CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

210361Orig1s000

PRODUCT QUALITY REVIEW(S)

Memorandum

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

Date: **June 12, 2018**

From: **Caroline Strasinger, Ph.D.**
Reviewer, 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: **Labeling Review #1 of NDA 210361**

Subject: **Final Recommendation**

Labeling Review #1 had noted the following pending issues:

A. Regarding PI

a) Highlight Section

HIGHLIGHTS OF PRESCRIBING INFORMATION
These highlights do not include all the information needed to use (b) (4) QBREXZA™ safely and effectively. See full prescribing information for (b) (4) QBREXZA.

(b) (4) QBREXZA (glycopyrronium) (b) (4) cloth, 2.4%, for topical use
Initial U.S. Approval: [YYYY]

----------DOSAGE FORMS AND STRENGTHS----------
Cloth: A single-use cloth pre-moistened with 2.4% glycopyrronium solution (b) (4)
(b) (4) 3).

b) Full Prescribing Information

#3: Dosage Forms and Strengths

3 DOSAGE FORMS AND STRENGTHS

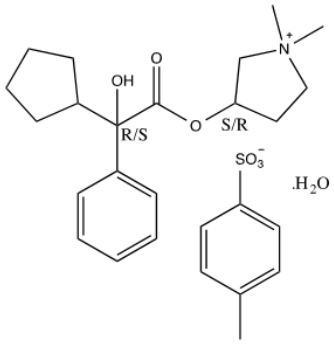
Cloth: A single-use cloth pre-moistened with 2.4% glycopyrronium solution

#11: Description

11 DESCRIPTION

Qbrexza (glycopyrronium) cloth, 2.4% (b) (4) is an anticholinergic drug available as a (b) (4) clear, colorless to pale yellow solution on a single-use pre-moistened (b) (4) cloth (an absorbent polypropylene pad) packaged in a pouch for topical administration. Each pouch contains (b) (4) (b) (4) 105 mg glycopyrronium tosylate, (b) (4) equivalent to 66 mg of glycopyrronium (b) (4) The inactive ingredients are citric acid, dehydrated alcohol, purified water, and sodium citrate.

Glycopyrronium tosylate (b) (4) is chemically described as pyrrolidinium, 3-[(2-cyclopentyl-2-hydroxy-2-phenylacetyl)oxy]-1,1-dimethyl-, 4-methylbenzensulfonate, hydrate (1:1:1) with an empirical formula of $C_{26}H_{37}NO_7S$ and a molecular weight of 507.6. The structural formula is represented below:



(b) (4)

#16: How Supplied/Storage and Handling

(b) (4)

(b) (4) Qbrexza is supplied as:

A sSingle-use cloth pre-moistened with a 2.4% glycopyrronium solution in a pouch (b) (4)

Carton of 30 (b) (4) pouches (b) (4) NDC 70428-011-12

16.2 Storage and Handling

Store at room temperature 20° - 25°C (68° - 77°F); excursions permitted to 15° - 30°C (59° - 86°F) [See USP Controlled Room Temperature].

(b) (4) Qbrexza is flammable; keep away from heat or flame.

(b) (4)

B. Regarding the Carton and Container

For both the Carton and Container

- The drug title should be expressed as:
  "Qbrexza (glycopyrronium) cloth"
  2.4%

- Remove (b) (4) from "single-use cloth (b) (4)"
- Change back panel contents to read:

Each pouch contains:
glycopyrronium……..66 mg
(equivalent to 105 mg of glycopyrronium tosylate) in a solution of citric acid, dehydrated alcohol, purified water, and sodium citrate

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

On June 11, 2018, the Applicant submitted updated labeling satisfactorily addressing all previous deficiencies (see the Attachment).

OVERALL ASSESSMENT AND RECOMMENDATION:

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

2 Page(s) of Draft Labeling have been Withheld in Full as b4 (CCI/TS) immediately following this page

Caroline Strasinger

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Moo Jhong Rhee

Digitally signed by Moo Jhong Rhee
Date: 6/12/2018 10:25:37AM
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Integrated Quality Assessment (IQA) for NDA 210361

Office of Pharmaceutical Quality (OPQ)

Executive Summary for NDA 210361

Recommendation:

From the OPQ perspective, this 505(b)(2) NDA is ***not*** deemed ready for approval as of this review in its present form per 21CFR 314.125(b)(6).

NDA 210361
Review # 1

Drug Name/Dosage Form	Qbrexza (glycopyrronium) Cloth
Strength	2.4%
Route of Administration	Topical
Rx/OTC Dispensed	Rx
Applicant	Dermira, Inc. Diane Ingolia 275 Middlefield Road, Suite 150 Menlo Park, CA 94025
US agent, if applicable	N/A

SUBMISSION(S) REVIEWED	DOCUMENT DATE	DISCIPLINE(S) AFFECTED
Original submission	08-31-2017	All
Amendment	10-31-2017	Quality microbiology and drug product manufacturing process
Amendment	11-15-2017	Drug product manufacturing process
Amendment	02-23-2018	Drug product labeling

Quality Review Team

DISCIPLINE	REVIEWER	BRANCH/DIVISION
Drug Substance	Fred Burnett	Branch II/Division of New Drug API
Drug Product	Caroline Strasinger	Branch V/Division of New Drug Products II
Process	Mesfin Abdi	Branch V/Division of Process Assessment III
Microbiology	Xia Xu	Branch II/Division of Microbiology Assessment
Facility	Carl Lee	Branch III/Division of Inspection Assessment
Biopharmaceutics	N/A	N/A
Regulatory Business Process Manager	Bamidele (Florence) Aisida	Branch I/Division of Regulatory and Business Management I/Office of Program and Regulatory Operations
Application Technical Lead	Yichun Sun	Branch V/Division of New Drug Products II

Quality Review Data Sheet

1. RELATED/SUPPORTING DOCUMENTS

A. DMFs:

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

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
CMC Type C Meeting Minutes (written responses)	IND 104160	Feedback on proposals of drug substance manufacturing process, stability study and qualification of drug substance reference standard.
CMC Type C Meeting Minutes (written responses)	IND 104160	Feedback on proposals of leachable testing and antimicrobial effectiveness testing (AET) of registration batches of the drug product.
End-of-Phase 2 Meeting Minutes	IND 104160	Discussions of development program for glycopyrrolate topical wipes.
Pre-NDA Meeting Minutes	IND 104160	Discussions of the content and format of the proposed NDA submission.

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 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 (OPF) has issued an "Acceptable" 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 pp. 16 - 18).

II. Summary of Quality Assessments

A. Product Overview

The NDA of Qbrexza (glycopyrronium) cloth, 2.4% is submitted as a 505(b)(2) application by Dermira, Inc. The listed drug used for the basis of this 505(b)(2) application is NDA 022571 [Cuvposa® (glycopyrrolate) oral solution].

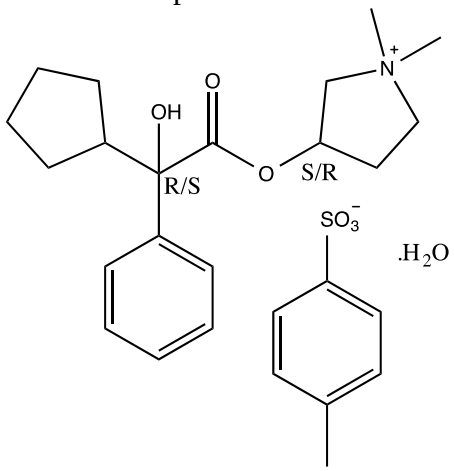
The indication and recommended dose of the drug product are summarized in the following Table.

Proposed Indication(s) including Intended Patient Population	Qbrexza is indicated for topical treatment of primary axillary hyperhidrosis in adults and children 9 years of age and older.
Duration of Treatment	N/A
Maximum Daily Dose	Qbrexza should not be used more frequently than once every 24 hours.
Alternative Methods of Administration	N/A

B. Quality Assessment Overview

Drug Substance

Qbrexza (glycopyrronium) Cloth, 2.4 % contains the active ingredient, glycopyrronium tosylate monohydrate (USAN: glycopyrronium tosylate), which is an anticholinergic. It is chemically named as pyrrolidinium, 3-[(2-cyclopentyl-2-hydroxy-2-phenylacetyl)oxy]-1,1-dimethyl-, 4-methylbenzensulfonate, hydrate (1:1:1). The structural formula is represented below:



It has a molecular formula of $C_{26}H_{37}NO_7S$ and the molecular weight is 507.6 g/mol.

Glycopyrronium tosylate monohydrate has two asymmetric centers in the glycopyrronium moiety and therefore may have four configurational isomers.

(b) (4)

(b) (4)

demonstration batch has been successfully produced using the proposed drug substance manufacturing process. The test results of the demonstration batch indicate that the proposed commercial-scale (b) (4) manufacturing process, and control strategy are adequate to produce the drug substance.

The data and information of elucidation of the chemical structure and characterization of the physiochemical properties of the drug substance were provided in the submission. The origin, identification, characterization and fate of specified organic impurities, observed unspecified organic impurities, starting material impurities, process impurities, and potential genotoxic impurities were adequately addressed by the NDA applicant. The identity, strength, purity and quality of the drug substance are adequately assured by the drug substance specification. The proposed retest period of (b) (4) months is supported by the stability data provided in the submission.

The review on the CMC information of the drug substance in the NDA has been conducted by Dr. Fred Burnett. The NDA is recommended for **approval** from the drug substances perspective (See **CHAPTER I: Review of Drug Substance**).

Drug Product

Qbrexza (glycopyrronium) Cloth is indicated for topical treatment of primary axillary hyperhidrosis in adults and children 9 years of age and older. The active pharmaceutical ingredient (API), glycopyrronium tosylate monohydrate, used in the topical solution is an anticholinergic.

The drug product is presented in individually-sealed, single-use, (b) (4) pouches containing a target of 2.8 g of the topical solution wetted onto a (b) (4) wipe (also referred to as a towelette or pad) with dimensions of approximately 6 × 3.75 inches. The topical solution contains 2.4% glycopyrronium (equivalent to (b) (4)% w/w of glycopyrronium tosylate monohydrate). The inactive ingredients used in the drug product include: citric acid (b) (4) sodium citrate (b) (4) dehydrated alcohol, and purified water. No novel excipients are used and the levels of the excipients in the drug product are below the limits found in the FDA's Inactive Ingredient Database for topical products approved. All excipients used are compendial and comply with the quality standards set in their respective current USP/NF monographs. The applicant has adequately addressed the concern of a genotoxic impurity, (b) (4) (b) (4) (b) (4)

The bulk drug product is prepared (b) (4) (b) (4)

The pouch is formed (b) (4) (b) (4)

(b) (4)

The specification of the drug product specification is deemed adequate to assure the identity, strength, purity, and quality of the drug product.

The long-term stability data up to 18 months and accelerated stability data for 6 months for the three registration batches of the drug product produced at pilot scale ((b) (4) kg, (b) (4) of the production scale) were provided in the NDA submission. The stability data submitted are sufficient to support the proposed expiration dating period of 24 months when stored at controlled room temperature. The results of photostability study indicated that light exposure did not adversely affect the drug product in terms of its assay, impurity level, pH and package integrity. The results of thermal cycling studies indicated that temperature cycle (-20°C and 40°C/75% RH) did not adversely affect the drug product in terms of its assay, weight, pH and package integrity.

The estimated EIC (expected introduction concentration) for the active moiety of the drug substance is estimated to be (b) (4) ppb. The claim of categorical exclusion is deemed acceptable per 21 CFR 25.31 (b).

The drug product is recommended for **approval** from the drug product perspective. The recommended expiration dating period of the drug product is 24 months. The review on the CMC information of the drug product has been conducted by Dr. Caroline Strasinger (See **CHAPTER II: Review of Drug Product**).

Labeling and Labels

The sections of the Package Insert related to CMC, and container and carton labels of the drug product of the NDA have been reviewed by Dr. Caroline Strasinger. Labeling and label issues have not been resolved satisfactorily as of this review (See **CHAPTER III: Review of Labeling and Labels**).

Drug Product Manufacturing Process

(b) (4)

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(b) (4)

The batch formula, manufacturing process parameters, and in-process controls are found to be adequate to ensure the robustness of the drug product manufacturing process. The NDA is recommended for **approval** from the perspective of drug product manufacturing process. The review on the drug product manufacturing process has been conducted by Dr. Mesfin Abdi (See **CHAPTER IV: Review of Drug Product Manufacturing Process**).

Quality Microbiology

The drug product is a single-use towelette (polypropylene (b) (4) wipe) pre-moistened with an aqueous, non-sterile, (b) (4) solution.

The drug substance, glycopyrronium tosylate monohydrate, is supplied as non-sterile API. The drug substance is tested for microbial limits and specified microorganisms with the acceptance criteria set in USP <1111> for non-sterile substances for pharmaceutical use.

The drug product is for single-use (b) (4)

(b) (4)

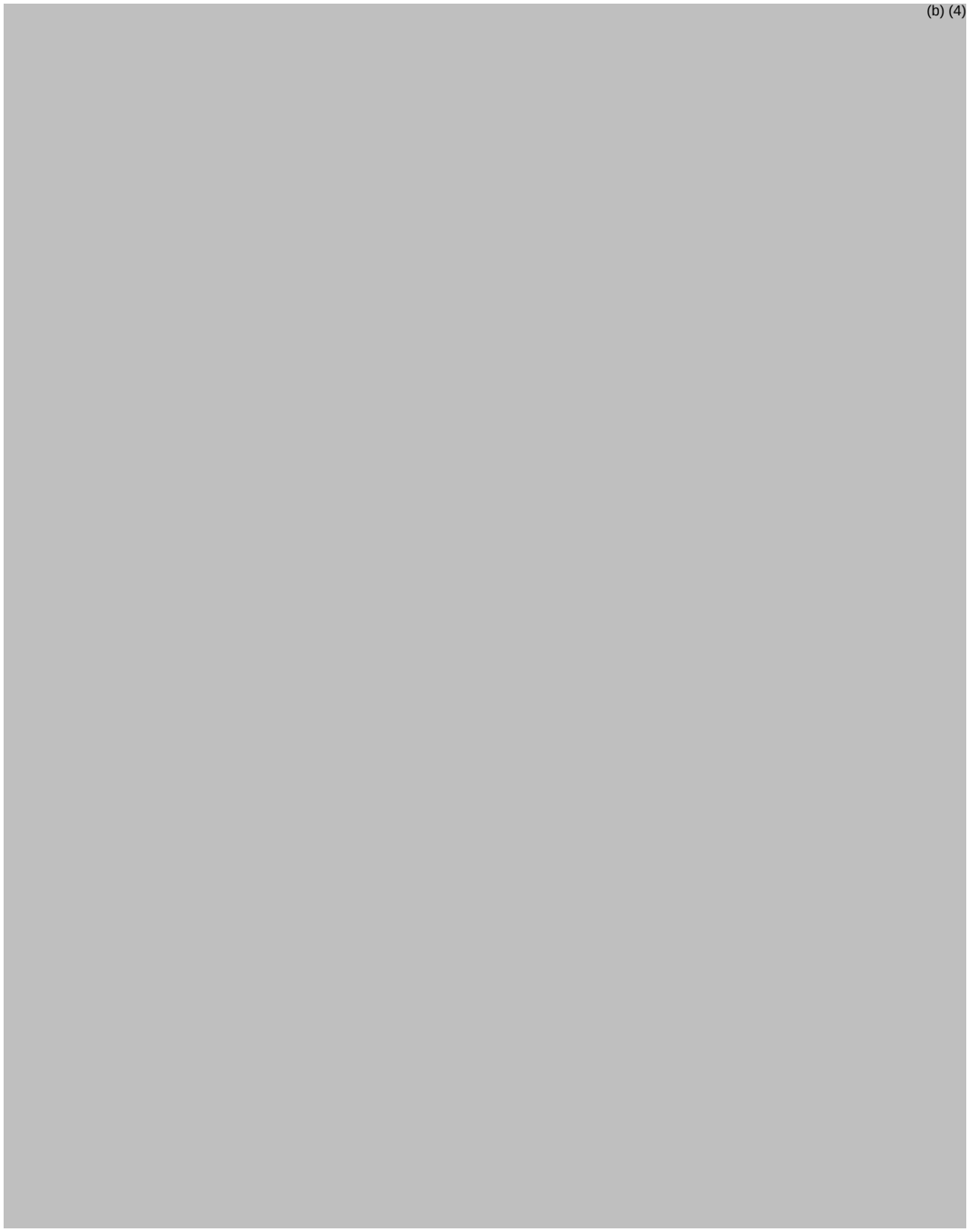
(b) (4) Validation results of microbial limits tests indicated that the current USP methods for microbial enumeration (TAMC and TYMC) and specified organisms (*P. aeruginosa and S. aureus*) are suitable to be used for microbial limit tests of the drug product. Validation results for the test method of *B. Cepacia* Complex (Bcc) indicated that test method is suitable to be used for monitoring *Burkholderia cepacia* complex (BCC) in the drug product. The results of stability studies indicated that stability samples of the drug product contained (b) (4) cfu/g TAMC and TYMC and were absent of *S. aureus* and *P. aeruginosa* during the long-term stability study.

The NDA is recommended for **Approval** from the perspective of quality microbiology. The review on microbiology controls of the drug product of the NDA has been conducted by Dr. Xia Xu (See **CHAPTER V: Review of Quality Microbiology**).

Facilities

Facilities Related to the Drug Substance Manufacturing and Testing:

(b) (4)



All the facilities are deemed acceptable in their identified functions and responsibilities to support the **approval** of NDA 210361. The facility review of the NDA has been conducted by Consumer Safety Officer, Carl Lee (See **CHAPTER VI: Review of Facilities**).

C. Special Product Quality Labeling Recommendations
N/A

D. Final Risk Assessment (Attachment I)

E. List of Deficiencies (Attachment II)

ATTACHMENT I: Final Risk Assessments

A. Final Risk Assessments - NDA

a) Drug Product

Final Risk Assessment for NDA 210361 [Qbrexza (glycopyrronium) Cloth, 2.4%]

Product Attribute/CQA	Factors that can impact the CQA	Probability (O)	Severity of Effect (S)	Detectability (D)	FMECA RPN Number	Comment
Appearance	• Process parameters • Scale/equipment • Site	2	4	2	16	Leakage of the pouches could be a concern. The appearance of the stability samples of the drug product remained unchanged after 18 months stored at long-term storage conditions, and 6 months at accelerated storage conditions. Package integrity also remained unchanged during the stability studies.
Assay (Glycopyrronium Assay)	• Formulation • Raw materials • Process parameters • Scale/equipment • Site	2	4	3	24	The content of the drug substance in the drug product is monitored using (b) (4) method. No significant change of the assay values was observed on the stability samples during stability studies.
Glycopyrronium Related Substances: (b) (4)	• Formulation • Raw materials • Process parameters • Scale/equipment	2	4	3	24	The related substances of the drug substance in the drug product are monitored using (b) (4) method at release and during stability studies. Levels of specified related substance, (b) (4) within the specification limit. Levels

Any Unspecified Related Substance **Total Related Substances**	• Site					of individual and total unspecified related substances (b) (4) (b) (4) the specification limits during stability studies.
Apparent pH (25 °C)	• Formulation • Raw materials • Process parameters • Scale/equipment • Site	2	4	2	16	The pH of the drug product is monitored at release and during stability studies. The pH of the stability samples remained within the range (b) (4) (b) (4) during stability studies.
Weight Loss	• Formulation • Raw materials • Process parameters • Scale/equipment • Site	2	3	3	18	Weight loss is monitored during long-term stability study. Results of weight loss test on the stability samples remained below the acceptance criterion (not more than (b) (4) %) during the long-term stability study.
Microbial Limits (Total aerobic microbial count, Total combined yeasts & molds count, *Staphylococcus aureus, Pseudomonas aeruginosa,*	• Formulation • Raw materials • Process parameters	2	3	3	18	Microbiological testing is included in the drug product specification, and performed at release and during stability studies. The results of microbiological tests met the acceptance criteria during the stability studies.
***Burkholderia cepacia species* (BCC))**	• Scale/equipment • Site					

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 - $25 < \text{RPN} \leq 60$

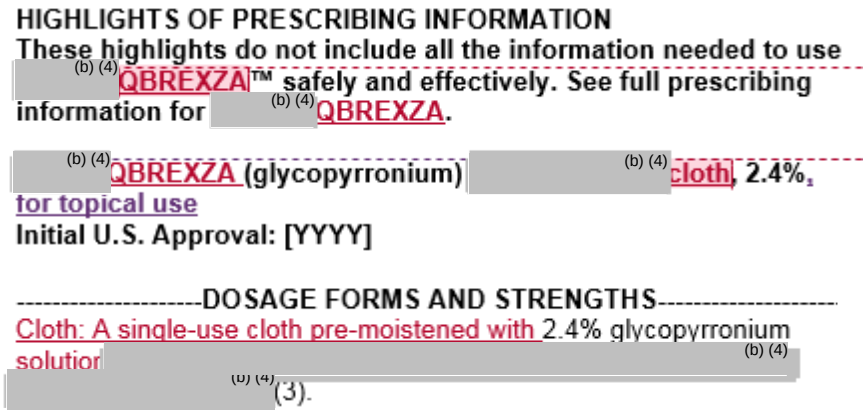
High Risk - RPN > 60

ATTACHMENT II: List of Deficiencies

A. Package Insert

Extensive edits to the content and format of each of the CMC sections in the PI are recommended. For ease of reference the below visuals have been compiled to aid in communicating the deficiencies:

a) Highlight Section



HIGHLIGHTS OF PRESCRIBING INFORMATION
These highlights do not include all the information needed to use (b) (4) QBREXZA™ safely and effectively. See full prescribing information for (b) (4) QBREXZA.

(b) (4) QBREXZA (glycopyrronium) (b) (4) cloth, 2.4%, for topical use
Initial U.S. Approval: [YYYY]

----------DOSAGE FORMS AND STRENGTHS----------
Cloth: A single-use cloth pre-moistened with 2.4% glycopyrronium solution (b) (4) (3).

b) Full Prescribing Information

#3: Dosage Forms and Strengths

3 DOSAGE FORMS AND STRENGTHS

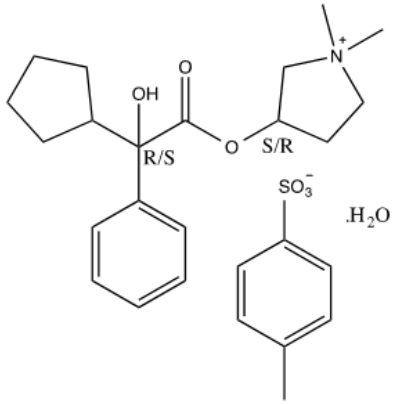
Cloth: A single-use cloth pre-moistened with 2.4% glycopyrronium solution

#11: Description

11 DESCRIPTION

Qbrexza (glycopyrronium) cloth, 2.4% (b) (4) is an anticholinergic drug available as a (b) (4) clear, colorless to pale yellow solution on a single-use pre-moistened (b) (4) cloth (an absorbent polypropylene pad) packaged in a pouch for topical administration. Each pouch contains (b) (4) 105 mg glycopyrronium tosylate, (b) (4) equivalent to 66 mg of glycopyrronium (b) (4) The inactive ingredients are citric acid, dehydrated alcohol, purified water, and sodium citrate.

Glycopyrronium tosylate (b) (4) is chemically described as pyrrolidinium, 3-[(2-cyclopentyl-2-hydroxy-2-phenylacetyl)oxy]-1,1-dimethyl-, 4-methylbenzensulfonate, hydrate (1:1:1) with an empirical formula of $C_{26}H_{37}NO_7S$ and a molecular weight of 507.6. The structural formula is represented below:



(b) (4)

#16: How Supplied/Storage and Handling

(b) (4)

(b) (4) Qbrexza is supplied as:

A sSingle-use cloth pre-moistened with a 2.4% glycopyrronium solution in a pouch (b) (4)

(b) (4) Carton of 30 pouches (b) (4) NDC 70428-011-12

16.2 Storage and Handling

Store at room temperature 20° - 25°C (68° - 77°F); excursions permitted to 15° - 30°C (59° - 86°F) [See USP Controlled Room Temperature].

(b) (4) Qbrexza is flammable; keep away from heat or flame.

(b) (4)

B. Carton and Container Labels

For both the carton and container labels

- The drug title should be expressed as:
  "Qbrexza (glycopyrronium) cloth" 2.4%

- Remove (b) (4) from "single-use cloth (b) (4)"

- Change back panel contents to read:

  Each pouch contains:
  glycopyrronium.....66 mg
  (equivalent to 105 mg of glycopyrronium tosylate) in a solution of citric acid, dehydrated alcohol, purified water, and sodium citrate

OVERALL ASSESSMENT AND SIGNATURES:

Application Technical Lead's Assessment and Signature

From the OPQ perspective, 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
4/26/2018

Yichun Sun

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Moo Jhong Rhee

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LABELING

R. Regional Information

1.14 Labeling

The dosage form for the product has been designated as cloth and the proprietary name has been designated as QBREXZA. The applicant will be provided a general comment requesting the dosage form and proprietary name be updated throughout the label.

I. Package Insert

1. HIGHLIGHTS OF PRESCRIBING INFORMATION

1) Title

HIGHLIGHTS OF PRESCRIBING INFORMATION
These highlights do not include all the information needed to use
(b) (4) QBREXZA™ safely and effectively. See full prescribing
information for QBREXZA.

(b) (4) QBREXZA (glycopyrronium) (b) (4) cloth, 2.4%,
for topical use
Initial U.S. Approval: [YYYY]

----------DOSAGE FORMS AND STRENGTHS----------
Cloth: A single-use cloth pre-moistened with 2.4% glycopyrronium
solution (b) (4)
(b) (4) (3).

Item	Information Provided in NDA	Reviewer's Comment and Recommendations
Drug name (201.57(a)(2))		
Proprietary name and established name	Proprietary: (b) (4) Established Name: (b) (4)	INADEQUATE proprietary name should be updated. Established name should include correct dosage form of cloth
Dosage form, route of administration	(b) (4)	INADEQUATE dosage form is cloth and for topical use should be added
Controlled drug substance symbol (if applicable)		NA
Dosage Forms and Strengths (201.57(a)(8))		

Summary of dosage form and strength	(b) (4)	INADEQUATE. The formatting and changes listed above should be made for accuracy and clarity

Reviewer Assessment: INADEQUATE

Applicant should modify the text of the dosage forms and strengths of the highlights for clarity as noted above. This information was communicated to OND labelling review team on 22-MAR-2018.

FULL PRESCRIBING INFORMATION

#3: DOSAGE FORM AND STRENGTHS

3 DOSAGE FORMS AND STRENGTHS

Cloth: A single-use cloth pre-moistened with 2.4% glycopyrronium solution

Item	Information Provided in NDA	Reviewer's Comment and Recommendations
Available dosage forms	(b) (4)	INADEQUATE Correct dosage form is cloth
Strengths: in metric system	2.4%	Adequate
Active moiety expression of strength with equivalence statement (if applicable)	2.4%	Adequate Although no equivalency statement is made, since that statement is made in the Description section as well as container and carton labels, it is deemed acceptable.
A description of the identifying characteristics of the dosage forms, including shape, color, coating, scoring, and imprinting, when applicable.	No description	INADEQUATE Should be revised to "A single-use cloth pre-moistened with solution"

Reviewer Assessment: Inadequate

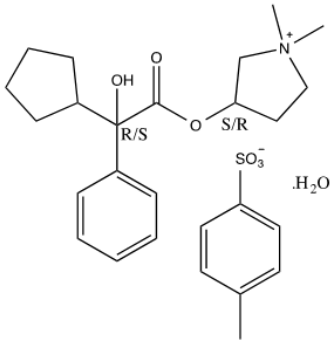
Applicant should modify the text of the dosage forms and strengths for clarity as noted above. This information was communicated to OND labelling review team on 22-MAR-2018.

#11: DESCRIPTION

11 DESCRIPTION

Qbrexza (glycopyrronium) cloth, 2.4% (b) (4) is an anticholinergic drug available as a (b) (4) clear, colorless to pale yellow solution on a single-use pre-moistened (b) (4) cloth (an absorbent polypropylene pad) packaged in a pouch for topical administration. Each pouch contains (b) (4) (b) (4) 105 mg glycopyrronium tosylate, (b) (4) equivalent to 66 mg of glycopyrronium (b) (4) The inactive ingredients are citric acid, dehydrated alcohol, purified water, and sodium citrate.

Glycopyrronium tosylate (b) (4) is chemically described as pyrrolidinium, 3-[(2-cyclopentyl-2-hydroxy-2-phenylacetyl)oxy]-1,1-dimethyl-, 4-methylbenzensulfonate, hydrate (1:1:1) with an empirical formula of $C_{26}H_{37}NO_7S$ and a molecular weight of 507.6. The structural formula is represented below:



(b) (4)

Item	Information Provided in NDA	Reviewer's Comment and Recommendations
Proprietary name and established name	Qbrexza glycopyrronium	INADEQUATE Include cloth as part of the established name
Dosage form and route of administration	Not correctly described	INADEQUATE Remove (b) (4)
Active moiety expression of strength with equivalence statement (if applicable)	105 mg glycopyrronium tosylate the active ingredient, equivalent to 66 mg of glycopyrronium base, the active moiety.	Adequate
Inactive ingredient information (quantitative, if injectables 21CFR201.100(b)(5)(iii)), listed by USP/NF names (if any) in alphabetical order (USP <1091>)	Dehydrated alcohol, purified water, citric acid, and sodium citrate.	INADEQUATE list alphabetically
Statement of being sterile (if applicable)	N/A	Adequate
Pharmacological/ therapeutic class	Anticholinergic drug	Adequate
Chemical name, structural formula, molecular weight	Structure, molecular weight, formula presented	Adequate
If radioactive, statement of important nuclear characteristics.	NA	Adequate
Other important chemical or physical properties (such as pKa or pH)	Clear, colorless to pale yellow solution	Adequate

Reviewer Assessment: INADEQUATE

Applicant should include the established name, list ingredients in alphabetical order and address the additional edits noted above of the Description for clarity. This information was communicated to OND labelling review team on 22-MAR-2018.

#16: HOW SUPPLIED/STORAGE AND HANDLING

(b) (4)

(b) (4) Qbrexza is supplied as:

A sSingle-use cloth pre-moistened with a 2.4% glycopyrronium solution in a pouch (b) (4)

(b) (4) (b) (4)
Carton of 30 pouches NDC 70428-011-12

16.2 Storage and Handling

Store at room temperature 20° - 25°C (68° - 77°F); excursions permitted to 15° - 30°C (59° - 86°F) [See USP Controlled Room Temperature].

(b) (4) Qbrexza is flammable; keep away from heat or flame.

(b) (4)

Item	Information Provided in NDA	Reviewer's Comment and Recommendations
Strength of dosage form	2.4%	INADEQUATE (formatting, see above)
Available units (e.g., bottles of 100 tablets)	(b) (4)	INADEQUATE (formatting, see above)
Identification of dosage forms, e.g., shape, color, coating, scoring, imprinting, NDC number	(b) (4)	INADEQUATE (formatting, see above)
Special handling (e.g., Dispense in tight and light resisteant container as defined in USP)	Flammable; keep away from heat or flame	Adequate
Storage conditions	20-25ºC (68º - 77ºF); excursions permitted 15º - 30ºC (59º - 86º) [See USP Controlled Room Temperature]	Adequate
Manufacturer/distributor name (21 CFR 201.1(h)(5))	Manufactured for: Dermira, Inc. Menlo Park, CA 94025	Adequate

Reviewer Assessment: INADEQUATE

Applicant should modify the text of the How Supplied and Storage and Handling for clarity as noted above. This information was communicated to OND labelling review team on 22-MAR-2018.

II. Labels (provided February 23, 2018)

1. IMMEDIATE CONTAINER LABEL

Container Label

Item	Information Provided in NDA	Reviewer's Assessment
Proprietary name, established name (font size and prominence (21 CFR 201.10(g)(2))	Qbrexa (glycopyrronium)	INADEQUATE The established name should include the dosage form, cloth with the same font size as the USAN name: (glycopyrronium) cloth
Dosage strength Active moiety expression of strength with equivalence statement (if applicable), if space is available	(b) (4)	INADEQUATE Each pouch contains Glycopyrronium….66 mg (equivalent to 105 mg of glycopyrronium tosylate) in a solution of citric acid, dehydrated alcohol, purified water, and sodium citrate
Net contents	1 cloth with 2.8 g of solution	Adequate
"Rx only" displayed prominently on the main panel	Rx only	Adequate
NDC number (21 CFR 207.35(b)(3)(i))	Present	Adequate
Lot number and expiration date (21 CFR 201.17)	Location present	Adequate
Storage conditions Special handling, e.g., "Dispense in tight and light resistant container as defined in USP".	Store at room temperature 20-25ºC (68º - 77ºF); excursions permitted 15º - 30ºC (59º - 86º) [See USP Controlled Room Temperature] Flamable	Adequate
Bar code (21CFR 201.25)	Included	Adequate
Name of manufacturer/distributor	Distributor is present	Adequate
And others, if space is available		

The following should be communicated to the Applicant:

- The drug title should be expressed as:
  "Qbrexza (glycopyrronium) cloth"
  2.4%
- Remove (b) (4) from "single-use cloth (b) (4)"

- Change back panel contents to read:
    - Each pouch contains:
      glycopyrronium……..66 mg
      (equivalent to 105 mg of glycopyrronium tosylate) in a solution of citric acid, dehydrated alcohol, purified water, and sodium citrate

2. CARTON LABELS:

Carton Labeling

(b) (4)

Item	Information Provided in NDA	Reviewer's Assessment
Proprietary name, established name (font size, prominence)	Qbrexa (glycopyrronium)	INADEQUATE The established name should include the dosage form, cloth with the same font size as the USAN name: (glycopyrronium) cloth
Dosage strength Active moiety expression of strength with equivalence statement (if applicable) in the side panel.	(b) (4)	INADEQUATE Each pouch contains Glycopyrronium….66 mg (equivalent to 105 mg of glycopyrronium tosylate) in a solution of citric acid, dehydrated alcohol, purified water, and sodium citrate
Net quantity of dosage form	30 single use cloth towlettes	INADEQUATE remove towlettes
"Rx only" displayed prominently on the main panel	Displayed on front;	Adequate
Lot number and expiration date	bottom flap	Adequate
Storage conditions Special handling, e.g., "Dispense in tight and light resistant container as defined in USP".	Store at room temperature 20-25ºC (68º - 77ºF); excursions permitted 15º - 30ºC (59º - 86º) [See USP Controlled Room Temperature]	Adequate
Bar code (21CFR 201.25)	Side panel	Adequate
NDC number (21 CFR 207.35(b)(3)(i))	Multiple Panels	Adequate
Manufacturer/distributor's name	Bottom	Adequate
Quantitative ingredient information (injectables)	Ingredients should be listed in alphabetical order (quantity not necessary)	Adequate
Statement of being sterile (if applicable)	N/A	Adequate
"See package insert for dosage information"	Back panel	Adequate

"Keep out of reach of children" (Required for OTC in CFR. Optional for Rx drugs)	Keep out of reach of children; Flammable	Adequate

The following should be communicated to the Applicant:

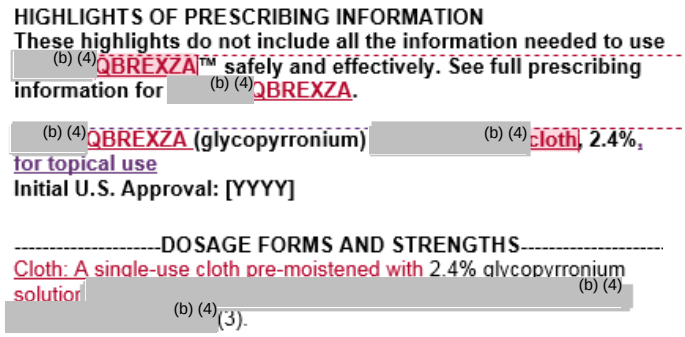
- The drug title should be expressed as:
  "Qbrexza (glycopyrronium) cloth"
  2.4%
- Remove (b) (4) from "single-use cloth (b) (4)"
- Change back panel contents to read:
  - Each pouch contains:
    glycopyrronium……..66 mg
    (equivalent to 105 mg of glycopyrronium tosylate) in a solution of citric acid, dehydrated alcohol, purified water, and sodium citrate

III. LIST OF DEFICIENCIES:

A. Regarding PI

Extensive edits to the content and format of each of the below sections is recommended. For ease of reference the below visuals have been compiled to aid in communicating the deficiencies:

a) Highlight Section



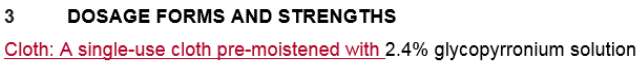
HIGHLIGHTS OF PRESCRIBING INFORMATION
These highlights do not include all the information needed to use (b) (4) QBREXZA™ safely and effectively. See full prescribing information for (b) (4) QBREXZA.

(b) (4) QBREXZA (glycopyrronium) (b) (4) cloth, 2.4%, for topical use
Initial U.S. Approval: [YYYY]

----------DOSAGE FORMS AND STRENGTHS----------
Cloth: A single-use cloth pre-moistened with 2.4% glycopyrronium solution (b) (4) (3).

b) Full Prescribing Information

#3: Dosage Forms and Strengths



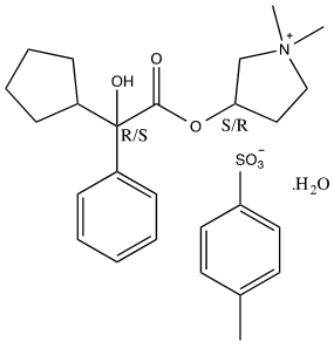
3 DOSAGE FORMS AND STRENGTHS
Cloth: A single-use cloth pre-moistened with 2.4% glycopyrronium solution

#11: Description

11 DESCRIPTION

Qbrexza (glycopyrronium) cloth, 2.4% (b) (4) is an anticholinergic drug available as a (b) (4) clear, colorless to pale yellow solution on a single-use pre-moistened (b) (4) cloth (an absorbent polypropylene pad) packaged in a pouch for topical administration. Each pouch contains (b) (4) (b) (4) 105 mg glycopyrronium tosylate, (b) (4) equivalent to 66 mg of glycopyrronium (b) (4) The inactive ingredients are citric acid, dehydrated alcohol, purified water, and sodium citrate.

Glycopyrronium tosylate (b) (4) is chemically described as pyrrolidinium, 3-[(2-cyclopentyl-2-hydroxy-2-phenylacetyl)oxy]-1,1-dimethyl-, 4-methylbenzensulfonate, hydrate (1:1:1) with an empirical formula of $C_{26}H_{37}NO_7S$ and a molecular weight of 507.6. The structural formula is represented below:



(b) (4)

#16: How Supplied/Storage and Handling

(b) (4)

(b) (4) Qbrexza is supplied as:

A sSingle-use cloth pre-moistened with a 2.4% glycopyrronium solution in a pouch (b) (4)

Carton of 30 (b) (4) pouches (b) (4) NDC 70428-011-12

16.2 Storage and Handling

Store at room temperature 20° - 25°C (68° - 77°F); excursions permitted to 15° - 30°C (59° - 86°F) [See USP Controlled Room Temperature].

(b) (4) Qbrexza is flammable; keep away from heat or flame.

(b) (4)

Carton and Container

For both the Carton and Container

- The drug title should be expressed as:
  "Qbrexza (glycopyrronium) cloth"
  2.4%

- Remove (b) (4) from "single-use cloth (b) (4)"
- Change back panel contents to read:

  Each pouch contains:
  glycopyrronium……..66 mg
  (equivalent to 105 mg of glycopyrronium tosylate) in a solution of citric acid, dehydrated alcohol, purified water, and sodium citrate

IV. OVERALL ASSESSMENT AND RECOMMENDATION:

The Label and Labeling of NDA 210361 is inadequate due to the deficiencies noted above for Highlights, Section 3, 11 and 16 of the PI and the Carton and Container. This information was communicated to OND labeling review team on April 20, 2018.

This application is not deemed ready for approval in its present form per 21CFR 314.125(b)(6) from the label/labeling perspective until the deficiencies noted above are satisfactorily resolved.

Primary Labeling Reviewer Name and Date:

Caroline Strasinger, PhD 20-APR-2018
OPQ, ONDP, DNDP II, BV

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

I agree with Dr. Strasinger's assessment on the labeling and labels and concur with her recommendation that this application is ***not*** deemed ready for approval as of this review.

Moo-Jhong Rhee, Ph.D. 20-APR-2018
Chief, Branch V
DNDP II/ONDP

Caroline Strasinger

Digitally signed by Caroline Strasinger
Date: 4/23/2018 04:40:29PM
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Moo Jhong Rhee

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Date: 4/24/2018 09:00:13AM
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MICROBIOLOGY

Product Background: Glycopyrronium tosylate is indicated for the topical treatment of primary axillary hyperhidrosis in adults and children 9 years of age and older.

NDA:210361

Drug Product Name / Strength: Glycopyrronium tosylate, 2.4%

Route of Administration: Topical

Applicant Name:
Dermira, Inc.
275 Middlefield Road, Suite 150
Menlo Park, CA 94025

Manufacturing Site:
(b) (4)

FEI # (b) (4)

Method of Sterilization: Drug product is not sterile.

Review Recommendation: The submission is **recommended** for approval from a quality microbiology perspective.

Review Summary: This is a single-use non-sterile topical drug product. The manufacturing process is to be controlled for microbial quality and absence of specified microorganisms.

List Submissions Being Reviewed:
Dates of Submission(s) Covered by this Review

Submit	Received	Review Request	Assigned to Reviewer
8/31/2017	8/31/2017	N/A	11/1/2017
10/31/2017	10/31/2017	N/A	N/A

Highlight Key Outstanding Issues from Last Cycle: None

Remarks: eCTD/Global submit review. This is a 505(b)(2) submission. The Reference Listed Drug is Cuvposa® (glycopyrrolate) oral solution, 1 mg/5 mL, indicated to reduce chronic severe drooling in patients aged 3-16 with neurologic conditions associated with problem drooling (e.g., cerebral palsy) (NDA 022571).

The Agency issued the CMC cumulative Information Request to the applicant on 18 October 2017. The applicant's Response of 31 October 2017 to the Information Request is incorporated in this review.

Concise Description Outstanding Issues Remaining: None

Supporting Documents: None

S Drug Substance

The drug substance, glycopyrronium tosylate monohydrate, manufactured by (b) (4) (b) (4) is supplied as non-sterile. The drug substance is tested for microbial limits and specified microorganisms with the following acceptance criteria (3.2.S.4.1-Specification.pdf):

Total Aerobic Microbial Count: NMT (b) (4) cfu/g
Total Combined Yeasts and Molds Count: NMT (b) (4) cfu/g
Tests for specified microorganisms *Staphylococcus aureus* and *Pseudomonas aeruginosa*: absent/1 g

Reviewer's Assessment: Microbiological quality acceptance criteria for drug substance comply with those specified by USP <1111> for non-sterile substances for pharmaceutical use.

ADEQUATE

P.1 Description of the Composition of the Drug Product

- **Description of drug product –**
  The drug product is an aqueous, non-sterile, (b) (4) solution containing 2.4% glycopyrronium, supplied on a pre-moistened single-use towelette (polypropylene (b) (4) wipe) with dimensions of approximately 6 × 3.75 inches, for topical administration.

- **Drug product composition –**
  (3.2.P.3.2- Batch Formula.pdf; 3.2.P.1-Description and Composition of the Drug Product.pdf)

Components	Function	Composition (% w/w)	Quantity per Pouch (mg)#
Glycopyrronium Tosylate Monohydrate	Active Pharmaceutical Ingredient	(b) (4)	
Citric Acid (b) (4) USP			
Sodium Citrate, (b) (4) USP			
Purified Water, USP			
Dehydrated Alcohol, USP			

* Equivalent to a label claim of 2.4% glycopyrronium
** Equivalent to a glycopyrronium content of 66 mg
# Total weight of 2.8 gram per pouch

- **Description of container closure system –**
(3.2.P.1- Description and Composition of the Drug Product.pdf)

A (b) (4) wipe wetted with the drug product is packaged in an individually-sealed, single-use, (b) (4) pouch. Each pouch is approximately 2.75 × 3.5 inches with a tear notch in the upper corner of the pouch.

Reviewer's Assessment: The drug product composition and container-closure system were adequately described. The container-closure system is adequate for the drug product topical route of administration.

Acceptable

P.2 Pharmaceutical Development

P.2.5 Microbiological Attributes

Container/Closure and Package Integrity - N/A

Antimicrobial Effectiveness Testing - The subject drug product is for single-use (b) (4)
(b) (4)

Stability data (up to twelve months' storage) provided demonstrated that the stored drug product contained (b) (4) cfu/g TAMC and TYMC and absence of *S. aureus* and P. *aeruginosa*, and therefore unlikely to support microbial growth. Microbiological testing on primary stability batches will also be performed at the 24- and 36-month test stations, and microbial limits testing (0, 12, 24, and 36 months) is included in the post approval stability protocol (See Section P.8.3, of this review). Similarly, no microbial growth was detected (b) (4) (See Section P.3.5 below).

P.3 Manufacture

P.3.1 Manufacturers

(b) (4)

FEI # (b) (4)

(b) (4)

(b) (4)

FEI # (b) (4)

(b) (4)

FEI # (b) (4)

Final product release and disposition:
Dermira, Inc.
275 Middlefield Road, Suite 150
Menlo Park, CA 94025

P. 3.3 Description of the Manufacturing Process and Process Controls

Overall Manufacturing Operation

(3.2.P.3.-Description of manufacturing process and process controls)

(b) (4)

Reviewer's Assessment: Acceptable

(b) (4)

P. 3.5 Process Validation and/or Evaluation

(b) (4)

(b) (4)

Reviewer's Assessment: Acceptable

P.5 Control of Drug Product

P. 5.1 Specification

The product release and stability specifications are as follows:

Test	Test Method	Acceptance Criteria	Exhibit Batch Results
Microbial Enumeration Tests:			
Total Aerobic Microbial Count (TAMC)	(b) (4) USP <61>	NMT (b) (4) cfu/g	11501688, 11500956, 11500955 ((b) (4) kg): (b) (4) cfu/g 11601626, 11601625, 11601624 ((b) (4) kg)*: (b) (4) cfu/g
Total Combined Yeasts and Molds Count (TYMC)		NMT (b) (4) cfu/g	11501688, 11500956, 11500955 ((b) (4) kg); 11601626, 11601625, 11601624 ((b) (4) kg)* : (b) (4) cfu/g
Tests for Specified Microorganisms:			
Staphylococcus aureus	(b) (4) USP <62>	Absent/1 g	11501688, 11500956, 11500955 ((b) (4) kg); 11601626, 11601625, 11601624 ((b) (4) kg)* : absent/1 g
Pseudomonas aeruginosa		Absent/1 g	11501688, 11500956, 11500955 ((b) (4) kg); 11601626, 11601625, 11601624 ((b) (4) kg)* : absent/1 g

*Burkholderia cepacia***	(b) (4)	Absent/ 1 g	Not tested

* Lots 11601624, 11601625 and 11601626 (b) (4)

(b) (4)

** Suitability results for test for *B. cepacia* were provided using two different *B. cepacia* strains. However, initially absence of *B. cepacia* was not included in the drug product or stability specifications.

Agency's Information Request (IR) of 18 October 2017

As per document 3.2.P.1-Description and Composition of the Drug Product.pdf, the drug product DRM04 is manufactured as a non-sterile aqueous topical solution. We acknowledge the provided information regarding the specifications of the drug product including TAMC (NMT (b) (4) cfu/g), TYMC (NMT (b) (4) cfu/g), and absence of Staphylococcus aureus and Pseudomonas aeruginosa. The drug product specification for non-sterile aqueous drug products should also include a test for the absence of Burkholderia cepacia complex (BCC). It is noted that 3.2.P.5.3-(b) (4) Validation Report (b) (4).pdf document provides the summary of the method verification studies for testing B. cepacia in drug product. However, the absence of B. cepacia is not included in the drug product release or stability specifications.

a. *Please provide a risk assessment to justify not performing BCC testing of the drug product. The assessment may include manufacturing in-process controls, microbial monitoring of components, drug product formulation properties, and supporting drug product quality microbiology test data.*

b. *Alternatively, please provide test methods and acceptance criteria to demonstrate the product is free of the objectionable microorganism B. cepacia. Please identify potential sources for introduction of BCC during the manufacturing process and describe the steps to minimize the risk of BCC organisms in the final drug product. We recommend that potential sources are examined and sampled as process controls, and these may include raw materials and the manufacturing environment. A risk assessment for this species in the product and raw materials is recommended to develop sampling procedures and acceptance criteria.*

   As there are currently no compendial methods for detection of BCC, we have provided suggestions for a potential validation approach and some points to consider when designing your validation studies. However, any validated method capable of detecting BCC organisms would be adequate. (b) (4)

(b) (4)

(b) (4)

For a recent review of FDA's perspective on BCC please see PDA J Pharm Sci Tech 2011; 65(5): 535-43. For more information, we also refer you to Envir Microbiol 2011; 13(1):1-12 and J. Appl Microbiol 1997; 83(3):322-6.

Applicant's IR Response of 31 October 2017

The applicant included the absence of *B. cepacia* to both release and stability specifications. Method for test for *B. cepacia*, the risk assessment of contamination with *B. cepacia*, and steps taken to minimize risk of BCC in finished drug product were provided in 1.11.1- Response to FDA – 31 Oct 2017.pdf.

Review of Applicant's IR Response of 31 October 2017

Procedure for test for *B. cepacia* is provided in 3.2.P.5.2-Analytical Procedures.pdf (page 17 of 17). (b) (4)

(b) (4)

(b) (4)

Microbiological quality acceptance criteria for the drug product comply with those specified by USP <1111> for non-sterile products for cutaneous use.

Reviewer's Assessment: Acceptable

P.5.2 Analytical Procedures – See P.5.1 and P.5.3

P.5.3 Validation of Analytical Procedures

Microbial Limits and test for specified microorganisms

(3.2.P.5.3-(b) (4) Validation Report (b) (4).pdf)

Test Methods: USP <61> for microbial limits; USP <62> for tests for *Staphylococcus aureus* and *Pseudomonas aeruginosa*; method # 12050 for test for *Burkholderia cepacia*

Report: Final report for the microbial limit testing recovery method validation of glycopyrronium tosylate solution, 2.4%, dated 02 June 2017.

The suitability studies for microbial limits and tests for specified microorganisms were performed (b) (4) (b) (4) Three lots drug products were tested in each microorganism test. In the suitability testing of TAMC, the recovery of *S. aureus* (b) (4) *P. aeruginosa* (b) (4) *Bacillus subtilis* (b) (4) *Candida albicans* (b) (4) and *Aspergillus brasiliensis* (b) (4) (b) (4) ranged from (b) (4)% to (b) (4)%. In the suitability testing of TYMC, the recovery of *C. albicans* and *A. brasiliensis* ranged from (b) (4)% to (b) (4)%. Both TAMC and TYMC suitability test results met the recovery requirements of (b) (4)% to (b) (4)%. In the suitability testing for tests for specified microorganisms, *S. aureus* (b) (4) *P. aeruginosa* (b) (4) *B. cereus* (b) (4) and *B. cepacia* (b) (4) were recovered in the presence of the drug product, Glycopyrronium Tosylate Solution, 2.4%. The suitability test results for tests for *S. aureus, P. aeruginosa* and *B. cepacia* met the recovery requirements.

Reviewer's Assessment: Acceptable

P.7 Container Closure – See P.1.

P.8 Stability

P. 8.1 Stability Summary and Conclusion

(3.2.P.8.1-Stability Summary and Conclusion.pdf)

Proposed Expiry: 24 months when stored at 20-25ºC (68-77ºF), with excursions permitted to 15-30ºC.

P. 8.2 Post-Approval Stability Protocol and Stability Commitment

(3.2.P.8.2-Post Approval Stability Protocol and Stability Commitment.pdf)

Post Approval Stability Commitment

The stability studies of the registration lots of DRM04 (glycopyrronium) Topical Solution, 2.4% will be continued to completion. The applicant commits to placing the first three commercial lots of the subject drug product into their stability program. Thereafter, a minimum of one production lot will be placed on stability studies annually at the long-term storage condition only. The microbial enumeration tests and tests for specified microorganisms will be performed at 0, 12, 24, 36 months at the 25ºC/60% RH storage condition.

Reviewer's Assessment: Acceptable

P.8.3 Stability Data

The stability data was provided up to 12 months. For the exhibit lots 11500631, 11500955, 11500956, 11501687, 11501688, 11501689, 11600184 and 11600185, TAMC and TYMC were (b) (4) cfu/g, and test results for *S. aureus* and P. *aeruginosa* were absent/1 g, at the 25ºC ± 2ºC/60% ± 5% RH storage condition.

Reviewer's Assessment: Acceptable

R Regional Information

Executed Batch Records

The batch records of lots 11501688 (batch size of (b) (4) kg) and 11601625 (batch size of (b) (4) kg) were provided.

Comparability Protocols - No CP was included in the application.

2. REVIEW OF COMMON TECHNICAL DOCUMENT – QUALITY (CTD-Q) MODULE 1

2.A. Package Insert

Storage temperature: 20-25ºC (68-77ºF), excursions permitted to 15-30ºC (59-86ºF)
Route of administration: Topical
Container: Single use

The drug product is used directly without any further dilution or reconstitution. It is noted that the drug product name is (b) (4) (glycopyrronium) topical solution, 2.4%, or (b) (4), in the package insert. Additionally, the package insert states that the drug product should not be applied to broken skin or used with occlusive dressings.

Reviewer's Assessment: Acceptable

Post-Approval Commitments: See P.8.2

List of Deficiencies: None

Primary Microbiology Reviewer Name and Date:

Xia Xu, Ph.D. 12/21/2017

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

Neal J. Sweeney, Ph.D. 12/21/2017

Xia Xu

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Neal Sweeney

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