CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

215985Orig1s000

PRODUCT QUALITY REVIEW(S)

RECOMMENDATION

☒ Approval
☐ Approval with Post-Marketing Commitment
☐ Complete Response

NDA 215985
Assessment 1

Drug Product Name	Zoryve (roflumilast) cream, 0.3%
Dosage Form	Cream
Strength	0.3%
Route of Administration	For topical use
Rx/OTC Dispensed	Rx
Applicant	Arcutis Biotherapeutics, Inc.
US agent, if applicable	NA

Submission(s) Assessed	Document Date	Discipline(s) Affected
Original Submission, eCTD SN 0001	09/29/2021	DS, DP, OPMA, Micro, labeling, and Biopharm
Amendment, SN 0007	12/10/2021	DP, micro, OPMA
Amendment, SN 0013	04/08/2022	DP
Amendment, SN 0014	04/19/2022	DP, OPMA
Amendment, SN 0016	04/29/2022	DP, OPMA
Amendment, SN 0017	05/03/2022	DP
Amendment, SN 0019	05/20/2022	DP
Amendment, SN 0021	06/22/2022	Labeling
Amendment, SN 0023	07/01/2022	Labeling

QUALITY ASSESSMENT TEAM

Discipline	Primary Assessor	Secondary Assessor
Drug Substance	Friedrich Burnett	Lawrence Perez
Drug Product	Jane Chang	Nina Ni
Manufacturing	Raeann Wu	Ying Zhang
Microbiology	Koushik Paul	Jesse Wells
Biopharmaceutics*	Assad Noory	Tapash Ghosh
Regulatory Business Process Manager	Grafton Adams	
Application Technical Lead (ATL)	Nina Ni	

Laboratory (OTR)	NA	NA
Environmental	Jane Chang	Nina Ni

*: No Biopharm review is provided for this NDA review cycle since the applicant proposes that the IVRT method will not be included in the commercial specification as a routine Quality Control test. (b) (4)

QUALITY ASSESSMENT DATA SHEET

For more details about the items in this template, please see the Quality Assessment Data Sheet chapter of the NDA IQA Guide

1. RELATED/SUPPORTING DOCUMENTS

A. DMFs:

DMF #	Type	Holder	Item Referenced	Status	Date Assessment Completed	Comments
(b) (4)	II		(b) (4)	Acceptable	11/02/2021	Reviewed by Dr. F. Burnett
	III			N/A	N/A	Adequate info provided in the NDA
	III			N/A	N/A	Adequate info provided in the NDA

B. OTHER DOCUMENTS: *IND, RLD, RS, Approved NDA*

Document	Application Number	Description
IND	135681 (cream), (b) (4)	Conducted clinical studies
NDA	22522	Reference to all relevant clinical, non-clinical, and CMC info

2. CONSULTS

Discipline	Status	Recommendation	Date	Assessor
Biostatistics	N/A			
Pharmacology/Toxicology	N/A			
CDRH	N/A			
Clinical	N/A			
Other	N/A			

NDA Executive Summary

1. Application/Product Information

NDA Number.	NDA 215985		
Applicant Name	Arcutis Biotherapeutics, Inc.		
Drug Product Name	Zoryve (roflumilast) cream, 0.3% (ARQ-151 cream)		
Dosage Form.	Cream		
Proposed Strength(s)	0.3%		
Route of Administration	Topical		
Maximum Daily Dose	(b) (4)		
Rx/OTC Dispensed	Rx		
Proposed Indication	Plaque psoriasis, including treatment of psoriasis in the intertriginous areas, in patients 12 years of age and older		
Drug Product Description	Roflumilast cream 0.3% (w/w) is a white to off-white cream. It is supplied as 60 g and 5 g in aluminum tubes with (b) (4) screw caps.		
Co-packaged product information	N/A		
Device information:	N/A		
Storage Temperature/ Conditions	Store at 20°C to 25°C (68°F to 77°F), excursions permitted between 15°C and 30°C (59°F and 86°F) [see USP Controlled Room Temperature].		
Review Team	**Discipline**	**Primary**	**Secondary**
	Drug Substance	Friedrich Burnett	Lawrence Perez
	Drug Product/ Labeling	Jane Chang	Nina Ni
	Manufacturing	Raeann Wu	Ying Zhang
	*Biopharmaceutics**	Assad Noory	Tapash Ghosh

	Microbiology	Koushik Paul	Jesse Wells
	Other (specify):	N/A	N/A
	RBPM	Grafton Adams	
	ATL	Nina Ni	
Consults	Le Zhang and David Lewis on compatibility protocol		

***:** No Biopharm review is provided for this NDA review cycle since the applicant proposes that the IVRT method will not be included in the commercial specification as a routine Quality Control test. [redacted] (b) (4)

2. Final Overall Recommendation - Approval

3. Action Letter Information

a. Expiration Dating: 24 months

b. Additional Comments for Action: None

4. Basis for Recommendation:

a. Summary of Rationale for Recommendation:

OPQ recommends APPROVAL of NDA 215985 for commercialization of Zoryve (roflumilast) cream, 0.3%. Based on our evaluation of the available information, the applicant provided sufficient information to support an approval recommendation from the product quality perspective. The applicant provided adequate information on the proposed drug product to ensure the identity, strength, purity, and quality of the proposed drug product. The overall manufacturing inspection recommendation is approval for all the facilities associated with this application. The proposed labeling and labels include adequate information to meet the regulatory requirements.

b. Is the overall recommendation in agreement with the individual discipline recommendations? Yes

[redacted]

Recommendation by Subdiscipline:

Drug Substance	**-**	**Adequate**
Drug Product	**-**	**Adequate**
Quality Labeling	**-**	**Adequate**
Manufacturing	**-**	**Adequate**
Biopharmaceutics	**-**	**Adequate**
Microbiology	**-**	**Adequate**

Environmental Assessment: Categorical Exclusion - Adequate
QPA for EA(s): Yes

5. Life-Cycle Considerations

Established Conditions per ICH Q12: No
Comments: N/A

Comparability Protocols (PACMP): Yes
Comments: The applicant plans (b) (4) In SDN-8, the applicant commits to submitting CBE-0 for information (b) (4) See drug product review on page 35 for details.

Additional Lifecycle Comments: Yes

In SDN-15, the applicant commits (b) (4) in CBE-0. (b) (4) See drug product review on page 10 for details.

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U.S. FOOD & DRUG ADMINISTRATION

CHAPTER IV: LABELING

See Chapter IV (Labeling) of the NDA IQA Guide

List Submissions being reviewed:

Document Reviewed (eCTD #)	Date Received	Information Provided
eCTD-0001 (SDN-1)	09/29/2021	PI, Container and Carton Labels
eCTD-0012 (SDN-13)	03/25/2022	Container and Carton Labels

1.0 PRESCRIBING INFORMATION

(refer to Labeling Review Tool (LRT) on the Labeling Development Team's website)

(b) (4)

Items	Information in Proposed Labeling	Assessor's Comments
Drug name [201.57(a)(2)]		
Established name[1]	Adequate	"roflumilast cream" as the established name
Dosage form, route of administration	Adequate	"cream" and "topical" provided
Controlled drug substance symbol (if applicable)	N/A	N/A
Initial U.S. Approval	Adequate	Roflumilast was first approved in 2011 (NDA 22522, (b) (4)).
Dosage Forms and Strengths [201.57(a)(8)]		
Dosage Forms and Strengths in metric system	Inadequate	Per 21 CFR 201.57(a)(8), strength in metric system, 3 mg of roflumilast per gram, should be provided. Per Labeling Review Tool (page 13), recommend including limited packaging information.
If the drug product contains an active ingredient that is a salt, clearly state whether the strength is based on the active moiety (e.g., Tablets: 10 mg of drug-x) or active ingredient (e.g., Tablets: 10 mg of drug-x hydrochloride).	N/A	The API is not a salt.

[1] Established name = [Drug] [Route of Administration] [Dosage Form]

Conclusion: Unsatisfactory

The recommended revision is shown below:

DOSAGE FORMS AND STRENGTHS:

Cream, 0.3%: 3 mg of roflumilast per gram in 60-gram tubes

1.2 FULL PRESCRIBING INFORMATION

(b) (4)

Items	Information in Proposed Labeling	Assessor's Comments
Available dosage forms	Adequate	"cream" provided
Strengths in metric system.	Adequate	Strength in metric system (3 mg of roflumilast per gram) provided. Minor format change is recommended.
If the active ingredient is a salt, apply the USP Salt Policy per FDA Guidance. Clearly state whether the strength is based on the active moiety.	N/A	N/A
A description of the identifying characteristics of the dosage forms, including shape, color, coating, scoring, and imprinting, and color and clarity of the solution, when applicable.	Inadequate	"white to off-white cream" provided. Recommend including limited package information per Labeling Review Tool (page 30 of 93).

Conclusion: **Unsatisfactory**

The recommended revisions are shown below:

Cream, 0.3%: 3 mg of roflumilast per gram (b) (4) -of white to off white cream in 60-gram tubes

1.2.2 Section 11: DESCRIPTION

(b) (4)

(b) (4)

Items	Information in Proposed Labeling	Assessor's Comments
Proprietary name and established name [21 CFR 201.57(c)(12)(i)(A)]	Inadequate	Per 201.10(g)(1), the established name shall accompany the proprietary name; "the established name shall be used at least once in the running text in association with such proprietary name or designation and in the same type size used in such running text".
Dosage form and route of administration [21 CFR 201.57(c)(12)(i)(B)]	Adequate	"cream" and "topical" are provided
Active moiety expression of strength with equivalence statement (if applicable) per 21 CFR 201.100(b)(4)	Adequate	Strength in metric system is included. A equivalence statement is not required since it is not a salt.
Inactive ingredient information [21 CFR 201.57(c)(12)(i)(C)] [quantitative, if injectables 21CFR201.100(b)(5)(iii), listed by USP/NF names (if any) in alphabetical order]. Not required for oral use, except for colorant. For ingredients added to adjust the pH or make isotonic, include the name and statement of effect. If alcohol is present, must provide the amount of alcohol in terms of percent volume of absolute alcohol at 60 °F (15.56 °C) per 21 CFR 201.10(d)(2).	Inadequate	The title of NF, i.e., cetostearyl alcohol" should be used in place of (b) (4) in alphabetical order.

Sterility statement [if applicable, 21 CFR 201.57(c)(12)(i)(D)]	N/A	N/A
Pharmacological/ therapeutic class [21 CFR 201.57(c)(12)(i)(E)]	Inadequate	PDE should be spelled out, i.e., phosphodiesterase.
Chemical name, structural formula, molecular weight [21 CFR 201.57(c)(12)(i)(F)]	Inadequate	Molecular weight should be 403.21.
If radioactive, statement of important nuclear characteristics [21 CFR 201.57(c)(12)(i)(G)]	N/A	N/A
Other important chemical or physical properties (such as pKa or pH) [21 CFR 201.57(c)(12)(ii)]	Inadequate	Recommend (b) (4)
For oral prescription drug products, include gluten statement if applicable	N/A	N/A
Remove statements that may be misleading or promotional (e.g., "synthesized and developed by Drug Company X," "structurally unique molecular entity"	N/A	N/A
If there is a USP monograph for the drug product and it contains a labeling requirement, ensure the labeling requirement is fulfilled. Note the labeling requirement may be applicable to another section of the PI (e.g., Section 2).	N/A	N/A No USP monograph established for roflumilast.

Conclusion: **Unsatisfactory**

The recommended revisions are shown below:

ZORYVE (roflumilast) cream, 0.3% is (b) (4) a white to off-white cream for topical use. The active ingredient, roflumilast, is a ~~PDE-4~~ phosphodiesterase 4 inhibitor.

Roflumilast is described chemically as 3-cyclopropylmethoxy-*N*-(3,5-~~D~~dichloropyridin-4-yl)-(b) (4) 4-(difluoromethoxy)-benzamide. The empirical formula is $C_{17}H_{14}Cl_2F_2N_2O_3$, and the molecular weight is (b) (4) 403.21.

Roflumilast is practically insoluble in water and hexane, sparingly soluble in ethanol, and freely soluble in acetone.

Each gram of ZORYVE contains 3 mg of roflumilast in a cream base containing ceteareth-10 phosphate, (b) (4) cetearyl phosphate, cetostearyl alcohol, diethylene glycol monoethyl ether, hexylene glycol, isopropyl palmitate, methylparaben, propylparaben, purified

water, sodium hydroxide, and white petrolatum. Hydrochloric acid may have been added to adjust pH (b) (4)

1.2.3 Section 16: HOW SUPPLIED/STORAGE AND HANDLING

(b) (4)

Items	Information in Proposed Labeling	Assessor's Comments
Dosage form	Adequate	"cream" provided
Strength(s) in metric system. If the active ingredient is a salt, apply the USP Salt Policy per FDA Guidance. Clearly state whether the strength is based on the active moiety.	Inadequate	Per 21 CFR 201.57(c)(17), strength in metric system (3 mg roflumilast) should be provided.
Available units (e.g., bottles of 100 tablets)	Adequate	"60-g tubes" provided
Identification of dosage forms, e.g., shape, color, coating, scoring, imprinting, and color and clarity of the solution, when applicable, NDC number. Assess if the tablet is scored. If product meets guidelines and criteria for a scored tablet, state "functionally scored"	Adequate	"white to off white cream" provided
Special handling (e.g., protect from light, refrigerate). If there is a statement to "Dispense in original container," provide reason why (e.g. to protect from light or moisture, to maintain stability, etc.) For hazardous drugs, state "DRUG X is a hazardous drug. Follow applicable special handling and disposal procedures.x" with	N/A	N/A

x numerical citation to "OSHA Hazardous Drugs."		
If the product contains a desiccant, ensure the size and shape differ from the dosage form and desiccant has a warning such as "Do not eat."	N/A	N/A
Storage conditions. Where applicable, use USP storage range rather than storage at a single temperature.	Adequate	Minor format edit
Latex: If product does not contain latex and manufacturing of product and container did not include use of natural rubber latex or synthetic derivatives of natural rubber latex, state: "Not made with natural rubber latex. Avoid statements such as "latex-free."	N/A	N/A
Include information about child-resistant packaging (if manufacturer choose to include)	N/A	N/A

Conclusion: Unsatisfactory

Per Labeling Review Tool (March 2022), page 70 of 93, it is recommended considering including the proprietary name (if any) and the nonproprietary name in Section 16.

The recommended revisions are shown below:

16.1 How Supplied

ZORYVE (roflumilast) cream is a white to off-white cream containing 3 mg (0.3%) of roflumilast per gram and is supplied in 60-g aluminum tubes (NDC 80610-130-60).

(b) (4)

16.2 Storage and Handling

Store at 20°C to 25°C (68°F to 77°F); excursions permitted (b) (4) between 15°C (b) (4) and 30°C (59°F (b) (4) and 86°F). [See USP Controlled Room Temperature.]

1.2.4 Other Sections of Labeling

1.2.5 Section 17: PATIENT COUNSELING INFORMATION

N/A

Item	Information in Proposed Labeling	Assessor's Comments
Name and location of business (street address, city, state, and zip code) of the manufacturer, distributor, and/or packer [21 CFR 201.1(h)(5)]	N/A	Not provided. Per Labeling Review Tool (page 74 of 93), the manufacturer information should be located **after** the PATIENT COUNSELING INFORMATION section, at the end of the PI.

2.0 PATIENT LABELING

(b) (4)

Item	Information in Proposed Labeling	Assessor's Comments
Established name[2]	Adequate	"roflumilast cream" provided
Special preparation instructions (if applicable)	N/A	N/A
Storage and handling information (if applicable)	Adequate	Minor edits to (b) (4) 68°F (b) (4) 77°F (20°C (b) (4) 25°C)"
If the product contains a desiccant, ensure the desiccant has a warning (e.g., "Do not eat.") and the size and shape of the desiccant differs from the dosage form.	N/A	N/A
Active ingredient(s) (if applicable)	Adequate	"roflumilast" provided
Alphabetical listing of inactive ingredients (if applicable)	Inadequate	The title of NF, i.e., cetostearyl alcohol" should be used in place of (b) (4) in alphabetical order.

[2] Established name = [Drug] [Route of Administration] [Dosage Form]

Name and location of business (street address, city, state, and zip code) of manufacturer, distributor, and/or packer	Adequate	The distributor's name, city and zip code are provided. Per Labeling Review Tool (page 74 of 93), the street address may be omitted if the address is shown in a current city or telephone directory. Per Google search, the street address of Arcutis Biotherapeutics, Inc. is: 3027 Townsgate Rd Ste 300 Westlake Village, CA 91361 Therefore, it is acceptable that no street address is listed.

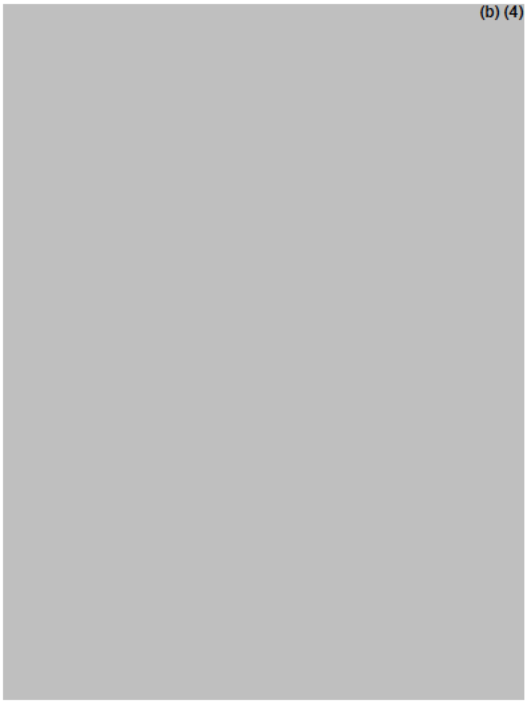
Conclusion: Unsatisfactory

The recommended revision is shown below:

> **How should I store ZORYVE cream?**
> Store ZORYVE (b) (4) at room temperature (b) (4) 68°F (b) (4) 77°F (20°C ~~to~~ (b) (4) 25°C).
>
> **Inactive ingredients:** ceteareth-10 phosphate, (b) (4) cetearyl phosphate, cetostearyl alcohol, diethylene glycol monoethyl ether, hexylene glycol, isopropyl palmitate, methylparaben, propylparaben, purified water, sodium hydroxide, and white petrolatum.

3.0 CARTON AND CONTAINER LABELS

3.1 CONTAINER LABEL (SDN-1)



(b) (4)

(b) (4)

Conclusion: **Unsatisfactory**

The recommended revision is shown below:

1. Since cetostearyl alcohol, NF is available, the title of the NF monograph should be used as the established name. Therefore, replace the inactive ingredient (b) (4) with cetostearyl alcohol and list inactive ingredients in alphabetical order, i.e., ceteareth-10 phosphate, cetearyl phosphate, cetostearyl alcohol, diethylene glycol monoethyl ether, hexylene glycol, isopropyl palmitate, methylparaben, propylparaben, purified water, sodium hydroxide, and white petrolatum.
2. Replace (b) (4) with "Store at 20°C to 25°C (68°F to 77°F); excursions permitted between 15°C and 30°C (59°F and 86°F) [See USP Controlled Room Temperature]."

In SDN-13, updated container labels, as shown below, are provided.

(b) (4)

Items	Information in Proposed Labeling	Assessor's Comments
Proprietary name, established name [FD&C Act 502(e)(1)(A)(i)] [font size at least half as large as the proprietary name, and prominence per FD&C Act 502(e)(1)(B), 21 CFR 201.10(g)(2)]	Adequate	"ZORYVE™ (roflumilast) cream" provided
Route of administration, if it is not for oral use [21 CFR 201.100(b)(3)]	Adequate	"topical" provided

Strength(s) in metric system	Adequate	"Each gram contains: 3 mg (0.3%) roflumilast" provided
Active moiety expression of strength with equivalence statement (if applicable) [FD&C Act 502(e)(1)(ii), 21 CFR 201.10(d)(1); 21 CFR 201.100(b)(4), USP <1121>]	N/A	Not a salt
Net content [FD&C Act 502(b)(2), 21 CFR 201.51(a)]&	Adequate	"60 g" and "5 g" provided
Name of all inactive ingredients, in alphabetical order required for OTC drugs [FD&C Act 502(e)(1)(A)(iii), 21 CFR 201.10(a)] [except for oral drug per 21 CFR 201.100(b)(5) or limited space per 21 CFR 201.10(i)(2)]; [Quantitative ingredient information is required for injectables per 21 CFR 201.100(b)(5)(iii)*]	Adequate	The title of NF, if available, is used as the established name for each excipient. Excipients are listed in alphabetical order.
"Rx only" displayed on principal display [21 CFR 201.100(b)(1)]	Adequate	Provided
NDC number [per 21 CFR 201.2, requested, but not required for all labels or labeling, also see 21 CFR 207.35(b)(3)(i)]	Adequate	60 g tube: NDC 80610-130-60 5 g tube Sample: NDC 80610-130-05 60 g tube Sample: NDC 80610-130-91
Lot number (21 CFR 201.18) and expiration date (21 CFR 201.17)	Adequate	Lot number and Expiration date are located at the bottom of the tube where the fold is, with Lot number on the front and expiration date on the back.
Storage conditions.	Adequate	Store at 20°C to 25°C (68°F to 77°F); excursions permitted between 15°C and 30°C (59°F and 86°F) [See USP Controlled Room Temperature]
Bar code [21CFR 201.25(c)(2)]**	Adequate	Provided for 60-g labels, not required for 5-g sample
Adequate directions for use [FD&C Act 502(f)(1), 21 CFR 201.5] or "Recommended Dosage: See Prescribing Information" (21 CFR 201.55)	Adequate	**"Recommended Dosage:** See prescribing information" provided
Name of manufacturer/distributor [502(b)(1), 21 CFR 201.1(a), 21 CFR 201.1(h)(5)]	Adequate	"**Manufactured for:** Arcutis Biotherapeutics, Inc. Westlake Village, CA 91361" provided
And others, if space is available	N/A	Not for oral, ophthalmic, or intravaginal use

If alcohol is present, must provide the amount of alcohol in terms of percent volume of absolute alcohol at 60 °F (15.56 °C) per 21 CFR 201.10(d)(2).	N/A	N/A

Conclusion: **Adequate**

The updated container labels meet the regulatory expectations.

3.2 CARTON LABELS

Carton label for 60 g tube (SDN-1):

4 Pages of Draft Labeling have been Withheld in Full as b4 (CCI/TS) immediately following this page

Items	Information in Proposed Labeling	Assessor's Comments
Proprietary name, established name [FD&C Act 502(e)(1)(A)(i)] [font size at least half as large as the proprietary name, and prominence per FD&C Act 502(e)(1)(B), 21 CFR 201.10(g)(2)]	Adequate	"ZORYVE™ (roflumilast) cream" provided
Strength(s) in metric system	Adequate	"Each gram contains: 3 mg (0.3%) roflumilast" provided
Route of Administration [not required for oral, 21 CFR 201.100(b)(3)]	Adequate	"Topical" provided
Active moiety expression of strength with equivalence statement (if applicable) [FD&C Act 502(e)(1)(ii), 21 CFR 201.10(d)(1); 21 CFR 201.100(b)(4), USP <1121>]	N/A	Not a salt
Net content [FD&C Act 502(b)(2), 21 CFR 201.51(a)]	Adequate	"60 g" and "Contains 6 tubes of Net Wt. 5 g per tube" provided
Name of all inactive ingredients, in alphabetical order required for OTC drugs [FD&C Act 502(e)(1)(A)(iii), 21 CFR 201.10(a)] [except for oral drug per 21 CFR 201.100(b)(5) or limited space per 21 CFR 201.10(i)(2)]; [Quantitative ingredient information is required for injectables per 21 CFR 201.100(b)(5)(iii)]	Adequate	The title of NF, if available, is used as the established name for each excipient. Excipients are listed in alphabetical order.
If alcohol is present, must provide the amount of alcohol in terms of percent volume of absolute alcohol	N/A	N/A
"Rx only" displayed on principal display [21 CFR 201.100(b)(1)]	Adequate	Provided
NDC number [per 21 CFR 201.2, requested, but not required for all labels or labeling, also see 21 CFR 207.35(b)(3)(i)]	Adequate	60 g: NDC 80610-130-60 5 g tube x 6: NDC 80610-130-96 60 g sample: NDC 80610-130-91
Lot number (21 CFR 201.18) and expiration date (21 CFR 201.17)	Adequate	Space allocated
Storage conditions. If applicable, include a space on the carton labeling for the user to write the new beyond-use-date (BUD).	Adequate	Store at 20°C to 25°C (68°F to 77°F); excursions permitted between 15°C and 30°C (59°F and 86°F) [See USP Controlled Room Temperature]
Bar code [21 CFR 201.25(c)(2)]*	Adequate	provided
Adequate directions for use [FD&C Act 502(f)(1), 21 CFR 201.5] or "Recommended Dosage: See Prescribing Information" (21 CFR 201.55)	Adequate	**"Recommended Dosage:** See prescribing information" provided

If there is a Medication Guide, must include a statement about dispensing a Medication Guide to each patient.	N/A	N/A
"Keep out of reach of children" (Required for OTC in CFR. Optional for Rx drugs)	Adequate	provided
Name of manufacturer/distributor [502(b)(1), 21 CFR 201.1(a), 21 CFR 201.1(h)(5)]	Adequate	"**Manufactured for:** Arcutis Biotherapeutics, Inc. Westlake Village, CA 91361" provided
And others, if space is available	Adequate	"Not for oral, ophthalmic, or intravaginal use" provided
If there is a USP monograph for the drug product and it contains a labeling requirement, ensure the labeling requirement is fulfilled.	N/A	No USP monograph established for roflumilast.
When a drug product differs from the relevant USP standard of strength, quality, or purity, as determined by the application of the tests, procedures, and acceptance criteria set forth in the relevant compendium, its difference shall be plainly stated on its label.	N/A	N/A

*Requests for an exemption can be made [21 CFR 201.25(d)(ii)(2)]. The bar code requirement does not apply to prescription drug samples [21 CFR 201.25(b)(1)(i)(A)].

Conclusion: ***Adequate***

The updated carton labels meet the regulatory expectations.

4.0 LIST OF DEFICIENCIES:

A. Regarding PI

a) Highlight Section

1. Include strength in metric system and limited packaging information, i.e., 3 mg of roflumilast per gram in 60-gram tubes, in Dosage Forms and Strengths section.

b) Full Prescribing Information

Section 3: Dosage Forms and Strengths

2. Include limited packaging information, e.g., in 60-gram tubes.

Section 11: Description

3. Per 201.10(g)(1), the established name shall accompany the proprietary name, i.e., ZORYVE (roflumilast) cream.
4. Regarding pharmacological class, PDE should be spelled out, i.e., phosphodiesterase 4 inhibitor.
5. Revise molecular weight from (b) (4) g/mol to 403.21.
6. List inactive ingredients in alphabetical order and replace (b) (4) with cetostearyl alcohol.
7. (b) (4).

Section 16: How Supplied/Storage and Handling

8. Include strength in metric system, i.e., 3 mg (0.3%) of roflumilast per gram.

B. Regarding the Container/Carton Labels

All issues pertaining to container and carton labels (see page 9) noted during the review have been resolved satisfactorily. There are no outstanding issues.

OVERALL ASSESSMENT:

Issues on strength (lack of strength in metric system) and inactive ingredient established name for Prescribing Information labeling are identified.

Recommendation:

From the ONDP perspective, this application is ***not*** ready for approval in its present form per 21 CFR 314.125(b)(6) until the deficiencies delineated above are satisfactorily resolved.

Primary Labeling Assessor Name and Date:

Jane Chang, Ph.D.
Master reviewer
ONDP/DNDP II
04/26/2022

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

Nina Ni, Ph.D.
Senior Pharmaceutical Quality Assessor
ONDP/DNDP II/Branch 4
04/26/2022

Jane Chang

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Nina Ni

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U.S. FOOD & DRUG ADMINISTRATION

MEMORANDUM

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

DATE: July 11, 2022

TO: Addendum of Assessment #1 of NDA 215985 Quality Assessment – Drug Product and Labeling

FROM: Jane Chang, Ph.D.
Master Chemistry Reviewer, OPQ/ONDP/DNDP II

THROUGH Nina Ni, Ph.D.
Senior Pharmaceutical Quality Assessor
OPQ/ONDP/DNDP II/Branch 4

SUBJECT: **Final Recommendation on Drug product and Labeling**

SUMMARY

The previous Quality Assessment – Labeling, Assessment Cycle #1 dated 26-Apr-2022, made a recommendation of not ready for approval for this NDA because of labeling deficiencies (see NDA 215985 Labeling R01 Section 4.0). These labeling issues have been satisfactorily resolved based on the revisions made in eCTD-0021 and eCTD-0023.

The previous Quality Assessment – Drug Product, Assessment Cycle #1 dated 13-May-2022, which included assessment of up to four weeks simulated leachable data for the drug product container closure system, concluded adequate. Subsequently, simulated leachable data for the 6-week interval was provided in eCTD-0019. The data also suggest a low risk for leachables.

RECOMMENDATION:

This application is now recommended for **Approval** from the CMC drug product and labeling perspective.

Assessment Notes

Assessor Comment: Labeling deficiencies from Quality Assessment were identified in Assessment Cycle #1 dated 26-Apr-2022 (see NDA 215985 Labeling R01 Section 4.0). Subsequently, labeling amendments, as listed below, were submitted. In addition, simulated leachable data for the drug product container closure system was provided in eCTD-0019. These amendments are the subject of this addendum.

List Submissions being reviewed:

Document Reviewed	Date Received	Information
eCTD-0019 (SDN-20)	05/20/2022	6-Week simulated leachable data
eCTD-0021 (SDN-22)	06/22/2022	PPI labeling, Container labels and carton labeling
eCTD-0023 (SDN-24)	07/01/2022	PI labeling

1.0 DRUG PRODUCT

In SDN-20, the leachable simulation study data were provided, including three separate lots for each of non-volatiles (HPLC-DAD/MS), volatiles (HS-GC/MS), and semi-volatiles (GC/MS) using isopropanol-water (15:85) as the simulation solvent in 60 g aluminum tubes and placed horizontally at 40°C/75% RH at t = 0, 2, 4, and 6 weeks. In addition, data of controls samples, i.e., the simulation solvent in absence of contact with the 60 g aluminum tubes, were also provided. Neither non-volatile nor semi-volatile was detected. Only two volatile compounds, i.e., (b) (4), were detected.

The simulated leachable data for up to 4 weeks were provided in SDN-13 (see Drug Product, Assessment Cycle #1 dated 13-May-2022), which did not reflect the recalculated values based on the FDA recommendation of using an analytical evaluation threshold (AET) of (b) (4) µg/tube due to the timing of the Agency's information request. The simulated leachable data summarized in the following table reflects the values based on an AET of (b) (4) µg/tube (for the 60 g tube).

Table 1: Leachables Data - Simulation Study at 40°C/75% RH

Analyte	Results (µg/day)				
	Control	T0	2 Weeks	4 Weeks	6 weeks
(b) (4)					

Assessment: ***Adequate***

The first 4 weeks of simulated leachable data were recalculated based on the Agency's recommended AET of (b) (4)µg/tube, which is based on a maximum daily dose (MDD) of (b) (4) g of cream, as opposed to a MDD of (b) (4) g originally used by the applicant. The 6 weeks data show that only two compounds, i.e., (b) (4) were detected. The recalculated values (for up to 4 weeks only) are reduced by a factor of (b) (4) was detected at up to (b) (4) µg/day, which is well below the PDE (b) (4) per ICH Q3C. (b) (4) was detected at up to (b) (4) µg/day of exposure level. If (b) (4) continues leaching from the container closure system at the same rate, it would reach to about (b) (4) µg/day at 60-week (the end of the simulation study), which presents no safety concern based on the 4/29/2022 email from Toxicologist, Dr. Jianyong (Jerry) Wang. See Drug Product, Assessment Cycle #1 dated 13-May-2022, page 12.

In conclusion, the interim simulated leachable data to date suggest a low risk for leachables. As more data become available, leachables should be further assessed.

2.0 PRESCRIBING INFORMATION LABELING

The information provided in eCTD-0023 dated 07/01/2022 is summarized below.

2.1 HIGHLIGHTS OF PRESCRIBING INFORMATION

(b) (4)

Items	Information in Proposed Labeling	Assessor's Comments
Drug name [201.57(a)(2)]		
Established name[1]	Adequate	"roflumilast cream" as the established name
Dosage form, route of administration	Adequate	"cream" and "topical" provided
Controlled drug substance symbol (if applicable)	N/A	N/A
Initial U.S. Approval	Adequate	Roflumilast was first approved in 2011 (NDA 22522, 250 mcg and 500 mcg; in NDA 215985 Labeling R01 Section 4.0, the strength was erroneously stated as (b) (4) for NDA 22522).

[1] Established name = [Drug] [Route of Administration] [Dosage Form]

Dosage Forms and Strengths [201.57(a)(8)]		
Dosage Forms and Strengths in metric system	Adequate	Per 21 CFR 201.57(a)(8), strength in metric system, i.e., 3 mg of roflumilast per gram, is provided. Limited packaging information is also provided per Labeling Review Tool (page 13).
If the drug product contains an active ingredient that is a salt, clearly state whether the strength is based on the active moiety (e.g., Tablets: 10 mg of drug-x) or active ingredient (e.g., Tablets: 10 mg of drug-x hydrochloride).	N/A	The API is not a salt.

Conclusion: ***Adequate***

Information in HIGHLIGHTS section meets the regulatory requirements.

2.2 FULL PRESCRIBING INFORMATION

(b) (4)

Items	Information in Proposed Labeling	Assessor's Comments
Available dosage forms	Adequate	"cream" provided
Strengths in metric system.	Adequate	Strength in metric system, i.e., 3 mg of roflumilast per gram, provided.
If the active ingredient is a salt, apply the USP Salt Policy per FDA Guidance. Clearly state whether the strength is based on the active moiety.	N/A	The API is not a salt.
A description of the identifying characteristics of the dosage forms, including shape, color, coating, scoring, and imprinting, and color and clarity of the solution, when applicable.	Adequate	"white to off-white cream" provided. Limited package information is provided per Labeling Review Tool (page 30 of 93).

Conclusion: ***Adequate***

Information in DOSAGE FORMS AND STRENGTHS meets the regulatory requirements.

Items	Information in Proposed Labeling	Assessor's Comments
Proprietary name and established name [21 CFR 201.57(c)(12)(i)(A)]	Adequate	"ZORYVE (roflumilast) cream" provided
Dosage form and route of administration [21 CFR 201.57(c)(12)(i)(B)]	Adequate	"cream" and "topical" are provided
Active moiety expression of strength with equivalence statement (if applicable) per 21 CFR 201.100(b)(4)	Adequate	Strength in metric system is included. An equivalence statement is not required since it is not a salt.
Inactive ingredient information [21 CFR 201.57(c)(12)(i)(C)] [quantitative, if injectables 21CFR201.100(b)(5)(iii), listed by USP/NF names (if any) in alphabetical order]. Not required for oral use, except for colorant. For ingredients added to adjust the pH or make isotonic, include the name and statement of effect. If alcohol is present, must provide the amount of alcohol in terms of percent	Adequate	The title of USP/NF, if available, is used for each excipient. Excipients are listed in alphabetical order.

volume of absolute alcohol at 60 °F (15.56 °C) per 21 CFR 201.10(d)(2).		
Sterility statement [if applicable, 21 CFR 201.57(c)(12)(i)(D)]	N/A	N/A
Pharmacological/ therapeutic class [21 CFR 201.57(c)(12)(i)(E)]	Adequate	" phosphodiesterase 4 inhibitor (PDE-4)" provided
Chemical name, structural formula, molecular weight [21 CFR 201.57(c)(12)(i)(F)]	Adequate	None
If radioactive, statement of important nuclear characteristics [21 CFR 201.57(c)(12)(i)(G)]	N/A	N/A
Other important chemical or physical properties (such as pKa or pH) [21 CFR 201.57(c)(12)(ii)]	N/A	It is acceptable that (b) (4) not to be included since the applicant considers the information confidential.
Remove statements that may be misleading or promotional (e.g., "synthesized and developed by Drug Company X," "structurally unique molecular entity"	N/A	No promotional statements
If there is a USP monograph for the drug product and it contains a labeling requirement, ensure the labeling requirement is fulfilled. Note the labeling requirement may be applicable to another section of the PI (e.g., Section 2).	N/A	N/A No USP monograph established for roflumilast.

Conclusion: ***Adequate***

Information in DESCRIPTION meets the regulatory requirements.

2.2.3 Section 16: HOW SUPPLIED/STORAGE AND HANDLING

(b) (4)

Items	Information in Proposed Labeling	Assessor's Comments
Dosage form	Adequate	"cream" provided
Strength(s) in metric system. If the active ingredient is a salt, apply the USP Salt Policy per FDA Guidance. Clearly state whether the strength is based on the active moiety.	Adequate	Per 21 CFR 201.57(c)(17), strength in metric system, i.e., 3 mg (0.3%) of roflumilast per gram, is provided.
Available units (e.g., bottles of 100 tablets)	Adequate	"60-g aluminum tubes" provided
Identification of dosage forms, e.g., shape, color, coating, scoring, imprinting, and color and clarity of the solution, when applicable, NDC number. Assess if the tablet is scored. If product meets guidelines and criteria for a scored tablet, state "functionally scored"	Adequate	"white to off-white cream" provided
Special handling (e.g., protect from light, refrigerate). If there is a statement to "Dispense in original container," provide reason why (e.g. to protect from light or moisture, to maintain stability, etc.) For hazardous drugs, state "DRUG X is a hazardous drug. Follow applicable special handling and disposal procedures.x" with x numerical citation to "OSHA Hazardous Drugs."	N/A	N/A
If the product contains a desiccant, ensure the size and shape differ from the dosage form and desiccant	N/A	N/A

has a warning such as "Do not eat."		
Storage conditions. Where applicable, use USP storage range rather than storage at a single temperature.	Adequate	None
Latex: If product does not contain latex and manufacturing of product and container did not include use of natural rubber latex or synthetic derivatives of natural rubber latex, state: "Not made with natural rubber latex. Avoid statements such as "latex-free."	N/A	N/A
Include information about child-resistant packaging (if manufacturer choose to include)	N/A	N/A

Conclusion: ***Adequate***

Information in HOW SUPPLIED/STORAGE AND HANDLING meets the regulatory requirements.

2.2.4 Section 17: PATIENT COUNSELING INFORMATION

N/A

Item	Information in Proposed Labeling	Assessor's Comments
Name and location of business (street address, city, state, and zip code) of the manufacturer, distributor, and/or packer [21 CFR 201.1(h)(5)]	N/A	Not provided. Per Labeling Review Tool (page 74 of 93), the manufacturer information should be located **after** the PATIENT COUNSELING INFORMATION section, at the end of the PI.

3.0 PATIENT LABELING (b) (4)

The information provided in eCTD-0021 dated 06/22/2022 is summarized below.

(b) (4)

Conclusion: ***Adequate***

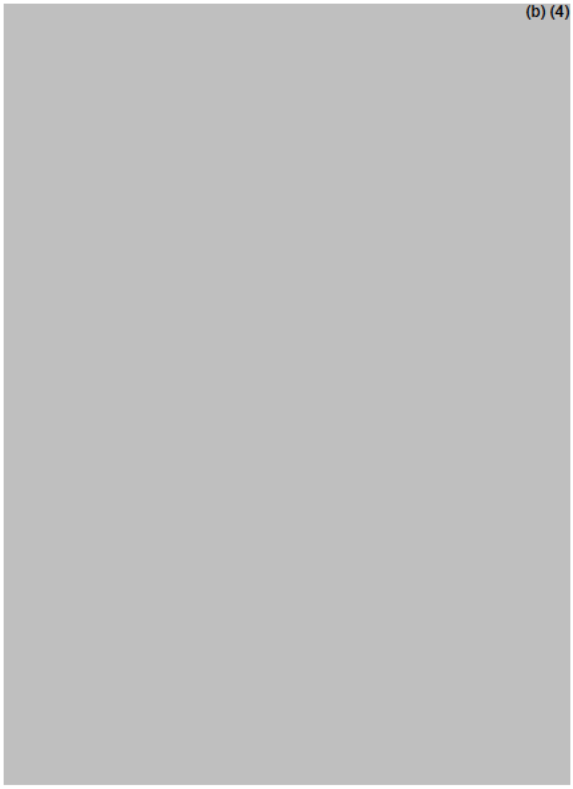
The information meets the regulatory expectation.

4.0 CARTON AND CONTAINER LABELS

4.1 CONTAINER LABEL

Assessor's Comment: *Acceptable container labels, including 5 g and 60 g physician samples as well as 60 g commercial product, were provided in eCTD-0012 (SDN-13) (see NDA 215985 Labeling R01 Section 4.0).*

Additional modifications, e.g., reducing font size of "Z" in the proprietary name, color, font thickness, and addition of part numbers, were made in eCTD-0021 (SDN-22). The updated container labels are shown below.



Professional Sample 5 g **Professional Sample 60 g**

(b) (4)

Items	Information in Proposed Labeling	Assessor's Comments
Proprietary name, established name [FD&C Act 502(e)(1)(A)(i)] [font size at least half as large as the proprietary name, and prominence per FD&C Act 502(e)(1)(B), 21 CFR 201.10(g)(2)]	Adequate	"ZORYVE™ (roflumilast) cream" provided
Route of administration, if it is not for oral use [21 CFR 201.100(b)(3)]	Adequate	"topical" provided
Strength(s) in metric system	Adequate	"Each gram contains: 3 mg (0.3%) roflumilast" provided
Active moiety expression of strength with equivalence statement (if applicable) [FD&C Act 502(e)(1)(ii), 21 CFR 201.10(d)(1); 21 CFR 201.100(b)(4), USP <1121>]	N/A	Not a salt
Net content [FD&C Act 502(b)(2), 21 CFR 201.51(a)]&	Adequate	"60 g" and "5 g" provided
Name of all inactive ingredients, in alphabetical order required for OTC drugs [FD&C Act 502(e)(1)(A)(iii), 21 CFR 201.10(a)] [except for oral drug per 21 CFR 201.100(b)(5) or limited space per 21 CFR 201.10(i)(2)]; [Quantitative ingredient information is required for injectables per 21 CFR 201.100(b)(5)(iii)*]	Adequate	The title of NF, if available, is used as the established name for each excipient. Excipients are listed in alphabetical order.
"Rx only" displayed on principal display [21 CFR 201.100(b)(1)]	Adequate	Provided

NDC number [per 21 CFR 201.2, requested, but not required for all labels or labeling, also see 21 CFR 207.35(b)(3)(i)]	Adequate	60 g commercial product: NDC 80610-130-60 5 g tube professional sample: NDC 80610-130-05 60 g tube professional sample: NDC 80610-130-91
Lot number (21 CFR 201.18) and expiration date (21 CFR 201.17)	Adequate	Lot number and Expiration date are located at the bottom of the tube where the fold is, with Lot number on the front and expiration date on the back.
Storage conditions.	Adequate	Store at 20°C to 25°C (68°F to 77°F); excursions permitted between 15°C and 30°C (59°F and 86°F) [See USP Controlled Room Temperature]
Bar code [21CFR 201.25(c)(2)]**	Adequate	Provided for 60 g labels, not required for 5 g professional sample
Adequate directions for use [FD&C Act 502(f)(1), 21 CFR 201.5] or "Recommended Dosage: See Prescribing Information" (21 CFR 201.55)	Adequate	**"Recommended Dosage:** See prescribing information" provided
Name of manufacturer/distributor [502(b)(1), 21 CFR 201.1(a), 21 CFR 201.1(h)(5)]	Adequate	"**Manufactured for:** Arcutis Biotherapeutics, Inc. Westlake Village, CA 91361" provided
And others, if space is available	N/A	Not for oral, ophthalmic, or intravaginal use
If alcohol is present, must provide the amount of alcohol in terms of percent volume of absolute alcohol at 60 °F (15.56 °C) per 21 CFR 201.10(d)(2).	N/A	N/A

Conclusion: ***Adequate***

The information for container labels meets the regulatory expectations.

4.2 CARTON LABELING

Assessor's Comment: Acceptable carton labeling, including 5 g and 60 g physician samples as well as 60 g commercial product, were provided in eCTD-0012 (SDN-13) (see NDA 215985 Labeling R01 Section 4.0).

Additional modifications, e.g., reducing font size of "Z" in the proprietary name, color, font thickness, and addition of part numbers, were made in eCTD-0021 (SDN-22). The updated carton labeling is shown below.

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Items	Information in Proposed Labeling	Assessor's Comments
Proprietary name, established name [FD&C Act 502(e)(1)(A)(i)] [font size at least half as large as the proprietary name, and prominence per FD&C Act 502(e)(1)(B), 21 CFR 201.10(g)(2)]	Adequate	"ZORYVE™ (roflumilast) cream" provided
Strength(s) in metric system	Adequate	"Each gram contains: 3 mg (0.3%) roflumilast" provided
Route of Administration [not required for oral, 21 CFR 201.100(b)(3)]	Adequate	"Topical" provided
Active moiety expression of strength with equivalence statement (if applicable) [FD&C Act 502(e)(1)(ii), 21 CFR 201.10(d)(1); 21 CFR 201.100(b)(4), USP <1121>]	N/A	Not a salt
Net content [FD&C Act 502(b)(2), 21 CFR 201.51(a)]	Adequate	"60 g" and "Contains 6 tubes of Net Wt. 5 g per tube" provided
Name of all inactive ingredients, in alphabetical order required for OTC drugs [FD&C Act 502(e)(1)(A)(iii), 21 CFR 201.10(a)] [except for oral drug per 21 CFR 201.100(b)(5) or limited space per 21 CFR 201.10(i)(2)]; [Quantitative ingredient information is required for injectables per 21 CFR 201.100(b)(5)(iii)]	Adequate	The title of NF, if available, is used as the established name for each excipient. Excipients are listed in alphabetical order.
If alcohol is present, must provide the amount of alcohol in terms of percent volume of absolute alcohol	N/A	N/A
"Rx only" displayed on principal display [21 CFR 201.100(b)(1)]	Adequate	Provided
NDC number [per 21 CFR 201.2, requested, but not required for all labels or labeling, also see 21 CFR 207.35(b)(3)(i)]	Adequate	60 g commercial product: NDC 80610-130-60 5 g x 6 professional sample: NDC 80610-130-96 60 g professional sample: NDC 80610-130-91
Lot number (21 CFR 201.18) and expiration date (21 CFR 201.17)	Adequate	Space allocated
Storage conditions. If applicable, include a space on the carton labeling for the user to write the new beyond-use-date (BUD).	Adequate	Store at 20°C to 25°C (68°F to 77°F); excursions permitted between 15°C and 30°C (59°F and 86°F) [See USP Controlled Room Temperature]
Bar code [21 CFR 201.25(c)(2)]	Adequate	provided

Adequate directions for use [FD&C Act 502(f)(1), 21 CFR 201.5] or "Recommended Dosage: See Prescribing Information" (21 CFR 201.55)	Adequate	**"Recommended Dosage:** See prescribing information" provided
If there is a Medication Guide, must include a statement about dispensing a Medication Guide to each patient.	N/A	N/A
"Keep out of reach of children" (Required for OTC in CFR. Optional for Rx drugs)	Adequate	provided
Name of manufacturer/distributor [502(b)(1), 21 CFR 201.1(a), 21 CFR 201.1(h)(5)]	Adequate	"**Manufactured for:** Arcutis Biotherapeutics, Inc. Westlake Village, CA 91361" provided
And others, if space is available	Adequate	"Not for oral, ophthalmic, or intravaginal use" provided
If there is a USP monograph for the drug product and it contains a labeling requirement, ensure the labeling requirement is fulfilled.	N/A	No USP monograph established for roflumilast.
When a drug product differs from the relevant USP standard of strength, quality, or purity, as determined by the application of the tests, procedures, and acceptance criteria set forth in the relevant compendium, its difference shall be plainly stated on its label.	N/A	N/A

Conclusion: ***Adequate***

The information for carton labeling meets the regulatory expectations.

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Jane Chang

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MICROBIOLOGY

Product Background: Zoryve™ is indicated for the topical treatment of plaque psoriasis, including treatment of psoriasis in the intertriginous areas, in patients 12 years of age and older.

NDA: 215985

Drug Product Name / Strength: Roflumilast (Zoryve) 0.3% (wt/wt).

Route of Administration: Topical Cream.

Applicant Name: Arcutis Biotherapeutics, Inc.

Manufacturing Site: (b) (4)

Method of Sterilization: This is a nonsterile product.

Review Recommendation: **Adequate**

Theme (ANDA only): **N/A**

Justification (ANDA only): N/A

Review Summary: (b) (4)

List Submissions Being Reviewed: 09/29/202 and 12/10/2021.

Highlight Key Outstanding Issues from Last Cycle: N/A

Remarks: The submission is **recommended** for approval on the basis of sterility assurance.

Concise Description Outstanding Issues Remaining: None.

Supporting Documents: Microbiology review N213872MR01.doc, dated 02/18/2021.

List Number of Comparability Protocols (NDA only): None.

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