CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

209575Orig1s000

PRODUCT QUALITY REVIEW(S)

Recommendation: Approve

NDA 209575
Review Cycle 2

Drug Name/Dosage Form	Cocaine Hydrochloride Topical Solution, 4% and 10% Topical Solution
Strength	40 mg/mL (4%) and (b) (4) (10%)
Route of Administration	Topical (intranasal)
Rx/OTC Dispensed	Rx
Applicant	Cody Laboratories, Inc.
US agent, if applicable	

Quality Review Team (For Resubmission)

DISCIPLINE	REVIEWER	BRANCH/DIVISION
Drug Substance	None for resubmission (N/A)	
Drug Product	Venkateswara Pavuluri	OPQ/ONDP/DNDPII/B4
Process /Facilities	Tarun Mehta	OPQ/OPF/DPAII/B6
Microbiology	N/A	
Biopharmaceutics	Not Required	
Regulatory Business Process Manager	Anika Lalmansingh	OPQ/OPRO/RBPMI/B1
Application Technical Lead	Venkateswara Pavuluri	OPQ/ONDP/DNDPII/B4
Laboratory (OTR)		
ORA Lead		
Environmental Analysis (EA)		

Reference ID: 4563625

Quality Review Data Sheet

1. RELATED/SUPPORTING DOCUMENTS

A. DMFs:

DMF #	Type	Holder	Item Referenced	Status	Date Review Completed	Comments
29120	Type II	Cody Laboratories, Inc.	Cocaine Hydrochloride, USP	Adequate	6/13/18	
(b) (4)	Type III	(b) (4)		Adequate	6/15/18	Information found in NDA
	Type III			Adequate	6/15/18	Information found in NDA
	Type III			Adequate	6/15/18	Information found in NDA
	Type III			Adequate	6/15/18	Information found in NDA
	Type III			Adequate	6/15/18	Information found in NDA

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

DOCUMENT	APPLICATION NUMBER	DESCRIPTION
N/A		
NDA	209575	IQA (CMC Review for Drug Product

Reference ID: 4583625

2. CONSULTS - None

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

Reference ID: 4563625

Executive Summary

I. Recommendations and Conclusion on Approvability

NDA 209575 for NUMBRINO (cocaine hydrochloride topical solution) is **APPROVABLE** from CMC perspective, in 40 mg/mL (4%) in 4 mL [redacted] (b) (4) dosage presentation, when packaged using (b) (4) Glass Bottle / (b) (4) (b) (4) cap as primary container closure system as proposed in the resubmission. [redacted] (b) (4) The NDA approval is based on review of additional quality information provided in the resubmission, subsequent requests for information (eCTD sequence # 0025, and seq. nos. 0028-0031) and from facilities and drug product perspective. All OPQ review disciplines have recommend the approval of the NDA from CMC perspective in previous review cycle (original submission).

II. Summary of Quality Assessments

A. Product Overview

The NDA 209575 for Cocaine hydrochloride topical solution, in 4% and 10% dosage strengths was filed as a 505(b)(2) with indication for the introduction of local (topical) anesthesia for diagnostic procedures and surgeries on or through the accessible mucous membranes of the nasal cavities. In the resubmission, applicant provided leachables test data from testing of additional batches of the 4% presentation in response to a non-clinical deficiency related to extractables and leachables studies, as written in the complete response letter Dt 20-JUL-2018. Applicant also provided the final study report from a 'Thermal cycling study' fulfilling commitment made during previous review cycle and clarifications on use of Source Overall manufacturing inspection recommendation is "APPROVE".

There are no flags or official action indicate (OAI) for any of the facilities listed in the NDA. Original IQA covered all the facilities review including the newly added (in Panorama) two facilities. [redacted] (b) (4) was initially included in the Form FDA 356h as a facility for storing stability samples, but it is removed from the 356h form later as it was only utilized for storage of stability samples at intermediate condition and will not be part of the facilities for commercial manufacturing and testing. In the resubmission applicant proposed to use only (b) (4) Glass Bottle / (b) (4) (b) (4) cap as primary container closure system [redacted] (b) (4) Refer Executive summary in the original CMC (IQA) review, written by Dr. Ciby Abraham, PhD, for complete details of information provided in the previous submissions.

Start of Applicant Material

Packaging Configuration	
Bottle Size & Description:	(b) (4) (b) (4) glass (USP Type III) bottle

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Bottle Code No.:	(b) (4)
Cap Size & Description:	(b) (4) cap, (b) (4) (b) (4)
Cap Code No.:	(b) (4)
Product Strength / Fill Size	4% - 4 mL and 10 mL; 10% - (b) (4)

End of Applicant Material.

The analytical methods used, and leachables testing on additional batches of 4 % drug product are adequate for approval of the NDA from CMC perspective. See the pharmacology/ Toxicology review for additional details on safety of the extractables / leachables detected. The proposed expiration dates are acceptable for each of the respective dosage strengths and presentations as described below, when the drug product is stored at controlled room temperature (20 -25°C as per USP) with excursion permitted between 15° - 30°C in the proposed primary container closure system, i.e. (b) (4) Glass Bottle / (b) (4) (b) (4) cap. 14-month expiry for Cocaine Hydrochloride Topical Solution, 4% (4 mL and 10 mL presentations) (b) (4)

B. Special Product Quality Labeling Recommendations (NDA only): Name of the drug product has been changed by the Division (DAAP) to Cocaine hydrochloride nasal solution – See labeling review for additional comments on the rationale for changing the drug product name.

C. Final Risk Assessment (see Attachment)

From Initial Quality Assessment			Review Assessment		
Product attribute/ CQA	**Factors that can impact the CQA**	**Risk Ranking***	**Risk Mitigation Approach**	**Risk Evaluation**	**Lifecycle Considerations/ Comments****
Assay, stability	• Formulation • Raw materials • Process parameters • Scale/equipment • Site	L	-	N/A	-
Physical stability (API)	• Formulation • Raw materials • Process parameters • Scale/equipment • Site	L	-	N/A	-
Content uniformity	• Formulation • Raw materials • Process parameters • Scale/equipment • Site	L	-	N/A	-.
Microbial Limits	• Formulation • Raw materials • Process parameters • Scale/equipment	L	-	-	-

Reference ID: 4583625

In Vitro Dissolution	• Formulation • Raw materials • Process parameters • Scale/equipment • Site • Exclude major reformulations • Alcohol dose dumping	L	-	-	-

Reference ID: 4563625

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CHAPTER IV: LABELING

IQA NDA Assessment Guide Reference

1.0 PRESCRIBING INFORMATION

Assessment of Product Quality Related Aspects of the Prescribing Information:

1.1 HIGHLIGHTS OF PRESCRIBING INFORMATION#

Item	Information Provided in the NDA	Assessor's Comments
Product Title in Highlights		
Proprietary name	Numbrino	none
Established name(s)	cocaine hydrochloride topical solution	Change to "cocaine hydrochloride nasal solution" †
Route(s) of administration	for nasal mucosa use	for application to intranasal mucosa
Dosage Forms and Strengths Heading in Highlights		
Summary of the dosage form(s) and strength(s) in metric system.	4% topical solution (40 mg/ mL) available in both 4mL and 10mL bottles. (b) (4) [redacted]	remove the word 'topical'
Assess if the tablet is scored. If product meets guidelines and criteria for a scored tablet, state "functionally scored"	Not applicable; solution	
For injectable drug products for parental 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.	Not applicable	

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† Though the type of dosage form was not defined (orange Book) earlier, OND Division wanted to retain this name for now, to be consistent with approved drug with similar composition. Once the citizen's petition on the drug product is resolved, Division want to send letters to both NDA holders, to change drug name. The RPM was asked to make a note of it.

[redacted] (b) (4)

1.2 FULL PRESCRIBING INFORMATION

1.2.1 Section 2 (DOSAGE AND ADMINISTRATION)

Item	Information Provided in the NDA	Assessor's Comments
DOSAGE AND ADMINISTRATION section		
Special instructions for product preparation (e.g., reconstitution and resulting concentration, dilution, compatible diluents, storage conditions needed to maintain the stability of the reconstituted or diluted product)	(b) (4) [redacted]	Change to: Draw up 4 ml NUMBRINO solution into a syringe calibrated in mL. Stack four pledgets and apply 2 mL of solution to the top of the stacked pledgets. Turn the stacked pledgets over and apply 2 mL of solution to the other side. NUMBRINO should be evenly distributed on all four pledgets.

1.2.2 Section 3 (DOSAGE FORMS AND STRENGTHS)

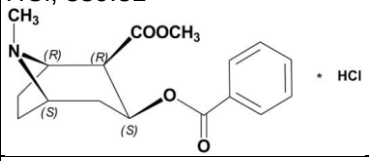
Item	Information Provided in the NDA	Assessor's Comments
DOSAGE FORMS AND STRENGTHS section		
Available dosage form(s)	(b) (4) [redacted]	NUMBRINO (cocaine hydrochloride) nasal solution† is a clear, blue-green solution provided in concentrations of 4% (40 mg/mL). The 4% nasal solution is provided in both a single-dose 4 mL (160 mg/4 mL) and multiple-dose 10 ml (400 mg/10 mL) bottles.
Strength(s) in metric system	(b) (4) [redacted]	Change to: Each 1 mL of the 4% solution contains 40 mg of cocaine hydrochloride, equivalent to 35.6 mg of cocaine as aqueous solution, for topical nasal administration.
If the active ingredient is a salt, apply the USP Salt Policy per FDA Guidance	equivalency information not provided	Add: 40 mg of cocaine hydrochloride, equivalent to 35.6 mg cocaine;
A description of the identifying characteristics of the dosage forms, including shape, color, coating, scoring, and imprinting	no identifying information included	Change to: NUMBRINO (cocaine hydrochloride) nasal solution is a clear, blue-green solution provided in concentrations of 4% (40 mg/mL).
Assess if the tablet is scored. If product meets guidelines and criteria for a scored tablet, state "functionally scored"	not applicable	
For injectable drug products for parental administration, use appropriate labeling term (e.g., single-dose, multiple-dose, single-patient-use). Other package type terms include pharmacy bulk package and imaging bulk package.	not applicable	

1.2.3 Section 11 (DESCRIPTION)

Appears this way on the original

Reference ID: 4563625

Item	Information Provided in the NDA	Assessor's Comments
DESCRIPTION section		
Proprietary and established name(s)	(b) (4)	Change to: NUMBRINO (cocaine hydrochloride) nasal solution
Dosage form(s) and route(s) of administration		Change to: nasal solution
If the active ingredient is a salt, apply the USP Salt Policy and include the equivalency statement per FDA Guidance.	(b) (4)	Change to: Each 1 mL contains cocaine hydrochloride 40 mg, equivalent to 35.6 mg of cocaine; 4% as160 mg/4 mL or 400 mg/10 mL.
List names of all inactive ingredients. Use USP/NF names. Avoid Brand names.	purified water, citric acid (anhydrous), sodium benzoate, D&C Yellow No. 10, and FD&C Green No. 3.	
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.	Not applicable	
If alcohol is present, must provide the amount of alcohol in terms of percent volume of absolute alcohol	not applicable	
Statement of being sterile (if applicable)	not applicable	
Pharmacological/ therapeutic class	local anesthetic	

Chemical name, structural formula, molecular weight	(1R,2R,3S,5S)-methyl 3-(benzoyloxy)-8-methyl-8-azabicyclo[3.2.1]octane-2-carboxylate hydrochloride,; $C_{17}H_{21}NO_4$ HCl; 339.81 	Acceptable
If radioactive, statement of important nuclear characteristics.	not applicable	
Other important chemical or physical properties (such as pKa or pH)	no information provided.	

Section 11 (DESCRIPTION) Continued

Item	Information Provided in the NDA	Assessor's Comments
For oral prescription drug products, include gluten statement if applicable	not applicable	
Remove statements that may be misleading or promotional (e.g., "synthesized and developed by Drug Company X," "structurally unique molecular entity"	none	

1.2.4 Section 16 (HOW SUPPLIED/STORAGE AND HANDLING)

Item	Information Provided in the NDA	Assessor's Comments
HOW SUPPLIED/STORAGE AND HANDLING section		
Available dosage form(s)	(b) (4) [redacted]	Nasal Solution
Strength(s) in metric system		4% (40 mg/ mL)
Available units (e.g., bottles of 100 tablets)		4% (40 mg/ mL) Nasal Solution: 4mL Single-use Bottles 10mL Multi-use Bottles
Identification of dosage forms, e.g., shape, color, coating, scoring, imprinting, NDC number	(b) (4) [redacted]	NUMBRINOTM (cocaine hydrochloride) nasal solution is a clear, blue-green solution available as follows: <u>4% (40 mg/ mL) Nasal Solution</u> NDC 0527-1961-74: 4mL Single-use Bottles NDC 0527-1961-73: 10mL Multi-use Bottles
Assess if the tablet is scored. If product meets guidelines and criteria for a scored tablet, state "functionally scored"	not applicable	
For injectable drug products for parental 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.	not applicable	

Section 16 (HOW SUPPLIED/STORAGE AND HANDLING) (Continued)

Item	Information Provided in the NDA	Assessor's Comments

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.)	Keep out of reach of children. Keep in a secure area and protect from diversion.	
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.”	not applicable	
Storage conditions. Where applicable, use USP storage range rather than storage at a single temperature.	(b) (4) [redacted]	Store at 20° to 25°C (68° to 77°F) with excursions permitted between 15° and 30°C (59° and 86° F) [see USP Controlled Room Temperature].
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.”	Not applicable	
Include information about child-resistant packaging	not a child resistant container	acceptable for hospital supply

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 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.

1.2.6 Manufacturing Information After Section 17 (for drug products)

Item	Information Provided in the NDA	Assessor's Comments
Manufacturing Information After Section 17		
Name and location of business (street address, city, state and zip code) of the manufacturer, distributor, and/or packer	Distributed by: Lannett Company, Inc. Philadelphia, PA 19136 Manufactured by: Cody Laboratories, Inc. Cody, WY 82414	

2.0 PATIENT LABELING

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

Above indicated changes are incorporated in to the working labeling (PI) document, to be sent to the applicant by the Division.

3.0 CARTON AND CONTAINER LABELING

3.1 Container Label

(b) (4)

2 Page(s) of Draft Labeling have been Withheld in Full as B4 (CCI/TS) immediately following this page

Item	Information Provided in the NDA	Assessor's Comments about Carton Labeling
Proprietary name, established name, and dosage form (font size and prominence	NUMBRINO (cocaine hydrochloride topical solution)	Font size of established name is acceptable from CMC perspective.
Dosage strength	4% and 10 %	4%# (see comment on above page, about 10% solution.
Route of administration	(b) (4) [redacted]	
If the active ingredient is a salt, include the equivalency statement per FDA Guidance	[redacted]	Each 1 mL contains cocaine hydrochloride 40 mg, equivalent to 35.6 mg cocaine
Net contents (e.g. tablet count)	(b) (4) [redacted]	
"Rx only" displayed on the principal display	Rx Only	
NDC number	NDC 0527-**1961**-74 NDC 0527-**1961**-73	
Lot number and expiration date	Lot No.: Exp. Date:	Provide the formats to be used for Lot number and Exp Dates for container labels Also identify the space and formats for Lot number and Exp Dates on cartons
Storage conditions. If applicable, include a space on the carton labeling for the user to write the new BUD.	**Store at 20° to 25°C (68° to 77°F).** [See USP Controlled Room Temperature].	Store at 20° to 25°C (68° to 77°F) with excursions permitted between 15° and 30°C (59° and 86° F) [see USP Controlled Room Temperature].

For injectable drug products for parental administration, use appropriate package type term (e.g., single-dose, multiple-dose, single-patient-use)	Unit of Use 4 mL Multi Dose 10 mL	to change to: Single-use 4 mL Multi-use 10 mL
Other package terms include pharmacy bulk package and imaging bulk package which require “Not for direct infusion” statement.	NOT FOR INJECTION OR OPHTHALMIC USE	
If alcohol is present, must provide the amount of alcohol in terms of percent volume of absolute alcohol	Not applicable	
Bar code	N 3 0 5 2 7 1 9 6 1 7 4 7 N 3 0 5 2 7 1 9 6 1 7 3 0	

Item	Information Provided in the NDA	Assessor's Comments about Carton Labeling
Name of manufacturer/distributor	Distributed by: Lannett Company, Inc. Philadelphia, PA 19154	
Medication Guide (if applicable)	Not applicable, Intended for clinic / hospital use	
No text on Ferrule and Cap overseal	not applicable for nasal solution	
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.	not applicable for non-compendial products. P. S: Only "Cocaine Hydrochloride Tablets for Topical Solution" has a USP monograph.	
And others, if space is available		

Assessment of Carton and Container Labeling: Inadequate

Labeling text (PI, carton, and container labels need modification as indicated above for both container labels and cartons.

ITEMS FOR ADDITIONAL ASSESSMENT

PI, carton, and container label for 4% solution (4 mL and 10mL):

1. Provide revised text with the following changes:
   A. Established name to NUMBRINO (cocaine hydrochloride) nasal solution†.
   B. Dosage strength statement to "Each 1 mL of the 4% solution contains 40 mg of cocaine hydrochloride, equivalent to 35.6 mg of cocaine".
   C. Storage statement to "Store at 20° to 25°C (68° to 77°F) with excursions permitted between 15° and 30°C (59° and 86° F) [see USP Controlled Room Temperature]."

Carton and Container Labels:

2. Revise the following text on cartons and container labels
   A. "unit of use 4 mL" to single use 4 mL" and
   B. "Multi-dose 10 mL" to multi-use 10 mL"

3. 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 lot number format to be used on the drug product labels. Also provided the format to be used for expiration dating, i.e. 11/2019 or NOV/2019 or DD/MM/YYYY.

Carton (4%, 4 ml and 10 mL):

4. Per 21 CFR 201.17, unless it is easily legible through such outer package, expiration dating must be displayed on both the immediate container label and carton for a drug product. Provide revised text for cartons, indicating the location for placing Lot no and expiration date.

Overall Assessment and Recommendation:

Approvable, subject to making changes to the text in PI (highlights, sections 2, 3, 11 and 16), and on carton and container labels, as suggested above.

Primary Labeling Assessor Name and Date:

Venkateswara R. Pavuluri, Ph.D., R. Ph.; 25-NOV-2019

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

Julia C. Pinto, Ph. D.; xx- NOV-2019

Venkateswara Pavuluri

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Recommendation: Approve

NDA 209575
Review #1

Drug Name/Dosage Form	Cocaine Hydrochloride Topical Solution, 4% and 10% Topical Solution
Strength	40 mg/mL (4%) and (b) (4) (10%)
Route of Administration	Topical
Rx/OTC Dispensed	Rx
Applicant	Cody Laboratories, Inc.
US agent, if applicable	

Quality Review Team

DISCIPLINE	REVIEWER	BRANCH/DIVISION
Drug Substance	Sam Bain	OPQ/ONDP/DNDPAPI/BII
Drug Product	Venkat Pavuluri	OPQ/ONDP/DNDPII/BIV
Process	Tarun Mehta	OPQ/OPF/DPAII/BVI
Microbiology	Renee Marcsisin	OPQ/OPF/DMA/BII
Facility	Frank Wackes	OPQ/OPF/DIA/BII
Biopharmaceutics	Not Required	
Regulatory Business Process Manager	Steven Kinsley	OPQ/OPRO/RBPMI/BI
Application Technical Lead	Ciby Abraham	OPQ/ONDP/DNDPII/BIV
Laboratory (OTR)		
ORA Lead	Caryn McNabb	
Environmental Analysis (EA)		

Reference ID: 4563674

Quality Review Data Sheet

1. RELATED/SUPPORTING DOCUMENTS

A. DMFs:

DMF #	Type	Holder	Item Referenced	Status	Date Review Completed	Comments
29120	Type II	Cody Laboratories, Inc.	Cocaine Hydrochloride	Adequate	6/15/18	
(b) (4)	Type III	(b) (4)	(b) (4)	Adequate	6/15/18	Information found in NDA
	Type III			Adequate	6/15/18	Information found in NDA
	Type III			Adequate	6/15/18	Information found in NDA
	Type III			Adequate	6/15/18	Information found in NDA
	Type III			Adequate	6/15/18	Information found in NDA
	Type III			Adequate	6/15/18	Information found in NDA
	Type III			Adequate	6/15/18	Information found in NDA
	Type III			Adequate	6/15/18	Information found in NDA
	Type III	(b) (4)		Adequate	6/15/18	Information found in NDA
	Type III	(b) (4)		Adequate	6/15/18	Information found in NDA
	Type III			Adequate	6/15/18	Information found in NDA

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

DOCUMENT	APPLICATION NUMBER	DESCRIPTION
N/A		

Reference ID: 4563674

2. CONSULTS - None

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

Reference ID: 4563674

Executive Summary

I. Recommendations and Conclusion on Approvability

Based on the recommendations from drug substance, process, microbiology, facilities, and drug product, CMC recommends the approval of NUMBRINO (Cocaine HCl Topical Solution) 40 mg/mL (4%) and (b) (4) (10%).

II. Summary of Quality Assessments

A. Product Overview

The applicant provided a letter of authorization to access DMF# 029120 Cocaine HCl by Cody laboratories, Inc. The DMF was reviewed by Dr. Sukhamaya Bain and found adequate for this submission on 6/13/2018. Cocaine HCl is a white crystal or powder that readily dissolves in water (1 gram in 0.4 mL). The melting point is approximately 195°C. The drug substance is stored at room temperature in (b) (4) in (b) (4) drums. The retest period is (b) (4) months.

Cocaine HCl Topical Solution 40 mg/ml and (b) (4) are clear blue-green solutions, proposed to be marketed in two dosage strengths, 4% (40 mg/mL) in 4 mL single-use (b) (4) vials and 10 mL multi-dose in (b) (4) vials (b) (4) ontainer closure configurations are shown below.

Start of Applicant Material.

Packaging Configuration 1	
Bottle Size & Description:	(b) (4) (b) (4) (b) (4) glass (USP Type III) bottle
Bottle Code No.:	(b) (4)
Cap Size & Description:	(b) (4) cap, (b) (4) (b) (4)
Cap Code No.:	(b) (4)
Product Strength / Fill Size	4% - 4 mL and 10 mL; 10% - (b) (4)

(b) (4)

Reference ID: 4563674

[redacted] (b) (4)

End of Applicant Material.

The applicant performed limited extractables/leachables [redacted] (b) (4) container closure systems. Additional information will be needed on the extractables/leachables study. See the Pharmacology/Toxicology review for additional details.

The proposed expiration dates are acceptable for each of the respective dosage strength and presentations as described below, when the drug product is stored at controlled room temperature (20 -25°C as per USP) in their proposed container closure system [redacted] (b) (4)). 14 month expiry for Cocaine Hydrochloride Topical Solution, 4% [redacted] (b) (4)

B. Special Product Quality Labeling Recommendations (NDA only) – N/A

Reference ID: 4563674

C. Final Risk Assessment (see Attachment)

From Initial Quality Assessment			Review Assessment		
Product attribute/ CQA	**Factors that can impact the CQA**	**Risk Ranking***	**Risk Mitigation Approach**	**Risk Evaluation**	**Lifecycle Considerations/ Comments****
Assay, stability	• Formulation • Raw materials • Process parameters • Scale/equipment • Site	L	-	N/A	-
Physical stability (API)	• Formulation • Raw materials • Process parameters • Scale/equipment • Site	L	-	N/A	-
Content uniformity	• Formulation • Raw materials • Process parameters • Scale/equipment • Site	L	-	N/A	-.
Microbial Limits	• Formulation • Raw materials • Process parameters • Scale/equipment	L	-	-	-
In Vitro Dissolution	• Formulation • Raw materials • Process parameters • Scale/equipment • Site • Exclude major reformulations • Alcohol dose dumping	L	-	-	-

Reference ID: 4563674

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MICROBIOLOGY

Product Background: Indicated for the introduction of local (topical) anesthesia for diagnostic procedures and surgeries on or through the accessible mucous membranes of the nasal cavities

NDA: 209575

Drug Product Name / Strength: Cocaine Hydrochloride Topical Solution, 4% and 10% (Proprietary name: Numbrino)

Route of Administration: Topical

Applicant Name: Cody Laboratories, Inc. (a wholly owned subsidiary of Lannett Company, Inc.)

Manufacturing Site: Cody Laboratories, Inc. (a wholly owned subsidiary of Lannett Company, Inc.), 601 Yellowstone Ave., Cody, WY 82414

Method of Sterilization: Not applicable for a non-sterile drug product

Review Recommendation: **Adequate**

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

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

Review Summary: **The drug product is administered as a topical solution and is therefore not required to be sterile. A sterility assurance review of this NDA was not performed; however, a review of the microbial limits is necessary.**

List Submissions Being Reviewed: 09/21/2017, 02/07/2018, 03/13/2018

Highlight Key Outstanding Issues from Last Cycle: N/A

Remarks: N/A

Concise Description Outstanding Issues Remaining: N/A

Supporting Documents: N/A

List Number of Comparability Protocols (ANDA only): N/A

Reference ID: 4563674

S Drug Substance: N/A

P.1 Description of the Composition of the Drug Product

(eCTD seq #0001: Section 3.2.P.1., Description and Composition of the Drug Product; Section 3.2.P.7., Summary of Container Closure System)

- **Description of drug product –**

Cocaine Hydrochloride Topical Solution, 4%	
Physical Description	Appearance: Clear, blue-green solution, no precipitate or sediment evident
	Odor: No stale or noxious odor
Strength (mg/ml)	40 mg/ml
Fill Volume (ml)	4 ml (unit of use) and 10 ml (multi-dose)

Cocaine Hydrochloride Topical Solution, 10%
(b) (4)

- **Drug product composition –**

Cocaine Hydrochloride Topical Solution, 4%				
Ingredient	**Quality Standard**	**mg per ml**	**% per w/w**	**Function**
Cocaine Hydrochloride, USP	USP	40	4.0	Active Ingredient
Sodium Benzoate, NF	NF	(b) (4)	(b) (4)	(b) (4)
D & C Yellow #10	N/A			
FD & C Green #3	N/A			
Citric Acid Anhydrous, USP	USP			
Purified Water, USP	USP			

Cocaine Hydrochloride Topical Solution, 10%				
Ingredient	**Quality Standard**	**mg per ml**	**% per w/w**	**Function**
		(b) (4)		(b) (4)

- **Description of container closure system –** (b) (4) container/closure systems are proposed for Cocaine Hydrochloride Topical Solution, 4% (b) (4)

Reference ID: 4563674

Packaging Component and Item Code	Component Description	Supplier/Manufacturer	Supplier Lot #	Cody Lot #
(b) (4) Bottle (b) (4)	(b) (4) (b) (4) Glass Bottle	(b) (4)		
Cap for (b) (4) Bottle ((b) (4) cap) (b) (4)	(b) (4) (b) (4) Cleaned			
Alternate Cap for (b) (4) Bottle (b) (4)	(b) (4) (b) (4)			
(b) (4) (b) (4)	(b) (4) Glass Bottle			
Cap for (b) (4) Bottle (b) (4)	(b) (4)			

[1] This lot was not utilized in a submission batch, but w data to support alternate container/closure systems.

Reviewer's Assessment: ***Adequate***

The description of the drug product and container closure system is adequate.

P.2 Pharmaceutical Development

P.2.5 Microbiological Attributes

Container/Closure and Package Integrity

Reviewer's Assessment: N/A

Antimicrobial Effectiveness Testing

(eCTD seq #0001: Section 3.2.P.2., Pharmaceutical Development Report)

The 4% and 10% drug products are (b) (4) Test strains evaluated as part of the study included (b) (4) concentrations (b) (4) the label claim, the drug product met the requirements of USP <51>. The data provided for the drug product formulated with (b) (4) of the label claim are summarized below:

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Reference ID: 4563674

Renee Marcsisin

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Erika Pfeiler

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