CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

207988Orig1s000

CHEMISTRY REVIEW(S)

Breakthrough Review: No

Recommendation: Approval

NDA 207988
Review #1
Review Date 08-SEP-2015

Drug Name/Dosage Form	Zurampic (lesinurad) oral tablets
Strength	200 mg
Route of Administration	Oral
Rx/OTC Dispensed	Rx
Applicant	Ardea Biosciences, Inc.
US agent, if applicable	None

SUBMISSION(S) REVIEWED	DOCUMENT DATES
Original	**12/29/2014**
Amendment (response to 74-day letter)	**04/09/2015**
Amendment (response to drug substance and drug product process IR)	**05/13/2015**
Amendment (response to general quality IR)	**07/16/2015**
Amendment (drug substance chirality info)	**08/11/2015**
Amendment (response to drug product IR)	**08/12/2015**
Amendment (response to biopharm IR)	**08/20/2015**

Quality Review Team

DISCIPLINE	REVIEWER	BRANCH/DIVISION
Drug Substance	Joseph Leginus	Branch II/New Drug API
Drug Product	Arthur B. Shaw, Ph.D.	ONDP/DNDPII
Process	Ted Chang	
Facility	Robert Wittorf	
Biopharmaceutics	Kimberly Raines	
Project/Business Process Manager	Florence Aisida	
Application Technical Lead	Craig Bertha	ONDP/DNDPII
Laboratory (OTR)	Laura C. Pogue	OTR/DPA
ORA Lead		
Environmental Assessment (EA)	N/A	

Table of Contents

Quality Review Data Sheet

1. **LEGAL BASIS FOR SUBMISSION:505(b)(1)**

2. **RELATED/SUPPORTING DOCUMENTS:**

   A. DMFs:
   DMFs for Type III DMFs for packaging materials and Type IV DMF (b) (4) for the color do not need reviews because there is sufficient information in the NDA to evaluate their suitability.
   B. Other Documents: *IND, RLD, or sister applications*

Document	APPLICATION NUMBER	DESCRIPTION
IND	102128	Development of the drug product

3. **CONSULTS:** None

Executive Summary

I. **Recommendations:** Approve

A. Recommendation and Conclusion on Approvability

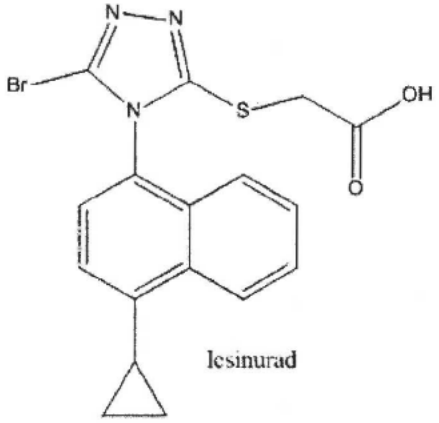
1. Summary of Complete Response issues : None
2. Action letter language, N/A
3. Benefit/Risk Considerations: N/A

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

II. **Summary of Quality Assessments**

A. Drug Substance [Lesinurad] Quality Summary

1. Chemical Name or IUPAC Name/Structure



lesinurad

2-((5-bromo-4-(4-cyclopropylnaphthalen-1-yl)-4*H*-1,2,4-triazol-3-yl)thio)acetic acid

2. Properties/CQAs Relevant to Drug Product Quality
The identity, purity (organic related, inorganic, residual solvents), and particle size of the drug substance are important to the attainment of the quality of the drug product.

3. List of starting materials
The starting materials for the synthesis of lesinurad are (b) (4)

4. Suppliers of starting materials (site)
There are multiple suppliers for each of the starting materials: (b) (4)

(b) (4)

5. Summary of Synthesis

(b) (4)

6. Process
   a. Sterilization processes of the sterile bulk, as applicable
      N/A
   b. Critical equipment
      None identified

7. Container Closure
   The drug substance is stored in (b) (4)

8. Retest Period & Storage Conditions
   A retest period of (b) (4) months with storage at (b) (4) is found to be acceptable.

B. Drug Product Quality Summary

1. Strength: 200 mg/tablet
2. Description/Commercial Image: Blue film-coated tablets
3. Summary of Product Design: Immediate release tablets
4. List of Excipients:
   Hypromellose 2910
   Microcrystalline Cellulose
   Lactose Monohydrate
   Crospovidone

Magnesium Stearate
Opadry Blue (b) (4)

5. Process Selection (Unit Operations Summary)

(b) (4)

6. Container Closure: HDPE bottled containing a desiccant
7. Expiration Date & Storage Conditions 36 months at Controlled Room Temperature
8. List of co-packaged components None

C. Summary of Drug Product Intended Use

Proprietary Name of the Drug Product	Zurampic
Non Proprietary Name of the Drug Product	N/A
Non Proprietary Name of the Drug Substance	Lesinurad
Proposed Indication(s) including Intended Patient Population	Uricosuric agent for treatment of hyperuricemia associated with gout in combination with a xanthine oxidase inhibitor (not for use as a monotherapy)[1]
Duration of Treatment	Unspecified; clinical trials were up to 12 months
Maximum Daily Dose	200 mg (once daily) oral administration
Alternative Methods of Administration	None

D. Biopharmaceutics Considerations

1. BCS Classification:
   - Drug Substance: class II

2. Biowaivers/Biostudies
   - Biowaiver Requests: N/A
   - IVIVC: See p. 117 of review

E. Novel Approaches

N/A

[1] According to the Applicant, Lesinurad is a selective uric acid reabsorption inhibitor (SURI) that inhibits uric acid transporter 1 (URAT1). The Agency has considered this and has determined this compound should be classified as a uricosuric agent.

F. Any Special Product Quality Labeling Recommendations
N/A

G. Process/Facility Quality Summary (see Attachment A)

H. Life Cycle Knowledge Information (see Attachment B)

Primary Quality Review

ASSESSMENT OF THE DRUG SUBSTANCE

2.3.S DRUG SUBSTANCE

NOTE: SOME OF THESE SECTIONS MAY BE PART OF A REFERENCED DMF REVIEW (including evaluation of a (b) (4) API). IF SO, PLEASE REFERENCE THE DMF REVIEW(S), AS NEEDED.

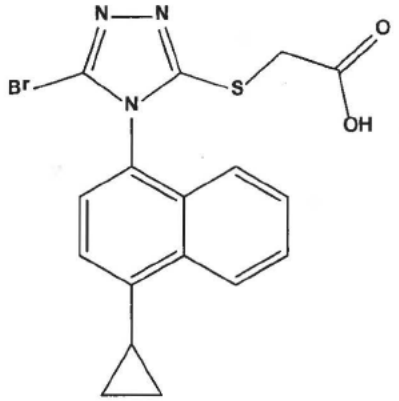
2.3.S.1 General Information

Applicant's Response:
Lesinurad is a new molecular entity (NME) that is formulated as an immediate release tablet for the treatment of hyperuricemia associated with gout.

Nomenclature

Compendial Name	N/A
USAN Name	Lesinurad
Chemical Names	Chemical Abstracts: Acetic acid, 2-[[5-bromo-4-(4-cyclopropyl-1-naphthalenyl)-4H-1,2,4-triazol-3-yl]thio]-
Company Code	RDEA594
CAS Registry #	[878672-00-5]

Chemical Structure



Molecular Formula: $C_{17}H_{14}BrN_3O_2S$
Molecular Weight: 404.28 g/mol

General Physico-Chemical Properties of Lesinurad

Appearance	White to off-white crystalline powder
Melting Point	169 - 171°C
Solubility	See table below
Water Absorption	Non-hygroscopic. [redacted] (b) (4)
Partition Coefficient	Log $P_{octanol/water}$ = 2.85
Polymorphism	[redacted] (b) (4)
pH (saturated solution)	4.5 (0.10 mg/mL)
pKa	Approximately 3.0
Optical Activity	Lesinurad exists as a [redacted] (b) (4) of enantiomeric atropisomers (stereoisomers due to hindered rotation) [redacted] (b) (4) [redacted] (b) (4)

Solvent	Solubility (mg/mL)	Description (as per USP)
Water at 25°C	0.10	Very Slightly Soluble
0.1 N HCl	0.0041	Practically Insoluble
pH 3 Buffer	0.0065	
pH 6.5 Buffer	2.1	Slightly Soluble
NaOH 0.01N	3.7	
NaOH 0.3N	117	Freely Soluble
Acetonitrile	18	Sparingly Soluble
Methanol	93	Soluble
Ethanol	52	
Ethyl Acetate	16	Sparingly Soluble
n-Hexane	Not Soluble	Insoluble

Reviewer's Assessment:

Adequate descriptions of the drug substance including general physico-chemical properties of lesinurad have been provided.

2.3.S.2 Manufacture

S.2.2 Description of the Manufacturing Process and Controls

1. Is the commercial manufacturing process adequately described and controlled to ensure consistent manufacturing of acceptable drug substance batches? (Note: add applicant's response and reviewers assessment box after this question)

2. Is there any proposal for online/at line/in line monitoring technologies for routine commercial production that allows for real-time process monitoring and control? If so, is it acceptable?

Applicant's Response:

(b) (4)

[redacted]

3 Page(s) have been Withheld in Full as B4 (CCI/TS) immediately following this page

(b) (4)

[redacted]

Reviewer's Assessment:

Adequate descriptions of each step in the two manufacturing processes for the drug substance have been provided. Starting materials have been identified and adequate justification provided for such designation.

The following CMC comment was included in the 3/12/2015 Day 74 Filing Communication to the Applicant:

> "Provide supplier information for each of the proposed starting materials (b) (4) [redacted] used in the manufacture of lesinurad drug substance. Also provide representative Certificates of Analysis for each material".

In a 4/9/2015 Amendment, the Applicant addressed this issue by providing specifications and Certificates of Analysis for:

(b) (4)

[redacted]

Evaluation of Response: The Applicant adequately provided supplier information and Certificates of Analysis of the starting materials for lesinurad drug substance.

There is no proposal for online/at line/in line monitoring technologies for routine commercial production that allows for real-time process monitoring and control.

Control of Critical Steps and Intermediates

3. What are the critical steps which could significantly affect the structure of the drug substance and impurity profiles? If so, are the critical process parameters (CPPs) adequate to ensure the identity and purity of the drug substance?

4. Are intermediates controlled adequately to assure the structure and impurity profile of the final drug substance?

Applicant's Response:

(b) (4)

[redacted]

12 Page(s) have been Withheld in Full as B4 (CCI/TS) immediately following this page

The following CMC comment was included in the 3/12/2015 Day 74 Filing Communication to the Applicant:

> "Provide updated structural characterization data/spectra (elemental analysis, high-resolution mass spectrum, FTIR, ^{1}H and ^{13}C NMR, UV and X-ray powder diffraction) from the most recent lesinurad lot used as the analytical reference standard (17JL02.HE00016) or other comparable lot of drug substance manufactured by [redacted] (b) (4) at the commercial manufacturing facility. The structural characterization data submitted in the NDA for lesinurad drug substance was obtained from the lesinurad analytical reference standard, Lot A10085-38-2 manufactured by [redacted] (b) (4) by Ardea Bioscience which is not representative of the commercial drug substance".

In a 4/9/2015 Amendment, the Applicant addressed this issue by updating Section 3.2.S.3.1 to include the structural characterization data/spectra for lesinurad drug substance Lot 17JL02.HE00016, manufactured using the [redacted] (b) (4) at the commercial manufacturing facility.

Evaluation of Response: The Applicant has adequately provided structural characterization data for the drug substance reference standard (Lot 17JL02.HE00016) which was manufactured using the [redacted] (b) (4) at the commercial manufacturing facility. Characterization data/spectra for Lot 17JL02.HE00016 has been incorporated and evaluated above as adequate.

A thorough discussion of the potential and actual impurities found in the lesinurad drug substance has been provided including inorganic impurities, [redacted] (b) (4) and residual solvents. Three process related impurities have been identified and none were found to exceed the qualification threshold according to ICH Guideline Q3A (R2). One potential degradation product has been identified, but it does not present an issue upon stability.

The analysis for potential genotoxic impurities was found to follow ICH M7 Guidelines and Guidance for Genotoxic and Carcinogenic Impurities. Risk associated with all impurities in the drug substance has been demonstrated to be extremely low.

A chiral assay to measure the ratio of atropisomers of lesinurad has been developed and data presented [redacted] (b) (4)

2.3.S.4 Control of Drug Substance

9. Is the proposed specification adequate to assure the identity, strength, purity, and quality of the drug substance?

10. Are all the analytical procedures appropriately described and validated for their intended use?

Applicant's Response:
Specifications
The specification for lesinurad drug substance is presented in the table below.

Lesinurad Drug Substance Specification

Test	Method	Acceptance Criteria
Description	Visual	White to off-white solid
Identification – IR Spectrum	FTIR, USP <197A>	Conforms to reference spectrum.
Identification – HPLC Retention Time	HPLC	The retention time of the major peak of the sample preparation corresponds to that of the standard preparation.
Assay	HPLC	(b) (4)
Inorganic Impurities		
(b) (4)		
Organic Impurities		
(b) (4)		
Residual Solvents		
(b) (4)		
Morphology		
Particle Size	Laser Diffraction	D(v, 0.5) (b) (4) µm D(v, 0.9) of NMT (b) (4) µm
(b) (4)	HPLC	(b) (4)

9 Page(s) have been Withheld in Full as B4 (CCI/TS) immediately following this page

(b) (4)

[redacted]

Reviewer's Assessment:

Based on the process understanding used to establish specifications, the process appears adequately controlled. Batch analysis data from 8 clinical and stability lots manufactured at commercial scale at the proposed site for commercial supply (b) (4) show that the drug substance can be manufactured repeatedly to meet the specifications proposed.

2.3.S.5 Reference Standards or Materials

12. Are the drug substance reference standards satisfactory?

Applicant's Response:
The current primary reference standard lot 17JL02.HE00016 is used for testing and release of the drug substance lesinurad and of the respective drug product. This lot of drug substance was manufactured by (b) (4) in June 2013 using the (b) (4) at the commercial manufacturing facility. A batch analysis for the reference standard has been provided.

Reviewer's Assessment:

Adequate descriptions of the lesinurad Reference Standards used during development have been provided including batch analyses. Updated spectral data has been provided for the current lesinurad reference standard, lot 17JL02.HE00016.

2.3.S.6 Container Closure System

13. Is the proposed container closure system(s) for commercial packaging of the drug substance adequate to protect the drug substance from the environment (oxygen, moisture, microorganism, etc.) during the storage?

Applicant's Response:
Lesinurad drug substance is stored in (b) (4)

Primary packaging complies with 21CFR 177.1520 (suitability for use in contact with U.S. foodstuffs). Specifications are in place for the (b) (4) used to store lesinurad drug substance.

Reviewer's Assessment:

The container closure system is appropriate for storage and/or shipment of drug substance. (b) (4) .

2.3.S.7 Stability

14. What is the proposed retest period for the drug substance? Do the drug substance stability data support the proposed retest period and storage conditions in the commercial container closure system? How does statistical evaluation of the stability data, if any and any observed trends support your proposed retest period?

15. Are the post-approval stability protocols and other stability commitments for the drug substance satisfactory?

Points to Consider

- What are the stability acceptance criteria? If applicable, what is the justification for acceptance criteria that differ from the drug substance release specification?
- Were any potential issues identified during the review for possible evaluation during inspection? (e.g., questionable development data, unexplained stability failures, potential data integrity issues, etc)
- What are the post-approval stability protocols and other stability commitments for the drug substance?

Applicant's Response:

(b) (4)

[redacted]

(b) (4)

[redacted]

1 Page(s) have been Withheld in Full as B4 (CCI/TS) immediately following this page

(b) (4)

[redacted]

Reviewer's Assessment:

The data from all stability studies demonstrate that lesinurad is chemically and physically stable under ICH Q1A(R2) conditions at all tested time points within a container closure system representative of the commercial container closure.

Stability data for both primary and supporting batches lesinurad drug substance met the proposed commercial specification criteria at all storage conditions studied. Lesinurad has been shown not to be hygroscopic and does not need to be protected from moisture.

Based on the photostability results, it has been concluded that lesinurad drug substance is

(b) (4)

(b) (4)

Based on this acceptable stability data, and following ICH Q1E Guidelines, a retest period of (b) (4) months at (b) (4) is granted for the drug substance when stored in (b) (4) This is in agreement with the applicant's proposed retest period of (b) (4) months for the drug substance.

An adequate post-approval stability protocol and stability commitment for the drug substance has been provided. The first three commercial lots of lesinurad drug substance will be added to the stability program according to the provided protocol. In addition, one lot of drug substance per year will be added to the stability program for every year that drug substance is manufactured.

OVERALL ASSESSMENT AND SIGNATURES: DRUG SUBSTANCE

Reviewer's Assessment and Signature:
There are no approvability issues for the drug substance portion of this application. There are no deficiencies that need to be reported to the applicant with respect to the drug substance portion of this application. The data is adequate to support the use of lesinurad drug substance in the manufacture of lesinurad drug product.

Joseph Leginus, Ph.D. 04-Sep-2015.

Supervisor Comments and Concurrence:

I concur with Dr. Leginus' assessment that the drug substance is acceptable for use in the drug product.

Donna F. Christner, Ph.D., 04-Sep-2015.

Note: additional reviewers can be added, as appropriate

ASSESSMENT OF THE DRUG PRODUCT

2.3.P DRUG PRODUCT

P DRUG PRODUCT

Direct quotes from the applicant are in *italics.*
Questions in our IR letter dated June 3, 2015 are in **bold.**

2.3.P.1 Description and Composition of the Drug Product

16. Are there any scientific or regulatory concerns about the proposed composition of the drug product?

Reviewer's Assessment:

No

Blue, oval, film-coated tablets (5.7 x 12.9 mm) containing 200 mg of lesinurad.
The following table is adapted from the table in P.3.1.2 (amended 7/16/2015), with the addition of an indicat actual uses of the materials (not in italics)

Component Name	*Quality Standard*	*Function*	*Quantity per Unit*	*% w/w*
				(b) (4)
Lesinurad	*In-house*	*Active*	*200.00*	(b) (4)
Hypromellose 2910	*USP, Ph Eur*	(b) (4)	(b) (4)	
Microcrystalline	*NF, Ph Eur*			
Lactose Monohydrate	*NF, Ph Eur*			
Crospovidone	*NF, Ph Eur*			
Magnesium Stearate	*NF, Ph Eur*			
				(b) (4)
Film Coating				
Opadry Blue (b) (4)	*Supplier*			
				(b) (4)
Total Target Weight:				***100.0%***

The composition of the film coat is provided in Section P.4.1. I have calculated the amount per tablet.

Ingredients	*Quality Standard*	*Function*	*Amount (% w/w)*	**Amount (mg/tablet)**
				(b) (4)

2.3.P.2 Pharmaceutical Development

17. Does the information described in the pharmaceutical development section support the proposed product design, commercial formulation, dosage form, compatibility, specification, and overall control strategy of the drug product?

Yes

P.2.1 Components of the Drug Product

Drug Substance: The drug substance exists in an (b) (4) . The latter was chosen for all Phase III trials and for stability studies. **ACCEPTABLE**

Excipients: All of the excipients, except the coating, are compendial and have been widely used. (b) (4) **ACCEPTABLE**

P.2.2 Drug Product

Formulation Development

(b) (4)

9 Page(s) have been Withheld in Full as B4 (CCI/TS) immediately following this page

See comment above about the ID test.

P.4.5 Excipients of Human or Animal Origin [Non-compendial]

See above. **ACCEPTABLE**

Reviewer's Assessment:

The control of the excipients is **ACCEPTABLE**

2.3.P.5 Control of Drug Product

19. Is the drug product specification adequate to assure the identity, strength, quality, purity, and potency, and bioavailability of the drug product so that future commercial production batches are comparable to the pivotal clinical batches for the clinical performance in terms of the safety and efficacy

Yes

P.5.1 Specification(s)

This table includes changes in the acceptance criteria for the [(b)(4)] from NMT [(b)(4)]% to NMT [(b)(4)]% and, for the Total degradants, from [(b)(4)]% to [(b)(4)]%. (July 16, 2015 amendment) and changes to the dissolution acceptance criterion (August 20, 2015 amendment). See discussion under "Justification for Specifications" below.

Attribute	***Test***	***Acceptance Criteria***	
Description	*Visual inspection*	*Blue oval tablet, debossed with LES200 on one side and blank on the other*	
Identification	*HPLC/UV Spectrum*	*The UV spectrum of the major peak of the sample preparation corresponds to that of the standard preparation.*	
	HPLC/Retention Time	*The retention time of the major peak of the sample preparation corresponds to that of the standard preparation.*	
Assay	*HPLC*	*[(b)(4)]% of label claim*	
Degradation Products	*HPLC*	*[(b)(4)]*	*NMT [(b)(4)]% w/w*
		Any individual unspecified degradation product	*NMT [(b)(4)]% w/w*
		Total degradation products	*NMT [(b)(4)]% w/w*
Dissolution	*USP Apparatus 2, 75 rpm, 900 mL, Acetate Buffer, pH 4.5 containing 1% SLS, 37 °C USP <711> HPLC or UV Spectrophotometry Sample Analysis*	*Shall comply with the requirements in USP Q = [(b)(4)]% released in 30 minutes.*	

Uniformity of Dosage Units	*Weight variation USP <905>, Ph Eur General chapter 2.9.40*	*Shall comply with requirements in USP/Ph Eur*

The applicant states:

> *"Microbiological quality for lesinurad tablets will not be performed at release. However, it will be tested at least annually using the microbial limit test method compliant with USP <61> and USP <62> and Ph Eur 2.6.12 and Ph Eur 2.6.13. All lots tested are required to pass the acceptance criteria described in the USP <1111>/Ph Eur 5.1.4 for non-sterile non-aqueous oral products."*

See ASSESSMENT OF MICROBIOLOGY below.
For the dissolution specification test and acceptance criterion, see ASSESSMENT OF BIOPHARMACEUTICS below

P.5.2 Analytical Procedures

1. Description: Visual **ACCEPTABLE**
2. Identification: This test uses the same HPLC method as is used for the Assay and impurities. The UV spectrum is collected from (b) (4) nm. Note that the wavelength for detection is (b) (4) nm.
3. Assay and Degradation Products
   These tests use the same HPLC method.

Parameter	**Setting**
Column	(b) (4)
Diluent	
Standard Solution	
Sample stock solution (SSS)	
Working standard solution (WSS)	
Practical limit of quantitation (b) (4) reference solution (PLOQ)	
Injection volume	
Mobile phase	
Column temperature	
Wavelength	
Column flow	
Autosampler temperature	
Total run time	

23 Page(s) have been Withheld in Full as B4 (CCI/TS) immediately following this page

Note that the applicant did not commit to providing data for the batches currently on stability for the remainder of the proposed expiration period.

Question 4 in June 3, 2015 IR Letter:

Provide a commitment to continue the long-term studies through the proposed shelf life.

This was already in P.8.2.

> *"The existing primary stability studies will continue through at least 36 months according to the protocols presented in Section 3.2.P.8.1, Stability Summary and Conclusion."*

ACCEPTABLE

P.8.3 Stability Data

It is not necessary to review the data, since there is no change over time and they support the conclusions.

Reviewer's Assessment:

ACCEPTABLE with a 36 month expiration date.

R.2 Comparability Protocols

26. Is a Comparability Protocol included in the application for post approval changes that might affect drug product quality including sterility assurance? If so, what post-approval changes are anticipated? How will the changes be reported and how will the validation studies be designed to support these changes?

Applicant's Response: This can be adopted from the QbR-QOS and Module 3 provided from the firm.

Reviewer's Assessment:

No Comparabiltiy Protocol proposed. ACCEPTABLE

OVERALL ASSESSMENT AND SIGNATURES: DRUG PRODUCT

Reviewer's Assessment and Signature:

The drug product is well-controlled and the data support the Specifications and the expiration date of 36 months.

Arthur Shaw, PhD
ONDP/DNDP II

CMC Lead Comments and Concurrence:
I concur (04-SEP-2015).

Craig M. Bertha
CMC Lead (for DPARP)
ONDP/DNDP II

Note: additional reviewers can be added, as appropriate

ASSESSMENT OF THE PROCESS

2.3.P DRUG PRODUCT

2.3.P.3 Manufacture

Batch Formula

27. Does the provided batch formula reflect the proposed composition and that of the registration batches?

Applicant's Response:

Batch Formula for Lesinurad Tablets, 200 mg (Amended 7/16/2015)

(b) (4)

[redacted]

(b) (4)

[redacted]

Reviewer's Assessment: ADEQUATE.

The proposed batch formula is the same as the primary stability batches, which were manufactured in the range of proposed commercial scale, based on the review of the executed batch records.

The batch formula supports the proposed drug product/tablet composition. The batch formula has been amended (in Response to Q6, 7/16/2015) (b) (4) [redacted] The batch formula, as amended 7/16/2015, is consistent with the tablet composition, process description, flow diagram, batch record, and is deemed satisfactory. (b) (4) [redacted].

A correspondence with the applicant regarding the batch formula is as follows:

FDA Request 6 in June 3, 2015 IR Letter:
Amend the batch formula to show the different composition of (b) (4) [redacted] consistent with the batch record.

Ardea Response in July 16, 2015 Amendment:
Module 3, Section 3.2.P.3.2, Batch Formula has been updated as requested to specify (b) (4) [redacted]

ACCEPTABLE

A schematic diagram for the Zurampic tablet (rendered by the reviewer) based on the batch formula and manufacturing process is presented next.

(b) (4)

[redacted]

Description of the Manufacturing Process and Process Controls

28. Is the commercial manufacturing process adequately described and controlled to ensure consistent manufacturing of acceptable drug product batches? (Note: add applicant's response and reviewers assessment box after this question)

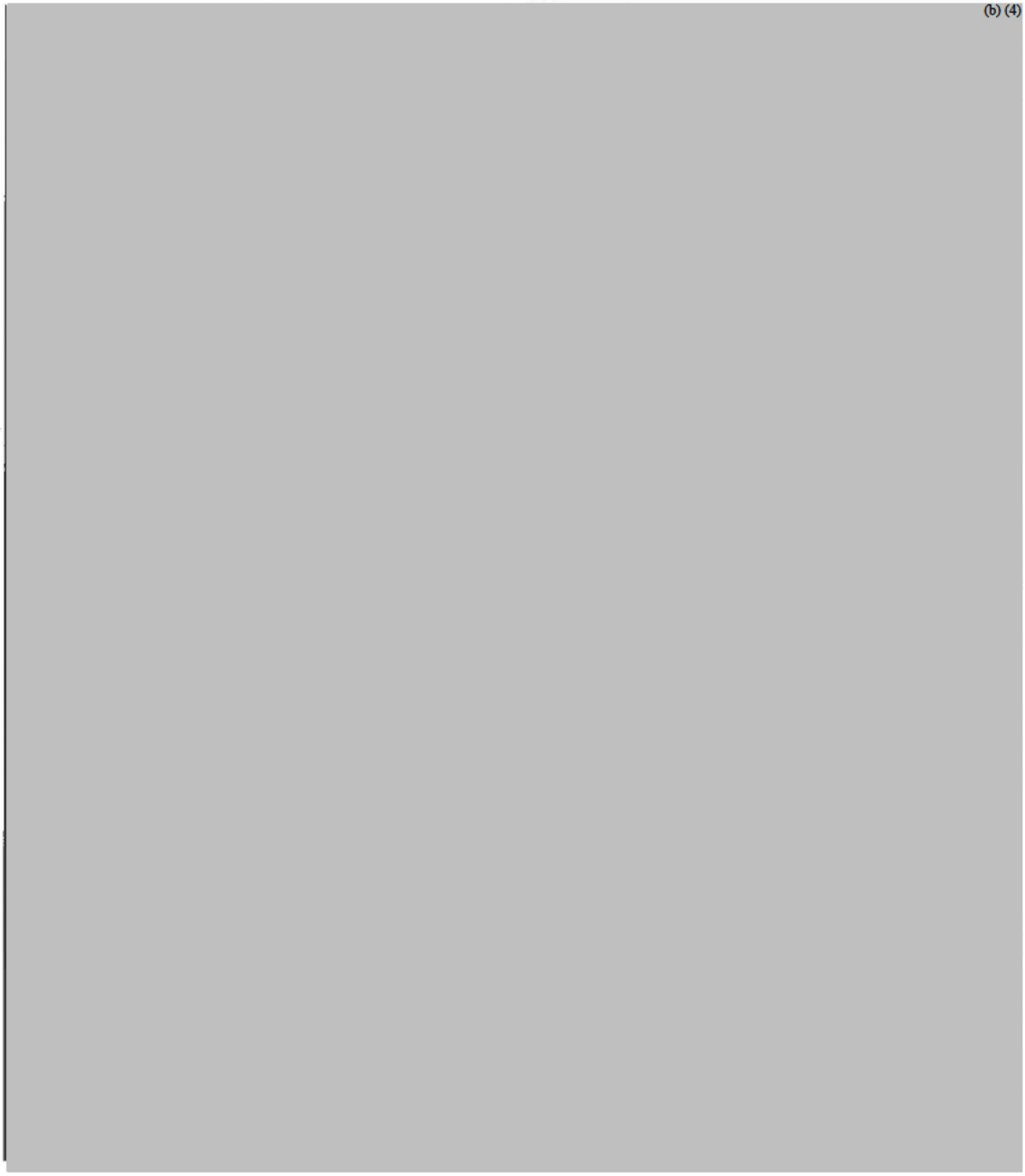
Applicant's Response for Manufacturing Pharmaceutical Development

(b) (4)

[redacted]

7 Page(s) have been Withheld in Full as B4 (CCI/TS) immediately following this page

(b) (4)



Applicant's Response for Process Validation for DP Manufacturing

In 3.2.P.3.5 PROCESS VALIDATION AND/OR EVALUATION the applicant stated that the prospective validation of the drug product manufacturing process will be completed prior to sales of drug product produced at the commercial manufacturing site. The validation batches will be processed according to an approved manufacturing batch record and per an approved Process Validation Protocol. The applicant also discussed continued process verification and improvement throughout the product lifecycle.

Reviewer's Assessment: ADEQUATE.

The post-approval commitment to validation the commercial manufacturing is acceptable. The applicant has actually provided batch analysis data several commercial-scale batches manufactured at the commercial site AstraZeneca in Sweden. The batches include five batches for each of the 200 mg (b) (4)) and 400 mg ((b) (4) tablets manufactured from Jan. 2013 to Oct. 2014. All results met specification criteria in place at the time—demonstrating the capability of AstraZeneca site to manufacture Zurampic tablets at commercial scale using the proposed manufacturing process.

29. Do the proposed manufacturing process and controls assure sterility/microbial limits of the final drug product?

Reviewer's Assessment: ADEQUATE.

The product is not a sterile product. The firm's compliance with the cGMP requirements will be critical to the control of microbial contamination in the product. See the section ASSESSMENT OF THE MICROBIOLOGY for more details.

R.2 Comparability Protocols

30. Is a Comparability Protocol included in the application for manufacturing process or manufacturing site post approval changes? If so, what post-approval changes are specified? What is the method of evaluation of the changes and the acceptance criteria for the change?? How will the changes be reported?

Applicant's Response: No provided.

Reviewer's Assessment: N/A

No Comparabiltiy Protocol proposed.

OVERALL ASSESSMENT AND SIGNATURES: PROCESS

Reviewer's Assessment and Signature:

ADEQUATE. – Huai Ted Chang 8/17/2015

Supervisor Comments and Concurrence:

ASSESSMENT OF THE FACILITIES

2.3.S DRUG SUBSTANCE

2.3.S.2 Manufacture

Manufacturer(s)

31. Are the manufacturers in conformity with current good manufacturing practice to assure that the drug meets the requirements of the FD&C Act as to safety and has the identity and strength, and meets the quality and purity characteristics which it purports?

Facility Name	FEI	Profile Code	Responsibilities	Facility Sub-Score	Process Sub-Score	Product Sub-Score	Overall Initial Facility Risk Assessment	Recommendation

Reviewer's Assessment:

Pre-Inspection Evaluation:

A pre-inspection risk analysis was covered for the drug substance manufacturers and tester. (b) (4) [redacted]

The risk analysis factored in the compliance history, complexity of process, and experience of the manufacturers in performing the (b) (4) **manufacturing operations. The compliance history, based on inspectional results, is acceptable and coverage is adequate for the CSN and** (b) (4) **manufacturing operations. All DS manufacturers were recently inspected (earliest** (b) (4) **FEI#** (b) (4)**) and were classified NAI.**

(b) (4) [redacted] **Based on this facility review,** (b) (4) **are acceptable.**

(b) (4) **has experience with the manufacturing of finished APIs.** (b) (4) [redacted] **Based on the facility review,** (b) (4) **is acceptable.**

QUALITY ASSESSMENT
NDA # 207988

A review of the testing activities performed at (b) (4) was performed. The firm is responsible for the quality control testing of the lesinurad drug substance. No unique testing is noted pertaining to the drug substance. A review of the firm's compliance history found that it was last inspected in (b) (4) and was classified VAI. A review of the firm's responses were reviewed and found to be adequate.

The risk analysis and assessment was discussed with the review team. The team agreed to waive inspections for all facilities pertaining to the DS. Therefore the DS facilities are acceptable with respect to NDA 207988.

2.3.P DRUG PRODUCT

2.3.P.3 Manufacture

Manufacturer(s)

32. Are the manufacturers in conformity with current good manufacturing practice to assure that the drug meets the requirements of the FD&C Act as to safety and has the identity and strength, and meets the quality and purity characteristics which it purports?

Points to consider

- Who manufactures the drug product? List each participant and facility involved in drug substance manufacturing/testing activities and clearly state their function. List the date of the last FDA inspection for each facility involved and the result of the inspection. Identify any historical inspectional findings that could impact the manufacturing of this product?
- For each of the facilities listed above, identify any potential GMP-related issues (e.g., expected in-process testing not being performed, questionable development, unexplained stability failures, data integrity issues, etc)?
- For each of the facilities listed above, are there any indicators that warrant a pre-approval inspection? Explain why or why not.
- For each of the facilities in which a pre-approval inspection was performed, list the date performed, summary of the inspection and any un-resolved observations. Indicate how any of the potential issues identified were/were not mitigated.

Facility Name	FEI	Profile Code	Responsibilities	Facility Sub-Score	Process Sub-Score	Product Sub-Score	Overall Initial Facility Risk Assessment	Recommendation
Astrazeneca Pharmaceuticals LP	2517100	TCM	Packaging and Release	5	6	10	21	AC- Based on File Review
Astrazeneca Sterile Operations	3003342394	TCM	DP Manufacturing	7	6	0	13	AC- Based on File Review
Astrazeneca	3002806411	CTL	DP QC and Micro Testing	1	5	0	6	AC- Based on File Review

Reviewer's Assessment:

Pre-inspection evaluation:

A pre-inspection risk analysis was covered for the drug product (DP) manufacturer, tester, and packaging. AstraZeneca Sterile Operations (FEI# 3003342394) manufactures lesinurad tablets (immediate release) (b) (4) A review of AstraZeneca's manufacturing capabilities has been conducted and the firm manufactures a variety of dosage forms, including immediate and extended release tablets. The compliance history review of EIRs and inspectional summaries listed in FACTs. The firm's most recent inspection was in (b) (4) The inspection was classified VAI with concerns around maintenance of HVAC, CIP and equipment qualifications. A view of the firm's corrective actions was also conducted. The firm's responses were adequate. Finally a district file review was conducted noting no additional observations or concerns.

The other two sites, AstraZeneca Pharmaceuticals LP (FEI# 2517100), and AstraZeneca (FEI# 3002806411) were reviewed for tablet packaging and testing operations, respectively. Both sites have been inspected and are capable of performing their respective functions. A review of the application notes no unique packaging operations or analytical testing. Finally, the compliance history for both sites is acceptable for their operations. AstraZeneca Pharmaceuticals, LP was most recently inspected in (b) (4) and classified VAI. The firm is acceptable for packaging operations. AstraZeneca was inspected in (b) (4) and was classified NAI. AstraZeneca is acceptable for laboratory operations.

The risk analysis and assessment was discussed with the review team. The team agreed with the proposal to waive inspections based on the risk analysis review. All drug product manufacturing firms are considered acceptable with respect to NDA 207988.

OVERALL ASSESSMENT AND SIGNATURES: FACILITIES

Reviewer's Assessment and Signature:

Acceptable- Robert H. Wittorf, PharmD. Facility Reviewer

Supervisor Comments and Concurrence:

Concur. Mahesh Ramanadham, 8/20/15

Note: additional reviewers can be added, as appropriate

ASSESSMENT OF THE BIOPHARMACEUTICS

Drug Substance

According to the Applicant, Lesinurad is a selective uric acid reabsorption inhibitor (SURI) that inhibits uric acid transporter 1 (URAT1).

(b) (4)

The crystalline free acid form (b) (4) was introduced in Phase 1 and used for the Phase 2 extension study and in **all** Phase 3 clinical trials. The crystalline free acid is the same form used in the commercial formulation (tablet). The drug substance manufacturing process produces (b) (4)

The physical and chemical properties of the drug substance were evaluated during drug product development. The attributes which were evaluated during development are summarized by this reviewer in Table 1-1.

Table 1-1. Physicochemical Properties and Attributes of Lesinurad Free Weak Acid

Property	Assessment
Molecular Weight (g/mole)	404.3
Appearance	crystalline powder (b) (4)
Proposed Particle Size Distribution*	D(v, 0.5) NMT (b) (4) µm D(v, 0.9) NMT (b) (4) µm
Solid State Form	crystalline free acid
Aqueous Solubility as a function of pH	low aqueous solubility at gastric pH but high solubility at intestinal pH (5.3 to 7.5)
Permeability	In vitro Caco-2 cell permeability (A - B Papp) results indicate high permeability of lesinurad
pKa	3.2 (carboxylate)
Log P (octanol/water)	2.85 at 25°C
Log D	-1.35 at pH7.4
Chemical Stability	crystalline free acid form (b) (4)
Biopharmaceutics Classification	BCS Class II

See Question #33 for detailed support of setting appropriate drug substance particle size distribution specification.

Lesinurad crystalline powder (b) (4) has a low aqueous solubility at gastric pH, but high solubility at intestinal pH (5.3 to 7.5). To be considered highly soluble, the BCS solubility class boundary for lesinurad (based on the tablet strength of 200 mg) is not less

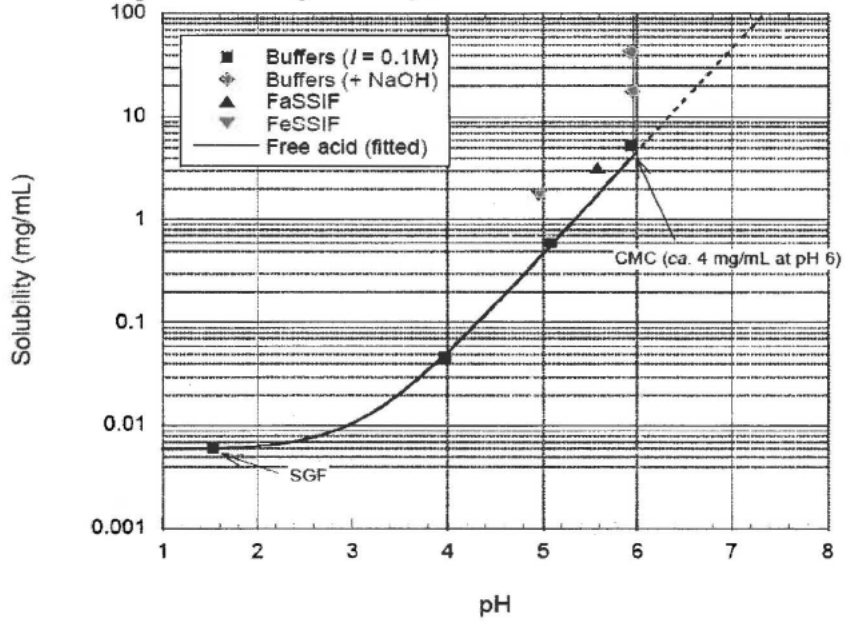
than 0.8 mg/mL over the physiologically relevant pH range of 1 to 7.5 (6.8). Lesinurad does not meet this criterion below approximately pH 5.3, but is highly soluble above pH 5.3. The solubility of Lesinurad is consistent with the behavior of a carboxylic weak acid. The aqueous pH solubility profile of lesinurad is presented in Table 1-2 and Figure 3 below.

Table 1-2. Lesinurad Aqueous Solubility, 37 °C

Media	pH (final)[a]	Solubility (mg/mL)
FaSSIF[b] pH 6.5	5.6	3.2
FeSSIF[c] pH 5.0	5.0	1.7
SGF[d] pH 1.6 (HCl 30 mM, I = 0.1 M)	1.5	0.0061
pH 4 buffer (Citrate 25 mM, I = 0.1 M)	4.0	0.045
pH 5 buffer (Acetate 25 mM, I = 0.1 M)	5.1	0.60
pH 6 buffer (Citrate 22 mM, I = 0.1 M)	5.9	5.2
pH 6.5 buffer (Phosphate 25 mM) plus NaOH[e]	6.0	17
pH 6 buffer (Citrate 22 mM) plus NaOH[e]	5.9	43
pH 4.5 buffer (Acetate, 50 mM) plus 1% SLS	4.5	1.77

Abbreviations: SLS = Sodium lauryl sulfate
a pH at solubility equilibrium
b FaSSIF: Fasted-state simulated intestinal fluid pH 6.5.
c FeSSIF: Fed-state simulated intestinal fluid, pH 5.0.
d SGF: Simulated gastric fluid, pH 1.6, consists of 0.03 M HCl and 0.079 M NaCl.
e Addition of NaOH (above the CMC) increases solubility without increasing pH.

Figure 1: Lesinurad pH-Solubility Profile, 37 °C



In vitro Caco-2 cell permeability (A - B P_{app}) results indicate high permeability of lesinurad, and the absolute bioavailability of lesinurad is 100% as determined by clinical study RDEA594-131 in which oral plasma data and IV data were obtained in the same healthy volunteer subjects.

Drug Product
Lesinurad drug product is provided as blue, oval, film-coated tablets containing 200 mg of the active pharmaceutical ingredient, lesinurad, as the free acid. The tablets are debossed with "LES200" on one side and are blank on the other. The drug product is intended for oral administration for the treatment of gout. The quantitative composition of the lesinurad IR tablets, 200 mg is provided in "Assessment of the Drug Product" Section 2.3.P of this review.

The 200 mg and 400 mg (*not proposed for commercial release*) tablet strengths (b) (4) A biowaiver is being sought for the 200 mg tablet based on established linear pharmacokinetics, similar *in vitro* dissolution, and the (b) (4) similarity of the (b) (4) 200 mg and 400 mg tablet strengths. This submission contains pre- and post- manufacturing site change in vitro dissolution data to support approval of the 200 mg strength.

33. **Are the in-vitro dissolution test and acceptance criteria adequate for assuring consistent bioavailability of the drug product?**

The dissolution method proposed as a quality control tool for lesinurad IR tablets is summarized below:

USP Apparatus	Speed of Rotation	Medium Volume	Temperature	Medium
II	75 rpm	900 mL	37°C	pH 4.5 sodium acetate buffer with 1% SLS

What data are provided to support the adequacy of the proposed dissolution method (e.g. medium, apparatus selection, etc.)?

Dissolution Method Development
The dissolution method was evaluated during the IND stage. At that stage of development (IND 102128 meeting minutes dated 24 OCT 2014), the review team considered the method acceptable.

The ultimate goal of the in vitro dissolution method development process was to arrive at a robust quality control tool to assess batch-to-batch quality, to allow quality control batch release and to assess product stability.

The dissolution method was evaluated to determine the effect that varying dissolution parameters would have on the *in vitro* drug release (for more details refer to dissolution method report under Module 3.2.P.2 Pharmaceutical Development submission date 07/16/2015). The following method parameters were evaluated: the effect dissolution apparatus and rotation speed, the effect of media type, and effect of surfactant type/concentration.

Dissolution Apparatus and Rotation Speed

(b) (4)

3 Page(s) have been Withheld in Full as B4 (CCI/TS) immediately following this page

(b) (4)

[redacted]

Reviewer's Comments
The Applicant submitted adequate/sufficient information to support the discriminating ability of the dissolution method.

What information is available to support the robustness (e.g. linearity, accuracy, etc.) of the dissolution methodology?

Dissolution Method Validation
The Applicant provided enough information to support the validity of the analytical method for dissolution testing for Lesinurad IR tablet (refer to CMC review for more details, see p. 63; also see **Sample Analysis Method** session at \\cdsesub1\evsprod\nda207988\0007\m3\32-body-data\32p-drug-prod\zurampic-tablets-200mg\32p2-pharm-dev\pharmaceutical-development.pdf).

What data are available to support the discriminating power of the method?

According to the Applicant, the discriminating capability and robustness of the dissolution method as a QC test were established through evaluation of factors that affect tablet dissolution such as:

Material Attributes:

18 Page(s) have been Withheld in Full as B4 (CCI/TS) immediately following this page

Is the proposed dissolution method biorelavant? What data is available to support this claim?

The submission contains data to support the assessment of the biorelevancy of the in vitro dissolution testing method (e.g. the ability of the method to reject batches that are not bioequivalent). Results from Study RDEA594-129 were used to support the selection of a biorelevant dissolution method with suitable discriminating power.

Designed as a phase 1, randomized, open-label, 2-treatment, 2-sequence, 2-period, balanced single-dose, crossover, pharmacokinetic study in healthy adult males subjects to assess the relative bioavailability of 400 mg lesinurad tablets, manufactured at two different sites, (b) (4) and AstraZeneca AB (located in Sodertalje, Sweden). The study was conducted in the fasted (Cohort 1) and fed (Cohort 2) conditions to evaluate the relative bioavailability of lesinurad in AZ Lot A against the reference lot (b) (4) The study then further evaluated the relative bioavailability of lesinurad in AZ Lot B against the reference lot (b) (4) (12A015) in the fasted (Cohort 3) and fed (Cohort 4) conditions. Each cohort enrolled 18 subjects randomized to 1 of 2 treatment sequences with a 4 day washout period.

Administration of Lot ELAB (400 mg) in Study RDEA594-129 to subjects in both the fed and fasted states resulted in point estimates for Cmax and AUC that were approximately 20% and 10% lower, respectively, than the reference batch, Lot 12A015 (400 mg) (Table 9).

Table 9: Summary of Bioequivalence Assessment from Cohorts 1 and 2 of Study RDEA594-129

Treatment	N	PK Parameters	Geomean Ratio (CI90%)
AstraZeneca AB Lot ELAB versus (b) (4) Lot 12A015 (Fasted Condition)	18	C_{max}	(b) (4)
		AUC_{last}	
		AUC_{∞}	
AstraZeneca AB Lot ELAB versus (b) (4) Lot 12A015 (Fed Condition)	18	C_{max}	
		AUC_{last}	
		AUC_{∞}	

(b) (4)

Reviewer's Assessment:

The data submitted as part of the original submission and during the review cycle contained sufficient information on the discriminating ability of the method towards (b) (4) and therefore is acceptable. In addition, in vivo data (BE data) and in silico model predictions support the biorelevant properties of the method.

ACCEPTANCE CRITERION

What is the proposed dissolution acceptance criterion for this product?

The following dissolution acceptance criterion was proposed by the Applicant as quality control for Lesinurad IR tablet:

Proposed Dissolution Acceptance criterion
Q= (b) (4) % in 30 min

What data are available to support it?

According to the Applicant, the proposed acceptance criterion is based on release data from batches tested in clinical trials formulations at the proposed manufacturing site. As shown in Figure 15 for the 200 mg strength.

Figure 15. Mean Dissolution Profiles of Phase 3 Lesinurad Tablets, 200 mg Using QC Dissolution Method (n = 12)

(b) (4)

Is the acceptance criterion acceptable? If not, what is the recommended criterion? Is the setting of the dissolution acceptance criterion based on data from clinical and registration batches?

The proposed acceptance criterion (b) (4)% at 30 min) is able to reject for non-bioequivalent batches of tablets that differ in formulation which is provided as an extreme variant (Figure 14). However, based on the provided data, it seemed that this criterion would not reject for batches with a dissolution profile close to this proposed criterion which dissolution profile was much slower compared to the clinical batches. Therefore, we recommended the dissolution acceptance criterion be tightened for the following reasons (communicated to the Applicant June 4, 2015):

The submitted dissolution profiles of lesinurad tablets 200 mg do not provide adequate support of the proposed 30-minute time point dissolution specification as follows:

(b) (4)

In an IR dated August 7, 2015 the Applicant was asked to provide the following information/data:

- *Batch numbers 12E058 and MPAC behave as outliers (e.g.* (b) (4) *. Provide an explanation for the observed dissolution behavior,* (b) (4)
- *If available, submit in vivo data (e.g. PK data) demonstrating that batches with a similar dissolution profile to batches 12E058 and MPAC do not have an impact on systemic exposure.*
    - *If in vivo data are not available, consider providing in silico predictions (e.g. GastroPlus predictions) on the impact of lower dissolution profiles (e.g. comparable to those observed for batch 12E058) on the systemic exposure of your drug product.*

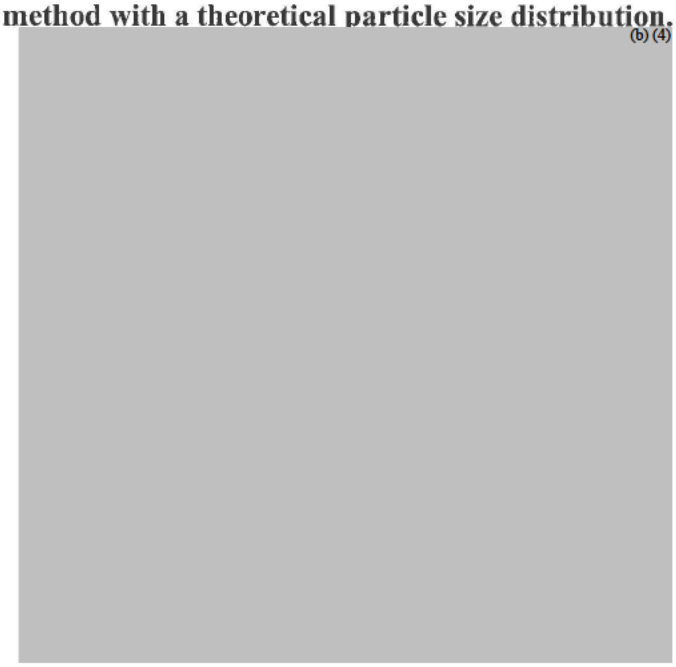
In response to the Information Request the Applicant provided in silico predictions, using a GastroPlus model, to evaluate the impact of lower dissolution profiles, comparable to those observed for lots 12E08 and MPAC, on the systemic exposure of lesinurad.

A detailed summary of the In silico biopharmaceutics modeling for Lesinurad tablets is provided above in Material Attributes (API Particle Size) page 102. Description of the IN VIVO-IN VITRO Extrapolation for exploring potential edge of failure for dissolution is provided below.

Incorporation of MPAC (200 mg) dissolution data into the modeling using Option A

The virtual particle size distribution was generated in Excel to use as input for the GastroPlus model. As MPAC is a 200mg tablet batch, simulations were performed at a 400mg dose (i.e. 2x200mg) to facilitate comparison to the simulations previously performed for ELAB and the reference batch 12A015 (Figure 16).

Figure 16: Fitting of dissolution profile for batch MPAC in the QC dissolution method with a theoretical particle size distribution.



A simulated trial using the virtual population was performed for batch MPAC. It can be seen that the predicted performance of MPAC is similar to the reference batch 12A015 for both AUC and Cmax (Figure 17 and Table 10).

Figure 17: Individual value plots for Cmax and AUC from the simulated trial with batches 12A015, ELAB and MPAC

Table 10: Paired comparison of ELAB and MPAC vs. 12A015 Cmax and AUC using the values obtained from the virtual trial (Predictions from GastroPlus; statistical analysis from Minitab software).

	Predicted C_{max}		Predicted AUC (0-96)	
	Geomean Ratio	90% CI	Geomean Ratio	90% CI
ELAB vs. 12A015				(b) (4)
MPAC vs. 12A015				

Batch MPAC, which passes the proposed dissolution specification, is anticipated to be bioequivalent to the reference clinical batch 12A015 according to the *in silico* modeling described above. The geomean ratios for both AUC and Cmax are very close to one; in an appropriately powered bioequivalence study these batches (12A015 and MPAC) would be expected to give confidence intervals that fall within the standard limits of (b) (4)

As batch 12E058 has a similar *in vitro* dissolution profile to batch MPAC, this batch is also expected to be bioequivalent *in vivo*, as well. This demonstrates that the proposed dissolution specification of Q= (b) (4) % at 30 minutes is justified, as it is able to pass batches which are anticipated to have suitable clinical performance, and rejects batches which have been shown to have reduced exposures *in vivo* (batch ELAB).

Simulations exploring potential edge of failure for dissolution:

To explore the dissolution space, an edge of failure for a dissolution profile that would keep the Cmax exposure ratio to 12A015 between approximately (b) (4) (which is expected to pass an adequately powered bioequivalence study) was investigated.

A virtual Batch A was generated with a dissolution profile that reaches complete release within (b) (4) (Figure 18-1). For input to the GastroPlus model, the dissolution profile was fitted to a theoretical particle size distribution using Option A (Figure 18-2).

Figure 18-1: Dissolution profile of Virtual Batch A vs. batches used in the in silico model

Figure 18-2: Fitting of dissolution profile for Virtual Batch A with a theoretical particle size distribution

A simulated trial was performed for Virtual Batch A using 25 subjects. The simulations demonstrate that Virtual Batch A would be anticipated to be bioequivalent to batch 12A015, as the geomean ratios for Cmax and AUC are close to one (Table 11). This exemplifies the robust *in vivo* performance of lesinurad, driven by high intestinal solubility and good permeability. Although the edge of failure for dissolution was not found, these data demonstrate that the proposed dissolution specification sits comfortably within a region of dissolution performance where bioequivalence is anticipated, and is not near an edge of failure for dissolution. This provides additional confidence in the proposed specification.

Table 11: Paired comparison of Virtual Batch A vs. 12A015 Cmax and AUC using the values obtained from the virtual trial

	Predicted C_{max}		Predicted AUC (0-96)	
	Geomean Ratio	90% CI	Geomean Ratio	90% CI
Virtual Batch A vs. 12A015	(b) (4)			

Applicant's Conclusions:
The design of Virtual Batch A demonstrates a dissolution "safe space" for lesinurad IR tablets, in which batches are anticipated to be bioequivalent to the clinical reference 12A015 are represented in the green area of Figure 19.

Figure 19: Proposed Dissolution "safe space" for lesinurad IR Tablets using the QC dissolution test

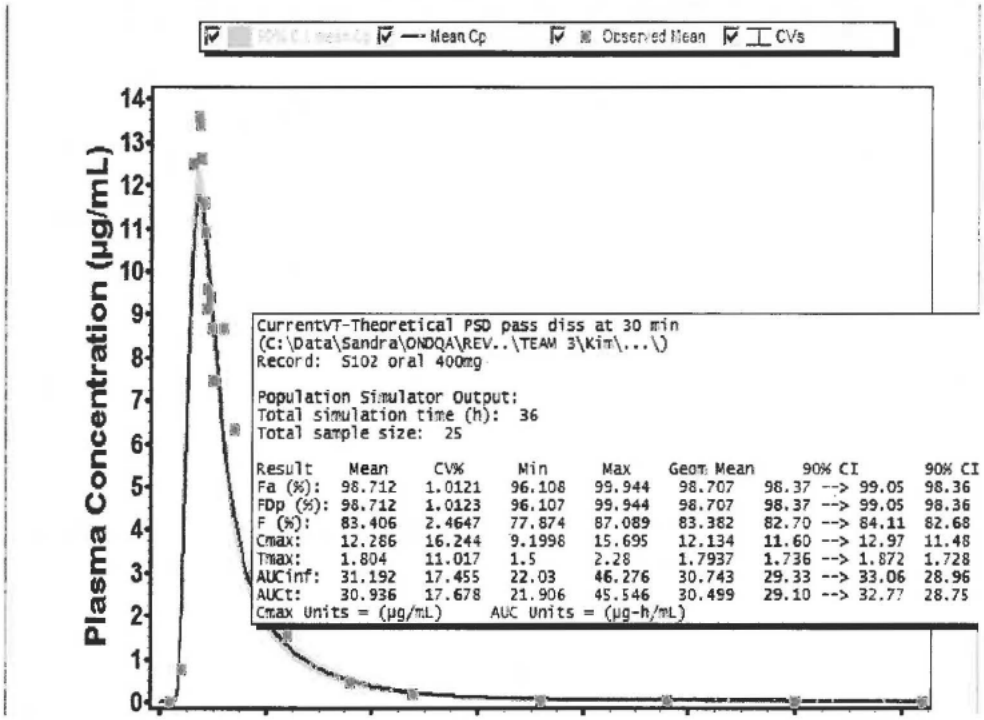
The lower limit is proposed based on the simulation results for Virtual Batch A, which GastroPlus modeling indicates will be bioequivalent to standard clinical batches such as 12A015 despite having a dissolution profile which would fail the proposed dissolution specification of Q=(b) (4)% in 30 minutes. For the upper limit, any batch showing dissolution quicker than 12A015 is also anticipated to be bioequivalent to standard clinical batches as dissolution does not impact the absorption rate which is rate-limited by permeability, and therefore AUC and Cmax will be independent of stomach emptying patterns.

It is proposed that this bioequivalence "safe space" gives further assurance that the proposed dissolution specification limits of Q=(b) (4)% in 30 minutes will not allow to release a drug product commercial batch that would be bio-inequivalent to pivotal clinical batches such as 12A015. The proposed dissolution specifications for the release of lesinurad tablets are well within the anticipated bioequivalent space using the current QC release dissolution method.

Reviewers' Comments

The review team ran the GastroPlus model using the calculated particle size distribution from the observed dissolution profile as an input for batch MPAC, a batch with similar dissolution profile for the clinical batch. Likewise, simulations were run for a batch with a dissolution profile on the edge of failure for a criterion of Q(b) (4)% at 30 min. The results of the simulation showed that the Point Estimates for the predicted Cmax and AUCt meet the goal post for BE for both MPAC (not shown in here) and the virtual profile (Figure 20).

Figure 20: Measured vs predicted plasma concentration time profile for a virtual batch with dissolution profile at the edge of failing the proposed dissolution specification



Reviewer's Assessment:

The Applicant's submitted in silico absorption modeling adequately assessed the impact of in vitro dissolution on in vivo performance of lesinurad tablets. The GastroPlus simulations provided supportive evidence for the acceptability of the proposed dissolution acceptance criterion of Q(b)(4)% in 30 minutes for lesinurad tablets, 200 mg. The proposed acceptance criterion securely is within the region of dissolution performance where bioequivalence is anticipated, "safe space", and not near the lower limit of predicted dissolution failure.

Biopharmaceutics Assessment of Risk based on Drug Product Dissolution Testing

PRODUCT PROPERTY/IMPACT OF CHANGE/CQAS	PROBABILITY OF OCCURRENCE (O)	SEVERITY OF EFFECT (S)	DETECTABILITY (D)	FMECA RPN	Assessment Comment
In vitro dissolution	**3**	**3**	**2**	**18**	**Based on the Risk Assessment and development work, the product and process were found to be robust with respect to dissolution CQA.**

The risk of dissolution failure is mitigated through (i) the use of a well justified and characterized in vitro dissolution testing method and (ii) acceptance criterion which assure clinical quality that discriminates between bio-in-equivalent products.

34. **Are the changes in the formulation, manufacturing process, manufacturing sites during the development appropriately bridged to the commercial product?**

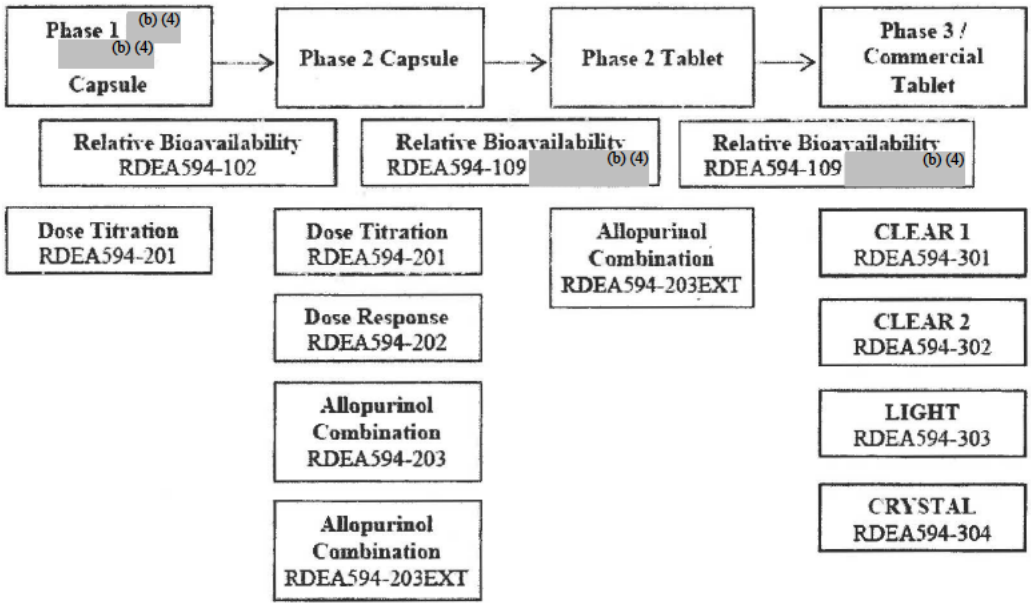
(b) (4)

(b) (4)

What are the highlights of the drug product formulation development?

Figure 21 gives a schematic overview on the lesinurad IR tablet Formulation Development and the data provided to bridge across stages. The Phase 3/commercial formulation is an immediate release lesinurad tablet. A summary of the formulations used in the Phase 2 and Phase 3 efficacy studies, and the relevant bridging pharmacokinetic (PK) studies is shown in Figure 21. All the BA studies listed in the diagram are being reviewed by OCP as agreed upon with the OCP reviewer via email communication on May 2, 2014.

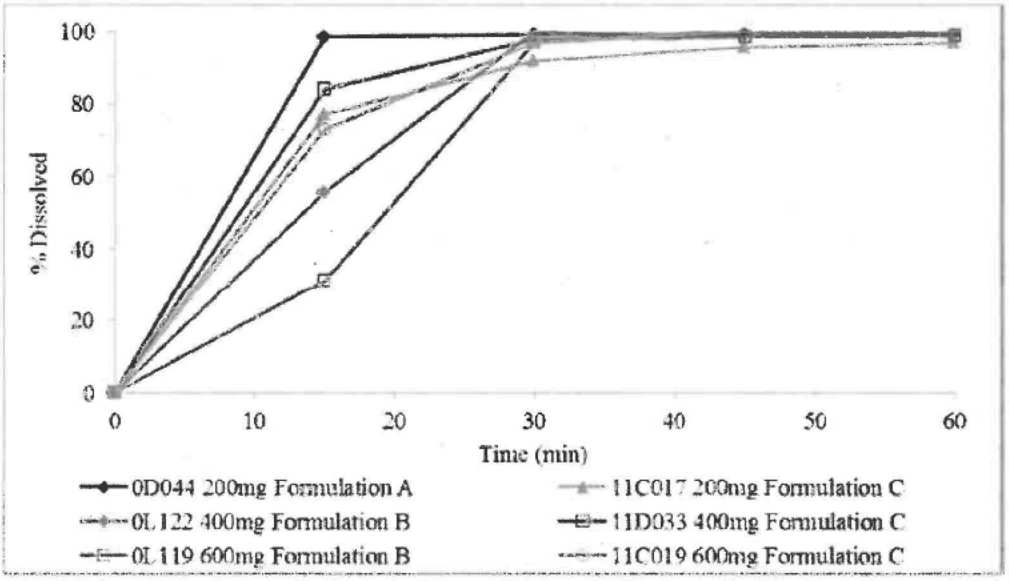
Figure 21: Listing of Biopharmaceutic Studies



The Phase 1 clinical studies used lesinurad sodium capsule and solution, the capsule formulation was also used in Phase 2 studies. The 3 formulation variants for lesinurad tablets, Formulation A, Formulation B and Formulation C, were each compared to the

lesinurad sodium capsule formulation used in Phase 2 studies and used as a reference. The results from this study indicated that lesinurad tablets have comparable bioavailability to the lesinurad sodium capsules. The differences between formulation C and A is: for formulation C, (b) (4) The in vitro release profile for Formulation C was similar to that observed for Formulation A. Formulation B has a lower exposure compared with the reference, which was likely due to (b) (4) nt (Figure 22).

Figure 22: Mean Dissolution Profile of Lesinurad Tablet Formulations Dosed in Study RDEA594-109



The proposed commercial product, lesinurad tablets, 200 mg, is identical to that used in Phase 3 studies. Transfer to the proposed commercial manufacturing site is established in bioequivalence studies (RDEA594-129 and RDEA594-132). To support the site change the Applicant submitted adequate pre- and post- in vitro dissolution testing data as indicated in SUPAC-IR.

Are there any manufacturing changes implemented (e.g. formulation changes, process changes, site change, etc.) to the clinical trial formulation? What information is available to support these changes?

Drug products (Formulation C) used in clinical studies (Phase 3) are identical to the commercial formulation. (\\cdsesub1\evsprod\nda207988\0000\m3\32-body-data\32p-drug-prod\zurampic-tablets-200mg\32p2-pharm-dev\pharmaceutical-development-1.pdf).

Are all the strengths evaluated in the pivotal clinical trials? What data are available to support the approval of lower strengths?

The 200 mg, 400 mg and 600 mg Lesinurad IR tablets were evaluated in phase 3 trials, while only the 200 mg strength is proposed for approval within this submission.

DISSOLUTION APPLICATIONS BIOWAIVERS

Is there a request for waiver of in vivo BE data (Biowaiver)? What is/are the purpose/s of the biowaiver request/s? What data support the biowaiver request/s?

There is a request for waiver of in vivo BE data for Lesinurad IR tablets, 200 mg. The request for biowaiver is not applicable. The manufacturing site change is supported by in vitro dissolution profile comparisons. Since site change is considered a minor change for an immediate release oral dosage form, BE studies are not required. Therefore, this application is evaluated for the approval of the manufacturing site changes for 200 mg strength. The following information/data was submitted to support the site change.

- **Formal biowaiver request**: The formal request can be located in Module 1.12.15 Request for Waiver of In Vivo Bioavailability Studies (\\cdsesub1\evsprod\nda207988\0000\m1\us\112-other-corr\waiver-rqst-in-vivo-ba.pdf).

- **Dissolution profile comparisons of Lesinurad Tablets, 200 mg pre- and post-manufacturing site change.**
  As per SUPAC-IR, a change in manufacturing site to a different campus, multi-point dissolution profile should be performed in the application/compendial medium at 15, 30, 45, 60 and 120 minutes or until an asymptote is reached. The dissolution profile of the drug product at the current and proposed site should be similar.

  Lesinurad 200 mg tablets manufactured at the new manufacturing site (AstraZeneca AB) exhibit similar in vitro dissolution profiles at (b) (4) and the application medium when compared to lesinurad 200 mg tablets manufactured at (b) (4) The f2-test was not applicable for comparing dissolution profiles in all media, (b) (4) (Figure23 and Table 13).

Figure 23: Comparative In Vitro Dissolution Profiles Lesinurad Tablets, 200 mg Old ((b) (4) vs. New (AZ) Manufacturing Site

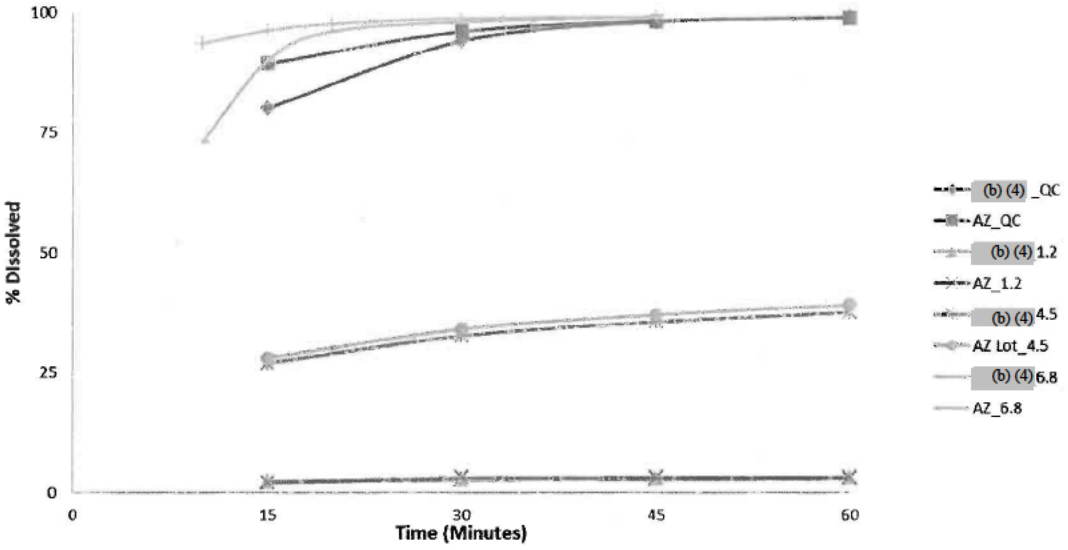


Table 13: In Vitro Dissolution Data for Lesinurad Tablets to Support Manufacturing Site Change: calculated by the Reviewer

Product Description	Dissolution Medium	Similarity Factor(f2)
Reference: 200 mg ((b) (4) Batch No. 12A014 Test: 200 mg (AZ) Batch No. MPAD	(b) (4)	N/A (incomplete release at 60 min)
		N/A (incomplete release at 60 min)
		N/A (b) (4)
		N/A (b) (4)

Reviewer's Assessment: Acceptable

Lesinurad 200 mg tablets manufactured at the new manufacturing site (AstraZeneca AB) exhibit similar in vitro dissolution profiles at different pH values and the application medium when compared to lesinurad 200 mg tablets manufactured at (b) (4) Inc. The f2-test was not applicable for comparing dissolution profiles in all media, as dissolution was incomplete (b) (4)

OVERALL ASSESSMENT AND SIGNATURES: BIOPHARMACEUTICS

Reviewer's Assessment and Signature:

SUMMARY OF BIOPHARMACEUTICS FINDINGS

Ardea Biosciences (A member of the AstraZeneca Group) is seeking approval of ZURAMPIC™ (lesinurad) tablets. Lesinurad is formulated as an immediate release (IR) tablet that is intended for once daily administration for the treatment of hyperuricemia associated with gout in combination with a xanthine oxidase (XO) inhibitor. The recommended dose is 200 mg once daily.

Relative bioavailability studies were conducted on 200 mg, 400 mg and 600 mg strengths of lesinurad tablets (b) (4) (b) (4) The proposed commercial strength is 200 mg.

A biowaiver is sought for the 200 mg strength lesinurad tablet to support a manufacturing site change from (b) (4). to AstraZeneca AB. The request for biowaiver is not applicable to this submission as the evaluation is for a manufacturing site change, considered a minor change (low risk). The manufacturing site change from (b) (4) to AstraZeneca AB is supported by comparative in vitro dissolution profiles from the old and new site for the 200 mg strength.

The manufacturing process development of lesinurad tablets comprises conventional manufacturing methods, (b) (4) . A control strategy is in place to ensure the critical quality attributes (CQAs) are met. Elements of the control strategy include control of input materials, controls for unit operations, in-process controls and final product testing.

This Biopharmaceutics review focuses on the evaluation and acceptability of the data provided to support:

1. Dissolution method and acceptance criterion;
2. Data supporting manufacturing site change (200mg);
3. The use of dissolution data to support the PSD specifications

1. Dissolution Method and Acceptance Criterion:

The in vitro dissolution testing method that is being proposed as a quality control tool for ZURAMPIC (lesinurad tablets), is summarized below:

USP Apparatus	Speed of Rotation	Medium Volume	Temperature	Medium	Proposed Acceptance Criterion
II	75 rpm	900 mL	37°C	pH 4.5 sodium acetate buffer with 1% SLS	Q(b)(4)% release in 30 minutes

The Applicant submitted adequate/sufficient information to support the discriminating ability of the dissolution method. The setting of the dissolution acceptance criterion is based on the mean dissolution profiles of pivotal clinical batches and supportive *in silico* predictions, using a GastroPlus model, which evaluated the impact of in vitro dissolution on in vivo performance of lesinurad. The dissolution testing method and acceptance criterion are **acceptable**.

2. Data supporting manufacturing site change for the 200mg strength
A waiver request for the requirement to submit in vivo BA/BE studies for the 200 mg strength of lesinurad was submitted to support a manufacturing site change. This request is supported by the following data:

- Comparative in vitro dissolution profiles in multiple-pH media ((b)(4) pH 4.5 with 1% SLS, which is the proposed QC method) for pre- and post- manufacturing site change of the 200 mg lesinurad tablets.

Lesinurad 200 mg tablets manufactured at AstraZeneca (new site) exhibit similar in vitro dissolution profiles at pH (b)(4) 4.5, (b)(4) to the 200 mg tablets manufactured at (b)(4) (old site). The f2-test was not applicable for comparing dissolution profiles across tablet strengths in all media, as dissolution was incomplete in the pH (b)(4) and pH 4.5 media and (b)(4) dissolved in 30 minutes. Nevertheless, the profiles were close to superimposable indicating similar in vitro performance. The manufacturing site change is **acceptable**.

3. The use of dissolution data to support the PSD specifications
The following two-point specification with limits for D(v0.5) and D(v, 0.9) are proposed for the drug substance particle size distribution (PSD):

Particle Size Distribution Specification	D(v, 0.5)	NMT	(b)(4) µm
	D(v, 0.9)	NMT	(b)(4) µm

The setting of the PSD specifications are based on the mean dissolution profiles of pivotal clinical batches and supportive *in silico* predictions to evaluate the impact of in vitro dissolution on in vivo performance of lesinurad. The GastroPlus model predicted the proposed specification limits for PSD {D(v, 05) = (b)(4) µm and D(v, 0.9) = (b)(4) µm} would be bioequivalent to the pivotal clinical batches. The PSD specifications are **acceptable**.

QUALITY ASSESSMENT
NDA # 207988

RECOMMENDATION

From the Biopharmaceutics perspective, NDA 207988 for Lesinurad IR film-coated tablets, 200 mg, is recommended for **APPROVAL.**

Kimberly Raines, Ph.D.
Biopharmaceutics Reviewer
Office of New Drug Products

09/03/2015

Supervisor Comments and Concurrence:

Sandra Suarez, Ph.D.
Biopharmaceutics Lead (acting)
Division of Biopharmaceutics
Office of New Drug Products

Note: additional reviewers can be added, as appropriate

ASSESSMENT OF MICROBIOLOGY

34. Are the tests and proposed acceptance criteria for microbial burden adequate for assuring the microbial quality of the drug product?

Applicant's Response:
Microbial limit test for will not be performed at release nor included in the drug product specification for the following reasons and using the ICH Q6A decision tree #8. Although it will be included as Periodic Quality Indicator Test (PQITs)—to be performed at least annually.

- Lesinurad drug substance does not support microbial growth (b) (4) This has been supported by mold challenge tests.
- Materials (excipients (b) (4)), manufacturing, and packaging controls are in place to ensure microbiological control during the manufacture of lesinurad tablets.

- Lesinurad drug substance is not hygroscopic. This has been supported by moisture sorption/desorption data at release and storage (b) (4).
- Historical data show that all microbial limit test data conformed to the pharmacopeial limits at release and throughout stability testing at all conditions and time points tested.

Reviewer's Assessment: ADEQUATE.
The drug product is not a sterile product. The applicant followed the ICH Q6A Decision Tree #8 (for Dry Dosage Form and Microbial Test Data), and the justification to not include Microbial Tests is supported adequately by the historical/development release and stability data (see P2 file named "pharmaceutical-development-5.pdf" and 3.2.P.5 Justification of Specification) and further by the drug substance's (b) (4) and non-hygroscopicity. The firm's compliance with the cGMP requirements will be critical to the control of microbial contamination in the product. The applicant also stated that microbiological quality will be tested annually as a periodic quality indicator test.

2.3.P.6 Reference Standards or Materials

35. Is the proposed container/closure system for the drug product validated to function as a barrier to microbial ingress? What is the container/closure design space and change control program in terms of validation?

Reviewer's Assessment: Not applicable.
This is not a sterile product.

A APPENDICES

A.2 Adventitious Agents Safety Evaluation

36. Are any materials used for the manufacture of the drug substance or drug product of biological origin or derived from biological sources? If the drug product contains material sourced from animals, what documentation is provided to assure a low risk of virus or prion contamination (causative agent of TSE)?

Reviewer's Assessment: Not Applicable

37. If any of the materials used for the manufacture of the drug substance or drug product are of biological origin or derived from biological sources, what drug substance/drug product processing steps assure microbiological (viral) safety of the component(s) and how are the viral inactivation/clearance capacity of these processes validated?

Reviewer's Assessment: Not Applicable

OVERALL ASSESSMENT AND SIGNATURES: MICROBIOLOGY

Reviewer's Assessment and Signature:

ADEQUATE. – Huai Ted Chang 8/17/2015

Supervisor Comments and Concurrence:

CONCUR. – Zhigang Sun 8/17/2015

I. Review of Common Technical Document-Quality (Ctd-Q) Module 1

Labeling & Package Insert

1. Package Insert

(a) "Highlights" Section (21CFR 201.57(a))

(Attach proposed text)

Item	Information Provided in NDA	Reviewer's Assessment
Product title, Drug name (201.57(a)(2))		
Proprietary name and established name	**ZURAMPIC™ (lesinurad)**	**ACCEPTABLE**
Dosage form, route of administration	**tablets, for oral use**	**ACCEPTABLE**
Dosage Forms and Strengths (201.57(a)(8))		
Dosage form, route of administration	**tablets, for oral use**	**ACCEPTABLE**

Conclusion: ACCEPTABLE

(b) "Full Prescribing Information" Section

 # 3: Dosage Forms and Strengths (21CFR 201.57(c)(4))

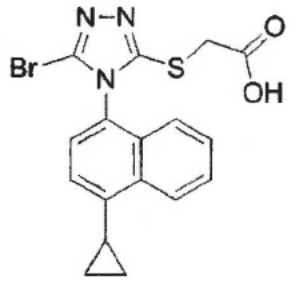
Item	Information Provided in NDA	Reviewer's Assessment
Available dosage forms	Tablets	**ACCEPTABLE**
Strengths:	200 mg	**ACCEPTABLE**
A description of the identifying characteristics of the dosage forms, including shape, color, coating, scoring, and imprinting, when applicable.	ZURAMPIC is available as film-coated tablets for oral administration containing 200 mg lesinurad and the following inactive ingredients: lactose monohydrate, microcrystalline cellulose, hypromellose, crospovidone, and magnesium stearate. ZURAMPIC tablets are coated with Opadry blue.	The word "blue" should be in the description.

Conclusion:

COMMENT: Change the description to:

ZURAMPIC is available as blue film-coated tablets for oral administration containing 200 mg lesinurad and the following inactive ingredients: lactose monohydrate, microcrystalline cellulose, hypromellose, crospovidone, and magnesium stearate. ZURAMPIC tablets are coated with Opadry blue.

#11: Description (21CFR 201.57(c)(12))

Item	Information Provided in NDA	Reviewer's Assessment
Proprietary name and established name	See above	**ACCEPTABLE**
Dosage form and route of administration	See above	**ACCEPTABLE**
Active moiety expression of strength	See above	**ACCEPTABLE**
Inactive ingredient information listed by USP/NF names.	lactose monohydrate, microcrystalline cellulose, hypromellose, crospovidone, and magnesium stearate	**ACCEPTABLE**
Chemical name, structural formula, molecular weight	2-((5-bromo-4-(4-cyclopropylnaphthalen-1-yl)-4*H*-1,2,4-triazol-3-yl)thio)acetic acid  MW 404.28	**ACCEPTABLE**
Other important chemical or physical properties (such as pKa, solubility, or pH)	None	**ACCEPTABLE**

Conclusion: ACCEPTABLE

#16: How Supplied/Storage and Handling (21CFR 201.57(c)(17))

Item	Information Provided in NDA	Reviewer's Assessment
Strength of dosage form	200 mg	**ACCEPTABLE**
Available units (e.g., bottles of 100 tablets)	Bottle of 5 tablets Bottle of 30 tablets Bottle of 90 tablets	**ACCEPTABLE**
Identification of dosage forms, e.g., shape, color, coating, scoring, imprinting, NDC number	blue in color, oval shaped, debossed with "LES200"	**ACCEPTABLE**
Special handling (e.g., protect from light, do not freeze)	Protect from light	**ACCEPTABLE**
Storage conditions	Store at 20° to 25°C (68° to 77°F); excursions permitted from 15° to 30°C (59° to 86°F) [*see USP Controlled Room Temperature*].	**ACCEPTABLE**

Conclusion: ACCEPTABLE

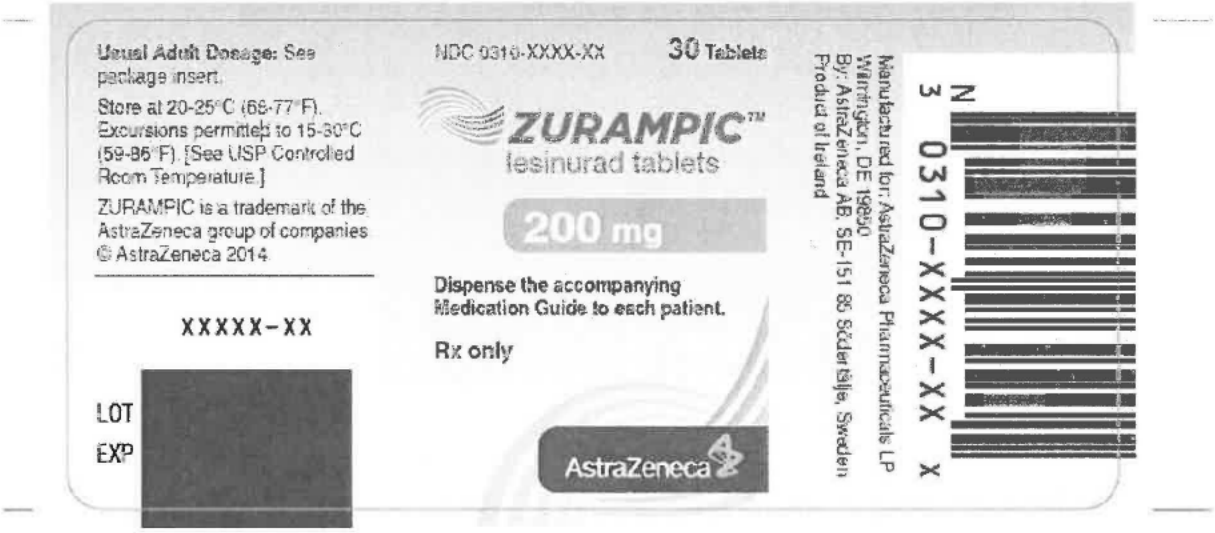
Manufacturer/distributor name listed at the end of PI, following Section #17

Item	Information Provided in NDA	Reviewer's Assessment
Manufacturer/distributor name (21 CFR 201.1)	Manufactured for: AstraZeneca Pharmaceuticals LP, Wilmington, DE 19850 By: AstraZeneca AB, S-151 85 Sodertalje, Sweden Product of Ireland	The API is manufactured in Ireland **ACCEPTABLE**

Conclusion: ACCEPTABLE

2. Labels

1) Immediate Container Label



QUALITY ASSESSMENT NDA # 207988		
Item	**Information Provided in NDA**	**Reviewer's Assessment**
Proprietary name, established name (font size and prominence (21 CFR 201.10(g)(2))	Zurampic	**ACCEPTABLE**
Strength (21CFR 201.10(d)(1); 21.CFR 201.100(b)(4))	200 mg	**ACCEPTABLE**
Net contents (21 CFR 201.51(a))	N/A	**ACCEPTABLE**
Lot number per 21 CFR 201.18	Blank space provided for Lot number	**ACCEPTABLE**
Expiration date per 21 CFR 201.17	Blank space provided for Expiration date	**ACCEPTABLE**
"Rx only" statement per 21 CFR 201.100(b)(1)	present	**ACCEPTABLE**
Storage (not required)	Store at 20° to 25°C (68° to 77°F); excursions permitted from 15° to 30°C (59° to 86°F) [*see USP Controlled Room Temperature*].	**ACCEPTABLE**
NDC number (per 21 CFR 201.2) (requested, but not required for all labels or labeling), also see 21 CFR 207.35(b)(3)	Blank space provided for NDC	**ACCEPTABLE**
Bar Code per 21 CFR 201.25(c)(2)**	Provided	
Name of manufacturer/distributor	Store at 20° to 25°C (68° to 77°F); excursions permitted from 15° to 30°C (59° to 86°F) [*see USP Controlled Room Temperature*].	**ACCEPTABLE**
Others	N/A	

Conclusion: ACCEPTABLE

2) **Cartons** The applicant will not package the drug product in a carton. **ACCEPTABLE**

II. List of Deficiencies To Be Communicated

A. Label/Labeling

Revise the DESCRIPTION section to:

ZURAMPIC is available as blue film-coated tablets for oral administration containing 200 mg lesinurad and the following inactive ingredients: lactose monohydrate, microcrystalline cellulose, hypromellose, crospovidone, and magnesium stearate. ZURAMPIC tablets are coated with Opadry blue.

III. Attachments

A. Facility

OVERALL RECOMMENDATION:				
DRUG SUBSTANCE				
FUNCTION	SITE INFORMATION	DUNS/FEI NUMBER	INITIAL RISK IDENTIFICATION	FINAL RECOMMENDATION
(b) (4)	(b) (4)		Moderate	Acceptable
			Moderate	Acceptable
CSN			Moderate	Acceptable
CTL			Moderate	Acceptable
DRUG PRODUCT				
FUNCTION	SITE INFORMATION	DUNS/FEI NUMBER	INITIAL RISK IDENTIFICATION	FINAL RECOMMENDATION
TCM	AstraZeneca Pharmaceuticals LP	2517100	Moderate	Acceptable
TCM	AstraZeneca Sterile Operations	3003342394	Moderate	Acceptable
CTL	AstraZeneca	3002806411	Low	Acceptable

B. Lifecycle Knowledge Management

a) Drug Substance – N/A

From Initial Risk Identification			Review Assessment		
Attribute/ CQA	Initial Risk Ranking*	Justification	Risk Mitigation Approach	Final Risk Evaluation	Lifecycle Considerations / Comments**
	H, M, or L			Acceptable or Not Acceptable	

b) Drug Product

From Initial Risk Identification			Review Assessment		
Attribute/ CQA	**Factors that can impact the CQA**	**Initial Risk Ranking***	**Risk Mitigation Approach**	**Final Risk Evaluation**	**Lifecycle Considerations/ Comments****
Identification (HPLC, UV)	(b) (4)	L	Adherence to CGMPs Validated ID tests in drug product	Acceptable	None
Assay, impurities (inorganics, solvents, degradants)		L	1.API Purity controlled 2.Excipients meet USP/NF 3.Controlled by process and by assay 4.No degradation seen on stability 5.Drug product not sensitive to moisture. Protected by CCS. Degradants controlled by assay (b) (4) 7.CU controlled by process and by Specifications.	Acceptable	None
Physical stability (solid state of API, dosage form)[5]		L	Not evaluated. Low risk	Acceptable	None
Content uniformity[3]		M	Controlled by process and by Specifications	Acceptable	None

[5] Not considered a CQA by applicant; but considering that this is not a QbD application, the implications are insignificant as long as the control strategy is sound.

	compression				
Microbial limits[3,6]	(b) (4)	L	1.Controlled at API and excipient level 2.Process control (b) (4)		
Drug Release or Dissolution[3]		L			

*Risk ranking applies to product attribute/CQA
**For example, critical controls, underlying control strategies assumptions, post marketing commitment, knowledge management post approval, etc.

[6] Evaluation to be done by the microbiology team.

IV. Administrative

A. ATL: Craig M. Bertha **Signature/Date**

Craig M. Bertha -S

Digitally signed by Craig M. Bertha -S
DN: c=US, o=U.S. Government, ou=HHS, ou=FDA, ou=People, 0.9.2342.19200300.100.1.1=1300103470, cn=Craig M. Bertha -S
Date: 2015.09.08 08:08:30 -04'00'

B. Endorsement Block

Reviewers' Names/Date: See above for reviewers and secondary reviewers' concurrence
Project Manager Name/Date:

Steven Kinsley -S

Digitally signed by Steven Kinsley -S
DN: c=US, o=U.S. Government, ou=HHS, ou=FDA, ou=People, cn=Steven Kinsley -S, 0.9.2342.19200300.100.1.1=2001720189
Date: 2015.09.08 08:29:24 -04'00'

PANORAMA My Work Projects Reporting Requests Timesheet

NDA 207988-Orig1-New - User Fee/NDA - Coversheet(1) » Manufacturing Facility Inspection

Overall Manufacturing Inspection Recommendation

Edit Task | Task Actions

Task Summary | Task Details | Issues | Updates | **Inspection Management Form**

Inspection Management Form As of 1:31 PM

Inspection Management Form

NDA 207988-Orig1-New - User Fee/NDA - Coversheet(1)

ASTRAZENECA PHARMACEUTICALS LP | 2517100 | TCM TABLETS, PROMPT RELEASE | Approve Facility

ASTRAZENECA | 3002806411 | CTL CONTROL TESTING LABORATORY | Approve Facility

(b) (4)

ASTRAZENECA STERILE OPERATIONS | 3003342394 | TCM TABLETS, PROMPT RELEASE | Approve Facility

(b) (4)

Overall Manufacturing Inspection Recommendation

- Approve
- Withhold

Cancel

Assigned To

Robert Wittorf

Edit Assignment

This was done on
Mar 24, 2015
(233 days ago)

Status
Complete

This task is waiting on
2 Tasks

Last Update: May 4, 2015
Submitted On: Dec 30, 2014

Reference Number
3671599

ONDP Initial Quality Assessment (IQA) and Filing Review
For Pre-Marking Applications
NDA #: 207988 Received Date: 22-DEC-2014

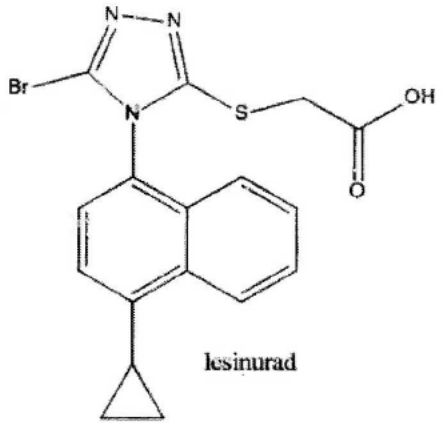
APPLICATION INFORMATION

1. NEW DRUG APPLICATION NUMBER: N207988

Submission Date	12/22/2014
Product name, generic name of the active	Zurampic (lesinurad tablets)
Dosage form and strength	tablets; 200 mg (proposed dose 200 mg qd)
Applicant	Ardea Biosciences, Inc.
Clinical Division	DPARP
Indication	Treatment for hyperuricemia associated with gout in combination with a xanthine oxidase inhibitor.
Type of Submission	505(b)(1) NDA
CMC Reviewer	To be determined
Acting CMC Lead	Craig M. Bertha, PhD
Acting Branch Chief	Julia Pinto, PhD
Biopharmaceutics Reviewer	Fang Wu, PhD
Acting Biopharmaceutics Lead	Sandra Suarez, PhD
Acting Biopharmaceutics Branch Chief	John Duan, PhD

Lesinurad is a new molecular entity (NME) that is formulated as an immediate release tablet for the treatment of hyperuricemia associated with gout. There are three firms involved in the synthesis of the drug substance. (b) (4)

Lesinurad is a class II as per the Biopharmaceutics Classification System (low solubility – high permeability).



lesinurad

2-((5-bromo-4-(4-cyclopropylnaphthalen-1-yl)-4*H*-1,2,4-triazol-3-yl)thio)acetic acid

The drug product for oral administration is a blue, oval, film-coated immediate-release tablet with a strength of 200 mg of lesinurad (as the free acid). The tablets are debossed with "LES200" on one side and they measure 5.7 by 12.9 mm. The excipients are said to comply with the USP/NF monograph requirements, with the exception (b) (4) used in the proprietary film coating from (b) (4), and all of these have been used in other approved oral drug products.

2. Drug Name: Zurampic (lesinurad tablets)

Although there is no formal policy, the chemistry classification codes for the drug product (see draft of MaPP 7500.3) would appear to be type 1 (**New Molecular Entity**).

3. RECEIVED DATE: 22-DEC-2014 (Applicant: Ardea Biosciences, Inc.)

4. RELATED REVIEW DOCUMENTS:

a. Drug Master Files (none listed on 356h form but LOAs provided):

DMF #	TYPE	HOLDER	ITEM REFERENCED	LOA DATE	COMMENTS
(b) (4)	3	(b) (4)	(b) (4)	10-SEP-2013	
	3			18-AUG-2014	
	3			24-JUN-2014	
	3			29-SEP-2014	
	3			23-JUN-2014	
	3			23-JUN-2014	
	3			20-JUN-2014	
	3			08-AUG-2014	(b) (4)
	4			22-SEP-2014	Note that composition is provided in NDA
	3			18-JUL-2014	(b) (4)

b. Recommended Consults

CONSULT	YES	NO	COMMENTS: (list date of request if already sent)
Biometrics	X	☐	Request evaluation of 24 month stability data if trends in parameters appear to limit expiry to less than requested 36 month shelf-life. Applicant does not provide any

			statistical analyses of stability data.
Clin Pharm	☐	X	
Establishment evaluation request	X	☐	ONDQA PM was informed of submission by the acting branch chief on 30-DEC-2014. Sites are pending submission into Panorama.
Pharm/Tox	X	☐	The pharmacologist may need to be consulted depending on the evaluation of the purging data for the potential for the presence of mutagenic impurities. The applicant also provides the results of the initial *in silico* screening (DEREK, MCASE) of various potential and actual impurities that may be present in the drug substance. Of the extensive list of compounds screened, (b) (4) . In section on impurities (S.3), the applicant indicates that (b) (4) had "sufficient data to demonstrate lack of mutagenicity." There are other compounds in the exhaustive list that also include commonly recognized structural alerts as well (e.g., (b) (4) plus those that scored (b) (4) in the screens. Note that the drug substance and the drug product specifications for impurities would appear to be consistent with the recommendations of ICH Q3A, B, and C in terms of the various thresholds.
Methods Validation	X	☐	Left to reviewer's discretion if any drug product methods are questionable and need assessment by the Agency laboratory, but a preliminary review indicates that the methods used for testing of the drug substance and the drug product are standard or are of compendial origin. However, as this is an NME, it is standard practice to submit the impurity method(s) for evaluation by the lab.
Environmental Assessment	☐	X	Applicant claims a categorical exclusion under 21 CFR 25.31(b) stating that their calculations estimate the aquatic concentration in the environment will be below 1 ppb. Calculations appear to be consistent with our Agency guidance document with an updated B factor.
New Drug Microbiology	☐	X	The drug product is not sterile. The drug product specification does not include any parameters related to microbial testing. The microbiology team has been notified (30-DEC-2014) of the application and will determine if any microbiology review is needed. Note that the applicant provides justification for the lack of microbial testing of the drug product in P.5.6.7
CDRH	☐	X	N/A
Other	☐	X	N/A

c. Other Applications or Submissions to note (if any):

DOCUMENT NAME	DATE	APPLICATION NUMBER	DESCRIPTION
IND	Submitted 01-OCT-2009, currently active	102128	IND opened with a 100 mg oral capsule formulation of lesinurad; the IND also includes information on 50, 200, and 400 mg tablets; there were various formulations studied during development

d. Previous Communications with the Applicant to note:

DOCUMENT NAME	DATE	APPLICATION NUMBER	DESCRIPTION
Written responses (pre-IND)	21-JUL-2008	IND 102128	• (b) (4) (now applicant provides justification for absence of this test) • Other minor information requests included to support safety review
Meeting Minutes (EoP2)	04-AUG-2011	IND 102128	• There was disagreement on the proposed starting material for the synthesis (b) (4) Refer to agreement cited in the minutes of the Pre-NDA meeting (question 4) • Note that phase 3 clinical studies used drug substance prepared via (b) (4) (applicant was reminded that toxicological qualification data would be needed to support phase 3 studies); focus of review should be on impurities (and qualification) resulting from the planned commercial route using (b) (4) • There was discussion of the dissolution methodology and clinical relevance, and information/data expected by the Pre-NDA meeting
Written Responses	01-NOV-2013	IND 102128	• Applicant provided with responses to dissolution methodology related questions
Meeting Minutes (Pre-NDA)	24-OCT-2014	IND 102128	• Agency agreed to applicant's chosen dissolution method (final method introduced late in the stability program)

			• Applicant was asked to request a biowaiver (b) (4) only the lower strength is proposed for use) • Applicant was asked to demonstrate the impact of tablet debossing on dissolution

OVERALL PRODUCT QUALITY CONCLUSIONS AND RECOMMENDATIONS

Is the Product Quality Section of the application fileable from a CMC perspective?

Yes	No	CMC Filing Issues
X	☐	N/A

Are there potential CMC review issues to be forward to the Applicant with the 74 day letter?

Yes	No
☐	X

Does the submission contain any of the following elements?

	Yes	No	Comments
Botanical Products	☐	X	
Combination Products	☐	X	
Nanotechnology	☐	X	
PET	☐	X	
QbD Elements	☐	X	Applicant states that "elements of a risk-based quality by design approach were employed" but these are not considered items to be "tracked" but they also state that the application is "not a Quality by Design submission and no design spaces are proposed."
SPOTS	☐	X	

Is a team review recommended?

Yes	No	Suggested expertise for team
☐	X	However, no longer relevant

ONDQA Initial Quality Assessment (IQA) and Filing Review
For Pre-Marking Applications
NDA #: 207988 Received Date: 22-DEC-2014

Drug Product Risk Assessment

DP attribute/ CQA	Factors that can impact the CQA	O[1]	S[1, 2]	D[1]	FMECA RPN #	Comment & considerations
Identification (HPLC, UV)	(b) (4)	1	3	1	3	• Probability of occurrence should be low and detectability high if applicant adheres to GMPs: specification for drug substance includes both specific (FTIR) and non-specific (HPLC retention) identification testing, consistent with Q6A • Severity of failure would depend on situation (incorrect or no drug present)[2] • Final drug product specification includes two non-specific orthogonal tests for the drug for identity confirmation (consistent with Q6A)
Assay, impurities (inorganics, solvents, degradants)		3	3	2	18	• Total impurities allowed in input API limited by respective specification • Inorganic impurities and residual solvents also tested for input API with limits proposed • Note heavy metal testing of API has been removed during development with justification to be considered • Exipients are of compendial quality, i.e., suitable for solid oral dosage forms (proprietary film coating prepared from compendial ingredients as well) • GMP adherence should prevent incorrect API amounts formulated • Applicant has addressed API/excipient

[1] O = Probability of Occurrence; S = Severity of Effect; D = Detectability
[2] Severity of effect can only be estimated; input from clinical, clinical pharmacology, and pharmacology/toxicology team would be necessary for more accurate assessment of clinical impact of failures of product CQAs.

Drug Product Risk Assessment

	(b) (4)					•	compatibility in P.2.1.2.1 (can also be gauged indirectly based on stability data provided in P.8) (b) (4)
Physical stability (solid state of API, dosage form)[3]		1	3	5	15	•	(b) (4)
Content uniformity[3]		3	3	3	27	•	(b) (4)
						•	Content uniformity is tested as part of drug product

[3] Not considered a CQA by applicant; but considering that this is not a QbD application, the implications are insignificant as long as the control strategy is sound.

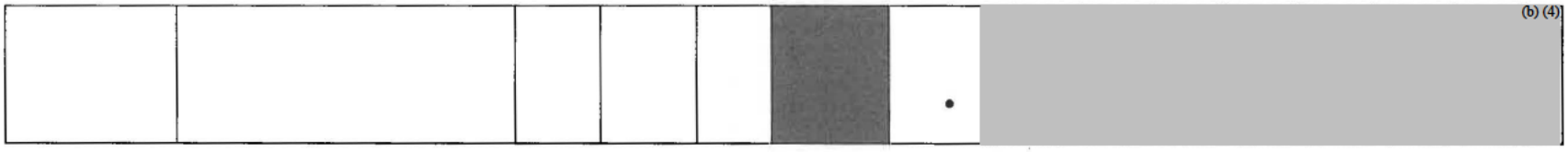
Drug Product Risk Assessment

						specification as per USP <905>
Microbial limits[3,4]	(b) (4)	1	3	5	15	• Applicant proposes to test one batch of drug product annually for microbial limits (periodic quality indicator test or PQIT) • Applicant claims (b) (4) of drug substance and the dosage form render these as non-viable for microbial growth (data provided for drug product in P.5.6.7 as per Q6A) • The applicant analyzed five batches of the drug product with microbial limits testing and these comply with the USP
Drug Release or Dissolution[3]		3	3	2	18	• (b) (4) • Excipients are also of compendial grade and in common use • (b) (4)

[4] Evaluation to be done by the microbiology team.

ONDQA Initial Quality Assessment (IQA) and Filing Review
For Pre-Marking Applications
NDA #: 207988 Received Date: 22-DEC-2014

Drug Product Risk Assessment



CMC Summary:
Critical Issues and Complexities

(This section is formatted to expand as far as needed by author.)

- Preliminary review has not revealed any issues that can be considered to be critical beyond the normal level of evaluation to assure sufficient quality control. However, there are extensive data/information presented associated with the potential and actual impurities in the drug product that may need to be coordinated with the evaluation of the pharmacology/toxicology team.

Description of Facility Related Risks or Complexities (i.e. foreign sites, large number of sites involved, etc.)

See Panorama for complete list of facilities related to this application.

There are three facilities involved in the synthesis of the NME lesinurad. (b) (4) [redacted]

The tablet drug product is manufactured by AstraZeneca AB (Sweden). Two other AZ sites are involved with QC, microbial testing, and packaging.

A total **7 sites** are involved in the production and QC of this drug product.

Biopharmaceutics Filing Review:
Summary, Critical Issues and Complexities

The following parameters for the ONDQA's Product Quality-Biopharmaceutics filing checklist are necessary in order to initiate a full biopharmaceutics review (i.e., complete enough to review but may have deficiencies).

<table>
<tr><th>Parameter</th><th>Yes</th><th>No</th><th>Comment</th></tr>
<tr><td>1. Does the application contains dissolution data?</td><td>X</td><td></td><td>The proposed dissolution method is as follows:
<table><tr><td>Apparatus</td><td>Apparatus II</td></tr><tr><td>Medium</td><td>pH 4.5 sodium acetate buffe with 1% SLS and sinker</td></tr><tr><td>Volume</td><td>900 mL</td></tr><tr><td>Temperature</td><td>37°C</td></tr><tr><td>Rotation Speed</td><td>75 RPM</td></tr><tr><td colspan="2">(b) (4)</td></tr><tr><td>Analysis</td><td>HPLC/UV</td></tr></table>The dissolution method ((b) (4)) was approved in the IND 102128 stage[5].

The link is Table 16 of session 2.3.P in NDA 207988 EDR files (\\CDSESUB1\evsprod\NDA207988\207988.enx)</td></tr>
<tr><td>2. Is the dissolution test part of the DP specifications?</td><td>X</td><td></td><td>The proposed dissolution acceptance criterion for Lesinurad Tablets (200 mg) is as follows:
<table><tr><td>Dissolution</td><td>USP Apparatus 2, 75 rpm, 900mL, pH 4.5 containing 1% SLS, 37°C USP <711> HPLC or UV spectrophotometry-Sample Analysis</td><td>Shall comply wit the requirements USP Q (b) (4)% released in (b) (4) minutes</td></tr></table>The Applicant provides the drug product specification in Table 16 of session 2.3.P in NDA 207988 EDR files (\\CDSESUB1\evsprod\NDA207988\207988.enx)</td></tr>
</table>

[5] Meeting minutes for IND 102128 by Jordan Garner, Michelle dated Oct 24, 2014.

3. Does the application contain the dissolution method development report?	X		A complete description of the dissolution method development is presented in Section 3.2.P.2.2 Appendix 1, Analytical Report AR-594-087-1.0 and Appendix 2, Report Addendum AR-594-087-A1-2.0. in NDA 207988 EDR files (\\CDSESUB1\evsprod\NDA207988\207988.enx)
4. Is there a validation package for the analytical method and dissolution methodology?	X		The Applicant provided data showing that the analytical procedure for dissolution of lesinurad tablets 200 mg and 400 mg in acetate buffer, pH 4.5 plus 1% SLS and UV analysis to be specific, linear, accurate, precise and robust. Refer to 3.2.P.5.3 in NDA 207988 EDR files (\\CDSESUB1\evsprod\NDA207988\207988.enx) The CMC reviewer will be responsible for the review of the analytical method validation report.
5. Does the application contain data from in vitro alcohol interaction studies?		X	N/A
6. Does the application include a biowaiver request?	X		The biowaiver request was included in section 2.7.1 of this NDA submission for the 200 mg strength.

7. Is there information provided to support the biowaiver request?	X		According to the Applicant, Lesinurad 200 mg tablets are (b) (4) as the 400 mg tablets and exhibit similar in vitro dissolution profiles at pH (b) (4) 4.5, and (b) (4) to the 400 mg tablets. The Applicant stated that the f2-test was not applicable for comparing dissolution profiles across tablet strengths in all media, as dissolution was incomplete in the pH (b) (4) (Figure 2 and Table 10) (b) (4) (From 3.2.5 Support for Biowaiver for the 200 mg Proposed Commercial Tablet in Section 2.7.1 "Summary of Biopharmaceutic Studies and Associated Analytical Methods" in the EDR files \\CDSESUB1\evsprod\NDA207988\207988.enx)
8. Does the application include a IVIVC model?		X	
9. Is information such as BCS classification mentioned, and supportive data provided?	X		Lesinurad is considered to be a BCS Class II molecule. The solubility of Lesinurad is pH dependent and ranges from 0.0041 mg/mL in 0.1 N HCl to more than 2.0 mg/mL at pH values of 5.8 or greater. Caco-2 cell permeability (A - B Papp) results indicate high permeability of lesinurad, and the absolute bioavailability of lesinurad is 100% as determined by clinical study RDEA594-131. The sponsor provides the justification data for being the BCS class II molecule in Section 3.2.P.2. (\\CDSESUB1\evsprod\NDA207988\207988.enx)

10. Is information on mixing the product with foods or liquids included?	X		PK information was provided following administration of Lesinurad free acid tablet in both the fed (high fat, high calorie) and fasted states following administration of the free acid tablet, whereas where plasma AUC was similar and Cmax was reduced by 18% with similar Tmax in the fed state as compared with the fasted state. (\\CDSESUB1\evsprod\NDA207988\207988.enx, Section 2.7.1 "Summary of Biopharmaceutic Studies and Associated Analytical Methods") These data will be reviewed by OCP.
11. Is there any in *vivo* BA or BE information in the submission?	X		A series of bioavailability studies were conducted on Free acid IR tablet (200, 400 and 600 mg) in Study 109 in Section 2.2.6. A BE study (study 132) in Section 2.1.10 was conducted between lesinurad 400 mg IR tablets manufactured at AstraZeneca AB and those manufactured at (b) (4) and showed bioequivalence. The BE study will be reviewed by ONDP-Biopharmaceutics.

B. FILING CONCLUSION				
	Parameter	**Yes**	**No**	**Comment**
1.	**IS THE BIOPHARMACEUTICS SECTIONS OF THE APPLICATION FILEABLE?**	X		
2.	If the NDA is not fileable from the biopharmaceutics perspective, state the reasons and provide **filing** comments to be sent to the Applicant.			N/A
3.	Are there any **potential review** issues to be forwarded to the Applicant for the 74-day letter?			Please see comments in biopharmaceutics aspects in 74-day letter

INITIAL BIOPHARMACEUTICS ASSESSMENT

SUMMARY OF BIOPHARMACEUTICS FINDINGS

Submission: Lesinurad is an IR tablet that is intended for once daily (qd) administration for the treatment of hyperuricemia associated with gout in combination with an XO inhibitor. A total of 41 clinical studies have been conducted with lesinurad, including 12 studies related to biopharmaceutic aspects (Table 3 of Section 2.7.1 "Summary of Biopharmaceutic Studies and Associated Analytical Methods" in \\CDSESUB1\evsprod\NDA207988\207988.enx). During its clinical development, lesinurad was formulated as an (b) (4) capsules, (b) (4), IR tablets, and an (b) (4). Three forms of the drug substance have been evaluated: (b) (4) The 200 mg strength tablet is the proposed commercial drug product. The submission includes both the 200 mg and 400 mg strength lesinurad tablets.

The key findings in the 12 clinical trials related to biopharmaceutics aspects and the formulation development processes are:

- (b) (4)
- Lesinurad plasma AUC was similar in both the fed (high fat, high calorie) and fasted states following administration of the free acid tablet, whereas Cmax was reduced by 18% with similar Tmax in the fed state as compared with the fasted state.
- A BE study (study 132) in Section 2.1.10 was conducted between lesinurad 400 mg IR tablets manufactured at AstraZeneca AB and those manufactured at (b) (4) and showed bioequivalence.

During development of the tablet formulations containing lesinurad free acid, a dissolution method using the USP Apparatus 2 (b) (4)
(b) (4)

(b) (4)

(b) (4). The final method utilizes pH 4.5 acetate buffer containing 1% sodium lauryl sulfate (SLS) as the dissolution medium at a paddle speed of 75 rpm and is the proposed quality control dissolution method.

Product's Description:

The API, Lesinurad is a (b) (4) Biopharmaceutics Classification System (BCS) Class II (b) (4), with high solubility in intestinal pH media and high permeability that results in complete absorption and oral bioavailability of approximately 100% (Study 131).

Lesinurad film-coated tablets were developed as an immediate-release oral formulation containing either 200 mg or 400 mg of the active ingredient. Lesinurad is intended for treatment of gout. (b) (4) According to the Applicant, the proposed commercial 200 mg formulation is identical to that dosed in the Phase 3 studies.

A biowaiver is sought for the 200 mg strength lesinurad tablet to support a manufacturing site change. The Applicant states that the manufacturing site change from (b) (4) to AstraZeneca AB is supported by clinical bioavailability and bioequivalence data for 400 mg tablet strength. A biowaiver is proposed for the 200 mg tablet strength and data submitted to support it include (b) (4)

Review: The biopharmaceutics review will be focused on the evaluation and acceptability of the data provided to support: 1) Dissolution method and acceptance criterion, and 2) Data supporting biowaiver request for the proposed strength (200mg).

Review Issues Identified:

- *The proposed dissolution method for 200mg IR tablets is the USP Apparatus 2, 75 rpm, 900mL, pH 4.5 acetate buffer containing 1% Sodium Lauryl Sulfate, at 37°C. The dissolution acceptance criterion is Q= (b) (4)% released in (b) (4) minutes. According to the guidance for industry "Dissolution Testing of Immediate Release Solid Oral Dosage Forms", for slowly dissolving or poorly water soluble drug product like Lesinurad (a BCS Class II drug), two-point specification, one at 15*

minutes to include a dissolution range (a dissolution window) and the other at a later point (30, 45 or 60 minutes) to ensure (b) (4)% dissolution is recommended for the setting as dissolution acceptance criterion.

- *As the sponsor requests biowaiver for 200 mg tablets, the Applicant needs to provide sufficient data to show (b) (4) f2 comparison between the dissolution profiles of 2*200mg IR tablet and 400 mg IR tablet to avoid the sink condition differences using proposed QC dissolution method. Whether biowaiver will be granted is based on the adequacy and totality of the provided data.*

Biopharmaceutics Comments for 74-Day Letter:

Provide the following information/data:

1. We acknowledge the data that you submitted to determine the impact of the Critical Material Attributes (CMA) and Critical Process Parameters (CPP) affecting dissolution. However, provide data e.g., dissolution profiles in graphical and tabular form as a function of the critical attributes identified using the proposed QC method supporting your conclusions in terms of the impact (or lack of impact) of these attributes on the dissolution profile of your proposed product to show the discriminatory power of the proposed QC dissolution method. In general, the testing conducted to demonstrate the discriminating ability of the selected dissolution method should compare the dissolution profiles of the drug product manufactured under target conditions vs. the drug products that are intentionally manufactured with meaningful variations (i.e. (b) (4)) for the most relevant manufacturing variables (e.g., (b) (4) etc.). In addition, if available, submit data showing the capability of the selected dissolution method to reject batches that are not bioequivalent. Note that the discriminating ability is not only determined by the dissolution method settings but also by the selected specification-sampling time point and specification value.

2. Your proposed dissolution acceptance criterion of "Not less than (b) (4)% (Q) of the labeled amount of Lesinurad is dissolved in (b) (4) minutes" may not be sufficient to ensure the quality control for BCS Class II drug. We recommend that you implement a two-point dissolution test to establish the acceptance criterion of the proposed strengths of lesinurad tablets. For this purpose, provide individual and mean dissolution values from all pivotal phase 3 batches used in setting the dissolution acceptance criterion.

3. Provide dissolution profile comparisons with similarity testing (e.g. f2 testing) between 2*200mg IR tablet and 400 mg IR tablet to avoid the sink condition differences achieved at the same volume of medium using the proposed QC dissolution method and additional media tested.

CMC FILING REVIEW CHECKLIST

The following parameters are necessary in order to initiate a full review, i.e., complete enough to review but may have deficiencies. On **initial** overview of the NDA application for filing:

A. GENERAL					
	Parameter	**Yes**	**No**	**N/A**	**Comment**
4.	Is the CMC section organized adequately?	X	☐	☐	
5.	Is the CMC section indexed and paginated (including all PDF files) adequately?	X	☐	☐	
6.	Are all the pages in the CMC section legible?	☐	☐		All pages examined for production of this IQA/filing review were legible.
7.	Has all information requested during the IND phase, and at the pre-NDA meetings been included?	X	☐	☐	It appears that information has been included to address the points covered during the pre-submission meetings; however the adequacy of these will be determined during review.

B. FACILITIES*					
	Parameter	**Yes**	**No**	**N/A**	**Comment**
8.	Is a single, comprehensive list of all involved facilities available in one location in the application?	X	☐	☐	Seven sites are indicated on form 356h

9.	For a naturally-derived API only, are the facilities responsible for critical intermediate or crude API manufacturing, or performing upstream steps, specified in the application? If not, has a justification been provided for this omission? **This question is not applicable for synthesized API.**	☐	☐	X	
10.	Are drug substance manufacturing sites identified on FDA Form 356h or associated continuation sheet? For each site, does the application list: • Name of facility, • Full address of facility including street, city, state, country • FEI number for facility (if previously registered with FDA) • Full name and title, telephone, fax number and email for on-site contact person. • Is the manufacturing responsibility and function identified for each facility?, and • DMF number (if applicable)	X	☐	☐	

11.	Are drug product manufacturing sites identified on FDA Form 356h or associated continuation sheet. For each site, does the application list: • Name of facility, • Full address of facility including street, city, state, country • FEI number for facility (if previously registered with FDA) • Full name and title, telephone, fax number and email for on-site contact person. • Is the manufacturing responsibility and function identified for each facility?, and • DMF number (if applicable)	X	☐	☐	
12.	Are additional manufacturing, packaging and control/testing laboratory sites are identified on FDA Form 356h or associated continuation sheet. For each site, does the application list: • Name of facility, • Full address of facility including street, city, state, country • FEI number for facility (if previously registered with FDA) • Full name and title, telephone, fax number and email for on-site contact person. • Is the manufacturing responsibility and function identified for each facility?, and • DMF number (if applicable)	X	☐	☐	

13.	Is a statement provided that all facilities are ready for GMP inspection at the time of submission?	X	☐	☐	

* If any information regarding the facilities is omitted, this should be addressed ASAP with the applicant and can be a *potential* filing issue or a *potential* review issue.

C. ENVIRONMENTAL ASSESMENT					
	Parameter	**Yes**	**No**	**N/A**	**Comment**
14.	Has an environmental assessment report or categorical exclusion been provided?	X	☐	☐	Exclusion requested as per 21 CFR 25.31(b), with calculations of expected introduction concentration; Applicant also claims that they know of no extraordinary circumstances regarding the EA.

D. MASTER FILES (DMF/MAF)					
	Parameter	**Yes**	**No**	**N/A**	**Comment**
15.	Is information for critical DMF references (i.e., for drug substance and important packaging components for non-solid-oral drug products) complete?	☐	☐	X	There are no critical DMF references.

E. DRUG SUBSTANCE/ACTIVE PHARMACEUTICAL INGREDIENT (DS/API)					
	Parameter	**Yes**	**No**	**N/A**	**Comment**
16.	Does the section contain a description of the DS manufacturing process?	X	☐	☐	
17.	Does the section contain identification and controls of critical steps and intermediates of the DS (in process parameters)?	X	☐	☐	
18.	Does the section contain information on impurities?	X	☐	☐	
19.	Does the section contain information regarding the characterization of the DS?	X	☐	☐	
20.	Does the section contain controls for the DS?	X	☐	☐	
21.	Has stability data and analysis been provided for the drug substance?	X	☐	☐	No statistical analysis has been performed for support of the retest period.
22.	Does the application contain Quality by Design (QbD) information regarding the DS?	☐	X	☐	
23.	Does the application contain Process Analytical Technology (PAT) information regarding the DS?	☐	X	☐	
24.	Does the section contain container and closure information?	X	☐	☐	

F. DRUG PRODUCT (DP)					
	Parameter	**Yes**	**No**	**N/A**	**Comment**
25.	Does the section contain quality controls of excipients?	X	☐	☐	
26.	Does the section contain information on composition?	X	☐	☐	
27.	Is there a description of manufacturing process and methods for DP production through finishing, including formulation, filling, labeling and packaging?	X	☐	☐	
28.	Does the section contain identification and controls of critical steps and intermediates of the DP, including analytical procedures and method validation reports for assay and related substances if applicable?	X	☐	☐	
29.	Is there a batch production record and a proposed master batch record?	☐	X	☐	There is only one executed batch record provided for the production of primary stability batch 12A014. No executed batch records could be found for primary stability batches 11H093 and 11H097 as required per 21 CFR 314.50(d)(1)(ii)(*b*). The presence of a proposed master batch record is irrelevant as this is not required for a 505(b)(1) application. There was no apparent agreement to only provide one executed batch record prior to the submission, but the reviewer can request the additional records if necessary.
30.	Has an investigational formulations section been provided? Is there adequate linkage between the investigational product and the proposed marketed product?	X	☐	☐	See P.2; formulation C was used in the phase 3 clinical studies and is proposed for commercialization. It is consistent with the formulation shown in P.1.
31.	Have any biowaivers been requested?	☐	☐	☐	The biopharmaceutics team has addressed any biowaiver requests (*vide infra*).

32.	Does the section contain description of to-be-marketed container/closure system and presentations?	X	☐	☐	There are three HDPE bottle sizes (45, 75, and 110 mL with 5, 30, and 90 counts, respectively), all with (b) (4) (b) (4) and silica gel desiccant.
33.	Does the section contain controls of the final drug product?	X	☐	☐	
34.	Has stability data and analysis been provided to support the requested expiration date?	X	☐	☐	Stability data are provided in a matrix fashion across bottle size/counts, but there has been no statistical analyses information included. Note that there are also changes to the methods (final dissolution method implemented in April 2014) indicated in P.8 that will need evaluation as this may complicate the interpretation of the stability data (e.g., for drug release). The CMC and biopharmaceutics reviewer may need to discuss any apparent changes in drug release to distinguish these as resulting from method changes as opposed to being stability related changes.
35.	Does the application contain Quality by Design (QbD) information regarding the DP?	☐	X	☐	
36.	Does the application contain Process Analytical Technology (PAT) information regarding the DP?	☐	X	☐	

G. METHODS VALIDATION (MV)					
	Parameter	**Yes**	**No**	**N/A**	**Comment**
37.	Is there a methods validation package?	X	☐	☐	The drug substance is an NME, so it is recommended that the reviewer send the related substances and any other method for which there is a concern, to the Agency laboratory for assessment. Upon request, the applicant has agreed to provide a list of samples, related CoAs, and MSDSs.

H. MICROBIOLOGY					
	Parameter	**Yes**	**No**	**N/A**	**Comment**

38.	If appropriate, is a separate microbiological section included discussing sterility of the drug product?	☐	☐		The microbiology team has been informed of the submission of this application and will make a determination of any review necessary, as per the pilot.

I. LABELING					
	Parameter	**Yes**	**No**	**N/A**	**Comment**
39.	Has the draft package insert been provided?	X	☐	☐	
40.	Have the immediate container and carton labels been provided?	X	☐	☐	
41.	Does section contain tradename and established name?	X	☐	☐	The *trademark* proposed for the oral tablet drug product is "Zurampic" and is owned by AstraZeneca (*tradename*). The established name is lesinurad.

A. FILING CONCLUSION					
	Parameter	**Yes**	**No**	**N/A**	**Comment**
42.	**IS THE PRODUCT QUALITY SECTION OF THE APPLICATION FILEABLE?**	X	☐	☐	
43.	If the NDA is not fileable from the product quality perspective, state the reasons and provide **filing** comments to be sent to the Applicant.	☐	☐	X	
44.	Are there any potential review issues identified?	☐	X	☐	
45.	Are there any comments to be sent to the Applicant as part of the 74-Day letter?	☐	X	☐	
46.	Are there any internal comments to other disciplines:	☐	☐	X	

REVIEW AND APPROVAL

This document will be signed electronically by the following:

Craig M. Bertha, PhD, Acting CMC Lead
Fang Wu, PhD, Biopharmaceutics Reviewer
Sandra Suarez, PhD., Acting Biopharmaceutics Lead
Julia Pinto, PhD, Acting Branch Chief

{See appended electronic signature page}

Craig M. Bertha -S

Digitally signed by Craig M. Bertha -S
DN: c=US, o=U.S. Government, ou=HHS, ou=FDA, ou=People, 0.9.2342.19200300.100.1.1=1300103470, cn=Craig M. Bertha -S
Date: 2015.01.21 06:23:11 -05'00'

Fang Wu -A

Digitally signed by Fang Wu -A
DN: c=US, o=U.S. Government, ou=HHS, ou=FDA, ou=People, cn=Fang Wu -A, 0.9.2342.19200300.100.1.1=2000994797
Date: 2015.01.21 06:29:50 -05'00'

Sandra Suarez -A

Digitally signed by Sandra Suarez -A
DN: c=US, o=U.S. Government, ou=HHS, ou=FDA, ou=People, cn=Sandra Suarez -A, 0.9.2342.19200300.100.1.1=1300147809
Date: 2015.01.21 07:27:56 -05'00'

Julia C. Pinto -A

Digitally signed by Julia C. Pinto -A
DN: c=US, o=U.S. Government, ou=HHS, ou=FDA, ou=People, cn=Julia C. Pinto -A, 0.9.2342.19200300.100.1.1=1300366849
Date: 2015.01.21 12:08:06 -05'00'