZLI'). However, the dosage form is more correctly a lyophilized powder "for inhalation solution". Furthermore, the USAN name 'aztreonam lysine' refers specifically to the 1:1 salt. The current drug product, with a (b) (4) of aztreonam to lysine, would appear to contain a (b) (4) Finally, the strength of the product, 75 mg, is expressed in terms of the free acid. The established name has been revised accordingly. Cayston®, the proposed proprietary name, has been found acceptable by the Division of Medication Error Prevention (DMEP). They have also made other recommendations regarding the container labels, carton labeling, and package and patient inserts. Because an 'approvable' action is being recommended from the clinical perspective, labeling negotiations have not been initiated.

III. Administrative

A. Reviewer's Signature

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B. Endorsement Block

{see electronic signature page}

C. CC Block

{see dfs}

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/s/

Mark Seggel
8/27/2008 10:17:23 AM
CHEMIST
N50814 Chem Rev #1

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8/27/2008 10:53:42 AM
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Initial Quality Assessment
Branch IV
Pre-Marketing Assessment Division II

OND Division:	Division of Anti-Infective and Ophthalmology Products
NDA:	50-814
Applicant:	Gilead Sciences, Inc.
Stamp Date:	16-Nov-07
PDUFA Date:	16-May-07
Trademark:	Cayston™
Established Name:	Aztreonam lysine
Dosage Form:	Powder for solution for inhalation
Route of Administration:	Nasal
Indication:	To improve respiratory symptoms and pulmonary function in cystic fibrosis patients with *P. aeruginosa*
PAL:	Rapti D. Madurawe
	YES NO
ONDQA Fileability:	☒ ☐
Comments for 74-Day Letter:	☒ ☐

Summary and Critical Issues:

A: Summary and Review

NDA 50-814 provides for Aztreonam Lysine for Inhalation for the improvement of respiratory symptoms and pulmonary function in cystic fibrosis patients with *Pseudomonas aeruginosa.* Aztreonam, the active pharmaceutical ingredient, is a β-lactam antibiotic which is currently marketed in the U.S. as an intravenous injection. In this application, the aztreonam lysine is formulated as a sterile lyophilized powder for reconstitution with a sterile solution of sodium chloride to form a solution for inhalation. The inhalation solution is administered using the PARI eFlow electronic nebulizer.

The corresponding IND for aztreonam lysine for inhalation is IND 64,402. CMC issues discussed at the CMC preNDA meeting held on May 30, 2007 are documented in the meeting minutes dated June 26, 2007. CMC issues were not discussed at the EOP2 meeting and there is no other CMC documentation in DARRTS.

Drug Substance

The drug substance of NDA 50-814 is aztreonam lysine. The lysine salt (b) (4)

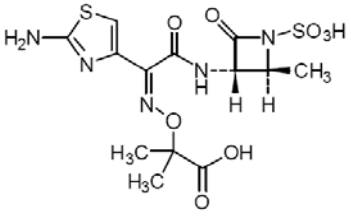
The applicant purchases aztreonam manufactured by (b) (4) and produces aztreonam lysine in the drug product manufacturing process. The NDA identifies aztreonam as the drug substance; a technicality which is OK.

The chemistry, manufacturing and controls for aztreonam are referred to DMF [redacted] "Aztreonam [redacted]" held by [redacted] A letter of authorization to refer to the DMF is provided. The DMF was reviewed on 13-April-2007 and found inadequate by Dr. Neeru Takiar, Office of Generic Drugs. Amendments dated 06-Jul-07 and Oct-25-07 are not yet reviewed. The 06-Jul-07 submission contains a response to the deficiency letter sent 19-Apr-07. Deficiencies need to be resolved and the DMF found adequate for NDA approval.

The NDA contains some information on aztreonam physical properties, impurities, specification, analytical tests, batch analysis data and stability. Only the limited information presented in the NDA is discussed and reviewed below.

The structure of aztreonam is given in Figure 1.

Figure 1: Structure of Aztreonam



Aztreonam is soluble in buffered aqueous solutions at pH greater than 4. The intrinsic solubility of aztreonam is 0.15 g/L. Of the 4 known polymorphic forms of aztreonam, the [redacted] and have similar physical and chemical properties. Data is presented to show the polymorphic form does not significantly affect the aztreonam lysine drug product bulk solution properties. [redacted]

[redacted]

The NDA gives the structures of 9 process impurities and degradation products. [redacted] Each unspecified

impurity limit is (b) (4)%. Acceptability of the impurity specification is a review issue. Limits for microbial and endotoxin levels are recommended to control the amounts entering the drug product manufacturing process.

Table 1: Aztreonam specification

Test Description	Test Method	Acceptance Limit
Appearance	Visual (TM-004)	White to off-white crystalline powder.
Identification – Infrared Spectrum	USP <197K> or Ph. Eur. 2.2.24	IR spectrum is consistent with that of the reference standard, similarly measured.
Water Content	USP <921> Method 1 or Ph. Eur. 2.5.32 or 2.5.12	(b) (4)
Assay	TM-096 or TM-099	(b) (4) calculated on a dried basis
Impurity Content	TM-098 or TM-099	(b) (4) Total Impurities (b) (4) of (b) (4) (b) (4) of (b) (4) (b) (4) each Unspecified Impurity
Heavy Metals	USP <231> or Ph. Eur. 2.4.8	(b) (4), as lead
Residue On Ignition	USP <281> or Ph. Eur. 2.4.14	(b) (4)
Organic Volatile Impurities	TM-101	(b) (4) of Ethanol (b) (4) of Methylene Chloride

Tables 2.3.S.4.4-1 to -3 in the NDA clearly identify the aztreonam batches used in toxicology, clinical and stability tests. No significant batch differences are seen in the water content, assay, impurities, heavy metals and residue on ignition. The (b) (4) content of two clinical batches differ from the average value (one high, one low), but are within the NMT (b) (4) specification.

Long-term (5°C) stability data up to 24-months is provided for 3 lots of aztreonam. Additional stability data is also provided. Aztreonam is stable at 5°C and -20°C for 24-months with only little changes in the impurity level, purity and (b) (4) content. Accelerated stability studies at 25°C/60% RH show an increase in the (b) (4) impurity level (b) (4) over 3 months and a corresponding increase in the total impurity level (b) (4) The (b) (4) content changed only slightly under accelerated stability. The applicant proposes to store aztreonam below 8 °C with a (b) (4) retest period. As this permits both refrigerated and frozen storage conditions, either cold storage at 2-8 °C or freezer storage at -25 to -10 °C should be specified.

Drug Product

Aztreonam lysine is provided as a sterile lyophilized powder in a single-use 2 mL amber glass vial with a (b) (4) rubber stopper and an overseal cap. Each vial contains 75 mg aztreonam, the nebulized dose. The aztreonam lysine vial is co-packaged with the diluent. The reconstituted solution for inhalation is to be used with the high efficiency PARI eFlow nebulizer. The nebulizer is to be purchased separately.

The drug product is manufactured at (b) (4) The facility is currently on a Withhold status and has received a warning letter from the Office of Compliance. Deficiencies need to be resolved and the facility found cGMP-compliant for NDA approval. As deficiencies could potentially get resolved during the review period, it was decided with supervisory concurrence to file the NDA from a CMC perspective.

The composition of the drug product is given in Table 2. Specification for lysine monohydrate based on the German Pharmacopeia is provided in the NDA. The USP monograph is for L-lysine. There are no novel excipients or excipients of animal origin.

Table 2: Quantitative composition of aztreonam lysine

Component	Reference to Quality Standard	Function	Quantity per Vial	Amount per batch (kg)
Aztreonam	In-house Standard	Drug Substance	75.0 mg	(b) (4)
Lysine Monohydrate	In-house Standard			(b) (4)
Water for Injection	USP			

1 The quantity used is adjusted on the basis of the purity (e.g., drug content factor) of each batch of aztreonam on a dried basis.
2 A suitable quantity of (b) (4), is used in the process and is removed during the (b) (4).

The source of the (b) (4) is unknown. Critical physicochemical properties are as follows: For physiological compatibility - pH 4.0 to 8.2 (maximum solubility and stability is at pH 4.5-6.0), osmolality 150 to 550 mOsm/kg and permeant anion (eg, chloride) concentration kept to a minimum; for nebulization - surface tension and dynamic viscosity.

The drug product manufacturing steps are: (b) (4) The manufacturing process appears to be adequately controlled with appropriate operating parameters and in-process steps. Although there is an in-process bioburden test before (b) (4) bioburden control of the drug product components is also recommended.

The lyophilized drug product container-closure system is a sterile, (b) (4), 2 mL USP Type I amber glass vial with a (b) (4) gray (b) (4) lyophilization stopper. A list of container-closure DMFs and letters of authorization are given in the NDA. All materials that come in contact with the drug product meet with the requirements of *21CFR 170-189* and USP <197> Spectrophotometric Identification Tests. Container-closure integrity tests have been performed.

The drug product specification is given in Table 3. Although aztreonam (drug substance) has (b) (4) water, the water content of aztreonam lysine drug product is controlled to NMT (b) (4) through the lyophilization process and the vial seal. Higher levels of degradants are specified during shelf-life than for release. The acceptability of this is a review issue. Inclusion of tests for endotoxin and the lysine counter-ion in the drug product specification is recommended. The other tests and acceptance criteria appear to be reasonable.

Table 3: Specification for Aztreonam Lysine for Inhalation

Test Description	Test Method	Acceptance Limit
Appearance	Visual (TM-004)	White to off-white powder.
Identification – IR	USP <197> or Ph. Eur. 2.2.24	IR Spectrum is consistent with that of the reference standard, similarly measured.
Reconstitution	TM-100	When reconstituted with 1.0 mL of a 0.17% w/v sodium chloride solution: • Reconstitution time is not more than 90 seconds. • No visible residue remains. • The reconstituted solution is not significantly less clear than an equal volume of the diluent in a similar vessel. • The reconstituted solution is colorless to lightly colored.
Water Content	USP <921> Method I or Ph. Eur. 2.5.12 or Ph. Eur. 2.5.32	(b) (4)
Assay	TM-097	**At Release:** (b) (4) of label strength. **Shelf-Life:** of label strength.
Degradation Product Content	TM-097	**At Release:** (b) (4) a total of (b) (4) impurities; and (b) (4) (b) (4) each unspecified impurity. **During Shelf Life:** (b) (4) a total of (b) (4) impurities; and (b) (4) (b) (4) each unspecified impurity.
Content Uniformity	USP <905> or Ph. Eur. 2.9.40	Meets USP or Ph. Eur. requirements for content uniformity.
pH of Solution	USP <791> or Ph. Eur. 2.2.3	When reconstituted with 1.0 mL of a 0.17% w/v sodium chloride solution, the pH is NLT 4.5 and NMT 6.0.
Sterility	USP <71> or Ph. Eur. 2.6.1	Meets USP or Ph. Eur. requirements of the test for sterility.

The drug product stability package contains data for long-term (5°C) and accelerated (25°C), short-term room temperature storage following long-term storage, thermal

cycling, photostability testing, reconstituted solution stability and statistical analysis. The proposed shelf-lives are (b) (4) Shelf-lives are based on real-time data.

The drug product accelerated storage condition does not appear to have included humidity control as recommended in ICH Q1A. The chemical stability of the drug product is said to be "not significantly affected by hydrolysis." However, as aztreonam lysine is hygroscopic and sensitive to hydrolysis, could a failed result be obtained if the drug product were stored at 25 °C/60%? The applicant should provide an explanation as to why humidity was not included in the accelerated stability test condition and provide available information on drug product stability at 25°C/60% RH.

All attributes of the drug product remained within the acceptance limits over 24-months of long-term and 6-months of 25 °C storage. Trends observed are (b) (4) Other drug product attributes such as appearance, lysine content, water content, pH of the reconstituted solution, osmolality, and particulate matter remained relatively unchanged. Five major degradation products (b) (4) were observed; the primary degradant was (b) (4)

Photostability tests showed some (but not a significant amount) degradation; the (b) (4) was the primary degradant. (b) (4) Information should be provided if (b) (4) are observed in the lyophilized and reconstitution drug product.

The reconstituted solution was stable up to 12 hours at room temperature, but failed stability at 24-hours due to excessive dimer formation. Some variation in the lysine content was also observed. Sterility data is not presented for the reconstituted solution. The division now requires sterility data for reconstituted solutions stored for more than 4 hours at room temperature. Patients are not likely to use sterile techniques for reconstituting the drug. The reconstituted solution should be used promptly.

Diluent

The diluent is co-packaged with the drug product. It is a single-use, 1 mL, sterile, preservative-free, 0.17% w/v sodium chloride solution in a (b) (4) ampoule. The diluent provides a minimum permeant anion concentration, keeps the osmolality of the reconstituted solution less than 550 mOsm/kg and does not significantly change the pH of the reconstituted solution from pH 4.5-6.0. Table 4 gives the diluent composition.

Table 4: Quantitative Composition of Diluent

Component	Reference to Quality Standard	Function	Quantity per Vial

Sodium Chloride	USP or Ph. Eur.	(b) (4)
Water for Injection	USP or Ph. Eur.	

The commercial manufacturers of the diluent are (b) (4) Clinical and stability batches were also manufactured by these two manufacturers. The manufacturing process (which includes (b) (4)), key processing parameters and equipment are described. The diluent is filled into sterile, LDPE, natural color ampoules by a (b) (4) process. Container closure extractable/leachable studies did not produce extractable components with water and 0.17% sodium chloride, but produced a (b) (4) This would require further evaluation.

The diluent specification is given in Table 4. The acceptance criterion for the deliverable volume of the diluent is lowered for shelf life. Is this justified? There are no specification tests for endotoxin, pH, metal and particulate matter. The need for additional tests should be determined upon detailed review.

Table 4: Diluent Specification

Test Description	Test Method	Acceptance Limit
Appearance	Visual	Colorless liquid essentially free of visible particles
Identification – Sodium Chloride	USP <191> or Ph. Eur. 2.3.1	Meets USP or Ph. Eur. requirements of the ID test for sodium. Meets USP or Ph. Eur. requirements of the ID test for chloride.
Assay	USP monograph for sodium chloride inhalation solution	(b) (4) of label strength.
Sterility	USP <71> or Ph. Eur. 2.6.1	Meets USP or Ph. Eur. requirements of the test for sterility.
Deliverable Volume	TM-102 (USP <698>)	At Release: Average volume from 10 containers is 1.0 - 1.2 mL No individual is outside the range of 0.9 - 1.4 mL During Shelf Life: Average volume from 10 containers is 0.9 - 1.2 mL No individual is outside the range of 0.8 - 1.4 mL

The NDA contains two separate 3.2.P sections for diluent made at (b) (4) and diluent made at (b) (4). I could not easily discern what the differences were for these two sections. The applicant should submit a summary table outlining the differences, if any, between the two submissions. If they are identical, one should be withdrawn.

Nebulizer

Aztreonam lysine for inhalation is nebulized using the eFlow® Electronic Nebulizer (eFlow), a high efficiency portable device, manufactured by PARI Innovative Manufacturers. The nebulizer is separately supplied to patients and is not co-packaged.

The Phase 3 clinical studies used the 510(k) cleared eFlow model 78G1004a (510(k) number K033833). The proposed commercial eFlow nebulizer in this NDA been slightly modified (b) (4) The nebulizer handset and the controls for delivery of the drug remain unaltered from the original eFlow 78G1004a model. PARI is to file a Special 510(k): Device Modification for the changes to the base unit. At the preNDA CMC meeting, the Agency agreed that the clinical data obtained with the 78G1004a eFlow is acceptable for the modified device, but asked the applicant to provide additional *in vitro* characterization data. The Agency indicated that NDA approval is contingent on 510(k) clearance of the device modification. Although the drug product 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 prior to the final NDA submission, I was not able to locate this information. The applicant should submit this information or indicate its exact location. CDRH should be consulted on the approvability of the device modification.

The nebulized solution is characterized for the emitted dose, particle size (geometry, distribution, etc), plume geometry, drug product degradation, and effect due to variability in bulk solution properties, drug product lots and device lots/usage. The study methods and data need careful evaluation. It appears (based on a quick review) that nebulization does not significantly affected particle size characteristics, but product degradation could occur during aerosolization. If drug product near the end of its expiration period is used, this may be a problem. Degradation information submitted for drug product aerosolization (3.2.P.2.6.2.3) should include impurity profile (data said to be obtained, but I did not see it) information for further evaluation.

Studies have been conducted to evaluate drug product and device interaction. (b) (4) , but none were detected with the aztreonam lysine for inhalation. The safety/amount of the sodium chloride extractables requires further review.

B. Review, Comments and Recommendation

Drug Substance

1. DMF (b) (4) for the aztreonam drug substance was reviewed in April 2007 and found inadequate. Resolution of these deficiencies is critical for NDA approval.
2. The drug substance has a high water content (b) (4). The applicant (or the DMF holder) should provide information on the susceptibility of aztreonam to hydrolysis.
3. Tests for optical rotation and (b) (4) may need to be added to the drug substance specification if DMF (b) ( ) does not provide information on the control of these two parameters.

4. A microbial and endotoxin specification may be needed to limit the amount entering the drug product manufacturing process.
5. The proposed storage temperature for aztreonam is "below 8 °C." As this permits both refrigerated and frozen storage conditions, a storage condition of either refrigerated at 2-8 °C or frozen at -25 to -10°C should be specified.

Drug Product

6. The drug product manufacturing facility, (b) (4) is currently on a Withhold status. An acceptable facility status is critical for NDA approval.
7. Accelerated stability studies were done at 25 °C and not at 25°C/60% RH. Given that aztreonam is hygroscopic, this omission (if it is not a typographical error) requires further explanation. The applicant should provide information on stability if tests were done at 25 °C/60% RH.
8. Sterility data is not provided for reconstituted solution stability. Early notification of the new Agency requirements for sterility tests (by the Product Quality Microbiology group) would enable the applicant to perform the required tests during the review period. However, my recommendation is not to store the reconstituted solution as patients are not likely to use sterile techniques.
9. The drug product specifications do not include tests for the counterion (lysine) and endotoxin. Inclusion of these tests is recommended.
10. A product quality microbiology consult for drug product, diluent and reconstituted solution for sterility and endotoxin is required.
11. Degradation of lyophilized, reconstituted and nebulized drug product should be evaluated carefully due to the high propensity for degradation.
12. Are (b) (4) (and other major degradants) soluble?
13. It is unclear if (b) (4) is of relevance during the usage period of the drug product (i.e. from reconstitution until nebulization). Applicant should indicate if (b) (4) is observed. This topic may require further follow-through as the (b) (4) are currently unidentified.

Diluent

14. The NDA contains two separate 3.2.P sections for diluent made at (b) (4) and diluent made at (b) (4) The applicant should submit a summary table outlining the differences between the two submissions. If they are identical, one diluent submission should be withdrawn.
15. There are no specification tests for endotoxin, pH, metal and particulate matter. Should additional tests be included?
16. The acceptance criterion for the deliverable volume of the diluent is lowered for shelf life. Is this justified?

Nebulizer

17. 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. I did not locate

this information which was requested at the preNDA CMC meeting. Applicant should indicate where this information is located or resubmit this information.

18. A CDRH consult is required for the device modification.

C: Critical issues for review

1. Drug product degradation.
2. DMF (b) (4) for the aztreonam drug substance was reviewed in April 2007 and found inadequate. Deficiencies should be resolved for NDA approval.

Items 3 and 4 are critical for NDA approval, but are not under the purview of CMC review.

3. The drug product manufacturing facility, (b) (4), is currently on a Withhold status. The facility should have an acceptable status for NDA approval.
4. 510(k) clearance for the eFlow device modification.

D: Comments for 74-Day Letter

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 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 withdraw one of the submissions.
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 has filed a 510(k) application with CDRH for the eFlow Device Modification and if it has received 510(k) clearance or is still under review.

__Rapti D. Madurawe_____ ___14-Dec-07____
Pharmaceutical Assessment Lead Date

__Norman R. Schmuff_____ ____14-Dec-07___
Branch Chief Date

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/s/

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1/18/2008 11:25:51 AM
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