

**CENTER FOR DRUG EVALUATION AND
RESEARCH**

APPLICATION NUMBER:

208794Orig1s000

CHEMISTRY REVIEW(S)

Memorandum

DEPARTMENT OF HEALTH AND HUMAN
SERVICES PUBLIC HEALTH SERVICE
FOOD AND DRUG ADMINISTRATION
CENTER FOR DRUG EVALUATION AND RESEARCH

Date: January 12, 2017
From: Hitesh Shroff, Ph.D.
Application Technical Lead, Branch V
Division of New Drug Products II
Office of New Drug Products

Through: Moo-Jhong Rhee, Ph.D.
Chief, Branch V
Division of New Drug Products II
Office of New Drug Products

To: CMC Review #1 of NDA 208794

Subject: Final Recommendation for NDA 208794

At the time when the CMC Review #1 was completed on November 28, 2016, it had noted the following pending issues:

- The label/labeling issues were not resolved.

Because of these deficiencies, the NDA was not recommended for approval from the OPQ perspective.

On December 7, 2016, the applicant submitted revised labeling. The CMC sections of the labeling were reviewed by Dr. Zhengfang Ge and found acceptable (**Attachment -1**) from CMC perspective.

Recommendation:

This NDA is now recommended for Approval from the OPQ perspective.

Application Technical Lead's Assessment and Signature

The NDA is recommended for Approval from quality perspective.

Hitesh Shroff, Ph.D.
Application Technical Lead, Branch V
Division of New Drug Products II
January 12, 2017

Attachment 1:

Labeling:

Memorandum DEPARTMENT OF HEALTH AND HUMAN SERVICES
PUBLIC HEALTH SERVICE
FOOD AND DRUG ADMINISTRATION
CENTER FOR DRUG EVALUATION AND RESEARCH

Date: Jan 3, 2017

From: Zhengfang Ge, Ph.D.
ONDP/Division II/Branch V

Through: Moo-Jhong Rhee, Ph.D.
Chief, ONDP/Division II/Branch V

To: CMC Review #1 of NDA 208794

Subject: Final labeling/labels

The Labeling review #1 has noted the following pending issues:

1. Regarding Highlight section
 - The established name should be changed to (telotristat ethy) tablets per CDER Salt Nomenclature policy
 - The Dosage Forms and Strengths should be displayed as "Tablets: 250 mg telotristat ethy"
2. Regarding # 3: Dosage Forms and Strengths
 - This section should be changed to "Tablets: 250mg telotristat ethyl is a white to"
3. Regarding #11: Description section
 - The 1st sentence should be changed to "Xermelo (telotristat ethyl) tablets contain telotristat ethyl as telotristat etiprate, a tryptophan hydroxylase inhibitor"
 - "Each Xermelo tablet contains 250 mg of telotristat ethyl (free base) which is equivalent to 328 mg telotristat etiprate" should be added.
 - (b)(4) should be removed from the active ingredients.
4. Regarding #16: How Supplied/Storage and Handling
 - In order to avoid potential medical errors using (b)(4) drug product samples have been requested through DMEPA. A final decision for a better description will be decided after receiving the drug product.

And because of these deficiencies, in the Labeling Review #1, this NDA was not recommended for approval from the labeling perspective.

On December 7, 2016, the applicant amended the labeling and the above issues are satisfactorily resolved. In addition, carton/container labels were also modified based on the recommendation from DMEPA (see the Attachment). These changes are acceptable from CMC perspective.

Recommendation:

This NDA is now recommended for approval from the labeling perspective.

Attachment: Final labeling and labels

Highlight

XERMELO (telotristat ethyl) tablets, for oral use

-----DOSAGE FORMS AND STRENGTHS-----

Tablets: 250 mg telotristat ethyl (3)

3. DOSAGE FORMS AND STRENGTHS

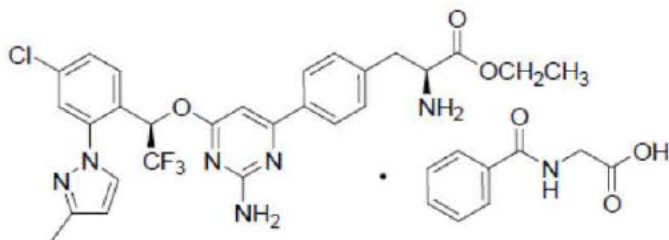
Tablets: 250 mg telotristat ethyl; white to off-white, coated and oval with "T-E" debossed on oneside and "250" debossed on the other side.

11. DESCRIPTION

Xermelo (telotristat ethyl) tablets contain telotristat ethyl as telotristat etiprate, a tryptophan hydroxylase inhibitor. Telotristat etiprate is the hippurate salt of telotristat ethyl [(S)-ethyl 2-amino-3-(4-(2-amino-6-((R)-1-(4-chloro-2-(3-methyl-1H-pyrazol-1-yl)phenyl)-2,2,2-trifluoroethoxy)pyrimidin-4-yl)phenyl)propanoate], which undergoes hydrolysis to the active metabolite, (S)-2-amino-3-(4-(2-amino-6-((R)-1-(4-chloro-2-(3-methyl-1H-pyrazol-1-yl)phenyl)-2,2,2-trifluoroethoxy)pyrimidin-4-yl)phenyl)propanoic acid.

The molecular formula of telotristat etiprate is $C_{27}H_{26}ClF_3N_6O_3 \cdot C_9H_9NO_3$ and its molecular weight is 754.2. The molecular weight of the free base (telotristat ethyl) is 575.0.

Chemical Structure:



Telotristat etiprate is a white to off-white solid. The solubility is a function of pH at 25°C; at pH 1 (0.1N HCl), the solubility is >71 mg/mL^(b) at pH 3 phosphate buffer, the solubility is 0.30 mg/mL, at pHs 5–9, the solubility is negligible. In organic solvents, telotristat etiprate is freely soluble in methanol, soluble in acetone, and sparingly soluble in ethanol.

Each Xermelo tablet contains 250 mg of telotristat ethyl (free base) which is equivalent to 328 mg telotristat etiprate. The inactive ingredients of Xermelo tablets include: colloidal silicon dioxide, croscarmellose sodium, hydroxypropyl cellulose, lactose anhydrous, macrogol/PEG, magnesium stearate, polyvinyl alcohol [part hydrolyzed], talc and titanium dioxide.

16 HOW SUPPLIED/STORAGE AND HANDLING

How Supplied

250 mg tablet: white to off-white coated oval tablet with "T-E" debossed on one side and "250" debossed on the other side.

Xermelo is dispensed in a monthly case for a total of 28 days of therapy. Each monthly case contains four weekly boxes. Each weekly box contains seven daily dose packs (day pack).

- NDC 70183-125-84: Monthly case of 84 tablets. Each child resistant daily dose pack (day pack) contains three 250 mg tablets.

Storage

Store at 25°C (77°F); excursions permitted to (b) (4). [see USP Controlled Room Temperature]

Label for 28 Day Case:



Label for 7-Day Box:

(b) (4)



Label for Daily Dose Pack:

(b) (4)





Moo Jhong
Rhee

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Zhengfang
Ge

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Recommendation: As of this review, this 505 (b)(1) NDA is Not Ready for Approval in its present form per **21 CFR 314.125(b)(6)**.

NDA 208794
Review 1

Drug Name/Dosage Form	Xermelo (telotristat ethyl) tablets
Strength	250 mg
Route of Administration	Oral
Rx/OTC Dispensed	Rx
Applicant	Lexicon Pharmaceuticals, Inc.; The Woodlands, TX
US agent, if applicable	N/A

SUBMISSION(S) REVIEWED	DOCUMENT DATE	DISCIPLINE(S) AFFECTED
Original	03/30/2016	OPQ
Amendment	07/01/2016	ONDP/OPF
Amendment	07/13/2016	ONDP/OPF
Amendment	08/05/2016	ONDP/BP
Amendment	08/19/2016	ONDP/OPF
Amendment	08/23/2016	ONDP
Amendment	08/25/2016	ONDP/OPF
Amendment	08/29/2016	ONDP/OPF
Amendment	08/10/2016	OPF
Amendment	08/12/2016	OPF
Amendment	09/01/2016	OPF
Amendment	07/20/2016	BP
Amendment	08/15/2016	BP

Quality Review Team

DISCIPLINE	REVIEWER	BRANCH/DIVISION
Drug Substance	Debasis Ghosh	CDER/OPQ/ONDP/ DNDAPI/NDBII
Drug Product	Zhengfang Ge	CDER/OPQ/ONDP/ DNDPII/NDPBV
Process	Jessica Liang	CDER/OPQ/OPF/ DPAI/PABI
Microbiology	Jessica Liang	CDER/OPQ/OPF/ DPAI/PABI
Facility	Vipulchandra Dholakia	CDER/OPQ/OPF/DIA/IABIII
Biopharmaceutics	Hansong Chen	CDER/OPQ/ONDP/ DB/BBII
Regulatory Business Process Manager	Vali Benjamin	CDER/OND/ODEIII/ DGIEP
Application Technical Lead	Hitesh Shroff	CDER/OPQ/ONDP/ DNDPII/NDPBV
Laboratory (OTR)	N/A	N/A
ORA Lead	Paul Perdue Jr.	ORA/OO/OMPTO/ DMPTPO/MDTP
Environmental Analysis (EA)	Raanan Bloom	CDER/OPQ/ONDP

Quality Review Data Sheet

1. RELATED/SUPPORTING DOCUMENTS

A. DMFs:

DMF #	Type	Holder	Item Referenced	Status	Date Review Completed	Comments
(b) (4)	IV		(b) (4)	N/A	N/A	N/A

N/A: There is enough data in the application, therefore, the DMD did not need to be reviewed

B. Other Documents: *IND, RLD, or sister applications*

DOCUMENT	APPLICATION NUMBER	DESCRIPTION
IND	078749	Lexicon has an active IND for treatment of GI symptoms associated with carcinoid syndrome.

2. CONSULTS: None

DISCIPLINE	STATUS	RECOMMENDATION	DATE	REVIEWER
Biostatistics	N/A			
Pharmacology/Toxicology	N/A			
CDRH	N/A			
Clinical	N/A			

Executive Summary

I. Recommendations and Conclusion on Approvability

The applicant has provided sufficient CMC information to assure the identity, strength, purity, and quality of the drug product.

The Office of Process and Facilities (OPF) has made a final overall “Approval” recommendation for the facilities involved in this application as of this review.

The claim for the Categorical Exclusion for the Environmental Assessment is granted.

The label/labeling issues have *not* been completely resolved as of this review.

Therefore, from the OPQ perspective this NDA is *not* deemed ready for approval at this time in its present form per 21 CFR 314.125(b)(6) until the above issues are satisfactorily resolved. (see **Attachment II**)

II. Summary of Quality Assessments

A. Product Overview

Xermelo tablet are immediate release, white to off-white, coated oval tablets with “T-E” debossed on one side and “250” debossed on the other side. Each tablet contains 250 mg of active ingredient telotristat ethyl (equivalent to 328 mg of telotristat etiprate). The 250 mg (b) (4) strength Xermelo tablets are supplied in child-resistant blister packs.

Proposed Indication(s) including Intended Patient Population	Xermelo (telotristat ethyl) tablets, 250 mg are indicated for the (b) (4) treatment of carcinoid syndrome in patients with metastatic neuroendocrine tumors who are receiving somatostatin analogue therapy
Duration of Treatment	(b) (4)
Maximum Daily Dose	(b) (4) mg three times a day
Alternative Methods of Administration	N/A

Quality Assessment Overview

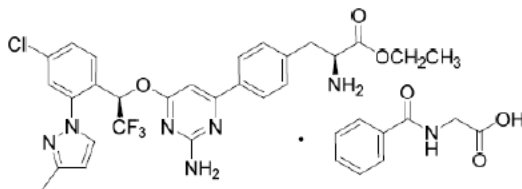
Drug Substance:

The drug substance, telotristat etiprate, is the hippuric acid salt of telotristat ethyl. It is manufactured by (b) (4)

Telotristat etiprate is a white to off-white solid. It has two chiral centers but no geometric isomers. It is non-hygroscopic and its solubility is a function of pH. It is practically insoluble in water, however, it is more soluble in organic solvents.

It is synthesized in (b) (4). The drug substance was characterized by spectroscopic methods such as (b) (4) analysis. The proposed telotristat ethyl (API) structure is also confirmed by (b) (4) structure analysis. Overall the proposed manufacturing process and in-process controls are deemed adequate to consistently produce (b) (4) the drug substance.

The chemical name of telotristat etiprate is [(1*S*)-1-[[4-[2-amino-6-[(1*R*)-1-[4-chloro-2-(3-methylpyrazol-1-yl)phenyl]-2,2,2-trifluoro-ethoxy]pyrimidin-4-yl]phenyl]methyl]-2-ethoxy-2-oxo-ethyl]ammonium; 2-benzamidoacetate. The molecular formula of telotristat etiprate is $C_{27}H_{26}ClF_3N_6O_3 \cdot C_9H_9NO_3$ and its molecular weight is 754.2. The molecular weight of telotristat ethyl (free base) is 575.0. The structural formula of telotristat etiprate is the following:



Telotristat etiprate

The quality of the drug substance is controlled by a specification including identification, assay, impurities ((b) (4), specified, unspecified and total), particle size, residual solvents and heavy metals etc., which are deemed adequate per Drug Substance reviewer, Dr. Debasis Ghosh (see his drug substance review).

The bulk drug substance is packaged in a (b) (4). The proposed retest period of (b) (4)-month is acceptable when stored in the proposed container closure system at (b) (4).

Drug Product:

Xermelo (telotristat epitrate) tablets, 250 mg are supplied in (b) (4) blister packs. The blister packaging consists of a (b) (4) film with paperbacked foil lidding. The blistered packs are then put into cartons. Xermelo tablets contain the following compendial grade inactive ingredients: colloidal silicon dioxide, croscarmellose sodium, hydroxypropyl cellulose, lactose anhydrous, macrogol/ PEG, magnesium stearate, polyvinyl alcohol [part hydrolyzed], talc and titanium dioxide.

The drug product manufacturing process includes (b) (4)

The drug product quality is controlled by a specification that includes identification, assay, degradation products (specified, unspecified and total), content uniformity and dissolution which is deemed adequate per Drug Product reviewer, Dr. Zhengfang Ge (see her drug product review).

The Division of Pharmaceutical Analysis, FDA performed validation of two drug substance and one drug product analytical procedures. The method validation report dated 30 Aug, 2016 stated that these methods were evaluated and deemed acceptable for quality control and regulatory purposes (see Attachment III).

Based on the submitted stability data, 48-month expiration dating period from the date of the manufacture of the drug product including holding time is justified when stored at room temperature in the proposed blister packs and cartons.

The applicant provided a claim for a categorical exclusion from an environmental assessment (EA) in accordance with 21 CFR Part 25.31(b). The required statement of no extraordinary circumstances was included. The claim was reviewed by Dr. Raanan Bloom and found to be acceptable (see his environmental analysis review).

The identity, strength, purity and quality of the drug product are assured by the adequate raw material controls, validated manufacturing process and drug product specification.

B. Special Product Quality Labeling Recommendations (NDA only)

None

Final Risk Assessment (see Attachment I)

ENVIRONMENTAL ANALYSIS**R Regional Information*****Environmental Analysis*****NDA 208794: Review of Claim of Categorical Exclusion**

Lexicon Pharmaceuticals, Inc. has submitted a claim of categorical exclusion citing 21CFR25.31(b) for Telotristat etiprate (Trade Name: Xermelo™). A statement of "no extraordinary circumstances" is provided.

The sponsor provides a production value of (b) (4) kg/year based on the highest annual quantity of the active moiety expected to be produced for use during the first 5 years of production. The EIC from patient use is calculated as (b) (4) ug/L (ppb).

Telotristat etiprate is a phenylalanine derivative and tryptophan hydroxylase inhibitor indicated for the treatment of GI symptoms associated with carcinoid syndrome. These symptoms are secondary to a rare tumor (carcinoid), arising from the neuroendocrine system which secretes excessive amounts of 5-HT. Tryptophan hydroxylase (TPH) is an enzyme that catalyzes the biosynthesis of the neurotransmitter, serotonin (5-HT). The maximum dose is (b) (4) mg/day.

Telotristat etiprate is metabolized to an active metabolite, LX-1033, with 46-58% of the administered dose excreted in the feces as LX-1033. The remaining metabolites are identified as inactive against TPH. No unchanged parent compound is excreted in the feces. Fecal excretion is the major route of elimination. The log D values for LX-1033 were 3.6 and 3.8 at pH 5 and 7.

Submitted non-clinical studies for Telotristat etiprate showed no adverse effects on fertility and early embryonic development in the rat at 500 mg/kg/day (highest dose tested). In the embryo-fetal development study in pregnant rats, telotristat etiprate showed no embryo/fetal toxicity at exposures approximately 11 times the human exposure to the active metabolite at the MRHD. In the embryo-fetal development study in pregnant rabbits, there was increased post-implantation loss (early and late) and decreased number of live fetuses at exposures approximately 19 times the human exposure to the active metabolite at the MRHD. There was no fetal, external, soft tissue, or a skeletal finding at exposures approximately 40 times the human exposure to the active metabolite at the MRHD.

Reviewer's Assessment:

Mammalian reproductive/developmental effects are not presented. Estrogenic, androgenic or thyroid pathway activity is not indicated. Log D values for LX-1033 indicate this compound may be considered in prioritization schemes for further chronic aquatic toxicity studies. A search of ecotoxicology literature did not locate any information on the ecological hazards or risks of Telotristat etiprate or tryptophan hydroxylase inhibitors on the development and reproduction of aquatic organisms. No information was located that indicates that at the expected level of exposure, there is the potential for serious harm to the environment. The cited claim of categorical is appropriate for the anticipated amount of drug to be used. No “extraordinary circumstances” are indicated.

The claim of categorical exclusion is accepted.

Primary EA Reviewer Name and Date:

Raanan A. Bloom, Ph.D. 10/19/2016

Secondary Reviewer Name and Date (and Secondary Summary, as needed):

Scott Furness, Ph.D. 10/19/2016



Michael
Furness

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Comments: EA secondary complete



Raanan
Bloom

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LABELING

R Regional Information

1.14 Labeling

Labeling & Package Insert

1. Package Insert

(a) “Highlights” Section

XERMELO (b) (4) **tablets, for oral use**

-----**DOSAGE FORMS AND STRENGTHS**-----
 (b) (4)

Item	Information Provided in NDA
Drug name (201.57(a)(2))	
Proprietary name and established name	(b) (4)
Dosage form, route of administration	Tablets for oral use Adequate.
Controlled drug substance symbol (if applicable)	N/A
Dosage Forms and Strengths (201.57(a)(8))	should display as Tablets:250 mg telotristat ethyl Not Adequate
Whether the drug product is scored	N/A

Evaluation: Not Adequate

- The established name should be changed to (telotristat ethyl) tablets per CDER Salt Nomenclature policy
- The Dosage Forms and Strengths should be displayed as Tablets: 250 mg telotristat ethyl

(b) “Full Prescribing Information” Section

3: Dosage Forms and Strengths

250 mg white to off-white coated (b) (4) with “T-E” debossed on one side and “250” debossed on the other side.

Item	Information Provided in NDA
Available dosage forms	Tablets. Adequate:
Strengths: in metric system	250 mg Adequate
Active moiety expression of strength with equivalence statement (if applicable)	It should be revised to “Tablets: 250mg telotristat ethyl is a white to”. The active moiety expression is added in section 11. Not Adequate
A description of the identifying characteristics of the dosage forms, including shape, color, coating, scoring, and imprinting, when applicable.	white to off-white coated (b) (4) with “T-E” debossed on one side and “250” debossed on the other side Adequate:

Evaluation: Not Adequate

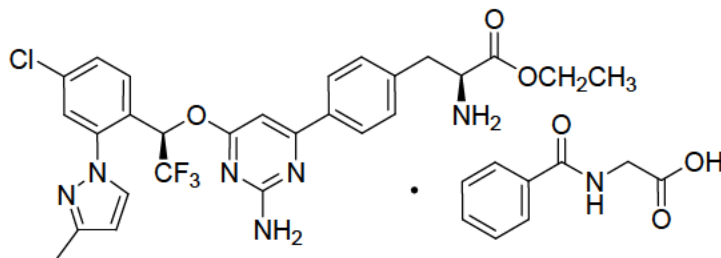
- It should be revised to: “Tablets: 250mg telotristat ethyl is a white to”

#11: Description

Telotristat etiprate is the hippurate salt of telotristat ethyl, [(S)-ethyl 2-amino-3-(4-(2-amino-6-((R)-1-(4-chloro-2-(3-methyl-1H-pyrazol-1-yl)phenyl)-2,2,2-trifluoroethoxy)pyrimidin-4-yl)phenyl)propanoate], which undergoes hydrolysis to the active metabolite, (S)-2-amino-3-(4-(2-amino-6-((R)-1-(4-chloro-2-(3-methyl-1H-pyrazol-1-yl)phenyl)-2,2,2-trifluoroethoxy)pyrimidin-4-yl)phenyl)propanoic acid.

The molecular formula of telotristat etiprate is $C_{27}H_{26}ClF_3N_6O_3 \cdot C_9H_9NO_3$ and its molecular weight is 754.2. The molecular weight of the free base (telotristat ethyl) is 575.0.

Chemical Structure:



Telotristat etiprate is a white to off-white solid. The solubility is a function of pH at 25°C; at pH 1 (0.1N HCl), the solubility is >71 mg/m (b) (4), at pH 3 phosphate buffer, the solubility is 0.30 mg/mL, at pHs 5–9, the solubility is negligible. In

organic solvents, telotristat etiprate is freely soluble in methanol, soluble in acetone, and sparingly soluble in ethanol.

(b) (4). The inactive ingredients of Xermelo tablets include: lactose anhydrous, hydroxypropyl cellulose, croscarmellose sodium, magnesium stearate, colloidal silicon dioxide, (b) (4) polyvinyl alcohol [part hydrolyzed], titanium dioxide, macrogol/PEG, and talc (b) (4)

Item	Information Provided in NDA
Proprietary name and established name	The 1 st sentence should be changed to: Xermelo (telotristat ethyl) tablets contain telotristat ethyl as telotristat etiprate, a tryptophan hydroxylase inhibitor. Not Adequate
Dosage form and route of administration	(b) (4) Adequate
Active moiety expression of strength with equivalence statement (if applicable)	“ Each Xermelo tablet contains 250 mg of telotristat ethyl (free base) which is equivalent to 328 mg telotristat etiprate” should be added. Not Adequate
Inactive ingredient information (quantitative, if injectables 21CFR201.100(b)(5)(iii)), listed by USP/NF names (if any) in alphabetical order (USP <1091>)	(b) (4) should be removed from the active ingredients. The ingredients of (b) (4) are included in the inactive ingredients. Not Adequate
Statement of being sterile (if applicable)	N/A
Pharmacological/ therapeutic class	Not provided. “tryptophan hydroxylase inhibitor” should be added Not Adequate
Chemical name, structural formula, molecular weight	Provided. Adequate
If radioactive, statement of important nuclear characteristics.	N/A
Other important chemical or physical properties (such as pKa or pH)	Solubility is provided. Adequate

Evaluation: **Not Adequate**

- The 1st sentence should be changed to: Xermelo (telotristat ethyl) tablets contain telotristat ethyl as telotristat etiprate, a tryptophan hydroxylase inhibitor.

- “Each Xermelo tablet contains 250 mg of telotristat ethyl (free base) which is equivalent to 328 mg telotristat etiprate” should be added.
- Pharmacologic/Therapeutic class “tryptophan hydroxylase inhibitor” should be added as shown in the 1st bullet

#16: How Supplied/Storage and Handling

How Supplied

250 mg tablets: white to off-white coated oval tablet with “T-E” debossed on one side and “250” debossed on the other side.

(b) (4)

(b) (4)

Storage

Store at 25°C (77°F); excursions permitted to 15°C to 30°C (59°F to 86°F). [see USP Controlled Room Temperature]

Item	Information Provided in NDA
Strength of dosage form	250 mg tablets Adequate
Available units (e.g., bottles of 100 tablets)	(b) (4) (b) (4) (b) (4) Adequate from CMC perspective. However in order to avoid potential medical errors using (b) (4) drug product samples have been requested through DMEPA. A final decision for a better description will be decided after receiving the drug product.
Identification of dosage forms, e.g., shape, color, coating, scoring, imprinting, NDC number	Provided Adequate
Special handling (e.g., protect from light)	N/A
Storage conditions	provided
Manufacturer/distributor name (21 CFR 201.1(h)(5))	Provided at the end of the labeling

Reviewer’s Assessment: Not Adequate

A. Regarding Highlighted section

- The established name should be changed to (telotristat ethy) tablets per CDER Salt Nomenclature policy
- The Dosage Forms and Strengths should be displayed as “Tablets: 250 mg telotristat ethy”

B. Regarding # 3: Dosage Forms and Strengths

- This section should be changed to “Tablets: 250mg telotristat ethyl is a white to”

C. Regarding the #11Description section

- The 1st sentence should be changed to “Xermelo (telotristat ethyl) tablets contain telotristat ethyl as telotristat etiprate, a tryptophan hydroxylase inhibitor”
- “Each Xermelo tablet contains 250 mg of telotristat ethyl (free base) which is equivalent to 328 mg telotristat etiprate” should be added.

- [REDACTED] ^{(b) (4)} should be removed from the active ingredients.

D. Regarding #16: How Supplied/Storage and Handling

- Drug product samples have been requested through DMEPA in order to better describe “How Supplied” to avoid potential medical errors.

2. Immediate Container Label



Item	Information Provided in NDA
Proprietary name, established name (font size and prominence (21 CFR 201.10(g)(2))	. The established name should be changed to “telotristat ethyl” Not Adequate
Dosage strength	Adequate
Net contents	Adequate
“Rx only” displayed prominently on the main panel	Adequate
NDC number (21 CFR 207.35(b)(3)(i))	Adequate
Lot number and expiration date (21 CFR 201.17)	Not Adequate
Storage conditions	Not Adequate
Bar code (21CFR 201.25)	Not Adequate
Name of manufacturer/distributor	Adequate
And others, if space is available	Adequate

Reviewer’s Final Assessment: Adequate

The applicant was requested to provide Lot number and expiration date, storage condition and bar code on the blister shellpak, also to change the established name to “telotristat ethyl”

In the amendment dated 23-Aug-2016, the applicant provided the revised shellpak and lidding shown below.

- Established name has been changed to telotristat ethyl as requested.
- Dose strength equivalence statement, lot number and expiration date, storage condition and bar code are provided at the back of the shell pack.
- Lot and expiration date are provided on the blister lidding.

The revised container labels are **adequate**.

Immediate Container:

1X 3 day pack front:

(b) (4)



1X 3 day pack back:

(b) (4)



Item	Information Provided in NDA
Proprietary name, established name (font size, prominence)	Not Adequate. The established name should be changed to “telotristat ethyl”. The dose strength telotristat ethyl (free base) 250 mg in the equivalence of the salt telotristat etiprate 328 mg should be added
Dosage strength	Provided
Net quantity of dosage form	Provided (b) (4) Review Note: The information provided is correct to CMC perspective but very confusing. DMEPA will need to decide if this could cause any prescription error.
“Rx only” displayed prominently on the main panel	provided
Lot number and expiration date	provided
Storage conditions	provided

Bar code (21CFR 201.25)	provided
NDC number (21 CFR 207.35(b)(3)(i))	provided
Manufacturer/distributor's name	provided
Quantitative ingredient information (injectables)	N/A
Statement of being sterile (if applicable)	N/A
"See package insert for dosage information"	Provided
"Keep out of reach of children" (Required for OTC in CFR. Optional for Rx drugs)	provided

Reviewer's Final Assessment: Adequate

The applicant was requested to change the established name [redacted] ^{(b) (4)} to telotristat ethyl. The applicant was also requested to add a foot note of the dose strength telotristat ethyl (free base) 250 mg in the equivalence of the salt telotristat etiprate 328 mg.

In the amendment dated 23-Aug-2016, the applicant provided the revised cartons as shown below.

- Established name has been changed to telotristat ethyl as requested.
- Dose strength equivalence statement has been provided on the side panel as requested.

The revised cartons are **adequate**.



(b) (4)

List of Deficiencies:

The following deficiencies for the Package Insert should be communicated to the Applicant

1. **Regarding Highlighted section**
 - *The established name should be changed to (telotristat ethyl) tablets per CDER Salt Nomenclature policy*
 - *The Dosage Forms and Strengths should be displayed as "Tablets: 250 mg telotristat ethyl"*
2. **Regarding # 3: Dosage Forms and Strengths**
 - *This section should be changed to "Tablets: 250mg telotristat ethyl is a white to"*
3. **Regarding the #11Description section**
 - *The 1st sentence should be changed to "Xermelo (telotristat ethyl) tablets contain telotristat ethyl as telotristat etiprate, a tryptophan hydroxylase inhibitor"*
 - *"Each Xermelo tablet contains 250 mg of telotristat ethyl (free base) which is equivalent to 328 mg telotristat etiprate" should be added.*
 - *(b) (4) should be removed from the active ingredients.*
4. **Regarding #16: How Supplied/Storage and Handling**

- *In order to avoid potential medical errors using [REDACTED] (b) (4) [REDACTED] drug product samples have been requested through DMEPA. A final decision for a better description will be decided after receiving the drug product.*

Overall Assessment and Recommendation: Not Adequate

The labeling is not adequate for approving this application until the above listed deficiencies are adequately resolved.

Primary Labeling Reviewer Name and Date:

Zhengfang Ge, Ph. D.

OFFICE OF NEW DRUG PRODUCT

DIVISION II/BRANCH V

Secondary Reviewer Name and Date (and Secondary Summary, as needed):

I concur with Dr, Ge's assessment on labeling and labels, and the deficiencies should be resolved before approval of this application.

Moo-Jhong Rhee, Ph. D.

Branch Chief, OFFICE OF NEW DRUG PRODUCT

DIVISION II/BRANCH V



Moo Jhong
Rhee

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Zhengfang
Ge

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FACILITIES

Product Background:

NDA/ANDA: *NDA 208-794*

Drug Product Name / Strength: *Telotristat etiprate Tablets 250 mg*

Route of Administration: *Oral*

Applicant Name: *Lexicon Pharmaceuticals, Inc.*

Review Summary:

Following a review of the application and inspectional documents, there are no significant, outstanding manufacturing or facility risks that prevent approval of this application. The manufacturing facilities for NDA 208-794 are found to be acceptable.

List Submissions being reviewed (table): Original Submission and Amendments

Highlight Key Outstanding Issues from Last Cycle: None

Concise Description Outstanding Issues Remaining: None

3.2.S.2 Manufacture

Summary of Facility Information:

Comparability Protocols**Reviewer's Assessment:**

No Comparability protocols are proposed.

Post-Approval Commitments**Reviewer's Assessment:**

No Post-Approval Commitments are proposed.

Lifecycle Management Considerations

Routine Surveillance inspections recommended.

List of Deficiencies: None

Primary Facilities Reviewer Name and Date:

BIOPHARMACEUTICS**Product Background:**

NDA/ANDA: NDA 208794

Drug Product Name / Strength: Xermelo (Telotristat Etiprate), coated tablets, 250 mg

Route of Administration: Oral

Applicant Name: Lexicon Pharmaceuticals, Inc.

Review Summary:

Lexicon Pharmaceuticals, Inc. developed Xermelo (Telotristat Etiprate), coated tablets, 250 mg (one strength only) and submitted the application under NDA 208794 seeking approval on 3/30/2016. It is indicated for the ^{(b) (4)} treatment of carcinoid syndrome in patients with metastatic neuroendocrine tumors who are receiving somatostatin analogue therapy.

The Biopharmaceutics review focuses on the dissolution method development, dissolution data, and dissolution specification.

From the Biopharmaceutics perspective, NDA 208426 for Xermelo (Telotristat Etiprate), coated tablets, 250 mg is reviewed and found adequate for approval.

The following dissolution specification has been set as agreed upon with the Applicant:

NLT ^{(b) (4)} % (Q) at 30 minutes

List Submissions being reviewed (table):

[Application 208794 - Sequence 0001 - 0001 \(1\) 03/30/2016 ORIG-1 /Multiple Categories/Subcategories](#)

[Application 208794 - Sequence 0019 - 0019 \(19\) 07/20/2016 ORIG-1 /Quality/Response To Information Request](#)

[Application 208794 - Sequence 0024 - 0024 \(24\) 08/05/2016 ORIG-1 /Quality/Response To Information Request](#)

[Application 208794 - Sequence 0027 - 0027 \(27\) 08/15/2016 ORIG-1 /Quality/Response To Information Request](#)

Module	Content

2.3.P	Quality overall summary- Drug product
2.7.1	Summary of Biopharmaceutic Studies and Associated Analytical Methods (in vitro dissolution data)
3.2.P.1	Description and composition of the drug product
3.2.P.2.2	Pharmaceutical Development-Drug product
3.2.P.5.1	Specifications
3.2.P.5.2	Analytical Procedures
3.2.P.5.2	Validation of Analytical Procedures
3.2.P.5.6	Justification of specifications

Highlight Key Outstanding Issues from Last Cycle:

Concise Description Outstanding Issues Remaining:

BCS Designation

Reviewer's Assessment: Not reported.

Solubility:

Table 1. Solubility of Telotristat Ethyl in aqueous solution and organic solvent

Approximate Solubility (25 °C)	
Solvent	Result (mg/ml)
pH 1 (0.1 N HCl)	>71 mg/mL ²
pH 3 (phosphate buffer)	0.30 mg/mL
pH 5 (phosphate buffer)	0.0083 mg/mL
pH 7 (phosphate buffer)	< 0.00059 mg/mL
pH 9 (borax buffer)	< 0.00059 mg/mL
pH 11 (0.001N NaOH)	Drug substance hydrolyses at this pH
Organic Solvents	Pharmacopeia Ranking
Acetone	Soluble
Acetonitrile	Slightly soluble
Dimethyl Sulfoxide	Freely soluble
Ethanol	Sparingly soluble
Methanol	Freely soluble
Tetrahydrofuran/Water (1:1)	Freely soluble

Permeability:

LogP=5.1

Both telotristat ethyl and its active metabolite LP- 778902 were shown to have poor permeability when tested at 20 µM, with an average apparent permeability (P_{app}) of 3.38 nm/sec and 1.66 nm/sec, respectively (Table 2 below).

Table 2. Apparent Permeability of Telotristat Ethyl and LP-778902 in Caco-2 Cells After Incubation at 20 µM

Compound	Average P _{app} (nm/sec)
Telotristat ethyl	3.38
LP-778902	1.66
Source: 160611	

Dissolution: See the Biopharm review below

Dissolution Method and Acceptance Criteria

Reviewer's Assessment:

I. Dissolution method

The Applicant used the following dissolution method to conduct dissolution tests.

Table 3. The Applicant's proposed dissolution method

	Telotristat Etiprate
Apparatus	USP apparatus 2 (paddles)
Speed	50 rpm
Dissolution media	0.01 N hydrochloric acid
Volume	900 mL
Sampling times	10, 20, 30, and 45 minutes
Temperature	37 ± 0.5 °C
Specification	NLT ^(b) / ₍₄₎ % (Q) in ^(b) / ₍₄₎ minutes (proposed)

II. Dissolution Method Development for Telotristat Etiprate

A. Selection of dissolution medium

(b) (4)

(b) (4)

**B. Selection of apparatus**

(b) (4)



C. Sink study

The Applicant stated sink conditions can be met for telotristat etiprate tablets in 900 mL of 0.01 N HCl.

III. The Discriminatory Power of the Proposed Dissolution Method

A. The power of the dissolution test method to discriminate

(b) (4)

The Applicant manufactured LX1606 250 mg (free base) tablets with different (b) (4) and used the proposed dissolution method to conduct dissolution tests. The proposed dissolution method is able to discriminate different (b) (4). However, the Applicant did not provide the complete dissolution data to support the statement. The information request was sent out to request the data.

Figure 2. Effect of (b) (4) on Dissolution



IV. Analytical Method for Dissolution

The applicant used HPLC with UV detection to determine the concentrations of the dissolution samples. The UV detection wavelength was set at (b) (4) nm. The percentage of drug release is calculated using the following equations:

$$\text{mg released} = U_n \times [V_{df} - (n - 1)V_a] + V_a \times (\text{sum of conc. from previous time points, i.e. } U_1 + U_2 + \dots + U_{n-1})$$

Where:

n = Sampling time point (i.e. 1st pull =1, 2nd pull = 2, etc.)

U_n = Concentration of sample solution at time point n

V_a = Aliquot in mL taken from the dissolution test solution at each time point

V_{df} = Initial dissolution fluid volume (900 mL)

$$\% \text{ of label claim} = \frac{\text{mg released} \times 100}{\text{Label Claim}}$$

The Applicant use the following HPLC parameters for its analytical method for dissolution

Parameter	
Column	Phenomenex Synergi (b) (4) μm particle size, or equivalent

Flow rate	(b) (4)
Detector	
Injection volume	
Runtime	
Column temperature	
Mobile phase	

V. Validation of Analytical procedures for Dissolution

The analytical method for dissolution was validated in the analytics laboratories of (b) (4). The validation includes specificity, linearity & range, accuracy, precision (repeatability and intermediate precision), stability in analytical solution, effect of Filter variation, and robustness. The summary of the validation is listed in Table 8.

Table 8. Validation Summary for Method QM3830 (Dissolution)

Reviewer's comment:

The Response is adequate.

VI. Dissolution data and specification**A. Information Request #2**

On 7/29/ 2016, the FDA sent three-item Biopharmaceutics IR #2 to the Applicant. On 8/5/2016, the Applicant responded to the IR with providing the request data. The following are the IR, the Applicant's response, and Reviewer's comment.

IR #2

1. Submit the complete dissolution data (individual, mean, SD, RSD, and mean profiles) of the following batches (including batch manufacturing date, site, and size, and also the dates of dissolution test) to the Agency for review. If you think you have already submitted the requested information, direct us to the proper section of your submission.
L0306856, L0308208, L0308531, L0309260, L0309261, L0401301, L0402483, L0406114, L0407696, L0408135, L0408136, L0409067, and L0502922
2. Your proposed commercial product is a coated oval tablet with "T-E" debossed on one side and "250" debossed on the other side. The test products used for pivotal clinical studies were coated oval tablets with (b) (4).
Provide supporting data to demonstrate that difference in debossing does not affect the dissolution performance and profiles.
3. You reported that the drug substance (DS) was manufactured by two suppliers. Therefore, provide your justification with comparative dissolution data to support/address that there is no difference in dissolution performance and profiles for the drug product batches made from these two DS manufacturers.

The Applicant's response to IR #2 Item 1

The Applicant provided the complete dissolution data of 14 batches as requested, which are listed in Appendix for details.

Reviewer's comment:

The response is adequate. However, the Applicant just used six units from each batch to conduct dissolution tests, which did not meet our expectation. It is considered to be acceptable because all batches can pass the Applicant's proposed specification "NLT (b) (4) % at (b) (4) minutes" at Stage 1, and all time points' variability is within the acceptance range.

Clinical relevance of dissolution method & acceptance criteria (e.g., IVIVR, IVIVC, In Silico Modeling, small scale in vivo)

Reviewer's Assessment: N/A

Application of dissolution/IVIVC in QbD

Reviewer's Assessment: N/A

Bridging of Formulations

Reviewer's Assessment: The formulation used for the pivotal studies is the same as the commercial one; therefore, the bridging of formulation is not needed.

Biowaiver Request

Reviewer's Assessment: N/A

R Regional Information

Comparability Protocols

Reviewer's Assessment:

Post-Approval Commitments

Reviewer's Assessment:

Lifecycle Management Considerations

List of Deficiencies:

Primary Biopharmaceutics Reviewer Name and Date:

Hansong Chen, 8/22/2016

Secondary Reviewer Name and Date (and Secondary Summary, as needed):

I concur. 09/16/16

Tien-Mien Chen, Ph.D.

Acting Biopharm Lead

DB/ONDP/OPQ



Tien Mien
Chen

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ATTACHMENT I: Method Validation Summary

DEPARTMENT OF HEALTH AND HUMAN SERVICES
Public Health Service
Food and Drug Administration
Center for Evaluation and Research

METHODS VALIDATION REPORT SUMMARY

TO: Zhengfang Ge, OPQ/ONDP/DNDPII/NDPBV
E-mail Address: Zhengfang.Ge@fda.hhs.gov
Phone: 301-798-1358

FROM: FDA
Division of Pharmaceutical Analysis
Michael Hadwiger, MVP Coordinator
645 S Newstead Avenue
St. Louis, MO 63110
Phone: (314) 539-3811

Through: Michael Trehy, Ph.D., Lab Chief, Branch II, CDER/OPQ/OTR/DPA
Phone: (314) 539-3815

SUBJECT: Methods Validation Report Summary

Application Number: NDA 208794

Name of Product: Telotristat 250mg Tablet

Applicant: Lexicon Pharmaceutical INC.

Applicant's Contact Person: Penny Logan

Address: 8800 Technology Forest Place, The Woodlands, TX 77381

Telephone: 281-863-3000

Email: plogan@lexpharma.com

Date Methods Validation Consult Request Form Received by DPA: 04/13/2016

Date Methods Validation Package Received by DPA: 04/13/2016

Date Samples Received by DPA: 5/13/2016 and 7/19/2016

Date Analytical Completed by DPA: 8/16/2016

Laboratory Classification: 1. Methods are acceptable for control and regulatory purposes.
2. Methods are acceptable with modifications (as stated in accompanying report).
3. Methods are unacceptable for regulatory purposes.

Comments: See attached summary for analyst comments and results.



Date: August 29, 2016
To: Zhengfang Ge, Chemist, OPQ/ONDP/DNDPII/NDPBV
Danuta Gromek-Woods, Chemist, OPQ/ONDP/DNDPII/NDPBV
Through: Michael L. Trehy, Acting Branch II Lab Chief, Division of Pharmaceutical Analysis
From: Daniel J. Mans, Chemist, Division of Pharmaceutical Analysis
Subject: Methods Validation for NDA 208794, Telotristat 250 mg Tablet, Lexicon
Pharmaceutical, Inc.

The following methods were evaluated and are acceptable for quality control and regulatory purposes:

- Assay, Identification and Impurities in Drug Product (3.2.P.5.2)
- (b) (4) HPLC for Identification (b) (4) assay of telotristat etiprate, assay of hippuric acid, and related substance (b) (4) (3.2.S.4.2.3.1)
- (b) (4) HPLC for identification (b) (4) and (b) (4) impurities (b) (4) (3.2.S.4.2.3.2)

Link to analyst worksheets: <http://ecmsweb.fda.gov:8080/webtop/drl/objectId/090026f880d9fce3>

The Division of Pharmaceutical Analysis (DPA) has the following comments pertaining to these methods below. See attached sheet for summary of results.

Assay, Identification and Impurities in Drug Product (3.2.P.5.2)

- No comments

- (b) (4) HPLC for Identification (b) (4) assay of telotristat etiprate, assay of hippuric acid, and related substances (b) (4) (3.2.S.4.2.3.1)
- Drug Substance supplied by firm fails the Related Substances test (observed related substance (b) (4) at (b) (4) Specification (b) (4) NMT (b) (4) (b) (4))
- Resolution solution (b) (4) retention time material provided by firm resulted in (b) (4) for related substance (b) (4). A freshly prepared (b) (4) mL solution of impurity (b) (4) provided by Lexicon Pharmaceuticals Inc. (b) (4) was not observed in the Drug Substance.

These impurities were not observed in the drug substance. Further, the method does permit detection and quantification of these two impurities in the drug substance even though the resolution of two impurities comprising (b) (4) is not completely optimal (R = (b) (4) rather than R = (b) (4)). DPA is available for discussion if needed.

- (b) (4) HPLC for identification (b) (4) and (b) (4) impurities (b) (4) (3.2.S.4.2.3.2)
- No comments

Summary of Results

NDA 208794

Method	Test item	Specification	Result	PASS/FAIL	
3.2.P.5.2 Identification, Assay, and Impurities in Drug Product using HPLC-UV	Identity	Sample AVG RT of Telotristat peak must be within $\pm$ (b) (4) % of AVG RT of Working STD (b) (4) min $\leq x \leq$ (b) (4) min	(b) (4) min	PASS	
	Assay	(b) (4) % of Label Claim	(b) (4) %	PASS	
	Impurities	[Redacted]	(b) (4)	(b) (4)	PASS
			(b) (4)	(b) (4)	PASS
			(b) (4)	(b) (4)	PASS
3.2.S.4.2.3.1 (b) (4) HPLC for Identification (b) (4) Assay of Telotristat Enirate, Assay of Hippuric Acid, and Related Substances (b) (4)	Identity	Sample AVG RT of Telotristat ethyl and Hippuric acid peaks must be within (b) (4) % of AVG RT of Working STDs (b) (4)	Telotristat ethyl (b) (4) % Hippuric acid (b) (4) %	PASS PASS	
	Assay	Telotristat enirate (b) (4) % Hippuric acid (b) (4) %	(b) (4) %	PASS	
			(b) (4) %	PASS	
	Related Substances	[Redacted]	(b) (4)	(b) (4)	PASS
			(b) (4)	(b) (4)	PASS
			(b) (4)	(b) (4)	PASS
			(b) (4)	(b) (4)	FAIL
			(b) (4)	(b) (4)	PASS
3.2.S.4.2.3.2 (b) (4) HPLC for Identification (b) (4) Impurities (b) (4)	(b) (4) Identification	Retention time of telotristat ethyl (LX1606) in Sample should be within (b) (4) % of retention time of LX1606 in the Resolution Solution	(b) (4) %	PASS	
	(b) (4)	[Redacted]	(b) (4)	PASS	

Case ID: 3978983

Impurities	(b) (4)	PASS
		PASS

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/s/

 MICHAEL E HADWIGER
 08/30/2016
 Final report for NDA 208794

MICHAEL L TREHY
 08/30/2016

Attachment II: Final Risk Assessment

Initial Risk Assessment for NDA 208794 Xermelo (telotristat ethyl) tablets, for oral use

Product Attribute / CQA	Factors that can impact the CQA	Risk Ranking	Risk Mitigation Approach	Risk Evaluation	LifeCycle consideration/ Comments
Blister and tablet Appearance	Blister sealing and moisture	M to L	During the DP manufacturing process blister integrity was assessed by leak test and appearance.	During the stability testing no blister or DP deterioration was found. Low to None	None
Assay	• Formulation • Raw materials • Process parameters • Scale/equipment • Site	L	Assay is determined by a validated HPLC method. During manufacturing process development critical steps were identified and in process controls (IPC) e.g. [REDACTED] (b) (4) [REDACTED] were instituted for a robust manufacturing process and to consistently produce quality DP. The long-term and accelerated stability studies of the registration batches demonstrated that there is no significant change in the quality of the DP during the time tested	The drug product is expected to be safe for oral administration during the entire shelf life from product quality perspective. Low to None	None
Related Substances Impurities / Degradants	• Raw materials • Process parameters • Container/closure system	L	The related substances/impurities are fully characterized and controlled by DS specification. The impurities are also controlled by DP specification at release and on stability. The impurities are assessed by validated HPLC methods.	Low to None	None

Dissolution	• Formulation • Raw materials • Process parameters • Scale/equipment • Site	L	The (b) (4) of the DS is controlled. During manufacturing the DP quality is controlled by IPC including (b) (4). Dissolution is also controlled by DP specification.	Low to None	None

ATTACHMENT III: List of Deficiencies for Complete Response

1. Labeling Deficiencies

1. Regarding Highlighted section

- *The established name should be changed to (telotristat ethyl) tablets per CDER Salt Nomenclature policy*
- *The Dosage Forms and Strengths should be displayed as “Tablets: 250 mg telotristat ethyl”*

2. Regarding # 3: Dosage Forms and Strengths

- *This section should be changed to “Tablets: 250mg telotristat ethyl is a white to”*

3. Regarding the #11 Description section

- *The 1st sentence should be changed to “Xermelo (telotristat ethyl) tablets contain telotristat ethyl as telotristat etiprate, a tryptophan hydroxylase inhibitor”*
- *“Each Xermelo tablet contains 250 mg of telotristat ethyl (free base) which is equivalent to 328 mg telotristat etiprate” should be added.*
- *(b) (4) should be removed from the active ingredients.*

4. Regarding #16: How Supplied/Storage and Handling

- *In order to avoid potential medical errors using (b) (4) drug product samples have been requested through DMEPA. A final decision for a better description will be decided after receiving the drug product.*

OVERALL ASSESSMENT AND SIGNATURES:

From the quality perspective this NDA is not deemed ready for approval at this time in its present form per 21 CFR 314.125(b)(6).

Application Technical Lead Name and Date:

Hitesh Shroff
Division of New Products II, Branch V
November 22, 2016

1 Document History

Document History		
Author: Integrated Quality Assessment Team, and Don Henry.		
Clearance Statement: This document is sponsored by the Integrated Quality Assessment Team. Jorge Rondon (OPRO/OE), Don Henry (OPRP/OE), and the Integrated Quality Assessment Team have cleared this template for use.	This process (CDER OPQ Integrated Quality Assessment Template) will be reviewed at the following intervals and changes to the work aid will be captured as needed: This process will be reviewed approximately 150 days from date issued (February 18, 2016).	
Version	Summary of Changes Issued	Date
03	Content update	02/18/2016



Hitesh
Shroff

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