CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

219474Orig1s000

PRODUCT QUALITY REVIEW(S)

NDA Executive Summary

- **Application/Product Information**

NDA Number	219474
Applicant Name	Acrotech Biopharma
Drug Product Name	Difamilast Ointment, 1%.
Dosage Form	Ointment
Proposed Strength(s)	1%
NDA Classification	Type 1 - NME
Route of Administration	Topical
Maximum Daily Dose	(b) (4) mg
Rx/OTC Dispensed	Rx
Proposed Indication	Treatment of mild to moderate atopic dermatitis (AD)
Drug Product Description	Acrotech Biopharma Inc. submitted a new NDA219474 for ADQUEY® (difamilast) ointment, 1% for topical use via 505 (b)(1) regulatory pathway for the treatment of mild to moderate atopic dermatitis (AD). This NDA is based on the IND 112973. The drug substance (DS), difamilast, is referred to DMF (b) (4). It is a white to off-white crystals or crystalline powder. It exists in two crystal forms ((b) (4)), in which (b) (4) is the stable form. (b) (4) The drug substance manufacturer, Otsuka, (b) (4); (b) (4) all Phase 3 studies and commercial production will use (b) (4) crystals. It has established a (b) (4)- months retest date; however, the drug product manufacturer, (b) (4) has an (b) (4) retest interval.

	Ointment formulation with 0.1%, 0.3%, 1% and 3% strength has been used in phase 1 clinical trial, 1% strength is considered for the clinical phase 3 study. Difamilast is formulated as a semi-solid ointment. The difamilast (b) (4) Propylene Carbonate, (b) (4) White petrolatum, Paraffin Wax, Mineral Oil and White Beeswax. The resultsing ointment is filled into (b) (4) tubes. Difamilast Ointment, 1% is packaged with 3 g, 27 g and 85 g three configurations in (b) (4) aluminium tubes sealed with (b) (4) cap. 3 g fill tube is a physician sample. 19 bulk batches including clinical and registration with each package of at least 3 batches manufactured at (b) (4) have been provided with their COAs. The applicant provided up to 36 months long-term stability data at 25°C/60%RH and 6 months accelerated data at 40°C/75%RH for three primary registration batches for three package configurations. The proposed expiry period for the drug product is 36 months for commercial 27g fill tube and 85g fill tube, and 18 months for 3g fill physician sample tubes when stored at 20ºC to 25ºC (68ºF to 77ºF); excursions permitted from 15ºC to 30ºC (59ºF to 86ºF) [see USP Controlled Room Temperature]. (b) (4)		
Co-packaged product information	N/A		
Device information	N/A		
Storage Temperature/ Conditions	at 20°C to 25°C (68°F to 77°F) and excursions permitted to 15°C to 30°C (59°F to 86°F). (b) (4)		
Review Team	**Discipline**	**Primary**	**Secondary**
	Drug Substance	Sam Bain, PhD	Lawrence Perez, PhD
	Drug Product/ Labeling	Ghaled Hamad, PhD	Baoqing Ma, PhD

	Manufacturing	Satheesh Podaralla, PhD	Kshitij Patkar, PhD
	Microbiology	Marijke Koppenol-Raab, PhD	Neal Sweeney, PhD
	Other (specify) Labeling	Ghaled Hamad, PhD	Julia Pinto, PhD
	RBPM	Emma Gimose	
	ATL	Baoqing Ma, PhD	
Consults	N/A		

2. Final Overall Recommendation - Approval

This application is recommended for approval with the expiration dating periods of 36 months when packaged in the proposed container closure and stored at 20-25 °C.

The CMC-recommended PI labeling as well as container and carton labels revisions have been communicated to the applicant. The applicant has accepted all CMC-recommended revision and will submit the finalized PI labeling as well as container and carton labels to the application prior to the action date. Therefore, no additional labeling memorandum is needed for the approval of this application from the OPQ perspective.

4. Basis for Recommendation:

a. Summary of Rationale for Recommendation:

- The applicant of this 505(b)(1) new drug application has provided sufficient CMC information to assure the identity, strength, purity, and quality of the drug substance, difamilast, and drug product, difamilas ointment, 1%.
- The Office of Pharmaceutical Manufacturing Assessment has made the overall recommendation of adequate for the facilities involved in this application.
- The CMC revisions on labels/labeling have been communicated to the applicant and the recommended CMC revisions have been accepted by the applicant.
- The applicant's request for categorical exclusion from preparation of environmental assessment has been found adequate and is granted.

Therefore, from the OPQ perspective this application is recommended for approval with an expiration dating period of 36 months when stored at 20-25 °C.

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

Recommendation by Subdiscipline:

Drug Substance	**-**	**Adequate**
Drug Product	**-**	**Adequate**
Quality Labeling	**-**	**Adequate**
Manufacturing	**-**	**Adequate**
Microbiology	**-**	**Adequate**
Biopharmaceutics	**-**	**N/A**

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

5. **Life-Cycle Considerations**
Established Conditions per ICH Q12: No
Comments:

Comparability Protocols (PACMP): No
Comments:

Additional Lifecycle Comments: None

Application Technical Lead Name and Date:

Baoqing Ma, PhD
Senior Pharmaceutical Quality Assessor
DPQA VII/OPQA II/OPQ

01/20/2026

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CHAPTER IV: LABELING

For more details about the items in this template, please see Chapter IV (Labeling) of the NDA IQA Guide (OPQ-ALL-WI-0006)

NDA Number	219474
Assessment Cycle Number	01
Drug Product Name	Adquey (Difamilast) Ointment, 1%

Assessment Recommendation: Adequate

Item	Assessment Conclusion	SDN # where labeling is adequate ("N/A" otherwise)
Prescribing Information Labeling	Adequate	01
Patient Information	Adequate	
Instruction for Use (IFU)	Adequate	
Container Labels	Adequate	
Carton Labeling	Adequate	

All labeling deficiencies identified during this review, including container and carton deficiencies, were conveyed to the applicant through information requests issued by the RPBM (Craig Johnson) via the DMEPA review team (Valerie Vaughan).

Labeling issues identified during Review:

- **1.0 Full Prescribing Information (FPI)**
  - Section 11 (DESCRIPTION):
    - Provide a description of the Active Pharmaceutical Ingredient (API), noting it is a crystalline solid or polymorph. Clearly state its solubility profile, for example: "Soluble in XX and insoluble in YY."
    - List all inactive ingredients by their USP/NF names, arranged in alphabetical order, as per USP <1091> guidelines.
- **2.0 Patient Labeling**
  - Inactive Ingredients: Inactive ingredients must be listed by their USP/NF names (where available) in alphabetical order, as per USP <1091>.
- **3.0 Container and Carton Labeling**

- Lot and Expiration Dates: Both the container and carton labels require updates to be fully compliant. The lot number and expiration date are missing on both labels. The format for the Lot number and expiration date should be included on both commercial and sample packs, and compliant with 21 CFR § 201.17.
    - As per 21 CFR § 201.18, the lot number on the label should be capable of yielding the complete manufacturing history of the package.
    - Provide the format to be used for the expiration date, e.g., DD/MM/YYYY or MMMYYYY.
- Storage Information: The container and carton labels should be consistent with the Patient Package Insert (PPI). Add the statement, "Store away from direct sunlight, heat and moisture," to the storage information on the container labels and carton labeling to minimize storage errors.
- Dosage Statement: For clarity and alignment with the Prescribing Information, revise the dosage statement to: "Apply a thin layer twice daily to affected areas."

Submissions being reviewed:

Document Reviewed (eCTD #, SDN #)	Date Received	Information Provided
0001, 1	02/13/2025	Difamilast USPI Draft Labeling
0001, 1	02/13/2025	Difamilast Draft patient package Insert and Patient Package Insert.
0001, 1	02/13/2025	Draft carton and tube label (3g, 27g, and 85g)

1.0 PRESCRIBING INFORMATION[1]

Assessment of Product Quality Related Aspects of the Prescribing Information: As submitted in SN 001; Date 13-Feb2025

[1] Labeling Review Tool (LRT) (March 2022), including use of consistent terminology for dosage form and unit of measure for strength in the product title and DOSAGE FORMS AND STRENGTHS heading in Highlights, in the DOSAGE AND ADMINISTRATION, DOSAGE FORMS AND STRENGTHS, DESCRIPTION, and HOW SUPPLIED/STORAGE AND HANDLING sections (see page 2 of LRT)

1.1 HIGHLIGHTS OF PRESCRIBING INFORMATION

(b) (4)

Item	Item in Proposed Labeling (choose "Adequate", "Inadequate", or "N/A")	Assessor's Comments (If an item is Inadequate, provide more details on the issues, as appropriate)
Product Title in Highlights[2] [21 CFR 201.57(a)(2)]		
Established name(s)[3]	Adequate	
Route(s) of administration	Adequate	
Controlled drug substance symbol (if applicable)	N/A	
Initial U.S. Approval [§201.57(a)(3)]	Adequate	
Dosage Forms and Strengths Heading in Highlights [§ 201.57(a)(8)]		
Dosage form(s)[4] and strength(s) in metric system[5]	Adequate	
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).[6]	N/A	

[2] Draft guidance: *Product Title and Initial U.S. Approval in the Highlights of Prescribing Information for Human Prescription Drug and Biological Products — Content and Format* (January 2018)
[3] Established name = [Drug] [Route of Administration] [Dosage Form]. Do use not "USP" descriptor in the product title or within the Highlights (see page 3 of LRT).
[4] Draft guidance: *Product Title and Initial U.S. Approval in the Highlights of Prescribing Information for Human Prescription Drug and Biological Products — Content and Format* (January 2018); USP <1151>; USP Nomenclature Guideline
[5] Labeling Review Tool (March 2022, page 13), include limited packaging information; USP <7>
[6] Guidance: *Naming of Drug Products Containing Salt Drug Substances* (June 2015); MAPP 5021.1

Item	Item in Proposed Labeling (choose "Adequate", "Inadequate", or "N/A")	Assessor's Comments (If an item is Inadequate, provide more details on the issues, as appropriate)
Assess if the tablet is scored. If product meets guidelines and criteria for a scored tablet, state "functionally scored."[7]	N/A	
For injectable drug products for parenteral administration, use appropriate package type term (e.g., single-dose, multiple-dose, single-patient-use). Other package terms include pharmacy bulk package and imaging bulk package.[8]	N/A	

Assessment: *Adequate*

(Provide any revision, if applicable, e.g., different color font, strikethrough, etc.) ***Any issues should be listed at the end in "OUTSTANDING ISSUES AND RECOMMENDATIONS"***

1.2 FULL PRESCRIBING INFORMATION

1.2.1 Section 2 (DOSAGE AND ADMINISTRATION)[9]

(b) (4)

[redacted]

[7] Guidance: *Tablet Scoring: Nomenclature, Labeling, and Data for Evaluation* (March 2013)
[8] Guidance: *Selection of the Appropriate Package Type Terms and Recommendations for Labeling Injectable Medical Products Packaged in Multiple-Dose, Single-Dose, and Single-Patient-Use Containers for Human Use* (October 2018); USP <659>
[9] See § 201.57(c)(3); draft guidance: *Dosage and Administration Section of Labeling for Human Prescription Drug and Biological Products — Content and Format* (January 2023); Labeling Review Tool (March 2022, page 25)

Item	Item in Proposed Labeling (choose "Adequate", "Inadequate", or "N/A")	Assessor's Comments (If an item is Inadequate, provide more details on the issues, as appropriate)
DOSAGE AND ADMINISTRATION section		
Special instructions for product preparation (e.g., reconstitution and resulting concentration, dilution, compatible diluents and/or soft food[10], storage conditions needed to maintain the stability of the reconstituted or diluted product).	N/A	Ointment, doesn't require special preparation.
Important administration instructions supported by product quality information (e.g., do not crush or chew extended-release tablets, instructions for mixing with food).	N/A	
For parenteral products: include statement: *"Parenteral drug products should be inspected visually for particulate matter and discoloration prior to administration, whenever solution and container permit."*[11]	N/A	Not a parenteral product.
If there is a USP monograph for the drug product and it contains a labeling requirement, ensure the labeling requirement is fulfilled.[12] Note the labeling requirement may be applicable to another section of the PI (e.g., Section 11).	N/A	
For radioactive products, include radiation dosimetry for the patient and healthcare practitioner(s) who administer the drug	N/A	
For hazardous products, include the statement *"DRUG X is a hazardous drug. Follow*	N/A	

[10] Draft Guidance: Use of Liquids and/or Soft Foods as Vehicles for Drug Administration: General Considerations for Selection and In Vitro Methods for Product Quality Assessments
[11] §201.57(c)(3)(iv)
[12] USP General Notices 2.30 Legal Recognition

Item	Item in Proposed Labeling (choose "Adequate", "Inadequate", or "N/A")	Assessor's Comments (If an item is Inadequate, provide more details on the issues, as appropriate)
applicable special handling and disposal procedures.[x]" with x numerical citation to "OSHA Hazardous Drugs."		

Assessment: *Adequate*

(Provide any revision, if applicable, e.g., different color font, strikethrough, etc.) ***Any issues should be listed at the end in "OUTSTANDING ISSUES AND RECOMMENDATIONS"***

1.2.2 Section 3 (DOSAGE FORMS AND STRENGTHS)[13]

(b) (4)

Item	Item in Proposed Labeling (choose "Adequate", "Inadequate", or "N/A")	Assessor's Comments (If an item is Inadequate, provide more details on the issues, as appropriate)
DOSAGE FORMS AND STRENGTHS section		
Available dosage form(s)	Adequate	
Strength(s) in metric system	Adequate	
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 (e.g., Tablets: 10 mg of drug-x) or active ingredient (e.g., Tablets: 10 mg of drug-x hydrochloride). No equivalency statement.	N/A	Not a salt.
A description of the identifying characteristics of the dosage forms, including shape, color, coating, scoring, imprinting, and color and clarity of the solution, when applicable.	Adequate	

[13] See § 201.57(c)(4); Labeling Review Tool (March 2022, page 29)

Item	Item in Proposed Labeling (choose "Adequate", "Inadequate", or "N/A")	Assessor's Comments (If an item is Inadequate, provide more details on the issues, as appropriate)
Assess if the tablet is scored. If product meets guidelines and criteria for a scored tablet, state "functionally scored."	N/A	Not a tablet.
For injectable drug products for parenteral administration, use appropriate package type term (e.g., single-dose, multiple-dose, single-patient-use). Other package type terms include pharmacy bulk package and imaging bulk package (see USP <659>).	N/A	Not injection.

Assessment: *Adequate*

(Provide any revision, if applicable, e.g., different color font, strikethrough, etc.) ***Any issues should be listed at the end in "OUTSTANDING ISSUES AND RECOMMENDATIONS"***

1.2.3 Section 11 (DESCRIPTION)[14]

(b) (4)

[redacted]

[14] See § 201.57(c)(12); Labeling Review Tool (March 2022, page 56)

Item	Item in Proposed Labeling (choose "Adequate", "Inadequate", or "N/A")	Assessor's Comments (If an item is Inadequate, provide more details on the issues, as appropriate)
DESCRIPTION section		
Proprietary and established name(s)[15] [§ 201.57(c)(12)(i)(A)].	Adequate	
Dosage form(s) and route(s) of administration [§ 201.57(c)(12)(i)(B)].	Adequate	
If the active ingredient is a salt, apply the USP Salt Policy and include the equivalency statement per Salt Guidance and MAPP. For example: "TRADENAME contains 100 mg of drug-x (equivalent to 123.7 mg of drug-x hydrochloride)" [§ 201.57(c)(12)(i)(C)].	N/A	Not a salt.
List inactive ingredients (not required for oral use, except for colorant) by the USP/NF names in alphabetical order.[16] Avoid brand names. [§ 201.57(c)(12)(i)(C)].	Inadequate	Inactive ingredients shall be listed by USP/NF names (where available) in alphabetical order, per USP <1091>.
For parenteral injectable dosage forms, include the name and quantities of all inactive ingredients. For ingredients added to adjust the pH or make isotonic, include the name and statement of effect. [§ 201.100(b)(5)(iii)].	N/A	Not a parenteral product.
If alcohol is present, must provide the amount of alcohol in terms of percent volume of	N/A	No Alcohol present.

[15] Use of "USP" descriptor is not required to be included next to the established name throughout Prescribing Information (PI) labeling. If an applicant wants to use the "USP" descriptor next to the established name in the PI, recommend limiting its use to the product quality sections of the Full Prescribing Information (FPI) (i.e., DOSAGE FORMS AND STRENGTHS, DESCRIPTION, HOW SUPPLIED/STORAGE AND HANDLING) (see page 3 of LRT).

[16] Per § 201.100(b)(5)(i) and (ii), flavoring and colorants may be designated as such without naming their components except for FD&C Yellow No 5 and FD&C Yellow No 6, which must be listed per § 201.20. Per § 201.100(b)(5)(iii), trace amounts of harmless substances added solely for individual product identification need not be named. If an applicant wants to use the National Formulary (NF) descriptor next to excipients, recommend limiting its use to the product quality sections of the FPI (see page 3 of LRT). Do not list brand names, e.g., Opadry, Eudragit, Polistirex, etc.

Item	Item in Proposed Labeling (choose "Adequate", "Inadequate", or "N/A")	Assessor's Comments (If an item is Inadequate, provide more details on the issues, as appropriate)
absolute alcohol at 60 °F. (15.56 °C) [§ 201.10(d)(2)].		
Sterility statement (if applicable) [§ 201.57(c)(12)(i)(D)].	N/A	
Pharmacological/Therapeutic class[17] [§ 201.57(c)(12)(i)(E)].	Adequate	
Chemical name[18], structural formula, molecular weight [§ 201.57(c)(12)(i)(F)].	Adequate	
If radioactive, statement of important nuclear characteristics [§ 201.57(c)(12)(i)(G)].	N/A	
Other important chemical or physical properties (such as pKa or pH) [201.57(c)(12)(ii)].	N/A	Not provided.
For oral prescription drug products, include gluten statement[19] (if applicable).	N/A	
Remove statements that may be misleading or promotional (e.g., "synthesized and developed by Drug Company X," "structurally unique molecular entity").	Adequate	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	No Monograph in USP.

Assessment: *Inadequate*

[17] Listed before "indicated for" in INDICATIONS AND USAGE of Highlights section [§ 201.57(a)(6)]; can also search the term "FDA EPC Text Phrases" in FDA's Labeling Resources for Human Prescription Drugs for the most recent EPC list.

[18] Chemical names do not need to be capitalized unless it appears at the beginning of a sentence (see *Preferred IUPAC Names Provisional Recommendation*, September 2004; Chapter 1, par. 16 Name writing, p.80-90).

[19] Draft guidance: *Gluten in Drug Products and Associated Labeling Recommendations* (December 2017)

- *Delete "wax-based" in the first sentence and it should read "tradename xxx difamilast is a white to off-white ointment for topical use. Then add the statement "Each gram of ointment contains 10 mg of difamilast.*
- *The API should be described, as a crystalline or polymorph with the following solubility profile: Soluble in xx and insoluble in yy.*
- *Inactive ingredients shall be listed by USP/NF names (where available) in alphabetical order, per USP <1091>.*

1.2.4 Section 16 (HOW SUPPLIED/STORAGE AND HANDLING)[20]

(b) (4)

Item	Item in Proposed Labeling (choose "Adequate", "Inadequate", or "N/A")	Assessor's Comments (If an item is Inadequate, provide more details on the issues, as appropriate)
HOW SUPPLIED/STORAGE AND HANDLING section		
Available dosage form(s) [§ 201.57(c)(17)].	Adequate	
Strength(s) in metric system. [§ 201.57(c)(17)(i)] 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. No equivalency statement.	Inadequate	Add the statement "Each gram of ointment contains 10 mg of difamilast".
Available units (e.g., bottles of 100 tablets) [§ 201.57(c)(17)(ii)].	Adequate	

[20] See § 201.57(c)(17); Labeling Review Tool (March 2022, page 70). Consider including proprietary name and established name.

Item	Item in Proposed Labeling (choose "Adequate", "Inadequate", or "N/A")	Assessor's Comments (If an item is Inadequate, provide more details on the issues, as appropriate)
Identification of dosage forms (e.g., shape, color, coating, scoring, imprinting, and color and clarity of the solution, when applicable); Include NDC(s) [§ 201.57(c)(17)(iii)].	Adequate	
Assess if the tablet is scored. If product meets guidelines and criteria for a scored tablet, state "functionally scored."	N/A	
For injectable drug products for parenteral administration, use appropriate package type term (e.g., single-dose, multiple-dose, single-patient-use). Other package terms include pharmacy bulk package and imaging bulk package (see USP <659>).	N/A	
Special handling about the supplied product (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." [§ 201.57(c)(17)(iv)]	Adequate	
Storage conditions. Where applicable, use USP storage range rather than storage at a single temperature. (see USP <659>).	Adequate	
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	N/A	

Item	Item in Proposed Labeling (choose "Adequate", "Inadequate", or "N/A")	Assessor's Comments (If an item is Inadequate, provide more details on the issues, as appropriate)
natural rubber latex, state: *"Not made with natural rubber latex. Avoid statements such as "latex-free."*[21]		
Include information about child-resistant packaging[22] (if chosen by manufacturer).	Adequate	Not Child resistant tube.

Assessment: *Inadequate*

(Provide any revision, if applicable, e.g., different color font, strikethrough, etc.) ***Any issues should be listed at the end in "OUTSTANDING ISSUES AND RECOMMENDATIONS"***

1.2.5 Other Sections of Labeling

There may be other sections of labeling that contain product-quality related information. For example, there are specific required/recommended warnings for certain inactive ingredients [e.g., aspartame, aluminum in large and small volume parenterals, sulfites, FD&C Yellow Number 5 (tartrazine), and benzyl alcohol]. Please notify the prescription drug review division if the product contains any of these inactive ingredients.

Please include your comments about other sections of labeling if they contain product quality information.

Not Applicable.

[21] Guidance: *Recommendations for Labeling Medical Products to Inform Users that the Product or Product Container is not Made with Natural Rubber Latex* (December 2014)
[22] Guidance: *Child-Resistant Packaging Statements in Drug Product Labeling* (August 2019)

1.2.6 Manufacturing Information After Section 17 (for drug products)[23]

Item	Item in Proposed Labeling (choose "Adequate" or "Inadequate")	Assessor's Comments (If an item is Inadequate, provide more details on the issues, as appropriate)
Manufacturing Information After Section 17		
Name and location of business (street address, city, state, and zip code) of the manufacturer, distributor, and/or packer.	Adequate	

Assessment: *Inadequate*

(Provide any revision, if applicable, e.g., different color font, strikethrough, etc.) ***Any issues should be listed at the end in "OUTSTANDING ISSUES AND RECOMMENDATIONS"***

2.0 PATIENT LABELING

Assessment of Product Quality Related Aspects of Patient Labeling (e.g., Medication Guides, Instructions for Use, Patient Information):

Item	Item in Proposed Labeling (choose "Adequate", "Inadequate", or "N/A")	Assessor's Comments about Labeling (If an item is Inadequate, provide more details on the issues, as appropriate)
Established name[24]	Adequate	
Special preparation instructions (if applicable).	N/A	
Storage and handling information (if applicable).	Adequate	
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 differ from the dosage form.	N/A	
Active ingredient(s) (if applicable).	Adequate	
Alphabetical listing of inactive ingredients (if applicable).	Inadequate	Inactive ingredients shall be listed

[23] § 201.1(h)(5) and 201.1(i); Labeling Review Tool (March 2022, page 74)
[24] Established name = [Drug] [Route of Administration] [Dosage Form]

Item	Item in Proposed Labeling (choose "Adequate", "Inadequate", or "N/A")	Assessor's Comments about Labeling (If an item is Inadequate, provide more details on the issues, as appropriate)
		by USP/NF names (where available) in alphabetical order, per USP <1091>.
Name and location of business (street address, city, state, and zip code) of manufacturer, distributor, and/or packer.	Adequate	

Assessment: *Inadequate*

(Provide any revision, if applicable, e.g., different color font, strikethrough, etc.) ***Any issues should be listed at the end in "OUTSTANDING ISSUES AND RECOMMENDATIONS"***

3.0 CONTAINER AND CARTON LABELING[25]

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[25] Carton and Container Labeling Resources

Item	Item in Proposed Carton Labeling (choose "Adequate", "Inadequate", or "N/A")	Is item in Container Labels same as that of Carton Labeling?	Assessor's Comments about Container Labels and Carton Labeling (If an item is Inadequate or different, provide more details, as appropriate)
Proprietary name and established name[27], (font size and prominence) [§ 201.10(g)(2)].	Adequate	Yes	Deferred to DMEPA for the requirements for font size and prominence.
Strength(s) in metric system [§ 201.100(b)(4) & 201.100(d)].[28]	Adequate	Yes	
Route(s) of administration, not required for oral use [§ 201.100(b)(3)].	Adequate	Yes	
If the active ingredient is a salt, include the equivalency statement per Salt Guidance and MAPP [§ 201.10(d)(1) & 201.100(b)(4), USP <1121>].	N/A	Yes	
Net contents (e.g., tablet count, volume of liquid) [§ 201.51(a)].[29]	Adequate	Yes	
"Rx only" displayed on the principal display [§ 201.100(b)(1)].	Adequate	Yes	
NDC (requested, but not required for all labels or labeling) [§ 201.2 & 207.35].	Adequate	Yes	
Lot number and expiration date [§ 201.18 & 201.17].	Inadequate	Yes	Both the container and carton labels require updates to be fully compliant. The most critical issues are the missing lot number and expiration date on both labels. The format of Lot number

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

[28] Express as " XX mg per tablet" or "XX mg per capsule" for strength of professional samples of solid oral dosage form with small net quantities per container (e.g., 5 or less) or blister pack/carton. See Guidance: *Safety Considerations for Container Labels and Carton Labeling Design to Minimize Medication Errors* (May 2022)

[29] § 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.

Item	Item in Proposed Carton Labeling (choose "Adequate", "Inadequate", or "N/A")	Is item in Container Labels same as that of Carton Labeling?	Assessor's Comments about Container Labels and Carton Labeling (If an item is Inadequate or different, provide more details, as appropriate)
			and expiry date should be included on both commercial and sample packs, and compliant with 21 CFR 201.17. Per 21 CFR 201.18, the lot number on the label of a drug should be capable of yielding the complete manufacturing history of the package. Provide the format to be used for expiration dating, i.e., DD/MM/YYYY or MMMYYYY.
Storage conditions. If applicable, include a space on the carton labeling for the user to write the beyond-use-date (BUD).	Adequate	Yes	
For injectable drug products for parenteral administration, use appropriate package type term (e.g., single-dose, multiple-dose, single-patient-use). Other package terms include pharmacy bulk package and imaging bulk package, and these products require a "Not for direct infusion" statement. (See USP <659>).	N/A	Yes	
Name of all inactive ingredients, in alphabetical order [§ 201.10(a)] [except for oral drug per § 201.100(b)(5) or limited space per § 201.10(i)(2)].	Adequate	Yes	
For parenteral injectable dosage forms, include	N/A	Yes	

Item	Item in Proposed Carton Labeling (choose "Adequate", "Inadequate", or "N/A")	Is item in Container Labels same as that of Carton Labeling?	Assessor's Comments about Container Labels and Carton Labeling (If an item is Inadequate or different, provide more details, as appropriate)
quantities of all inactive ingredients. For ingredients added to adjust the pH or make isotonic, include the name and statement of effect. [§ 201.100(b)(5)(iii)].			
If alcohol is present, must provide the amount of alcohol in terms of percent volume of absolute alcohol at 60 °F. (15.56 °C) [§ 201.10(d)(2)].	N/A	Yes	
Linear Bar code [§ 201.25(c)(2)].[30]	Adequate	Yes	
Adequate directions for use: "Recommended Dosage: See Prescribing Information" [§ 201.5 & 201.55].	Adequate	Yes	
Name of manufacturer/distributor /packer [§ 201.1(a), 201.1(h)(5)].	Adequate	Yes	
"Keep out of reach of children" statement, optional for Rx, required for OTC [§ 201.66(c)(5)(x)].	N/A	Yes	
If there is a Medication Guide, must include a statement about dispensing a Medication Guide to each patient.	N/A	Yes	
No text on Ferrule and Cap overseal of a vial of injectable products unless a cautionary statement is required. (USP <7>).	N/A	Yes	
If there is a USP monograph for the drug product and it	N/A	Yes	

[30] See § 201.25(b)(1)(i) for a list where bar code is not required, e.g., prescription drug samples, medical gases, radiopharmaceuticals, etc.

Item	Item in Proposed Carton Labeling (choose "Adequate", "Inadequate", or "N/A")	Is item in Container Labels same as that of Carton Labeling?	Assessor's Comments about Container Labels and Carton Labeling (If an item is Inadequate or different, provide more details, as appropriate)
contains a labeling requirement, ensure the labeling requirement is fulfilled.			
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.[31]	N/A	Yes	
And others if space is available.	Adequate	Yes	

Assessment of Carton Labels and Container Labeling: *Inadequate*

Any issues should be listed at the end in "OUTSTANDING ISSUES AND RECOMMENDATIONS"

4. OUTSTANDING ISSUES AND RECOMMENDATIONS

- **1.0 Full Prescribing Information (FPI)**
  - Section 11 (DESCRIPTION):
    - In the first sentence, delete the phrase "wax-based" so it reads: "tradename xxx difamilast is a white to off-white ointment for topical use."
    - Immediately following the first sentence, add the statement: "Each gram of ointment contains 10 mg of difamilast."
    - Provide a description of the Active Pharmaceutical Ingredient (API), noting it is a crystalline solid or polymorph. Clearly state its solubility profile, for example: "Soluble in XX and insoluble in YY."

[31] USP General Notices 3.20 Indicating Conformance

- List all inactive ingredients by their USP/NF names, arranged in alphabetical order, as per USP <1091> guidelines.

- Section 16 (HOW SUPPLIED/STORAGE AND HANDLING):
  - Add the statement, "Each gram of ointment contains 10 mg of difamilast."

- **2.0 Patient Labeling**
  - Inactive Ingredients: Inactive ingredients must be listed by their USP/NF names (where available) in alphabetical order, as per USP <1091>.
  - "Name and location of business": The address is incomplete, lacking the street number and name. The labeling must be updated to include the complete street address as required by 21 CFR §§ 201.1(h)(5) and 201.1(i).
- **3.0 Container and Carton Labeling**
  - Lot and Expiration Dates: Both the container and carton labels require updates to be fully compliant. The lot number and expiration date are missing on both labels. The format for the Lot number and expiration date should be included on both commercial and sample packs, and compliant with 21 CFR § 201.17.
    - As per 21 CFR § 201.18, the lot number on the label should be capable of yielding the complete manufacturing history of the package.
    - Provide the format to be used for the expiration date, e.g., DD/MM/YYYY or MMMYYYY.
  - Storage Information: The container and carton labels should be consistent with the Patient Package Insert (PPI). Add the statement, “Store away from direct sunlight, heat and moisture,” to the storage information on the container labels and carton labeling to minimize storage errors.
  - Dosage Statement: For clarity and alignment with the Prescribing Information, revise the dosage statement to: “Apply a thin layer twice daily to affected areas.”

Primary Drug Product Assessor Name and Date:

Ghaled Hamad, Ph.D.
Drug Product Reviewer
OPQ/OPQA II/ Division VII/Unit 1
Date:09/02/2025

Secondary Assessor Name and Date:

Julia Pinto, Ph.D.
Supervisory chemist
OPQ/OPQAII/DPQAVIII
Date:09/02/2025

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CHAPTER VII: MICROBIOLOGY

IQA NDA Assessment Guide Reference

Product Information	Ointment for the treatment of mild to moderate atopic dermatitis (AD)
NDA Number	219474
Assessment Cycle Number	MR01
Drug Product Name/ Strength	Difamilast Ointment 1% (3g physician sample, 27g, 85g tube)
Route of Administration	Topical
Applicant Name	Acrotech Biopharma Inc.
Therapeutic Classification/ OND Division	CDER/OND/OII/DDD
Manufacturing Site	(b) (4)
Method of Sterilization	Non-sterile fill

Assessment Recommendation: **Adequate**

Assessment Summary: The proposed drug product is a non-sterile, non-aqueous, non-preserved ointment formulation of the API for topical administration.

List Submissions being assessed (table):

Document(s) Assessed	Date Received
0001 Original Submission	13 February 2025

Highlight Key Issues from Last Cycle and Their Resolution: N/A

Remarks: The API is a new chemical entity. During development, the API was also referred to as OPA-15406 and OPC-271. Numerous stability and EBR documents refer to the drug product as OPA-15406 ointment.

Concise Description of Outstanding Issues
(List bullet points with key information and update as needed): N/A

Supporting Documents: N/A

S DRUG SUBSTANCE

The drug product is non-sterile. The drug substance will not be reviewed here.

P.1 DESCRIPTION OF THE COMPOSITION OF THE DRUG PRODUCT
(eCTD 0001 Section 3.2.P.1 description-and-composition.pdf)

Description of drug product – The difamilast topical drug product is a white to off-white ointment (b) (4) (b) (4) The ointment contains 1% w/w difamilast API. It is supplied in aluminum tubes. The DP is intended to treat mild to moderate atopic dermatitis (AD).

Drug product composition –

Ingredient	Function	Concentration (%w/w)
Difamilast	API	1.0
White petrolatum, USP	(b) (4)	
Paraffin, NF		
Mineral oil, USP		
White wax, NF		
Propylene carbonate, USP/NF		

Description of container closure system – The cream drug product is filled in aluminum tubes with 3g (physician sample), 27g, and 85g fill:

Component	Description	Manufacturer
Tube	5g, 30g, 90g aluminum tube with (b) (4)	(b) (4)
Cap	(b) (4) screw cap	

Assessment: *Adequate*

The applicant provided an adequate description of the drug product composition and the container closure system designed to maintain microbial control of the product.

P.2 PHARMACEUTICAL DEVELOPMENT

(b) (4)

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