CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

207695Orig1s000

CHEMISTRY REVIEW(S)

Memorandum

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

Date: **November 28, 2016**
From: **Yichun Sun, 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 207695

Subject: Final Approval Recommendation for NDA 207695

At the time when the CMC review #1 was written, resolution of issues on Labels and Labeling was pending.

Additionally, on September 9, 2016, the applicant sent a letter to the Agency indicating their intention of submitting an erratum to the response dated on April 11, 2016, which was related to potential mutagenic impurities (b) (4). On October 19, 2016, the applicant sent another letter to the Agency indicating to revise the crisaborole drug substance specification to include controls for the two mutagenic impurities observed in the final drug substance (b) (4) The applicant proposed to submit the intended changes in two separate submissions. On October 26, 2016, the applicant submitted an amendment to amend the response to the Agency's request dated on April 04, 2016 for information on potential genotoxic/carcinogenic impurities (b) (4) A new testing site, Pfizer Groton (Pfizer Laboratories Div, Pfizer, Inc.) was added to the NDA for the two new specified impurities in the amendment. On November 21, 2016, the applicant submitted another amendment providing summaries of validation reports of the (b) (4) analytical methods used in the determination of the aforementioned two new specified impurities, (b) (4)

<u>Concern of Genotoxic/Carcinogenic Impurities Present in the Drug Substance</u>
The amendments have been reviewed by Dr. Joseph Leginus, who is the drug substance reviewer of the NDA. Dr. Leginus has concluded that the control strategy for reducing

these impurities proposed by the applicant, and the acceptance criteria for (b) (4) with limits of "NMT (b) (4) ppm" in the crisaborole drug substance specification are acceptable. Additionally, descriptions of the analytical methods for (b) (4) in the proposed drug substance specification and the method validation reports are deemed acceptable. The addendum to the drug substance review is attached below (**Attachment - 1**).

Update of the Status of Facility Inspection

Dr. Vipulchandra Dholakia, who is the facility reviewer of the NDA, has reviewed the inspection status of the newly added testing facility (Pfizer Groton, Pfizer Laboratories Div, Pfizer, Inc.). He still recommended approval for the manufacturing and test facilities of the NDA with addition of the new testing facility. The updated overall manufacturing inspection recommendation (OMIR) is attached below (**Attachment - 2**).

Label/Labeling

On September 21, 2016, the NDA applicant submitted an amendment providing the finalized mock up container and carton labels. Additionally, the applicant also agreed to all the CMC changes made to the package insert. All the labels/labeling issues are now satisfactorily resolved. The review of the CMC sections of the final package insert, and mock up container and carton labels was conducted by Dr. Bhavishya Mittal, and is attached below (**Attachment - 3**).

Recommendation:

The revised package insert and mock-up container and carton labels are now satisfactory from the CMC perspective. Additionally, issues related to potential mutagenic impurities (b) (4) have been satisfactorily resolved. Therefore, from the OPQ's perspective, this NDA is recommended for **APPROVAL** with an expiration dating period of 24 months.

Application Technical Lead's Assessment and Signature

The NDA is recommended for approval from a quality perspective.

Yichun Sun, Ph.D.
Application Technical Lead, Branch V
Division of New Drug Products II
11/28/2016

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showing that [redacted] (b) (4) impurities can be detected at limits proposed in the crisaborole drug substance specifications.

The NDA is recommended for approval from the Drug Substance perspective.

Joseph Leginus, PhD
Review Chemist

Donna Christner, PhD
Office of New Drug API, Chief (Acting), Branch II

Donna Christner

Digitally signed by Donna Christner
Date: 11/22/2016 11:20:49AM
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Joseph Leginus

Digitally signed by Joseph Leginus
Date: 11/22/2016 11:16:57AM
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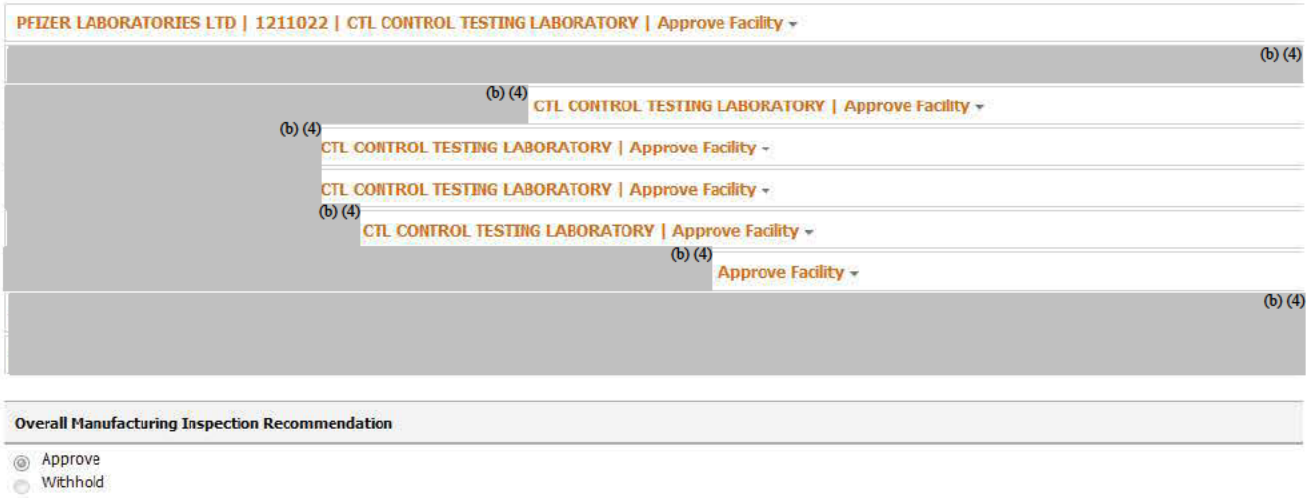
Attachment - 2 (Updated Overall Manufacturing Inspection Recommendation)

NDA-207695-ORIG-1



Attachment - 3 (Review of CMC Sections of the Finalized Labeling and Labels)

Memorandum

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

Date: November 22, 2016

From: Bhavishya Mittal, Ph.D.
Reviewer
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 207695

Subject: Final Labeling/label Recommendation for NDA 207695

At the time when the CMC review #1 was written, resolution of issues on **Labels and Labeling** was pending. These issues were communicated to the applicant, and based on the applicant's responses; all the issues were satisfactorily resolved. The revised labels for the container and the carton are included in this memo.

Recommendation:
All pending issues on container and carton labels are now satisfactorily resolved for the NDA. Therefore, from the labeling/label's perspective, this NDA is recommended for **APPROVAL**.

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Memorandum

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

Date: **November 22, 2016**

From: **Bhavishya Mittal, Ph.D.**
Reviewer
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 207695

Subject: Final Labeling/label Recommendation for NDA 207695

At the time when the CMC review #1 was written, resolution of issues on **Labels and Labeling** was pending. These issues were communicated to the applicant, and based on the applicant's responses; all the issues were satisfactorily resolved. The revised labels for the container and the carton are included in this memo.

Recommendation:

All pending issues on container and carton labels are now satisfactorily resolved for the NDA. Therefore, from the labeling/label's perspective, this NDA is recommended for **APPROVAL**.

Attachment - 1 (CMC Sections of the Finalized Labeling and Labels)

1. Container and Carton Labeling

1) Immediate Container Label

The following amended container label was provided with the NDA

Container Label for Package Content: 2.5 g (Physician's sample)

Package Content: 2.5 g (Physician's sample)

Item	Comments on the Information Provided in NDA	Conclusions
Proprietary name, established name (font size and prominence (21 CFR 201.10(g)(2))	• The proprietary name is "EUCRISA" • Since the product is a topical ointment, the established name is correctly given as "(crisaborole) Ointment, 2%"	Adequate
Strength (21CFR 201.10(d)(1); 21.CFR 201.100(b)(4))	Strength is provided	Adequate
Route of administration 21.CFR 201.100(b)(3))	"For Topical Use Only" statement is provided	Adequate
Net contents* (21 CFR 201.51(a))	The phrase "Net Wt." is missing before the contents given in grams. Based on discussions with DMEPA, it was clarified that 21 CFR 201.51 requires that the labels bear a net quantity statement; however, the regulation is not specific as to the need to include the words "Net wt." and there is ample precedent for the inclusion of the net quantity without the words "Net wt."	Adequate
Name of all inactive ingredients (Quantitative ingredient information is required for injectables) 21CFR 201.100(b)(5)**	Information not provided	Acceptable due to limited space
Lot number per 21 CFR 201.18	Space is provided for lot number	Adequate
Expiration date per 21 CFR 201.17	Space is provided for expiration date	Adequate
"Rx only" statement per 21 CFR 201.100(b)(1)	Complies	Adequate
Storage (not required)	Provided	Adequate
NDC number (per 21 CFR 201.2) (requested, but not required for all labels or labeling), also see 21 CFR 207.35(b)(3)	Provided	Adequate
Bar Code per 21 CFR 201.25(c)(2)***	Provided	Adequate
Name of manufacturer/distributor (21 CFR 201.1)	Name of sponsor is provided. However, name of manufacturer is not provided. Based on the discussions with DMEPA, it was clarified that 21 CFR 201.1(h)(5) states "If the distributor is named on the label, the name shall be qualified by one of the following phrases: "Manufactured for _____", "Distributed by _____", "Manufactured by _____ for _____", "Manufactured for _____ by _____", "Distributor: _____", "Marketed by _____". The qualifying phrases may be abbreviated." Therefore, the applicants proposal complies with the regulations.	Adequate
Others	Includes statements such as "Physician Sample – Not for Sale" and "Not for ophthalmic, oral, or intravaginal use"	Adequate

*21 CFR 201.51(h) A drug shall be exempt from compliance with the net quantity declaration required by this section if it is an ointment labeled ''sample'', ''physician's sample'', or a substantially similar statement and the contents of the package do not exceed 8 grams.

**For solid oral dosage forms, CDER policy provides for exclusion of "oral" from the container label

**Not required for Physician's samples. The bar code requirement does not apply to prescription drugs sold by a manufacturer, repacker, relabeler, or private label distributor directly to patients, but versions of the same drug product that are sold to or used in hospitals are subject to the bar code requirements.

Container Label for Package Content: 60 g

Package Content: 60 g

Item	Comments on the Information Provided in NDA	Conclusions
Proprietary name, established name (font size and prominence (21 CFR 201.10(g)(2))	• The proprietary name is "EUCRISA" • Since the product is a topical ointment, the established name is correctly given as "(crisaborole) Ointment, 2%"	Adequate
Strength (21CFR 201.10(d)(1); 21.CFR 201.100(b)(4))	Strength is provided	Adequate
Route of administration 21.CFR 201.100(b)(3))	"For Topical Use Only" statement is provided	Adequate
Net contents* (21 CFR 201.51(a))	The phrase "Net Wt." is missing before the contents given in grams. Based on discussions with DMEPA, it was clarified that 21 CFR 201.51 requires that the labels bear a net quantity statement; however, the regulation is not specific as to the need to include the words "Net wt." and there is ample precedent for the inclusion of the net quantity without the words "Net wt."	Adequate
Name of all inactive ingredients (Quantitative ingredient information is required for injectables) 21CFR 201.100(b)(5)**	Information on all inactive ingredients is provided.	Adequate
Lot number per 21 CFR 201.18	Space is provided for lot number	Adequate
Expiration date per 21 CFR 201.17	Space is provided for expiration date	Adequate
"Rx only" statement per 21 CFR 201.100(b)(1)	Complies	Adequate
Storage (not required)	Provided	Adequate
NDC number (per 21 CFR 201.2) (requested, but not required for all labels or labeling), also see 21 CFR 207.35(b)(3)	Provided	Adequate
Bar Code per 21 CFR 201.25(c)(2)***	Provided	Adequate
Name of manufacturer/distributor (21 CFR 201.1)	Name of sponsor is provided. However, name of manufacturer is not provided. Based on the discussions with DMEPA, it was clarified that 21 CFR 201.1(h)(5) states "If the distributor is named on the label, the name shall be qualified by one of the following phrases: "Manufactured for _____", "Distributed by _____", "Manufactured by _____ for _____", "Manufactured for _____by _____", "Distributor: _____", "Marketed by _____". The qualifying phrases may be abbreviated." Therefore, the applicants proposal complies with the regulations.	Adequate
Others	Includes statements such as "Not for ophthalmic, oral, or intravaginal use"	Adequate

*21 CFR 201.51(h) A drug shall be exempt from compliance with the net quantity declaration required by this section if it is an ointment labeled ''sample'', ''physician's sample'', or a substantially similar statement and the contents of the package do not exceed 8 grams.
**For solid oral dosage forms, CDER policy provides for exclusion of "oral" from the container label
**Not required for Physician's samples. The bar code requirement does not apply to prescription drugs sold by a manufacturer, repacker, relabeler, or private label distributor directly to patients, but versions of the same drug product that are sold to or used in hospitals are subject to the bar code requirements.

Container Label for Package Content: 100 g

Package Content: 100 g

Item	Comments on the Information Provided in NDA	Conclusions
Proprietary name, established name (font size and prominence (21 CFR 201.10(g)(2))	• The proprietary name is "EUCRISA" • Since the product is a topical ointment, the established name is correctly given as "(crisaborole) Ointment, 2%"	Adequate
Strength (21CFR 201.10(d)(1); 21.CFR 201.100(b)(4))	Strength is provided	Adequate
Route of administration 21.CFR 201.100(b)(3))	"For Topical Use Only" statement is provided	Adequate
Net contents* (21 CFR 201.51(a))	The phrase "Net Wt." is missing before the contents given in grams. Based on discussions with DMEPA, it was clarified that 21 CFR 201.51 requires that the labels bear a net quantity statement; however, the regulation is not specific as to the need to include the words "Net wt." and there is ample precedent for the inclusion of the net quantity without the words "Net wt."	Adequate
Name of all inactive ingredients (3.Quantitative ingredient information is required for injectables) 21CFR 201.100(b)(5)**	Information on all inactive ingredients is provided.	Adequate
Lot number per 21 CFR 201.18	Space is provided for lot number	Adequate
Expiration date per 21 CFR 201.17	Space is provided for expiration date	Adequate
"Rx only" statement per 21 CFR 201.100(b)(1)	Complies	Adequate
Storage (not required)	Provided	Adequate
NDC number (per 21 CFR 201.2) (requested, but not required for all labels or labeling), also see 21 CFR 207.35(b)(3)	Provided	Adequate
Bar Code per 21 CFR 201.25(c)(2)***	Provided	Adequate
Name of manufacturer/distributor (21 CFR 201.1)	Name of sponsor is provided. However, name of manufacturer is not provided. Based on the discussions with DMEPA, it was clarified that 21 CFR 201.1(h)(5) states "If the distributor is named on the label, the name shall be qualified by one of the following phrases: "Manufactured for _____", "Distributed by _____", "Manufactured by _____ for _____", "Manufactured for _____by _____", "Distributor: _____", "Marketed by _____". The qualifying phrases may be abbreviated." Therefore, the applicant's proposal complies with the regulations.	Adequate
Others	Includes statements such as "Not for ophthalmic, oral, or intravaginal use"	Adequate

*21 CFR 201.51(h) A drug shall be exempt from compliance with the net quantity declaration required by this section if it is an ointment labeled ''sample'', ''physician's sample'', or a substantially similar statement and the contents of the package do not exceed 8 grams.
**For solid oral dosage forms, CDER policy provides for exclusion of "oral" from the container label
**Not required for Physician's samples. The bar code requirement does not apply to prescription drugs sold by a manufacturer, repacker, relabeler, or private label distributor directly to patients, but versions of the same drug product that are sold to or used in hospitals are subject to the bar code requirements.

Conclusion: The container labels are satisfactory.

Satisfactory.

2) Carton Labeling

EUCRISA will be supplied in 2.5 g (physician sample size), 60 g, and 100 g laminate tubes containing 2% white to off-white petrolatum-based ointment. The carton dimensions for each tube size are as follows:

Carton Label for Package Content: 2.5 g (Physician's sample)

Package Content: 2.5 g (Physician's sample)

Item	Comments on the Information Provided in NDA	Conclusions
Proprietary name, established name (font size and prominence (FD&C Act 502(e)(1)(A)(i), FD&C Act 502(e)(1)(B), 21 CFR 201.10(g)(2))	• The proprietary name is "EUCRISA" • Since the product is a topical ointment, the established name is correctly given as "(crisaborole) Ointment, 2%"	Adequate
Strength (21CFR 201.10(d)(1); 21.CFR 201.100((d)(2))	Strength is provided	Adequate
Net contents (21 CFR 201.51(a))	The phrase "Net Wt." is missing before the contents given in grams. Based on discussions with DMEPA, it was clarified that 21 CFR 201.51 requires that the labels bear a net quantity statement; however, the regulation is not specific as to the need to include the words "Net wt." and there is ample precedent for the inclusion of the net quantity without the words "Net wt."	Adequate
Lot number per 21 CFR 201.18	Space is reserved for lot #	Adequate
Expiration date per 21 CFR 201.17	Space is reserved for expiration date	Adequate
Name of all inactive ingredients (except for oral drugs); Quantitative ingredient information is required for injectables)[201.10(a), 21CFR201.100(d)(2)]	Information on all inactive ingredients is provided.	Adequate
Sterility Information (if applicable)	Not applicable	Not applicable
"Rx only" statement per 21 CFR 201.100(d)(2), FD&C Act 503(b)(4)	Complies	Adequate
Storage Conditions	Provided	Adequate
NDC number (per 21 CFR 201.2) (requested, but not required for all labels or labeling), also see 21 CFR 207.35(b)(3)	Provided	Adequate
Bar Code per 21 CFR 201.25(c)(2)**	Provided	Adequate
Name of manufacturer/distributor	Name of sponsor is provided. However, name of manufacturer is not provided. Based on the discussions with DMEPA, it was clarified that 21 CFR 201.1(h)(5) states "If the distributor is named on the label, the name shall be qualified by one of the following phrases: "Manufactured for _____", "Distributed by _____", "Manufactured by _____ for _____", "Manufactured for _____by _____", "Distributor: _____", "Marketed by _____". The qualifying phrases may be abbreviated." Therefore, the applicant's proposal complies with the regulations.	Adequate
"See package insert for dosage information" (21 CFR 201.55)	Provided	Adequate
"Keep out of reach of children" (optional for Rx, required for OTC)	Provided	Adequate
Route of Administration (not required for oral, 21 CFR 201.100(d)(1) and (d)(2))	"For Topical Use Only" statement is provided	Adequate

Carton Label for Package Content: 60 g

Package Content: 60 g

Item	Comments on the Information Provided in NDA	Conclusions
Proprietary name, established name (font size and prominence (FD&C Act 502(e)(1)(A)(i), FD&C Act 502(e)(1)(B), 21 CFR 201.10(g)(2))	• The proprietary name is "EUCRISA" • Since the product is a topical ointment, the established name is correctly given as "(crisaborole) Ointment, 2%"	Adequate
Strength (21CFR 201.10(d)(1); 21.CFR 201.100((d)(2))	Strength is provided	Adequate
Net contents (21 CFR 201.51(a))	The phrase "Net Wt." is missing before the contents given in grams. Based on discussions with DMEPA, it was clarified that 21 CFR 201.51 requires that the labels bear a net quantity statement; however, the regulation is not specific as to the need to include the words "Net wt." and there is ample precedent for the inclusion of the net quantity without the words "Net wt."	Adequate
Lot number per 21 CFR 201.18	Space is reserved for lot #	Adequate
Expiration date per 21 CFR 201.17	Space is reserved for expiration date	Adequate
Name of all inactive ingredients (except for oral drugs); Quantitative ingredient information is required for injectables)[201.10(a), 21CFR201.100(d)(2)]	Information on all inactive ingredients is provided.	Adequate
Sterility Information (if applicable)	Not applicable	Not applicable
"Rx only" statement per 21 CFR 201.100(d)(2), FD&C Act 503(b)(4)	Complies	Adequate
Storage Conditions	Provided	Adequate
NDC number (per 21 CFR 201.2) (requested, but not required for all labels or labeling), also see 21 CFR 207.35(b)(3)	Provided	Adequate
Bar Code per 21 CFR 201.25(c)(2)**	Provided	Adequate
Name of manufacturer/distributor	Name of sponsor is provided. However, name of manufacturer is not provided. Based on the discussions with DMEPA, it was clarified that 21 CFR 201.1(h)(5) states "If the distributor is named on the label, the name shall be qualified by one of the following phrases: "Manufactured for _____", "Distributed by _____", "Manufactured by _____ for _____", "Manufactured for _____by _____", "Distributor: _____", "Marketed by _____". The qualifying phrases may be abbreviated." Therefore, the applicant's proposal complies with the regulations.	Adequate
"See package insert for dosage information" (21 CFR 201.55)	Provided	Adequate
"Keep out of reach of children" (optional for Rx, required for OTC)	Provided	Adequate
Route of Administration (not required for oral, 21 CFR 201.100(d)(1) and (d)(2))	"For Topical Use Only" statement is provided	Adequate

Carton Label for Package Content: 100 g

Package Content: 100 g

Item	Comments on the Information Provided in NDA	Conclusions
Proprietary name, established name (font size and prominence (FD&C Act 502(e)(1)(A)(i), FD&C Act 502(e)(1)(B), 21 CFR 201.10(g)(2))	• The proprietary name is "EUCRISA" • Since the product is a topical ointment, the established name is correctly given as "(crisaborole) Ointment, 2%"	Adequate
Strength (21CFR 201.10(d)(1); 21.CFR 201.100((d)(2))	Strength is provided	Adequate
Net contents (21 CFR 201.51(a))	The phrase "Net Wt." is missing before the contents given in grams. Based on discussions with DMEPA, it was clarified that 21 CFR 201.51 requires that the labels bear a net quantity statement; however, the regulation is not specific as to the need to include the words "Net wt." and there is ample precedent for the inclusion of the net quantity without the words "Net wt."	Adequate
Lot number per 21 CFR 201.18	Space is reserved for lot #	Adequate
Expiration date per 21 CFR 201.17	Space is reserved for expiration date	Adequate
Name of all inactive ingredients (except for oral drugs); Quantitative ingredient information is required for injectables)[201.10(a), 21CFR201.100(d)(2)]	Information on all inactive ingredients is provided.	Adequate
Sterility Information (if applicable)	Not applicable	Not applicable
"Rx only" statement per 21 CFR 201.100(d)(2), FD&C Act 503(b)(4)	Complies	Adequate
Storage Conditions	Provided	Adequate
NDC number (per 21 CFR 201.2) (requested, but not required for all labels or labeling), also see 21 CFR 207.35(b)(3)	Provided	Adequate
Bar Code per 21 CFR 201.25(c)(2)**	Provided	Adequate
Name of manufacturer/distributor	Name of sponsor is provided. However, name of manufacturer is not provided. Based on the discussions with DMEPA, it was clarified that 21 CFR 201.1(h)(5) states "If the distributor is named on the label, the name shall be qualified by one of the following phrases: "Manufactured for _____", "Distributed by _____", "Manufactured by _____ for _____", "Manufactured for _____by _____", "Distributor: _____", "Marketed by _____". The qualifying phrases may be abbreviated." Therefore, the applicant's proposal complies with the regulations.	Adequate
"See package insert for dosage information" (21 CFR 201.55)	Provided	Adequate
"Keep out of reach of children" (optional for Rx, required for OTC)	Provided	Adequate
Route of Administration (not required for oral, 21 CFR 201.100(d)(1) and (d)(2))	"For Topical Use Only" statement is provided	Adequate

Conclusion: There are no issues with the carton labels.

Satisfactory.

OVERALL ASSESSMENT AND SIGNATURES: LABELING

Reviewer's Assessment and Signature:
No deficiencies were found in the carton and container labels. This NDA is recommended for approval from an ONDP perspective.

Reviewer's Signature
Bhavishya Mittal, Ph.D.
Branch V
Division of New Drug Products II/ONDP

Secondary Review Comments and Concurrence:

I concur with Dr. Mittal's assessment and his recommendation on the labeling and labels.

Secondary Reviewer's Signature

Moo-Jhong Rhee, Ph.D.
Chief, Branch V
Division of New Drug Products II/ONDP

Moo Jhong Rhee

Digitally signed by Moo Jhong Rhee
Date: 11/22/2016 03 29:03PM
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Bhavishya Mittal

Digitally signed by Bhavishya Mittal
Date: 11/22/2016 02 25:19PM
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Recommendation:

This 505(b)(1) NDA is not deemed ready for approval as of this review in its present form per 21CFR 314.125(b)(6).

NDA 207695
Review 1

Drug Name/Dosage Form	Crisaborole Topical Ointment
Strength	2%
Route of Administration	Topical
Rx/OTC Dispensed	Rx
Applicant	Anacor Pharmaceuticals, Inc.
US agent, if applicable	N/A

SUBMISSION(S) REVIEWED	DOCUMENT DATE	DISCIPLINE(S) AFFECTED
Original NDA submission	1/7/2016	All disciplines of the review team
Amendment	4/7/2016	Biopharmaceutics
Amendment	4/11/2016	Drug product manufacturing process, drug substance and quality microbiology
Amendment	6/2/2016	Biopharmaceutics

Quality Review Team

DISCIPLINE	REVIEWER	BRANCH/DIVISION
Drug Substance	Joseph Leginus	Branch II/New Drug API
Drug Product	Bhavishya Mittal	Branch V/New Drug Products II
Drug Product Process	Kejun Cheng	Branch VIII/Division of Process Assessment III
Quality Microbiology	Samata Tiwari	Branch II/Division of Microbiology Assessment
Facility	Vipulchandra Dholakia	Branch III/Division of Inspectional Assessment
Biopharmaceutics	Vidula Kolhatkar	Branch II/Division of Biopharmaceutics
Regulatory Business Process Manager	Maria Cowan	Branch I/Division of Regulatory and Business Management I/Office of Program and Regulatory Operations
Environmental Assessment (EA)	Raanan (Ron) A. Bloom	Environmental Assessment Team/Office of New Drug Products
Application Technical Lead	Yichun Sun	Branch V/Division of New Drug Products II

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Quality Review Data Sheet

1. RELATED/SUPPORTING DOCUMENTS:

A. DMFs:

DMF #	TYPE	HOLDER	ITEM REFERENCED	CODE[1]	STATUS[2]	DATE REVIEW COMPLETED	COMMENTS
(b) (4)	Type III		(b) (4)	3	Adequate	DMF last reviewed by Dr. Joel Hathaway on May 4, 2016	None

1 Action codes for DMF Table:

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

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

DOCUMENT	APPLICATION NUMBER	DESCRIPTION
EOP2 meeting minutes (11/3/2011)	77537	Discussions of the development plan of Crisaborole topical ointment.
EOP2 meeting minutes (3/6/2014)	77537	Discussions of the development plan of Crisaborole topical ointment.
Pre-NDA meeting minutes (9/17/2015)	77537	Discussions of the plan of development and submission of the NDA.

2. CONSULTS:

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

Executive Summary

I. Recommendations

A. Recommendation and Conclusion on Approvability

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

The facility review team from the Office of Process and Facility has issued an "Approval" recommendation for the facilities involved in this application.

However, the issues on labels/labeling are not completely resolved at this time.

Therefore, from the OPQ perspective, this NDA is not ready for approval in its present form per 21 CFR 314.125(b)(6) until the aforementioned issues are satisfactorily resolved (See the **List of Deficiencies** on p. 127).

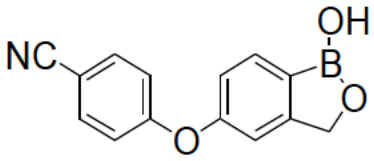
B. Recommendation on Phase 4 (Post-Marketing) Commitments, Agreements, and/or Risk Management Steps, if Approvable

N/A

II. Summary of Quality Assessments

A. Drug Substance [USAN Name] Quality Summary

The drug substance/active pharmaceutical ingredient (API) used in the drug product, ((b) (4)), is crisaborole. The chemical name of crisaborole is: 5-(4-cyanophenoxy)-1,3-dihydro-1-hydroxy-[2,1]-benzoxaborole. It has the following structural formula:



Crisaborole is a white to pale yellow solid that has an empirical formula of $C_{14}H_{10}BNO_3$ and a molecular weight of 251.1. The melting range of crisaborole is 128.8°C - 134.6°C.

Crisaborole is freely soluble in N,N-dimethylformamide, tetrahydrofuran, propylene glycol and isopropyl alcohol. It is soluble in alcohol, acetonitrile, isopropyl acetate and acetic acid/Water (90:10 v/v). It is sparingly soluble in methanol. It is insoluble in Milli-Q water, hydrochloric acid, 18%, acetic acid, 0.9% (w/w) and n-Heptane.

The partition coefficient (logP) of the drug is determined to be 3.24. The dissociation constant (pKa) of crisaborole was determined to be 6.98. (b) (4)

(b) (4)

The identity, strength, purity and quality of the drug substance are deemed assured by the drug substance specification. The drug substance is packaged in (b) (4)

(b) (4) A retest period of (b) (4) months is proposed for crisaborole drug substance when stored at (b) (4), with excursions permitted to (b) (4) (b) (4) in the recommended container closure system.

B. Drug Product [Eucrisa] Quality Summary

The drug product, Crisaborole Topical Ointment, is white to off-white, petrolatum based ointment containing 2.0% of crisaborole, which is a low molecular weight benzoxaborole PDE-4 inhibitor, indicated for topical treatment of mild to moderate atopic dermatitis in patients 2 years of age and older. Each gram of the cream contains 20 mg of crisaborole in an ointment vehicle containing white petrolatum, propylene glycol, mono- and di-glycerides, paraffin, butylated hydroxytoluene, and edetate calcium disodium. Crisaborole ointment is packaged in laminate tubes with 3 packaging presentations: 60 g, 100 g and a physician sample.

(b) (4)

(b) (4)

The in-process controls and tests implemented during the drug product manufacturing process include the following:

(b) (4)

The identity, strength, purity including microbial limits, and quality of the drug product are deemed assured by the drug product specification. No in vitro release test (IVRT) for the ointment is planned to be developed. An expiration dating period of 24 months is recommended for the 60 g and 100 g presentations of Crisaborole Topical Ointment, 2% based on statistical analysis of the 12 months of long-term primary stability data submitted. An expiration dating period of 22 months is recommended for the physician sample presentation of Crisaborole Topical Ointment, 2% based on statistical analysis of the 12 months of long-term primary stability data submitted. The Environmental Assessment (EA) team finds that the NDA applicant's request for a categorical exclusion from an EA is acceptable. The facility review team from the Office of Process and Facilities has provided an **Overall Acceptable** recommendation for the facilities involved in the manufacture and tests of the drug substance and drug product.

C. Summary of Drug Product Intended Use

Proprietary Name of the Drug Product	EUCRISA
Non Proprietary Name of the Drug Product	Crisaborole ointment
Non Proprietary Name of the Drug Substance	Crisaborole

Proposed Indication(s) including Intended Patient Population	Indicated for topical treatment of mild to moderate atopic dermatitis in patients 2 years of age and older.
Duration of Treatment	N/A
Maximum Daily Dose	N/A (twice daily to affected areas)
Alternative Methods of Administration	N/A

D. Biopharmaceutics Considerations

1. BCS Classification: N/A
    - Drug Substance: N/A
    - Drug Product: N/A

2. Biowaivers/Biostudies
    - Biowaiver Requests: N/A
    - PK studies: N/A
    - IVIVC: N/A
    - IVRT: The applicant does not plan to develop an IVRT method.

E. Novel Approaches

N/A

F. Any Special Product Quality Labeling Recommendations

N/A

G. Life Cycle Knowledge Information (see Attachment A)

OVERALL ASSESSMENT AND SIGNATURES: EXECUTIVE SUMMARY

Application Technical Lead Signature:

The NDA is not deemed ready for approval as of this review in its present form per 21CFR 314.125(b)(6).

Yichun Sun, Ph.D.
Application Technical Lead, Branch V
Division of New Drug Products II
8/17/2016

Yichun Sun -S

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ASSESSMENT OF THE BIOPHARMACUETICS

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

In the 74-day letter (March 21, 2016), the Division of Biopharmaceutics recommended that the Applicant develop an in vitro release test (IVRT) methodology and propose in vitro release acceptance criteria (range) for the proposed drug product to be used at release and during stability as a quality control parameter.

Applicant's Response:
The applicant provided the following response on April 07, 2016:

The applicant referred to USP <3> (Topical and Transdermal Drug Products – Product Quality Tests) that in-vitro release testing (IVRT) is not required for quality control for a topical ointment. They acknowledged that IVRT is required as a measure of "sameness" as per the Agency's "Guidance for Industry Nonsterile Semisolid Dosage Forms Scale-Up and Postapproval Changes: Chemistry, Manufacturing, and Controls; In Vitro Release Testing and In Vivo Bioequivalence Documentation," May 1997 (SUPAC-SS).

(b) (4)

The proposed product lots used in the Phase 3 studies and registration lots were manufactured at the same facility, using the same equipment and scale as the lots to be used for commercial launch. The applicant is confident that the quality of the proposed Crisaborole Topical Ointment, 2% is adequately controlled by the currently proposed and established specifications.

The applicant submits that the implementation of IVRT to be used at release and during stability as a quality control parameter is not necessary. The applicant is confident that the already rigorous specifications currently proposed in the NDA are adequate to assure the quality of the drug product. It is further stated that the Agency did not communicate a request for IVRT during the recent communications (the two End of Phase 2 meetings; meeting minutes November 03, 2011 and March 06, 2014 and pre-NDA meeting; meeting minutes October 08, 2015).

Based on the reasons discussed above, there is not sufficient justification contained in the applicable guidance or an otherwise compelling rationale for the addition of an IVRT

acceptance criteria as a quality control parameter for the release and stability specification of Crisaborole Topical Ointment, 2%.

Reviewer's Assessment: The Agency recommended the applicant to develop IVRT as a quality control tool and to support any future changes. This is a recommendation and not a requirement from the Biopharmaceutics perspective. The applicant provided their justification for not developing an IVRT method. The lack of an IVRT method and in vitro release acceptance criteria will not affect the approvability of this NDA.

In vitro skin flux studies during formulation development

(b) (4)

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(b) (4)

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

Applicant's Response:
Phase 3 and long-term safety studies were conducted using the to-be-marketed formulation.

Reviewer's Assessment: N/A

OVERALL ASSESSMENT AND SIGNATURES: BIOPHARMACUETICS

Reviewer's Assessment and Signature: Adequate.

Reviewer's Signature
Vidula Kolhatkar, Ph.D.
Branch II
Division of Biopharmaceutics/ONDP
July 20, 2016

Vidula R Kolhatkar -S

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Date: 2016.08.18 15:01:16 -04'00'

Secondary Review Comments and Concurrence:
I concur with the reviewer's assessment.

Secondary Reviewer's Signature
Kelly M. Kitchens, Ph.D.
Quality Assessment Lead (Acting)
Division of Biopharmaceutics, Branch II
July 25, 2016

Kelly M. Kitchens -S

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ASSESSMENT OF MICROBIOLOGY

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

Description of the Composition of the Drug Product-
Description of drug product – The drug product is a petrolatum-based ointment containing 2% (w/w) crisaborole. The drug product is filled in to three packaging presentations [60 g, 100 g, and 2.5 g (physician sample)].

- Drug product composition – The composition was provided in submission section 3.2.P.1. The quantitative composition of the drug product is presented in the table below.

Components	Quality Standard	Function	Concentration (% w/w)
Crisaborole	In-house	Active	2.0000
White Petrolatum	USP	Ointment base	(b) (4)
Propylene Glycol	USP	(b) (4)	
Mono- and Di-glycerides	NF		
Paraffin	NF		
Butylated Hydroxytoluene	NF		
Edetate Calcium Disodium	USP		

- Description of container closure system – The drug product is packaged in (b) (4) laminated tubes with a (b) (4) cap, (b) (4) (b) (4) tube head, and (b) (4) seal.

Antimicrobial Effectiveness Test (AET) –
The sponsor stated that Antimicrobial Effectiveness tests were performed per USP <51> on one clinical lot of crisaborole topical ointment, 2% (lot DHE-C) and six clinical lots related crisaborale topical ointments (lots DBF-C, DBE-C, CMI-C, CMH-C, BHF-C, and BHD-C).
The AET was performed at 0, 12 and 24 months. All lots passed antimicrobial effectiveness testing at release and throughout stability, and met the log reduction requirements for USP <51> category 2 products (data not provided).

The sponsor states that since the product (b) (4) (b) (4) it does not support microbial growth. Therefore AET will not be performed for the commercial batch.

Acceptable.

Drug Product Specifications

Analytical Procedures
Endotoxin – NA
Sterility – NA
Microbial Limits –

- Microbial limits are tested per per USP <61> and USP <62> on the nine primary stability lots of Crisaborole Topical Ointment, 2% in three presentations (60 g, 100 g, and physician samples) and thirteen (13) supporting stability lots with the following specifications:

TAMC NMT (b) (4) cfu/g
TYMC: NMT cfu/g
Absence of *S. aureus* and *P. aeruginosa* (Absence/1g)

Method suitability testing was not provided.

Note to Reviewer: Applicant has stated that all drug product lots, including all primary and supporting stability lots, met the USP <1111> criteria for total aerobic microbial count, total combined yeasts and molds, *S. aureus*, and *P. aeruginosa* on release and stability (data provided). (b) (4)

(b) (4)

Information Request of April 04, 2016:
Microbial limits method suitability results for USP <61> and <62> drug product testing could not be located in the submission. Please provide the respective reports.

Response of April 11, 2016:
The method verifications reports for the drug product microbial limit tests for USP <61> and <62> were amended to section 3.2.P.5.3.

Review of Report:

Note to Reviewer: The testing of Crisaborole Topical Ointment, 2% lots used for the Phase 3 clinical studies, and primary and supporting stability studies has been conducted by the manufacturing site (b) (4) for release and

contract testing laboratory and (b) (4) for stability. Applicant has provided two different reports; (b) (4) verification (report #5731) and (b) (4) verification (protocol 616.009.019.02 , report#64.VAL.CPT.01) for the microbial limits method suitability results for USP <61> and <62> drug product testing. A memorandum for the rational to waive additional validation work for report#64.VAL.CPT.01 has been provided pertaining to the minor change in the EDTA concentration from (b) (4)%. It is not clear if the Report#5731 used the new concentration of EDTA. It is stated that the change in concentration of EDTA has no impact on the microbiology test methods. As per both the reports, the method suitability was performed per USP <61> and <62> and supports the routine testing for TAMC and TYMC for the product and test for specified microorganisms. Both the reports are reviewed below.

Report#64.VAL.CPT.01, performed at (b) (4)
Date: (b) (4)
The Applicant has not provided a detail report and a test data sheet is provided. As per the report, 1:10 dilution of product lots CMI-C,963-0125D01 and 963-0127D01 was tested for the adequate recovery of compendia organisms and it can be concluded that the test method as per USP□61> and <62> are suitable for detecting and enumerating microorganisms which may contaminate the product.

Report#5731, performed at (b) (4)
Date: (b) (4)
The drug product lot DHF-C topical ointment 2% and placebo were tested to validate the test parameters. The samples were tested at the 1:100 dilutions. Positive and negative controls were used for testing. The average inoculum concentration used for each compendia organisms was <100 CFU. The test result showed adequate recovery of each organisms with the recovery factors (b) (4) as compared to the respective positive controls. The negative controls exhibited no observable growth. It is stated that there was no recovery of *B. spizizenii* in the test sample as compared to the positive control.

The results are summarized in the table below:

Result at 1:100 dilution of the product

Microorganism	Negative Controls	Positive Control Recovery Average (CFU)	Sample Prep Recovery Average (CFU)	Recovery Factor
P. aeruginosa	No Growth	(b) (4)		
S. aureus				
B. spizizenii				
C. albicans	No Growth			
A. brasiliensis				

The placebo demonstrated similar result as the test with exception of the growth of *B. spizizenii.* For testing the specified microorganisms, the test sample was inoculated with 100µL of the suspension of the test microorganisms and incubated at 30-35°C for 1 day in the appropriate media. Comparable recovery of *P. aeruginosa* was obtained and compared to the respective positive control. It is stated that the recovery of *S. aureus* was evident; however it was not comparable to the positive control. The negative controls exhibited no observable growth. The results are summarized below:

Microorganism	Negative Control	Positive Control	Sample	Comparable Growth (Yes / No)	Inoculum Verification (CFU)
P. aeruginosa	-	+	+	Yes	(b) (4)
S. aureus	-	+	+	No	

+ = growth; - = no growth

Note to Reviewer:
The Applicant has referred to an expert from USP <61> and <62> to address undetectable and low recovery of the microorganisms due to lack of suitable neutralization method for the microbicidal activity of product. Based on this, it is assumed that the inhibited microorganisms will not be present in the product.

Acceptable.

Stability
Stability Summary and Conclusion
Proposed shelf life is 24 months at 20-25°C (68–77°F) with excursions permitted to 15–30°C (59–86°F).

Post-Approval Stability Protocol and Stability Commitment
The first three commercial lots will be placed on stability with one lot annually thereafter. The applicant states that if a production lot is not produced within a one year period, the next production lot produced will be placed on stability.

Stability Data
Long Term: 25°C/60% RH
Microbial enumeration and microbial specific organism tests performed at initial, 12, 18, 24 and 36 months on three primary stability lots (GGA-C, GGB-C and GGC-C) of 60 g presentation and 3 primary stability lots designated for physician sample of 2.5 g presentation (GFN, GFP and GFR). Three supporting stability lots (FHX-C, FCT-C, and DMD-C) of 60 g presentation are also on stability.

The TAMC and TYMC for initial and 12 month time points for all the above lots were LT (b)(4) cfu/g. *S. aureus* and *P. aeruginosa* were also absent/1g in all the lots. The remaining time point data are not yet available.

Intermediate: 30°C/65% RH
Accelerated: 40°C/75% RH
No microbial enumeration and microbial specific organism tests performed at Intermediate and accelerated stability.

Microbial limits – ML was tested at each time point for TAMC, TYMC and the absence of *S. aureus* and *P. aeruginosa*.

Acceptable.

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

Reviewer's Assessment: The information provided in support of drug product quality microbiology for NDA 207695 is acceptable.

2.3.P.7 Container/Closure System

41. *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?*

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

Reviewer's Assessment: N/A From a quality microbiology perspective, container closure is not a critical attribute for non-sterile topical dosage forms.

A APPENDICES

A.2 Adventitious Agents Safety Evaluation

42. *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)?*

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

Reviewer's Assessment: No materials are obtained or derived from animal sources.

43. *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?*

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

Reviewer's Assessment: N/A

OVERALL ASSESSMENT AND SIGNATURES: MICROBIOLOGY

Reviewer's Assessment and Signature:

There were no quality microbiology deficiencies identified in the information provided. The application is recommended for approval from a quality microbiology perspective.

Reviewer's Signature
Samata Tiwari, Ph.D.
Branch II
Division of Microbiology Assessment/OPF
05/13/16

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Date: 2016.08.19 09:31:05 -04'00'

Secondary Review Comments and Concurrence:

I concur with Dr. Tiwari's product quality microbiology assessment and approval recommendation.

Secondary Reviewer's Signature
Neal J. Sweeney, Ph.D.
Microbiology Quality Assessment Lead (Acting), Branch II
Division of Microbiology Assessment/OPF
13 May 2016

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ASSESSMENT OF ENVIRONMENTAL ANALYSIS

44. *Is the applicant's claim for categorical exclusion acceptable?*

45. *Is the applicant's Environmental Assessment adequate for approval of the application?*

Applicant's Response: N/A

Reviewer's Assessment:

The applicant has submitted a claim of categorical exclusion citing 21CFR25.31(b). A statement of "no extraordinary circumstances" is provided.

The sponsor provides a production value of (b) (4) kg Crisaborole/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) µg/L (ppb). The cited categorical is appropriate for the anticipated amount of drug to be used.

Crisaborole suppresses the release of cytokines and other inflammatory signals that may mediate the pathophysiologic process underlying the development and maintenance of atopic dermatitis. Crisaborole is substantially metabolized into inactive metabolites once it crosses the skin barrier and reaches the bloodstream. Renal excretion is the major route of elimination. Crisaborole C_{max} plasma concentration indicated minimal systemic exposure following topical application. This low concentration further reduces potential release into the environment through excretion pathways.

Submitted non-clinical studies demonstrated no effects on mating and fertility in male or female rats or Caesarean-sectioning and litter parameters of female rats dosed as high as 600 mg/kg/day at exposures 25 times the maximum recommended human dose. The reproductive NOAEL in the dams was 600 mg/kg/day. The drug does not appear to exhibit estrogen, androgen or thyroid pathway activity.

A search of ecotoxicology literature did not locate any information on the ecological hazards or risks of PDE-4 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. Therefore, no extraordinary circumstances are indicated.

The claim of categorical exclusion is acceptable.

OVERALL ASSESSMENT AND SIGNATURES: ENVIRONMENTAL

Reviewer's Assessment and Signature: Adequate. The claim of categorical exclusion is acceptable.

Reviewer's Signature
Raanan Bloom, Ph.D.
Environmental Assessment Team, ONDP

Raanan A. Bloom -S
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Date: 2016.08.18 09:09:00 -04'00'

Secondary Review Comments and Concurrence: Concur.

Secondary Reviewer's Signature
Scott Furness, Ph.D.
Deputy Director, ONDP

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

Labeling & Package Insert

1. Package Insert

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

(b) (4)

Item	Information Provided in NDA	Reviewer's Assessment
Product title, Drug name (201.57(a)(2))		
Proprietary name and established name	**EUCRISA, crisaborole**	**Not adequate as the word "TRADENAME" needs to be replaced by "EUCRISA" "(b) (4) should be changed to "ointment, for topical use"**
Dosage form, route of administration	Ointment, Topical	Adequate
Controlled drug substance symbol (if applicable)	Not applicable	Not applicable
Dosage Forms and Strengths (201.57(a)(8))		
A concise summary of dosage forms and strengths	Ointment, 2%	Adequate

Conclusion:
The word "TRADENAME" needs to be replaced by "EUCRISA" throughout the document.

"(b) (4) should be changed to "ointment, for topical use"

Not Satisfactory.

(b) "Full Prescribing Information" Section

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

(b) (4)

Item	Information Provided in NDA	Reviewer's Assessment
Available dosage forms	Ointment	Adequate
Strengths: in metric system	2%	Adequate
A description of the identifying characteristics of the dosage forms, including shape, color, coating, scoring, and imprinting, when applicable.	White to off-white ointment	(b) (4) (b) (4) cannot be found in the drug product section of the NDA, and hence is difficult to justify including it here. **Not Adequate**

Conclusion:
The phrase (b) (4) " needs to be removed.

Not Satisfactory.

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

(b) (4)

[redacted]

Item	Information Provided in NDA	Reviewer's Assessment
Proprietary name and established name	**EUCRISA, crisaborole**	**Not adequate as the word "TRADENAME" needs to be replaced by "EUCRISA"**
Dosage form and route of administration	Ointment, Topical	Adequate
Active moiety expression of strength with equivalence statement for salt (if applicable)	Not applicable	Not applicable
Inactive ingredient information (quantitative, if injectables 21CFR201.100(b)(5)(iii)), listed by USP/NF names.	Information on all inactive ingredients is provided.	Adequate
Statement of being sterile (if applicable)	Not applicable	Not applicable
Pharmacological/ therapeutic class	(b) (4) PDE-4 inhibitor	Adequate
Chemical name, structural formula, molecular weight	**Provided but add g/mol after molecular weight**	**Not adequate**
If radioactive, statement of important nuclear characteristics.	Not applicable	Not applicable
Other important chemical or physical properties (such as pKa, solubility, or pH)	Information is provided on appearance, and solubility.	Adequate

Conclusion:

The molecular weight should be expressed correctly, 251.1g/mole.

Not Satisfactory.

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

(b) (4)

Item	Information Provided in NDA	Reviewer's Assessment
Strength of dosage form	2%	Adequate
Available units (e.g., bottles of 100 tablets)	Provided	The drug product is also provided as a physician-sample but based on internal discussions with the ATL, it was determined that the inclusion of the physician sample was not necessary. Adequate.
Identification of dosage forms, e.g., shape, color, coating, scoring, imprinting, NDC number	NDC number is provided	Adequate
Special handling (e.g., protect from light, do not freeze)	Statements such as (b) (4) (b) (4) "keep tube tightly closed" and " (b) (4) (b) (4) are provided	Adequate
Storage conditions	Provided	Adequate

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

(b) (4)

Item	Information Provided in NDA	Reviewer's Assessment
Manufacturer/distributor name (21 CFR 201.1)	Name of distributor is properly provided.	Adequate

Conclusion:

Satisfactory.

2. Container and Carton Labeling

Container Label for Package Content: 2.5 g (Physician's sample)

Package Content: 2.5 g (Physician's sample)

Item	Comments on the Information Provided in NDA	Conclusions
Proprietary name, established name (font size and prominence (21 CFR 201.10(g)(2))	• **The word "TRADENAME" needs to be replaced by "EUCRISA"** • **Since the product is a topical ointment, as per the guidelines provided on Dec. 1, 2014 by USP Expert Committee on Nomenclature, Safety and Labeling, the established name should be given as "(crisaborole) Ointment, 2%"**	**Not adequate**
Strength (21CFR 201.10(d)(1); 21.CFR 201.100(b)(4))	Strength is provided	Adequate
Route of administration 21.CFR 201.100(b)(3))	"For Topical Use Only" statement is provided	Adequate
Net contents* (21 CFR 201.51(a))	The phrase "Net Wt." is missing before the contents given in grams. Based on discussions with DMEPA, it was clarified that 21 CFR 201.51 requires that the labels bear a net quantity statement; however, the regulation is not specific as to the need to include the words "Net wt." and there is ample precedent for the inclusion of the net quantity without the words "Net wt."	Adequate
Name of all inactive ingredients (Quantitative ingredient information is required for injectables) 21CFR 201.100(b)(5)**	Information not provided	Acceptable due to limited space
Lot number per 21 CFR 201.18	**Information not provided**	**Not adequate**
Expiration date per 21 CFR 201.17	**Information not provided**	**Not adequate**
"Rx only" statement per 21 CFR 201.100(b)(1)	Complies	Adequate
Storage (not required)	Provided	Adequate
NDC number (per 21 CFR 201.2) (requested, but not required for all labels or labeling), also see 21 CFR 207.35(b)(3)	Provided	Adequate
Bar Code per 21 CFR 201.25(c)(2)***	Provided	Adequate
Name of manufacturer/distributor (21 CFR 201.1)	Name of sponsor is provided. However, name of manufacturer is not provided. Based on the discussions with DMEPA, it was clarified that 21 CFR 201.1(h)(5) states "If the distributor is named on the label, the name shall be qualified by one of the following phrases: "Manufactured for _____", "Distributed by _____", "Manufactured by _____ for _____", "Manufactured for _____by _____", "Distributor: _____", "Marketed by _____". The qualifying phrases may be abbreviated." Therefore, the applicants proposal complies with the regulations.	Adequate
Others	Includes statements such as "Physician Sample – Not for Sale" and "Not for ophthalmic, oral, or intravaginal use"	Adequate

*21 CFR 201.51(h) A drug shall be exempt from compliance with the net quantity declaration required by this section if it is an ointment labeled ''sample'', ''physician's sample'', or a substantially similar statement and the contents of the package do not exceed 8 grams.
**For solid oral dosage forms, CDER policy provides for exclusion of "oral" from the container label
**Not required for Physician's samples. The bar code requirement does not apply to prescription drugs sold by a manufacturer, repacker, relabeler, or private label distributor directly to patients, but versions of the same drug product that are sold to or used in hospitals are subject to the bar code requirements.

Container Label for Package Content: 60 g

Package Content: 60 g

Item	Comments on the Information Provided in NDA	Conclusions
Proprietary name, established name (font size and prominence (21 CFR 201.10(g)(2))	• **The word "TRADENAME" needs to be replaced by "EUCRISA"** • **Since the product is a topical ointment, as per the guidelines provided on Dec. 1, 2014 by USP Expert Committee on Nomenclature, Safety and Labeling, the established name should be given as "(crisaborole) Ointment, 2%"**	**Not adequate**
Strength (21CFR 201.10(d)(1); 21.CFR 201.100(b)(4))	Strength is provided	Adequate
Route of administration 21.CFR 201.100(b)(3))	"For Topical Use Only" statement is provided	Adequate
Net contents* (21 CFR 201.51(a))	The phrase "Net Wt." is missing before the contents given in grams. Based on discussions with DMEPA, it was clarified that 21 CFR 201.51 requires that the labels bear a net quantity statement; however, the regulation is not specific as to the need to include the words "Net wt." and there is ample precedent for the inclusion of the net quantity without the words "Net wt."	Adequate
Name of all inactive ingredients (Quantitative ingredient information is required for injectables) 21CFR 201.100(b)(5)**	Information on all inactive ingredients is provided.	Adequate
Lot number per 21 CFR 201.18	**Information not provided**	**Not adequate**
Expiration date per 21 CFR 201.17	**Information not provided**	**Not adequate**
"Rx only" statement per 21 CFR 201.100(b)(1)	Complies	Adequate
Storage (not required)	Provided	Adequate
NDC number (per 21 CFR 201.2) (requested, but not required for all labels or labeling), also see 21 CFR 207.35(b)(3)	Provided	Adequate
Bar Code per 21 CFR 201.25(c)(2)***	Provided	Adequate
Name of manufacturer/distributor (21 CFR 201.1)	Name of sponsor is provided. However, name of manufacturer is not provided. Based on the discussions with DMEPA, it was clarified that 21 CFR 201.1(h)(5) states "If the distributor is named on the label, the name shall be qualified by one of the following phrases: "Manufactured for _____", "Distributed by _____", "Manufactured by _____ for _____", "Manufactured for _____by _____", "Distributor: _____", "Marketed by _____". The qualifying phrases may be abbreviated." Therefore, the applicants proposal complies with the regulations.	Adequate
Others	Includes statements such as "Not for ophthalmic, oral, or intravaginal use"	Adequate

*21 CFR 201.51(h) A drug shall be exempt from compliance with the net quantity declaration required by this section if it is an ointment labeled ''sample'', ''physician's sample'', or a substantially similar statement and the contents of the package do not exceed 8 grams.
**For solid oral dosage forms, CDER policy provides for exclusion of "oral" from the container label
**Not required for Physician's samples. The bar code requirement does not apply to prescription drugs sold by a manufacturer, repacker, relabeler, or private label distributor directly to patients, but versions of the same drug product that are sold to or used in hospitals are subject to the bar code requirements.

Container Label for Package Content: 100 g

Package Content: 100 g

Item	Comments on the Information Provided in NDA	Conclusions
Proprietary name, established name (font size and prominence (21 CFR 201.10(g)(2))	• **The word "TRADENAME" needs to be replaced by "EUCRISA"** • **Since the product is a topical ointment, as per the guidelines provided on Dec. 1, 2014 by USP Expert Committee on Nomenclature, Safety and Labeling, the established name should be given as "(crisaborole) Ointment, 2%"**	**Not adequate**
Strength (21CFR 201.10(d)(1); 21.CFR 201.100(b)(4))	Strength is provided	Adequate
Route of administration 21.CFR 201.100(b)(3))	"For Topical Use Only" statement is provided	Adequate
Net contents* (21 CFR 201.51(a))	The phrase "Net Wt." is missing before the contents given in grams. Based on discussions with DMEPA, it was clarified that 21 CFR 201.51 requires that the labels bear a net quantity statement; however, the regulation is not specific as to the need to include the words "Net wt." and there is ample precedent for the inclusion of the net quantity without the words "Net wt."	Adequate
Name of all inactive ingredients (3.Quantitative ingredient information is required for injectables) 21CFR 201.100(b)(5)**	Information on all inactive ingredients is provided.	Adequate
Lot number per 21 CFR 201.18	**Information not provided**	**Not adequate**
Expiration date per 21 CFR 201.17	**Information not provided**	**Not adequate**
"Rx only" statement per 21 CFR 201.100(b)(1)	Complies	Adequate
Storage (not required)	Provided	Adequate
NDC number (per 21 CFR 201.2) (requested, but not required for all labels or labeling), also see 21 CFR 207.35(b)(3)	Provided	Adequate
Bar Code per 21 CFR 201.25(c)(2)***	Provided	Adequate
Name of manufacturer/distributor (21 CFR 201.1)	Name of sponsor is provided. However, name of manufacturer is not provided. Based on the discussions with DMEPA, it was clarified that 21 CFR 201.1(h)(5) states "If the distributor is named on the label, the name shall be qualified by one of the following phrases: "Manufactured for _____", "Distributed by _____", "Manufactured by _____ for _____", "Manufactured for _____by _____", "Distributor: _____", "Marketed by _____". The qualifying phrases may be abbreviated." Therefore, the applicants proposal complies with the regulations.	Adequate
Others	Includes statements such as "Not for ophthalmic, oral, or intravaginal use"	Adequate

*21 CFR 201.51(h) A drug shall be exempt from compliance with the net quantity declaration required by this section if it is an ointment labeled ''sample'', ''physician's sample'', or a substantially similar statement and the contents of the package do not exceed 8 grams.
**For solid oral dosage forms, CDER policy provides for exclusion of "oral" from the container label
**Not required for Physician's samples. The bar code requirement does not apply to prescription drugs sold by a manufacturer, repacker, relabeler, or private label distributor directly to patients, but versions of the same drug product that are sold to or used in hospitals are subject to the bar code requirements.

Conclusion:

- **The established name should be given as "(crisaborole) Ointment**
- **Lot number and expiry date should be added.**

Not Satisfactory.

2) Carton Labeling

EUCRISA will be supplied in 2.5 g (physician sample size), 60 g, and 100 g laminate tubes containing 2% white to off-white petrolatum-based ointment. The carton dimensions for each tube size are as follows:

(b) (4)

Package Content: 2.5 g (Physician's sample)

Item	Comments on the Information Provided in NDA	Conclusions
Proprietary name, established name (font size and prominence (FD&C Act 502(e)(1)(A)(i), FD&C Act 502(e)(1)(B), 21 CFR 201.10(g)(2))	• **The word "TRADENAME" needs to be replaced by "EUCRISA"** • **Since the product is a topical ointment, as per the guidelines provided on Dec. 1, 2014 by USP Expert Committee on Nomenclature, Safety and Labeling, the established name should be given as "(crisaborole) Ointment, 2%"**	**Not adequate**
Strength (21CFR 201.10(d)(1); 21.CFR 201.100((d)(2))	Strength is provided	Adequate
Net contents (21 CFR 201.51(a))	The phrase "Net Wt." is missing before the contents given in grams. Based on discussions with DMEPA, it was clarified that 21 CFR 201.51 requires that the labels bear a net quantity statement; however, the regulation is not specific as to the need to include the words "Net wt." and there is ample precedent for the inclusion of the net quantity without the words "Net wt."	Adequate
Lot number per 21 CFR 201.18	Space is reserved for lot #	Adequate
Expiration date per 21 CFR 201.17	Space is reserved for expiration date	Adequate
Name of all inactive ingredients (except for oral drugs); Quantitative ingredient information is required for injectables)[201.10(a), 21CFR201.100(d)(2)]	Information on all inactive ingredients is provided.	Adequate
Sterility Information (if applicable)	Not applicable	Not applicable
"Rx only" statement per 21 CFR 201.100(d)(2), FD&C Act 503(b)(4)	Complies	Adequate
Storage Conditions	Provided	Adequate
NDC number (per 21 CFR 201.2) (requested, but not required for all labels or labeling), also see 21 CFR 207.35(b)(3)	Provided	Adequate
Bar Code per 21 CFR 201.25(c)(2)**	Provided	Adequate
Name of manufacturer/distributor	Name of sponsor is provided. However, name of manufacturer is not provided. Based on the discussions with DMEPA, it was clarified that 21 CFR 201.1(h)(5) states "If the distributor is named on the label, the name shall be qualified by one of the following phrases: "Manufactured for _____", "Distributed by _____", "Manufactured by _____ for _____", "Manufactured for _____by _____", "Distributor: _____", "Marketed by _____". The qualifying phrases may be abbreviated." Therefore, the applicants proposal complies with the regulations.	Adequate
"See package insert for dosage information" (21 CFR 201.55)	Provided	Adequate
"Keep out of reach of children" (optional for Rx, required for OTC)	Provided	Adequate
Route of Administration (not required for oral, 21 CFR 201.100(d)(1) and (d)(2))	"For Topical Use Only" statement is provided	Adequate

(b) (4)

Carton Label for Package Content: 60 g

Package Content: 60 g

Item	Comments on the Information Provided in NDA	Conclusions
Proprietary name, established name (font size and prominence (FD&C Act 502(e)(1)(A)(i), FD&C Act 502(e)(1)(B), 21 CFR 201.10(g)(2))	• **The word "TRADENAME" needs to be replaced by "EUCRISA"** • **Since the product is a topical ointment, as per the guidelines provided on Dec. 1, 2014 by USP Expert Committee on Nomenclature, Safety and Labeling, the established name should be given as "(crisaborole) Ointment, 2%"**	**Not adequate**
Strength (21CFR 201.10(d)(1); 21.CFR 201.100((d)(2))	Strength is provided	Adequate
Net contents (21 CFR 201.51(a))	The phrase "Net Wt." is missing before the contents given in grams. Based on discussions with DMEPA, it was clarified that 21 CFR 201.51 requires that the labels bear a net quantity statement; however, the regulation is not specific as to the need to include the words "Net wt." and there is ample precedent for the inclusion of the net quantity without the words "Net wt."	Adequate
Lot number per 21 CFR 201.18	Space is reserved for lot #	Adequate
Expiration date per 21 CFR 201.17	Space is reserved for expiration date	Adequate
Name of all inactive ingredients (except for oral drugs); Quantitative ingredient information is required for injectables)[201.10(a), 21CFR201.100(d)(2)]	Information on all inactive ingredients is provided.	Adequate
Sterility Information (if applicable)	Not applicable	Not applicable
"Rx only" statement per 21 CFR 201.100(d)(2), FD&C Act 503(b)(4)	Complies	Adequate
Storage Conditions	Provided	Adequate
NDC number (per 21 CFR 201.2) (requested, but not required for all labels or labeling), also see 21 CFR 207.35(b)(3)	Provided	Adequate
Bar Code per 21 CFR 201.25(c)(2)**	Provided	Adequate
Name of manufacturer/distributor	Name of sponsor is provided. However, name of manufacturer is not provided. Based on the discussions with DMEPA, it was clarified that 21 CFR 201.1(h)(5) states "If the distributor is named on the label, the name shall be qualified by one of the following phrases: "Manufactured for _____", "Distributed by _____", "Manufactured by _____ for _____", "Manufactured for _____by _____", "Distributor: _____", "Marketed by _____". The qualifying phrases may be abbreviated." Therefore, the applicants proposal complies with the regulations.	Adequate
"See package insert for dosage information" (21 CFR 201.55)	Provided	Adequate
"Keep out of reach of children" (optional for Rx, required for OTC)	Provided	Adequate
Route of Administration (not required for oral, 21 CFR 201.100(d)(1) and (d)(2))	"For Topical Use Only" statement is provided	Adequate

(b) (4)

Carton Label for Package Content: 100 g

Package Content: 100 g

Item	Comments on the Information Provided in NDA	Conclusions
Proprietary name, established name (font size and prominence (FD&C Act 502(e)(1)(A)(i), FD&C Act 502(e)(1)(B), 21 CFR 201.10(g)(2))	• **The word "TRADENAME" needs to be replaced by "EUCRISA"** • **Since the product is a topical ointment, as per the guidelines provided on Dec. 1, 2014 by USP Expert Committee on Nomenclature, Safety and Labeling, the established name should be given as "(crisaborole) Ointment, 2%"**	**Not adequate**
Strength (21CFR 201.10(d)(1); 21.CFR 201.100((d)(2))	Strength is provided	Adequate
Net contents (21 CFR 201.51(a))	The phrase "Net Wt." is missing before the contents given in grams. Based on discussions with DMEPA, it was clarified that 21 CFR 201.51 requires that the labels bear a net quantity statement; however, the regulation is not specific as to the need to include the words "Net wt." and there is ample precedent for the inclusion of the net quantity without the words "Net wt."	Adequate
Lot number per 21 CFR 201.18	Space is reserved for lot #	Adequate
Expiration date per 21 CFR 201.17	Space is reserved for expiration date	Adequate
Name of all inactive ingredients (except for oral drugs); Quantitative ingredient information is required for injectables)[201.10(a), 21CFR201.100(d)(2)]	Information on all inactive ingredients is provided.	Adequate
Sterility Information (if applicable)	Not applicable	Not applicable
"Rx only" statement per 21 CFR 201.100(d)(2), FD&C Act 503(b)(4)	Complies	Adequate
Storage Conditions	Provided	Adequate
NDC number (per 21 CFR 201.2) (requested, but not required for all labels or labeling), also see 21 CFR 207.35(b)(3)	Provided	Adequate
Bar Code per 21 CFR 201.25(c)(2)**	Provided	Adequate
Name of manufacturer/distributor	Name of sponsor is provided. However, name of manufacturer is not provided. Based on the discussions with DMEPA, it was clarified that 21 CFR 201.1(h)(5) states "If the distributor is named on the label, the name shall be qualified by one of the following phrases: "Manufactured for _____", "Distributed by _____", "Manufactured by _____ for _____", "Manufactured for _____by _____", "Distributor: _____", "Marketed by _____". The qualifying phrases may be abbreviated." Therefore, the applicants proposal complies with the regulations.	Adequate
"See package insert for dosage information" (21 CFR 201.55)	Provided	Adequate
"Keep out of reach of children" (optional for Rx, required for OTC)	Provided	Adequate
Route of Administration (not required for oral, 21 CFR 201.100(d)(1) and (d)(2))	"For Topical Use Only" statement is provided	Adequate

Conclusion:

Not Satisfactory.

OVERALL ASSESSMENT AND SIGNATURES: LABELING

Reviewer's Assessment and Signature:
Numerous deficiencies were found in the labels and the package insert. Till these deficiencies are resolved, the NDA is not recommended for approval from an ONDP perspective (see the **List of Deficiencies**).

Reviewer's Signature
Bhavishya Mittal, Ph.D.
Branch V
Division of New Drug Products II/ONDP

Bhavishya Mittal -S
Digitally signed by Bhavishya Mittal -S
DN: c=US, o=U.S. Government, ou=HHS, ou=FDA, ou=People, 0.9.2342.19200300.100.1.1=2001708640, cn=Bhavishya Mittal -S
Date: 2016.08.18 08:34:00 -04'00'

Secondary Review Comments and Concurrence:

I concur with Dr. Mittal's assessment and his recommendation on the labeling and labels.

Secondary Reviewer's Signature

Moo-Jhong Rhee, Ph.D.
Chief, Branch V
Division of New Drug Products II/ONDP

Moojhong Rhee -S
Digitally signed by Moojhong Rhee -S
DN: c=US, o=U.S. Government, ou=HHS, ou=FDA, ou=People, cn=Moojhong Rhee -S, 0.9.2342.19200300.100.1.1=1300041261
Date: 2016.08.18 08:46:37 -04'00'

II. List of Deficiencies To Be Communicated

Drug Substance: None.

Drug Product: None.

Process: None.

Facility: None.

Biopharmaceutics: None.

Microbiology: None.

Environmental: None.

Label/Labeling:

1) **Package Insert**

- The tradename, EUCRISA should be used through out labeling.
- The term "(b) (4)" should be deleted from the **# 3: Dosage Forms and Strengths in the Full Prescribibig** section.
- The molecular weight should be described correctly, 251.1 g/mole in the #11: **Description** section.

2) **Immediate Container Labels**

- The label needs to be revised with the trade name, EUCRISA.
- The established name and dosage form should be given as "(crisaborole) ointment".
- Lot number and expiry date should be added.

3) **Carton labels**

- The label needs to be revised with the trade name, EUCRISA.
- The established name and dosage form should be given as "(crisaborole) ointment".

III. Attachments

A. Lifecycle Knowledge Management

a) 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**
Assay (Crisaborole)	• Formulation • Raw materials • Process parameters • Scale/equipment • Site	L (24)	(b) (4)	Acceptable	N/A
Impurities (b) (4) **individual unspecified, and total impurities)**	• Formulation • Raw materials • Process parameters • Scale/equipment • Site	M (36)		Acceptable	N/A
(b) (4) **(Butylated Hydroxytoluene)**	• Formulation • Raw materials • Process parameters • Scale/equipment • Site	L (18)		Acceptable	N/A
Microbial Limits	• Formulation • Raw materials • Process parameters • Scale/equipment • Site	M (27)		Acceptable	N/A
Apparent Viscosity (cps)	• Formulation • Raw materials • Process parameters • Scale/equipment • Site	M (48)		Acceptable	N/A

			(b) (4)		
Content Uniformity in the Container, USP <3>	• Formulation • Raw materials • Process parameters • Scale/equipment • Site	M (32)		Acceptable	N/A
Minimal Fill	• Process parameters • Scale/equipment • Site	L (18)		Acceptable	N/A

RPN: Risk Priority Number

$$RPN = \begin{bmatrix} 5 \\ 4 \\ 3 \\ 2 \\ 1 \end{bmatrix} O \times \begin{bmatrix} 5 \\ 4 \\ 3 \\ 2 \\ 1 \end{bmatrix} S \times \begin{bmatrix} 1 \\ 2 \\ 3 \\ 4 \\ 5 \end{bmatrix} D$$

Low Risk- RPN ≤ 25
Moderate Risk - $25 < RPN \leq 60$
High Risk - $RPN > 60$