CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

209963Orig1s000

PRODUCT QUALITY REVIEW(S)

Recommendation: Approve

NDA 209963
Review #1

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

Quality Review Team

DISCIPLINE	REVIEWER	BRANCH/DIVISION
Drug Substance	Sam Bain	OPQ/ONDP/DNDPAPI/BII
Drug Product	Valerie Amspacher	OPQ/ONDP/DNDPII/BIV
Process	Tarun Mehta	OPQ/OPF/DPAII/BVI
Microbiology	Denise Miller	OPQ/OPF/DMA/BII
Facility	Wenzheng Zhang	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/Michael Tollon	
Environmental Analysis (EA)		

Quality Review Data Sheet

1. RELATED/SUPPORTING DOCUMENTS

A. DMFs:

DMF #	Type	Holder	Item Referenced	Status	Date Review Completed	Comments
(b) (4)	Type II		(b) (4)	Adequate	9/25/17	
	Type III			Adequate	9/25/17	Information found in NDA
	Type III			Adequate	9/25/17	Information found in NDA
	Type III			Adequate	9/25/17	Information found in NDA

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

DOCUMENT	APPLICATION NUMBER	DESCRIPTION
IND	IND 118527	

2. CONSULTS - None

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

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 Cocaine HCl Topical Solution 40 mg/mL (4%).

II. Summary of Quality Assessments

A. Product Overview

The applicant provided a letter of authorization to access DMF# (b) (4) The DMF was reviewed by Dr. Sukhamaya Bain and found adequate for this submission on 4/17/2017. (-) Cocaine is the naturally occurring alkaloid extracted from coca leaves. Cocaine HCl is a white powder that readily dissolves in water (1 gram in 0.4 mL). The melting point is approximately 195ºC. The drug substance (b) (4) The retest period is (b) (4) months.

Cocaine HCl Topical Solution 40 mg/ml is a clear green colored liquid packaged in a 0.5 oz. amber glass bottle with lined, ribbed closure with a fill volume of 4 mL. Cocaine Hydrochloride Topical Solution is an ester-based anesthetic indicated for the induction of local anesthesia when performing diagnostic procedures and surgeries on or through the mucous membranes of the nasal cavities in adults. Cocaine Hydrochloride Topical Solution is for intranasal use only. The recommended dose of Cocaine Hydrochloride Topical Solution is two pledgets, each containing 40 mg of cocaine hydrochloride, applied to each nasal cavity. Based on the stability data provided, a 18-month expiry at 25°C ± 2°C/60% RH ± 5% RH is granted.

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

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	L	-	N/A	-

	• Scale/equipment • Site				
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	-	-	-

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QUALITY ASSESSMENT

MICROBIOLOGY

Product Background: This is a currently marketed unapproved drug product for local anesthesia in diagnostic procedures and surgeries on or through the mucous membranes of the nasal cavities in adults. This is a topically applied product to be marketed in a 0.5 oz amber glass bottle with a 4.0 mL fill.

NDA: **209-963**

Drug Product Name / Strength: Cocaine Hydrochloride Topical Solution, 4%

Route of Administration: topical

Applicant Name: Genus LifeSciences Inc. (b) (4)

Manufacturing Site: Genus LifeSciences Inc. (b) (4)
514 North 12th Street
Allentown Pennsylvania 18102
FEI # 3003851100

Method of Sterilization: NA; this is a non-sterile drug product.

Review Recommendation: Approve from a quality microbiology perspective.

Review Summary: This is a non-sterile (b) (4) drug product that is administered topically. The critical aspects of the process from the quality microbiology perspective are the release testing and the effectiveness of the antimicrobial agent. These aspects were reviewed and deemed acceptable.

List Submissions Being Reviewed:

Submit	Received	Review Request	Assigned to Reviewer
23 November 2016	23 November 2016	N/A	06 December 2016
06 March 2017	06 March 2017	N/A	N/A
06 April 2017	06 April 2017	N/A	N/A

Highlight Key Outstanding Issues from Last Cycle: NA

Remarks:
Information request was sent on 13 February 2017 requesting information on testing for the absence of *B. cepacia* and performing antimicrobial effectiveness testing at end of shelf life. A partial response was received on 06 March 2017 and a complete response was received on 06 April 2017. The IR and response are reviewed in the appropriate sections of this review.

Concise Description Outstanding Issues Remaining: None

Supporting Documents: NA

List Number of Comparability Protocols (ANDA only): NA

S Drug Substance: NA

P Drug Product

P.1 Description of the Composition of the Drug Product

- **Description of drug product –** The drug product is non-sterile preserved clear green solution. It is a topical (b) (4) product.

- **Drug product composition –** The drug product composition is Cocaine Hydrochloride, USP at 40.00 mg/mL. The excipients include anhydrous citric acid, sodium benzoate (b) (4) coloring, and purified water.

- **Description of container closure system –**
  - Bottle: (b) (4) Round amber glass bottle, 0.5 oz
  - Closure: 18 mm (b) (4) ribbed closure
  - Liner: (b) (4) foam liner

Reviewer's Assessment: ***Adequate.*** The information provided for description and the composition of the drug is sufficient.

P.2 Pharmaceutical Development

P.2.5 Microbiological Attributes

Antimicrobial Effectiveness Testing (AET)

Note: This product is a USP <51> Category 2 product. Category 2 products are topical products with aqueous bases, nonsterile nasal product and emulsions including those applied to mucous membranes.

Verification of the microbial counting method: The microbial counts could be reliably recovered from product (b) (4). This microbial counting method was verified for all three exhibit lots with recoveries ranging from (b) (4)% for all organisms (specification was ≥ (b) (4)%).

Selection of preservative concentration: The sponsor performed AET on the drug product with preservatives levels of 0%, 0.05%, 0.1%, 0.15%, and 0.2%. All concentrations met the USP <51> for a Category 2 product. The sponsor selected the preservative level of (b) (4)% as this level also reduced mold counts by (b) (4) logs at the 7 day time point. The proposed acceptable range for the preservative is (b) (4)%.

AET testing: AET testing was performed on the three exhibits lots (Report R-318459-RO) following USP <51>. The report included the count recovery method already described and the results of the AET testing for the three exhibit batches. All three batches met the acceptance criteria for USP <51> Category 2 product

Reviewer's Assessment: ***Adequate.*** The AET testing supports the effectiveness of the preservative system over the acceptable preservative concentration range. The AET is included in the stability program to demonstrate effectiveness over the shelf life of the product.

P.3 Manufacture

P.3.1 Manufacturers

Genus LifeSciences Inc (b) (4)
514 N. 12th Street
Allentown PA 18102

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

P. 3.3 Description of the Manufacturing Process and Process Controls

Overall Manufacturing Operation

(b) (4)

Batch size is (b) (4) Kg (40 mg/mL with 4.0 mL/bottle)

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

P.5 Control of Drug Product

P. 5.1 Specification

Microbial Limits

Total Aerobic Microbial Counts: NMT (b) (4) cfu/gram
Total Mold and Yeast Counts: NMT (b) (4) cfu/gram
Absence of *Pseudomonas aeruginosa, Staphylococcus aureus, and Burkholderia cepacia*

Reviewer Note: Originally, the release specifications did not include the absence of *B. cepacia*. The request of this testing was sent to the sponsor in an information request dated 13 February 2017. The sponsor responded on 06 April 2017 with an updated release specification to include the absence of *B. cepacia*.

Information Request #1 Question 1: Non-sterile aqueous drug product may potentially be contaminated with organism in the *Burkholderia cepacia* complex (BCC). BCC stains have a well-documented ability to ferment a wide variety of substrates and are known to proliferate in the presence of many traditional preservative systems. Thus, despite the presence of otherwise adequate preservative systems, BCC strains can survive and even proliferate in product during storage. For a recent review of FDA's perspective on BCC please see PDA J Pharm Sci Tech 2011; 65(5):535-43.

In order to control for the presence of BCC in your product you should consider the following:

A) 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. These may include raw materials and the manufacturing environment. A risk assessment for this species in the product and raw material is recommended to develop sampling procedures and acceptance criteria.

B) Provide test methods and acceptance criteria to demonstrate the drug product is free of BCC. Your test method should be validated and a discussion of those methods should be provided. Test method validation should address multiple strains of the species and cells should be acclimated to the conditions in the manufacturing environments (e.g. temperature) before testing.
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 do detecting BCC organisms would be adequate. It is currently sufficient to precondition representative strain(s) of BCC in water and/or your drug product without preservatives to demonstrate that your proposed method is capable of detecting small number of BCC. Your submission should describe the preconditions step (time, temperature, and solution(s) used), the total number of inoculated organisms, and the detailed test method to include growth medium and incubation conditions. It is essential that sufficient preconditioning of the organisms occurs during these method validation studies to insure that the proposed recovery methods are adequate to recover organisms potentially present in the environment.

For more information, we refer you to *Envir Microbiol* 2011; 13(1):1-12 and *J. Appl Microbiol* 1997; 83(3):322-6.

Response: The sponsor added the absence of *B. cepacia* to the release specifications and provided the validation study described below in review section P.5.3.

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

P.5.2 Analytical Procedures

Microbial Limits testing is performed following USP <61> and <62>.

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

P.5.3 Validation of Analytical Procedures

Two method suitability reports were provided.

The first was report R-317755 supporting the release testing for the TAMC, TYMC and the absence of P. aeruginosa and S. aureus by USP <61> and <62>. The method suitability was performed on three lots of drug product and supports the release testing. Recovery of counts for the TAMC and TYMC ranged from (b) (4)% and the presence of *P. aeruginosa* and *S. aureus* was detected.

The second was report R-442732-RO supporting the release testing the absence of *Burkholderia cepacia* . The method includes an enrichment phase in Trypticase Soy Broth and then subculture on Burkholderia cepacia Selective Agar (BCSA). Any growth on BCSA will be identified to confirm the identity of the microorganism. The method suitability supports the release testing for the absence of *B. cepacia*. The suitability report supports the ability of the method to detect the presence of *B. cepacia* in the drug product.

Reviewer's Assessment: ***Adequate.*** The microbial limits testing meets the minimum recommended USP <1111> limits and Agency expectations for route of administration. The testing for is supported by the method suitability studies.

P.7 Container Closure

Summary table of the container closure system proposed

- Bottle: (b) (4) Round amber glass bottle, 0.5 oz
- Closure: 18 mm (b) (4) ribbed closure

- Liner: (b) (4) foam liner

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

P.8 Stability

P. 8.1 Stability Summary and Conclusion

Microbial Limits is performed at T 0, 12, 15, 18, 19, and 20 months

Information request #2: *Provide a commitment to conduct antimicrobial effectiveness testing according to USP <51> or equivalent methodology on at least one primary stability batch at the end of the proposed shelf life (reference ICH Q1A Stability Testing of New Drug Substances and Products).*

Summary of Response (06 March 2017): The three stability submission batches have already exceeded the proposed shelf life of 20 months, therefore the Antimicrobial Effectiveness Testing will be tested on stability batch S35900115 at the 20 month time point (scheduled for June 12, 2017). A review of the pending data is not required for the completion of the DMA assessment for this drug product. The proposal to perform AET at the 20 month time point is acceptable.

Reviewer's Assessment: ***Adequate. The response is acceptable.***

P. 8.2 Post-Approval Stability Protocol and Stability Commitment

Stability for the commercial batches will be under long term storage conditions.

Testing for ML will be performed at initial and at 20 months. One commercial batch will be added yearly.

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

P.8.3 Stability Data

Long Term: 25 ± 2°C/60 ± 5% RH (20 months)
Accelerated: 40 ± 2°C/75 ± 5% RH (6 months)
Intermediate: 30 ± 2°C/65 ± 5% RH (12 months)

Testing followed the recommendations outlined in Guidance for Industry *Q1A9R2) Stability Testing of New Drugs Substances and Products*, ICH, November 2003, Revision 2.
The stability information provided included the three exhibit batches S3500113, S35900213, and S03500313. Testing was completed on all three batches. The microbial limits testing meet the acceptance criteria.

Reviewer's Assessment: *Adequate*

A Appendices: NA

R Regional Information

Executed Batch Records

Batch records for three exhibit batches were submitted, S35900113, S3500213 and S359313.

Reviewer's Assessment: *Adequate.*

Comparability Protocols: NA

Reviewer's Assessment: *NA.*

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

2.A. Package Insert: NA

Reviewer's Assessment: *NA.* There are no quality microbiology concerns for the package insert.

Post-Approval Commitments: NA

Reviewer's Assessment: There are no post-approval commitments from a quality microbiology perspective.

List of Deficiencies: None

Primary Microbiology Reviewer Name and Date: Denise A. Miller, 06 June 2017

Secondary Reviewer Name and Date: Neal J. Sweeney, Ph.D., 18 June 2017

Denise Miller

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Date: 7/24/2017 07:30:07AM
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Neal Sweeney

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Ciby Abraham

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OFFICE OF PHARMACEUTICAL QUALITY

NDA FILING REVIEW

Application #: 209963	**Established/Proper Name: Cocaine Hydrochloride Topical Solution, 4%**
Applicant (b) (4)	**Dosage Form: Solution**
Submission Type:	**Strength(s):40 mg/mL (4%)**
Chemical Type:	**Cross Referenced Applications:**

A. FILING CONCLUSION				
	Parameter	**Yes**	**No**	**Comment**
1.	**DOES THE OFFICE OF PHARMACEUTICAL QUALITY RECOMMEND THE APPLICATION TO BE FILED?**	x		
2.	If the application is not fileable from the product quality perspective, state the reasons and provide **filing** comments to be sent to the Applicant.			N/A
3.	Are there any **potential review** issues to be forwarded to the Applicant, not including any filing comments stated above?		x	

A. OVERVIEW OF CRITICAL PRODUCT QUALITY REVIEW CONSIDERATIONS

The applicant is proposing to market Cocaine HCl Topical Solution 4% for the proposed indication of the induction of local anesthesia when performing diagnostic procedures and surgeries on or through the mucous membranes of the nasal cavities in adults. The proposed cocaine HCl topical solution, 40 mg/mL (4%) is a clear green colored liquid packaged in a 0.5 oz amber bottle with a lined, ribbed closure. The fill volume is 4 mL.

B. FILING CONSIDERATIONS					
	Parameter	**Yes**	**No**	**N/A**	**Comment**
	GENERAL/ADMINISTRATIVE				
1.	Has an environmental assessment report (NME, API with estrogenic, androgenic, or thyroid activity; API derived from plants and animals) or appropriate categorical exclusion (21 CFR 25.31 **AND** 25.15(d) been provided?	x			
2.	For DMFs, are DMF #'s identified and authorization letter(s) from the US agent provided in the application and referenced DMF?	x			
3.	Is the Quality Overall Summary (QOS) organized adequately and legible? Is there sufficient information in the QOS to conduct a review?	x			
	FACILITY INFORMATION				
4.	Are drug substance manufacturing sites, drug product manufacturing sites, and additional manufacturing, packaging and control/testing laboratory sites identified on FDA Form 356h or associated continuation sheet with complete identifying information?	x			
5.	Is a statement provided that all facilities are ready for GMP inspection at the time of submission? For BLA: ❑ Is a manufacturing schedule provided? ❑ Is the schedule feasible to conduct an inspection within the review cycle?	x			
	DRUG SUBSTANCE INFORMATION				
6.	Is the Drug Substance section [3.2.S] organized adequately and legible? Is there sufficient information in this section to conduct a review?	X			A DMF ((b) (4)) is referenced. Summaries of critical information are included in the NDA.
	DRUG PRODUCT INFORMATION				
7.	Is the Drug Product section [3.2.P] organized adequately and legible? Is there sufficient information in this section to conduct a review?	x			
	BIOPHARMACEUTICS –N/A				
8.					
9.					

B. FILING CONSIDERATIONS					
10.					
11.					
12.					
13.					
REGIONAL INFORMATION AND APPENDICES					
14.	Are any study reports or published articles in a foreign language? If yes, has the translated version been included in the submission for review?		x		
15.	Are Executed Batch Records for drug substance (if applicable) and drug product available?			x	
16.	If applicable, is the required information provided in 3.2.A for Biotech Products?			x	
17.	For Biotech Products, is sufficient information provided in compliance with 21 CFR 610.9 and 601.2(a)?			x	

Conclusion: From a CMC perspective, the application can be filed. CMC does not have any comments for the 74-day letter. Note: There will be no biopharmaceutics review on this application since it is an immediate release solution.

Application Technical Lead Name and Date:

Ciby J. Abraham -S

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DN: c=US, o=U.S. Government, ou=HHS, ou=FDA, ou=People, 0.9.2342.19200300.100.1.1=2000827346, cn=Ciby J. Abraham -S
Date: 2017.01.23 09:48:40 -05'00'

Ciby J. Abraham, Ph.D.
Acting Quality Assessment Lead
OPQ/ONDP/DIVII/Branch IV

PRODUCT QUALITY MICROBIOLOGY NON-STERILE

DRUG PRODUCT FILING CHECKLIST

NDA Number: 209-963 **Applicant:** [redacted] (b) (4) **Letter Date:** 23 November 2016

Drug Name: Cocaine Hydrochloride Topical Solution, 4% **NDA Type:** 505(b)(2) **Stamp Date:** 23 November 2016

Dosage Form: Solution **Reviewer:** Denise A. Miller

The following are necessary to initiate a review of the NDA application:

	Content Parameter	Yes	No	Comments
1	Is the product quality microbiology information described in the NDA and organized in a manner to allow substantive review to begin? Is it legible, indexed, and/or paginated adequately?	√		
2	Has the applicant submitted an overall description of the manufacturing processes and microbiological controls used in the manufacture of the drug product?	√		
3	Has the applicant submitted microbiological specifications for the drug product and a description of the test methods?	√		The absence of specified organisms does not include the absence of *Burkholdaria cepacia*.
4	Has the applicant submitted the results of analytical method verification studies?	√		
5	Has the applicant submitted preservative effectiveness studies (if applicable)?	√		No AET stability data provided for expiry.
6	Is this NDA fileable? If not, then describe why.	√		

Additional Comments: This is a topical nasal spray.

Product Quality Microbiology Information Request:

1) Non-sterile aqueous drug products may potentially be contaminated with organisms in the *Burkholderia cepacia* complex (BCC). BCC strains have a well-documented ability to ferment a wide variety of substrates and are known to proliferate in the presence of many traditional preservative systems. Thus, despite the presence of otherwise adequate preservative systems, BCC strains can survive and even proliferate in product during storage. For a recent review of FDA's perspective on BCC please see *PDA J Pharm Sci Tech* 2011; 65(5): 535-43.

In order to control for the presence of BCC in your product you should consider the following:

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2. Provide test methods and acceptance criteria to demonstrate the drug product is free of BCC. Your test method should be validated and a discussion of those methods should be provided. Test method validation should address multiple strains of the species and cells should be acclimated to the conditions in the manufacturing environment (e.g., temperature) before testing.

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For more information, we refer you to *Envir Microbiol* 2011; 13(1):1-12 and *J. Appl Microbiol* 1997; 83(3):322-6.

2) Provide a commitment to conduct antimicrobial effectiveness testing according to USP <51> or equivalent methodology on at least one primary stability batch at the end of the proposed shelf life (reference ICH Q1A Stability Testing of New Drug Substances and Products).

Denise Miller
OPF/DMA/Branch II Sr. Microbiology Reviewer

Neal Sweeney Ph.D.
OPF/DMA/Branch II Acting AQL

Neal Sweeney

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Denise Miller

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