

**CENTER FOR DRUG EVALUATION AND
RESEARCH**

APPLICATION NUMBER:

209963Orig1s000

ADMINISTRATIVE and CORRESPONDENCE
DOCUMENTS

ACTION PACKAGE CHECKLIST

APPLICATION INFORMATION ¹		
NDA # 209963 BLA #	NDA Supplement # BLA Supplement #	If NDA, Efficacy Supplement Type: Type 5 <i>(an action package is not required for SE8 or SE9 supplements)</i>
Proprietary Name: GOPRELTO Established/Proper Name: Cocaine hydrochloride nasal solution, 4% Dosage Form: Solution, 4%, 40 mg/mL		Applicant: Genus Life Sciences Agent for Applicant (if applicable): Melissa Goodhead, (b) (4)
RPM: Diana Walker		Division: DAAAP
NDA Application Type: ☐ 505(b)(1) ☒ 505(b)(2) Efficacy Supplement: ☐ 505(b)(1) ☐ 505(b)(2) BLA Application Type: ☐ 351(k) ☐ 351(a) Efficacy Supplement: ☐ 351(k) ☐ 351(a)		<u>For ALL 505(b)(2) applications, two months prior to EVERY action:</u> - Review the information in the 505(b)(2) Assessment and submit the draft² to CDER OND IO for clearance. - Check Orange Book for newly listed patents and/or exclusivity (including pediatric exclusivity) ☒ No changes ☐ New patent/exclusivity (notify CDER OND IO) Date of check: December 14, 2017 <i>Note: If pediatric exclusivity has been granted or the pediatric information in the labeling of the listed drug changed, determine whether pediatric information needs to be added to or deleted from the labeling of this drug.</i>
❖ Actions		
- Proposed action - User Fee Goal Date is <u>December 23, 2017</u>		☒ AP ☐ TA ☐ CR
Previous actions (<i>specify type and date for each action taken</i>)		☒ None
❖ If accelerated approval or approval based on efficacy studies in animals, were promotional materials received? Note: Promotional materials to be used within 120 days after approval must have been submitted (for exceptions, see http://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/ucm069965.pdf). If not submitted, explain _____		☐ Received
❖ Application Characteristics ³		

¹ The **Application Information** Section is (only) a checklist. The **Contents of Action Package** Section (beginning on page 2) lists the documents to be included in the Action Package.

² For resubmissions, 505(b)(2) applications must be cleared before the action, but it is not necessary to resubmit the draft 505(b)(2) Assessment to CDER OND IO unless the Assessment has been substantively revised (e.g., new listed drug, patent certification revised).

³ Answer all questions in all sections in relation to the pending application, i.e., if the pending application is an NDA or BLA supplement, then the questions should be answered in relation to that supplement, not in relation to the original NDA or BLA.

Review priority: ☒ Standard ☐ Priority
Chemical classification (new NDAs only): Type 5
(confirm chemical classification at time of approval)

- | | |
|---|---|
| ☐ Fast Track | ☐ Rx-to-OTC full switch |
| ☐ Rolling Review | ☐ Rx-to-OTC partial switch |
| ☐ Orphan drug designation | ☐ Direct-to-OTC |
| ☐ Breakthrough Therapy designation | |

(NOTE: Set the submission property in DARRTS and notify the CDER Breakthrough Therapy Program Manager;
Refer to the "RPM BT Checklist for Considerations after Designation Granted" for other required actions: [CST SharePoint](#))

NDAs: Subpart H

- ☐ Accelerated approval (21 CFR 314.510)
☐ Restricted distribution (21 CFR 314.520)

Subpart I

- ☐ Approval based on animal studies

- ☐ Submitted in response to a PMR
☐ Submitted in response to a PMC
☐ Submitted in response to a Pediatric Written Request

BLAs: Subpart E

- ☐ Accelerated approval (21 CFR 601.41)
☐ Restricted distribution (21 CFR 601.42)

Subpart H

- ☐ Approval based on animal studies

- REMS: ☐ MedGuide
☐ Communication Plan
☐ ETASU
☐ MedGuide w/o REMS
☐ REMS not required

Comments:

❖ BLAs only: Is the product subject to official FDA lot release per 21 CFR 610.2 (approvals only)	☐ Yes ☐ No
❖ Public communications (approvals only)	
• Office of Executive Programs (OEP) liaison has been notified of action	☒ Yes ☐ No
• Indicate what types (if any) of information were issued	☐ None ☐ FDA Press Release ☐ FDA Talk Paper ☒ CDER Q&As ☐ Other
❖ Exclusivity	
• Is approval of this application blocked by any type of exclusivity (orphan, 5-year NCE, 3-year, pediatric exclusivity)?	☒ No ☐ Yes
• If so, specify the type	
❖ Patent Information (NDAs only)	
• Patent Information: Verify that form FDA-3542a was submitted for patents that claim the drug for which approval is sought.	☒ Verified ☐ Not applicable because drug is an old antibiotic.
CONTENTS OF ACTION PACKAGE	
Officer/Employee List	
❖ List of officers/employees who participated in the decision to approve this application and consented to be identified on this list (approvals only) (link)	☒ Included
Documentation of consent/non-consent by officers/employees (link)	☒ Included

Action Letters	
❖ Copies of all action letters <i>(including approval letter with final labeling)</i>	Action and date: Approval: December 14, 2017
Labeling	
❖ Package Insert <i>(write submission/communication date at upper right of first page of PI)</i>	
Most recent draft labeling <i>(if it is division-proposed labeling, it should be in track-changes format)</i>	☒ Included
❖ Medication Guide/Patient Package Insert/Instructions for Use/Device Labeling <i>(write submission/communication date at upper right of first page of each piece)</i>	☐ Medication Guide ☐ Patient Package Insert ☐ Instructions for Use ☐ Device Labeling ☒ None
Most-recent draft labeling <i>(if it is division-proposed labeling, it should be in track-changes format)</i>	☐ Included
❖ Labels (full color carton and immediate-container labels) <i>(write submission/communication date on upper right of first page of each submission)</i>	
Most-recent draft labeling	☒ Included
❖ Proprietary Name - Acceptability/non-acceptability letter(s) <i>(indicate date(s))</i> - Review(s) <i>(indicate date(s))</i>	<u>Reviews:</u> March 10, 2017 August 16, 2017 <u>Letters:</u> August 17, 2017 July 7, 2017 March 15, 2017 December 30, 2016
❖ Labeling reviews <i>(indicate dates of reviews)</i>	RPM: ☐ None - January 19, 2017 DMEPA: ☐ None August 9, 2017 May 24, 2017 May 11, 2017 DMPP/PLT (DRISK): ☒ None OPDP: ☐ None September 26, 2017 SEALD: ☒ None CSS: ☐ None - See Final Review August 8, 2017 Product Quality ☐ None See Final OPQ Review MHT: ☒ None August 18, 2017
Administrative / Regulatory Documents	

❖ RPM Filing Review ⁴ /Memo of Filing Meeting (<i>indicate date of each review</i>)	January 25, 2017
❖ All NDA 505(b)(2) Actions: Date each action cleared by 505(b)(2) Clearance Committee	☐ Not a (b)(2) September 11, 2017
❖ NDAs/NDA supplements only: Exclusivity Summary (<i>signed by Division Director</i>)	☒ Completed (Do not include)
❖ Application Integrity Policy (AIP) Status and Related Documents http://www.fda.gov/ICECI/EnforcementActions/ApplicationIntegrityPolicy/default.htm	
• Applicant is on the AIP	☐ Yes ☒ No
• This application is on the AIP	☐ Yes ☒ No
○ If yes, Center Director's Exception for Review memo (<i>indicate date</i>)	
○ If yes, OC clearance for approval (<i>indicate date of clearance communication</i>)	☐ Not an AP action
❖ Pediatrics (<i>approvals only</i>)	
• Date reviewed by PeRC <u>August 9, 2017</u> If PeRC review not necessary, explain: _____	PeRC Meeting August 9, 2017
❖ Breakthrough Therapy Designation	☒ N/A
• Breakthrough Therapy Designation Letter(s) (granted, denied, an/or rescinded)	
• CDER Medical Policy Council Breakthrough Therapy Designation Determination Review Template(s) (<i>include only the completed template(s) and not the meeting minutes</i>)	
• CDER Medical Policy Council Brief – Evaluating a Breakthrough Therapy Designation for Rescission Template(s) (<i>include only the completed template(s) and not the meeting minutes</i>) (<i>completed CDER MPC templates can be found in DARRTS as clinical reviews or on the MPC SharePoint Site</i>)	
❖ Outgoing communications: letters, emails, and faxes considered important to include in the action package by the reviewing office/division (e.g., clinical SPA letters, RTF letter, Formal Dispute Resolution Request decisional letters, etc.) (<i>do not include OPDP letters regarding pre-launch promotional materials as these are non-disclosable; do not include Master File letters; do not include previous action letters, as these are located elsewhere in package</i>)	Included
❖ Internal documents: memoranda, telecons, emails, and other documents considered important to include in the action package by the reviewing office/division (e.g., Regulatory Briefing minutes, Medical Policy Council meeting minutes)	Included
❖ Minutes of Meetings	
• If not the first review cycle, any end-of-review meeting (<i>indicate date of mtg</i>)	☒ N/A or no mtg
• Pre-NDA/BLA meeting (<i>indicate date of mtg</i>)	☐ No mtg July 14, 2015
• EOP2 meeting (<i>indicate date of mtg</i>)	☒ No mtg
• Mid-cycle Communication (<i>indicate date of mtg</i>)	☒ N/A
• Late-cycle Meeting (<i>indicate date of mtg</i>)	☒ N/A
• Other milestone meetings (e.g., EOP2a, CMC focused milestone meetings) (<i>indicate dates of mtgs</i>)	August 20, 2013 January 29, 2015

⁴ Filing reviews for scientific disciplines are NOT required to be included in the action package.

❖ Advisory Committee Meeting(s)	☒ No AC meeting
• Date(s) of Meeting(s)	
Decisional and Summary Memos	
❖ Office Director Decisional Memo (<i>indicate date for each review</i>)	☒ None
Division Director Summary Review (<i>indicate date for each review</i>)	☐ None December 14, 2017
Cross-Discipline Team Leader Review (<i>indicate date for each review</i>)	☒ None See Deputy Director Summary Review
PMR/PMC Development Templates (<i>indicate total number</i>)	☐ None Nine PMR templates
Clinical	
❖ Clinical Reviews	
• Clinical Team Leader Review(s) (<i>indicate date for each review</i>)	☒ No separate review
• Clinical review(s) (<i>indicate date for each review</i>)	Final: Filing: January 19, 2017
• Social scientist review(s) (if OTC drug) (<i>indicate date for each review</i>)	☒ None
❖ Financial Disclosure reviews(s) or location/date if addressed in another review OR If no financial disclosure information was required, check here ☐ and include a review/memo explaining why not (<i>indicate date of review/memo</i>)	See Final Clinical Review
❖ Clinical reviews from immunology and other clinical areas/divisions/Centers (<i>indicate date of each review</i>) ⁵	☐ None QT-IRT Review: April 24, 2017
❖ Controlled Substance Staff review(s) and Scheduling Recommendation (<i>indicate date of each review</i>)	☐ N/A Final – August 8, 2017 Filing – February 7, 2017 and January 25, 2017
❖ Risk Management - REMS Documents and REMS Supporting Document (<i>indicate date(s) of submission(s)</i>) - REMS Memo(s) and letter(s) (<i>indicate date(s)</i>) - Risk management review(s) and recommendations (including those by OSE and CSS) (<i>indicate date of each review and indicate location/date if incorporated into another review</i>)	N/A N/A ☒ None
❖ OSI Clinical Inspection Review Summary(ies) (<i>include copies of OSI letters to investigators</i>)	☐ None requested Summary Review: July 26, 2017 Letters: June 28, 2017
Clinical Microbiology ☒ None	
❖ Clinical Microbiology Team Leader Review(s) (<i>indicate date for each review</i>)	☐ No separate review
Clinical Microbiology Review(s) (<i>indicate date for each review</i>)	☐ None
Biostatistics ☐ None	
❖ Statistical Division Director Review(s) (<i>indicate date for each review</i>)	☒ No separate review
Statistical Team Leader Review(s) (<i>indicate date for each review</i>)	☒ No separate review
Statistical Review(s) (<i>indicate date for each review</i>)	☐ None Final: September 7, 2017

⁵ For Part 3 combination products, all reviews from the reviewing Center(s) should be entered into the official archive (for further instructions, see “Section 508 Compliant Documents: Process for Regulatory Project Managers” located in the CST electronic repository).

		Filing: January 13, 2017
Clinical Pharmacology ☐ None		
❖ Clinical Pharmacology Division Director Review(s) <i>(indicate date for each review)</i>	☒ No separate review	
Clinical Pharmacology Team Leader Review(s) <i>(indicate date for each review)</i>	☒ No separate review	
Clinical Pharmacology review(s) <i>(indicate date for each review)</i>	☐ None Final: August 18, 2017 Filing: January 18, 2017	
❖ OSI Clinical Pharmacology Inspection Review Summary <i>(include copies of OSI letters)</i>	☐ None requested	
Nonclinical ☐ None		
❖ Pharmacology/Toxicology Discipline Reviews		
• ADP/T Review(s) <i>(indicate date for each review)</i>	☒ No separate review	
• Supervisory Review(s) <i>(indicate date for each review)</i>	☒ No separate review	
• Pharm/tox review(s), including referenced IND reviews <i>(indicate date for each review)</i>	☐ None Final – December 7, 2017 Filing – January 20, 2017	
❖ Review(s) by other disciplines/divisions/Centers requested by P/T reviewer <i>(indicate date for each review)</i>	☒ None	
❖ Statistical review(s) of carcinogenicity studies <i>(indicate date for each review)</i>	☒ No carc	
❖ ECAC/CAC report/memo of meeting	☒ None Included in P/T review, page	
❖ OSI Nonclinical Inspection Review Summary <i>(include copies of OSI letters)</i>	☒ None requested	
Product Quality ☐ None		
❖ Product Quality Discipline Reviews ⁶		
• Tertiary review <i>(indicate date for each review)</i>	☒ None	
• Secondary review (e.g., Branch Chief) <i>(indicate date for each review)</i>	☒ None	
• Integrated Quality Assessment (contains the Executive Summary and the primary reviews from each product quality review discipline) <i>(indicate date for each review)</i>	☐ None Final IQA – October 30, 2017 Filing – January 23, 2017 Micro Filing – January 3, 2017	
❖ Reviews by other disciplines/divisions/Centers requested by product quality review team <i>(indicate date of each review)</i>	☒ None	
❖ Environmental Assessment (check one) (original and supplemental applications)		
☒ Categorical Exclusion <i>(indicate review date)(all original applications and all efficacy supplements that could increase the patient population)</i>	(See Final CMC Review - October 30, 2017)	
☐ Review & FONSI <i>(indicate date of review)</i>		
☐ Review & Environmental Impact Statement <i>(indicate date of each review)</i>		

⁶ Do not include Master File (MF) reviews or communications to MF holders. However, these documents should be made available upon signatory request.

❖ Facilities Review/Inspection	
☒ Facilities inspections (indicate date of recommendation; within one week of taking an approval action, confirm that there is an acceptable recommendation before issuing approval letter) (<i>only original applications and efficacy supplements that require a manufacturing facility inspection(e.g., new strength, manufacturing process, or manufacturing site change)</i>)	☒ Acceptable (See Final CMC Review - October 30, 2017) ☐ Withhold recommendation ☐ Not applicable

Day of Approval Activities	
❖ For all 505(b)(2) applications: Check Orange Book for newly listed patents and/or exclusivity (including pediatric exclusivity)	☒ No changes ☐ New patent/exclusivity <i>(Notify CDER OND IO)</i>
Finalize 505(b)(2) assessment	☒ Done
❖ For Breakthrough Therapy (BT) Designated drugs: Notify the CDER BT Program Manager	☐ Done N/A <i>(Send email to CDER OND IO)</i>
❖ For products that need to be added to the flush list (generally opioids): Flush List Notify the Division of Online Communications, Office of Communications	☐ Done N/A
❖ Send a courtesy copy of approval letter and all attachments to applicant by fax or secure email	☒ Done
❖ If an FDA communication will issue, notify Press Office of approval action after confirming that applicant received courtesy copy of approval letter	☒ Done
❖ Ensure that proprietary name, if any, and established name are listed in the <i>Application Product Names</i> section of DARRTS, and that the proprietary name is identified as the “preferred” name	☒ Done
❖ Ensure Pediatric Record is accurate	☒ Done
❖ Send approval email within one business day to CDER-APPROVALS	☒ Done
❖ Take Action Package (if in paper) down to Document Room for scanning within two business days	

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/s/

DIANA L WALKER
12/14/2017

From: [Walker, Diana](#)
To: [Melissa Goodhead](#) (b) (4)
Subject: NDA 209963 Labeling Comments 12Dec17
Date: Tuesday, December 12, 2017 8:27:17 AM
Attachments: [Draft PI label for NDA 209963-FDA edits - 12Dec17.docx](#)
Importance: High

Dear Melissa,

Please find attached the package insert label in track changes for NDA 209963, containing edits and comments in response to your proposed labeling.

Please review this document, and:

1. Accept the changes with which you agree. You can also respond to the balloon comments with your response by adding your own balloon comment. If you accept the change and have no responses, you can delete those comment bubbles from the Agency.
2. Make revisions (**in track-changes!!**) and add a rationale comment for any language with which you do not agree (the rationale can be added as a comment balloon).
3. Please check for the accuracy of the cross references, TOC, etc.
4. Please check for any formatting or typographical errors and make those corrections.

Please return the label to me via email only. The label you send back should be in track-changes with only the new edits you have added (per #1 above, accept all the track changes you agree with) and the comment bubbles. There is no need to submit formally to your NDA at this time, as there may be additional negotiation of the language before the action date. If you could review this label and return your comments **if at all possible by tomorrow, Wednesday, December 13 or as soon after that as possible**, so that we can keep the process moving as quickly as possible to finalize the label.

Kindly acknowledge receipt of this email.

Warm regards,

Diana

Diana L. Walker, Ph.D.
Sr. Regulatory Health Project Manager
FDA/CDER/ODE II/DAAAP
Tel: 301-796-4029
Email: Diana.Walker@fda.hhs.gov

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/s/

DIANA L WALKER
12/13/2017

From: [Walker, Diana](#)
To: [Melissa Goodhead](#) (b) (4)
Subject: NDA 209963 Labeling Information Request 07dec17
Date: Thursday, December 07, 2017 11:23:36 AM
Attachments: [Carton and Container Final.pdf](#)
Importance: High

Dear Melissa,

Given that your proprietary name was conditionally approved, please resubmit your draft labels with the new name as soon as possible, or by no later than Tuesday, December 12, 2017.

I have attached your current labels for reference, but in the place of Cocaine Hydrochloride Topical Solution, insert this in the container label and carton: **GOPRELTO (cocaine hydrochloride) nasal solution.**

Warm regards,

Diana

Diana L. Walker, Ph.D.
Sr. Regulatory Health Project Manager
FDA/CDER/ODE II/DAAAP
Tel: 301-796-4029
Email: Diana.Walker@fda.hhs.gov

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/s/

DIANA L WALKER
12/13/2017

From: [Walker, Diana](#)
To: [Melissa Goodhead](#) (b) (4)
Subject: NDA 209963 Labeling Comments draft 30Nov17
Date: Thursday, November 30, 2017 10:15:33 AM
Attachments: [draft NDA 209963 PI label to GLS 30Nov17.docx](#)
Importance: High

Dear Melissa,

Please find attached the package insert label in track changes for NDA 209963, containing edits and comments in response to your proposed labeling.

Please review this document, and:

1. Accept the changes with which you agree. You can also respond to the balloon comments with your response by adding your own balloon comment. If you accept the change and have no responses, you can delete those comment bubbles from the Agency.
2. Make revisions (**in track-changes!!**) and add a rationale comment for any language with which you do not agree (the rationale can be added as a comment balloon).
3. Please check for the accuracy of the cross references, TOC, etc.
4. Please check for any formatting or typographical errors and make those corrections.

Please return the label to me via email only. The label you send back should be in track-changes with only the new edits you have added (per #1 above, accept all the track changes you agree with) and the comment bubbles. There is no need to submit formally to your NDA at this time, as there may be additional negotiation of the language before the action date. If you could review this label and return your comments **if at all possible by Tuesday, December 5 or as soon after that as possible**, so that we can keep the process moving as quickly as possible to finalize the label. Note that, the Maternal Health Team requested a reference for a statement in Section 8.1. If it will take longer to retrieve that reference, go ahead and send your edited label in advance and you can follow with the reference in a few days after, if that would be helpful in expediting your review and return of the edited label.

Kindly acknowledge receipt of this email, and please provide an estimated date by which you will return the document with your edits and comments.

Warm regards,

Diana

Diana L. Walker, Ph.D.
Sr. Regulatory Health Project Manager
FDA/CDER/ODE II/DAAAP
Tel: 301-796-4029

Email: Diana.Walker@fda.hhs.gov

APPEARS THIS WAY ON ORIGINAL

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/s/

DIANA L WALKER
12/04/2017

From: [Walker, Diana](#)
To: [Melissa Goodhead](#) (b) (4)
Subject: NDA 209963 Nonclinical Information Request 03Nov17
Date: Friday, November 03, 2017 10:25:49 AM
Importance: High

Dear Melissa,

I have received the following nonclinical request for information. Given our short timeline, please submit a response as soon as possible.

1. Although you have provided 14-day intranasal toxicity data in support of the proposed specification for the drug substance impurity (b) (4) which exceeds ICH Q3A(R2) qualification thresholds, the studies do not include full histopathology and the (b) (4). As such, we are unable to concur with the proposed specification for systemic safety based on our understanding of the information submitted to the NDA to date. To adequately address the systemic safety of (b) (4) provide histopathological data for the full standard set of tissues in a 14-day toxicology study.
2. We acknowledge that you have previously submitted a literature-based safety justification for (b) (4) to the IND as part of a meeting package. Submit your safety justification for (b) (4) and copies of all referenced citations to the NDA.
3. The existing in vivo comet assay for (b) (4) suggested a positive response in this assay. We note that the response was apparently within the historical control range, but is higher than the concurrent vehicle control data. Given the inherent potential for variability in this assay due to tissue collection experience, provide historical control data, if available, for recent comet assays conducted by that laboratory and specifically address the range and incidence of control values that define the upper range of the curve.
4. The NDA does not currently include the literature citations that you referenced during the IND stage of development to complete the standard battery of genetic toxicology studies for cocaine. Submit these references to the NDA and update the literature summaries accordingly.
5. We are unable to identify the literature references supporting your statement that cocaine accumulates in rat milk. Provide these references or identify where in the current NDA submission these references are located.

Warm regards,

Diana

Diana L. Walker, Ph.D.
Sr. Regulatory Health Project Manager
FDA/CDER/ODE II/DAAAP
Tel: 301-796-4029
Email: Diana.Walker@fda.hhs.gov

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/s/

DIANA L WALKER
11/17/2017

From: Steven Kinsley
To: (b) (4)
Cc: Diana Walker
Subject: NDA 209963 CMC Information Request 10-17-17
Date: October 17, 2017

Dear Melissa,

I have received the following information request from our CMC review team. Please respond to the following with a submission to your NDA by Thursday, October 19, 2017. Also, please verify receipt of this Information Request via return e-mail.

Drug Product

1. Tighten the (b) (4) in the drug product specification to (b) (4) % of the concentration in the formulation, so that it would be (b) (4) %. Update the specification tables to reflect this spec.

If you have any questions, contact me.
Best Regards,
Steve

Steven Kinsley, Ph.D.
Regulatory Business Process Manager

Office of Program and Regulatory Operations
U.S. Food and Drug Administration
Tel: 240-402-2773
Steven.Kinsley@fda.hhs.gov





Steven
Kinsley

Digitally signed by Steven Kinsley

Date: 10/17/2017 02:11:43PM

GUID: 555cc3bc000836e194b17e8bf695ce5f

From: [Walker, Diana](#)
To: [Melissa Goodhead](#) (b) (4)
Subject: NDA 209963 Pediatric Information Request and request for teleconference 02Oct17
Date: Monday, October 02, 2017 9:47:19 AM
Importance: High

Dear Melissa,

We have met with the Pediatric Review Committee regarding your proposed pediatric study plan, from which we will derive postmarketing PREA studies. During that meeting, we were advised to shorten the milestone dates and potentially overlap or consolidate studies. After reviewing your proposed studies in order to shorten the milestone dates, we have the following requests for information and clarification. We would like to schedule a teleconference to discuss the following points. Please respond prior to the teleconference so that we can have a productive meeting.

(b) (4)

2. Provide additional details regarding the proposed formulation, including the proposed concentration and how it was selected. If there are any proposed changes to the excipients in the pediatric formulation, they may need to be tested in animals prior to initiation of any pediatric clinical studies.

3. As discussed in the FDA guidance for industry *Analgesic Indications: Developing Drug and Biologic Products (2014)*, the cutoff for extrapolation of efficacy for pediatric subjects down to the age of 2 years may be appropriate. This recommendation is based on systemic exposure, and because cocaine HCl is a topically-administered local anesthetic, the age cutoff in the guidance may not be applicable. There may be data or rationale to support adjustment of this age cutoff.

4. Provide a status update on the protocol development for the animal studies.

We have the following time available for a teleconference: October 12, 2017; 3:30 – 4:00 pm (Eastern). Please let me know if this will work for your team, and kindly provide a call-in number.

Warm regards,

Diana

Diana L. Walker, Ph.D.
Sr. Regulatory Health Project Manager

FDA/CDER/ODE II/DAAAP
Tel: 301-796-4029
Email: Diana.Walker@fda.hhs.gov

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/s/

DIANA L WALKER
10/02/2017

From: [Walker, Diana](#)
To: [Melissa Goodhead](#) (b) (4)
Subject: NDA 209963 Labeling Comments draft 02Oct17
Date: Monday, October 02, 2017 2:51:17 PM
Attachments: [NDA 209963 Draft Label to Genus 02Oct17.docx](#)

Dear Melissa,

Please find attached the package insert label in track changes, containing edits and comments in response to your proposed labeling. Please note that this is a work in progress "version 1" only, and that these are not the final comments from FDA. As previously conveyed, the labeling is still pending comments from nonclinical (therefore they will likely revise Sections 8 and 13 again) and final review and comment from management. So although we have provided substantial comments, there will likely be additional comments made after we receive your revised version back.

Please review this document, and:

1. Accept the changes with which you agree. You can also respond to the balloon comments with your response by adding your own balloon comment.
2. Make revisions (in track-changes!!) and add a rationale comment for any language with which you do not agree (the rationale can be added as a comment balloon).
3. Please check for the accuracy of the cross references.
4. Please check for any formatting or typographical errors and make those corrections.

Please return the label to me via email only. The label you send back should be in track-changes with only the new edits you have added (per #1 above, accept all of the track changes you agree with) and the comment bubbles. There is no need to submit formally to your NDA at this time, as there will be additional negotiation of the language before the action date. If you could review this label and return your comments as soon as possible it would be appreciated so that the nonclinical team can begin to add their comments to the label as soon as they have finalized their review of the studies submitted prior to the clock extension.

Kindly acknowledge receipt of this email, and please provide an estimated date by which you will return the document with your edits and comments.

Warm regards,

Diana

Diana L. Walker, Ph.D.
Sr. Regulatory Health Project Manager
FDA/CDER/ODE II/DAAAP
Tel: 301-796-4029
Email: Diana.Walker@fda.hhs.gov

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/s/

DIANA L WALKER
11/17/2017



NDA 209963

**PROPRIETARY NAME REQUEST
CONDITIONALLY ACCEPTABLE**

Genus Lifesciences Inc.
11705 Boyette Road Suite 171
Riverview, FL 33569

ATTENTION: Melissa L. Goodhead, MSc, RAC
Regulatory Agent for Genus Lifesciences, Inc.

Dear Ms. Goodhead:

Please refer to your New Drug Application (NDA) dated and received November 23, 2016, submitted under section 505(b)(2) of the Federal Food, Drug, and Cosmetic Act for Cocaine Hydrochloride Topical Solution, 4%.

We also refer to your correspondence, dated and received June 26, 2017, requesting review of your proposed proprietary name, Goprelto.

We have completed our review of the proposed proprietary name, Goprelto and have concluded that it is conditionally acceptable.

If any of the proposed product characteristics as stated in your June 26, 2017, submission are altered prior to approval of the marketing application, the proprietary name should be resubmitted for review. Additionally, if your application receives a complete response, a new request for name review for your proposed name should be submitted when you respond to the application deficiencies.

If you require information on submitting requests for proprietary name review or PDUFA performance goals associated with proprietary name reviews, we refer you to the following:

- Guidance for Industry Contents of a Complete Submission for the Evaluation of Proprietary Names
(<http://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/UCM075068.pdf>)
- PDUFA Reauthorization Performance Goals and Procedures Fiscal Years 2013 through 2017,
(<http://www.fda.gov/downloads/ForIndustry/UserFees/PrescriptionDrugUserFee/UCM270412.pdf>)

If you have any questions regarding the contents of this letter or any other aspects of the proprietary name review process, contact Davis Mathew, Safety Regulatory Project Manager in the Office of Surveillance and Epidemiology, at (240) 402-4559. For any other information regarding this application, contact Diana L. Walker, Regulatory Project Manager in the Office of New Drugs, at (301) 796-4029.

Sincerely,

{See appended electronic signature page}

Todd Bridges, RPh
Director
Division of Medication Error Prevention and Analysis
Office of Medication Error Prevention and Risk Management
Office of Surveillance and Epidemiology
Center for Drug Evaluation and Research

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/s/

DANIELLE M HARRIS on behalf of TODD D BRIDGES
08/17/2017



NDA 209963

**REVIEW EXTENSION –
MAJOR AMENDMENT**

Genus Lifesciences, Inc.
514 North 12th Street
Allentown, PA 18102

Attention: William Reightler
Vice President of Regulatory Affairs

Dear Mr. Reightler:

Please refer to your New Drug Application (NDA) dated and received November 23, 2016, submitted pursuant to section 505(b)(2) of the Federal Food, Drug, and Cosmetic Act (FDCA), for Cocaine Hydrochloride Topical Solution, 4%.

On July 31, 2017, we received your major amendment to this application. Therefore, we are extending the goal date by three months to provide time for a full review of the submission. The extended user fee goal date is December 23, 2017.

In addition, we are establishing a new timeline for communicating labeling changes and/or postmarketing requirements/commitments in accordance with “PDUFA Reauthorization Performance Goals and Procedures – Fiscal Years 2013 through 2017.” If major deficiencies are not identified during our review, we plan to communicate proposed labeling and, if necessary, any postmarketing requirement/commitment requests by November 25, 2017.

If you have any questions, call Diana L. Walker, PhD, Regulatory Project Manager, at (301) 796-4029.

Sincerely,

{See appended electronic signature page}

Sharon Hertz, MD
Director
Division of Anesthesia, Analgesia, and
Addiction Products
Office of Drug Evaluation II
Center for Drug Evaluation and Research

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/s/

SHARON H HERTZ
08/14/2017

From: Steven Kinsley
To: (b) (4)
Cc: Diana Walker
Subject: NDA 209963 CMC Information Request 7-28-17
Date: July 28, 2017

Dear Melissa,

I have received the following information request from our CMC review team. Please respond to the following with a submission to your NDA by Friday, August 4, 2017.

Drug Product

1. We acknowledge your response dated 11 July 2017 to an information request sent 28 June 2017. As part of the response to question 3, methods AS-TM-CH-TS-014 Assay, Related Substances and (b) (4) content and AS-TM-CH-TS-061 PDA Spectrum Identification Test include in the Equipment section 4 different HPLC systems from 3 different manufacturers. Confirm that all of the HPLCs listed in the methods have been used for the method validation.

If you have any questions, contact me. Also, please verify receipt of this Information Request via return e-mail.

Best Regards,
Steve

Steven Kinsley, Ph.D.
Regulatory Business Process Manager

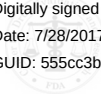
Office of Program and Regulatory Operations
U.S. Food and Drug Administration
Tel: 240-402-2773
Steven.Kinsley@fda.hhs.gov





Steven
Kinsley

Digitally signed by Steven Kinsley
Date: 7/28/2017 12:49:59PM
GUID: 555cc3bc000836e194b17e8bf695ce5f



From: [Walker, Diana](#)
To: [Melissa Goodhead](#) (b) (4)
Subject: NDA 209963 Clinical Information Request 26Jul17
Date: Wednesday, July 26, 2017 10:36:34 AM

Dear Melissa,

Please respond to the following request for information with a submission to your NDA no later than August 3, 2017.

(b) (4)
[Redacted]
[Redacted]
[Redacted]
Specifically, the exclusion criteria included the following:

Medications

- Serotonin-norepinephrine reuptake inhibitors (SNRSs) and selective serotonin-reuptake inhibitors (SSRIs)
- Monoamine oxidase inhibitors (MAOIs)
- Amphetamines, stimulant prescription and nonprescription products such as catecholamines (direct and indirect acting sympathomimetics), bronchial inhalers containing sympathomimetics (epinephrine or other beta-receptor agonists), or herbal products

Cardiac conditions

- History of myocardial infarction, coronary artery disease, congestive heart failure, or uncontrolled hypertension (defined as an average systolic blood pressure =140 mmHg or an average diastolic blood pressure =90 mmHg at the dosing visit)
- Screening 12-lead ECG had findings of any abnormalities, including current or prior myocardial infarction, dysrhythmia, or risk of serious dysrhythmia (such as prolonged QT interval)

Provide justification as to why the prohibited medications and history of specific cardiac conditions used as exclusion criteria in your Phase 3 study have not been incorporated into the relevant sections of the product label. Provide your response by the close of business on August 3, 2017.

Warm regards,

Diana

Diana L. Walker, Ph.D.
Sr. Regulatory Health Project Manager
FDA/CDER/ODE II/DAAAP
Tel: 301-796-4029
Email: Diana.Walker@fda.hhs.gov

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/s/

DIANA L WALKER
07/26/2017

Walker, Diana

From: Walker, Diana
Sent: Wednesday, July 26, 2017 10:37 AM
To: Melissa Goodhead (b) (4)
Subject: NDA 209963 Pediatric Information Request 26Jul17

Importance: High

Dear Melissa,

Please refer to your Agreed PSP, dated November 15, 2016, and to your submission of a complete set of proposed milestone dates via email on July 18, 2017. We note that, while some of the dates had not been previously specified in the PSP (draft protocol and final protocol submission and final study report), the dates that had been previously specified, such as date of study completion are substantially later than those in the Agreed PSP (please refer to the table below). Provide an explanation as to your proposed extension of the milestone timelines as compared to the Agreed PSP. Submit your response, including the table of proposed milestone dates that was previously submitted via email, to your NDA no later than August 3, 2017.



Warm regards,

Diana

Diana L. Walker, Ph.D.
Sr. Regulatory Health Project Manager
FDA/CDER/ODE II/DAAAP
Tel: 301-796-4029
Email: Diana.Walker@fda.hhs.gov

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DIANA L WALKER
07/26/2017

From: [Walker, Diana](#)
To: [Melissa Goodhead](#) (b) (4)
Subject: NDA 209963 Carton and Container comments 25Jul17
Date: Tuesday, July 25, 2017 10:48:07 AM
Importance: High

Dear Melissa,

I have received the following additional comment from our CMC review team. Please respond to these comments with a submission to your NDA of revised carton and container labels.

Container Label and Carton Labeling

In addition to 40 mg/mL, include percent strength "4%" on the carton and container labeling. We recommend placing the percent strength directly below the established name, and ensure the percent strength is prominently displayed on the principal display panel. Revise the carton and container labels to reflect these changes.

Warm regards,

Diana

Diana L. Walker, Ph.D.
Sr. Regulatory Health Project Manager
FDA/CDER/ODE II/DAAAP
Tel: 301-796-4029
Email: Diana.Walker@fda.hhs.gov

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/s/

DIANA L WALKER
07/25/2017

From: [Walker, Diana](#)
To: [Melissa Goodhead](#) (b) (4)
Subject: NDA 209963 Pediatric Information Request 14Jul17
Date: Friday, July 14, 2017 10:51:21 AM
Importance: High

Dear Melissa,

Part of the review of an NDA is an additional review at the PerC committee of your planned pediatric studies, including the milestone dates. Please send me the following proposed dates for your studies listed in your Agreed PSP:



4. Phase 4 single-dose, multicenter study of the PK, efficacy, and safety of 4% RX0041-002 as a topical nasal anesthetic in pediatric patients from 0 years to 2 years; enrollment in this study will be tiered by age.

You must include all 4 milestone dates for each study (see below). If the (b) (4) studies will be conducted at the same time, they can have the same dates, if not please provide separate dates. I also suggest that, for the time interval between the draft and final protocol submission, you allow 4 to 6 months, as it can take time to review the protocols and provide comments.

PMR Schedule Milestones

Draft Protocol Submission: MM /YYYY

Final Protocol Submission: MM /YYYY

Study/Trial Completion: MM /YYYY

Final Report Submission: MM /YYYY

Please provide me with the proposed milestone dates all of these studies via email no later than Tuesday, July 18, 2017.

Warm regards,

Diana

Diana L. Walker, Ph.D.
Sr. Regulatory Health Project Manager
FDA/CDER/ODE II/DAAAP
Tel: 301-796-4029
Email: Diana.Walker@fda.hhs.gov

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/s/

DIANA L WALKER
07/17/2017

From: [Walker, Diana](#)
To: [Melissa Goodhead](#) (b) (4)
Subject: NDA 209963 Carton and Container comments 12Jul17
Date: Wednesday, July 12, 2017 1:23:53 PM

Dear Melissa,

I have received the following comments from our CMC review team. Please respond to these comments with a submission to your NDA of revised carton and container labels.

A. Container Label and Carton Labeling

Add a base equivalency statement to the front panel of the carton and container labels. For example “Cocaine hydrochloride* xx (*equivalent to yy cocaine base). The strength must be expressed as xx mg/ml rather than as a percent. Revise the carton and container labels to reflect these changes.

Warm regards,

Diana

Diana L. Walker, Ph.D.
Sr. Regulatory Health Project Manager
FDA/CDER/ODE II/DAAAP
Tel: 301-796-4029
Email: Diana.Walker@fda.hhs.gov

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/s/

DIANA L WALKER
07/12/2017



NDA 209963

**PROPRIETARY NAME
ACKNOWLEDGEMENT**

Genus Lifesciences Inc.
11705 Boyette Road
Suite 171
Riverview, FL 33569

ATTENTION: Melissa L. Goodhead, MSc, RAC
Regulatory Agent for Genus Lifesciences Inc.

Dear Ms. Goodhead:

Please refer to your New Drug Application (NDA) dated and received November 23, 2016, submitted under section 505(b)(2) of the Federal Food, Drug, and Cosmetic Act for Cocaine Hydrochloride Topical Solution, 4%.

We acknowledge receipt of your correspondence, dated and received June 26, 2017, requesting a review of your proposed proprietary name, Goprelto.

The user fee goal date is September 24, 2017.

If you have any questions regarding the contents of this letter or any other aspects of the proprietary name review process, contact Davis Mathew, Safety Regulatory Project Manager in the Office of Surveillance and Epidemiology, at (240) 402-4559. For any other information regarding this application, contact Diana Walker, Regulatory Project Manager, in the Office of New Drugs at (301) 796-4029.

Sincerely,

{See appended electronic signature page}

Davis Mathew, PharmD
Safety Regulatory Project Manager
Office of Surveillance and Epidemiology
Center for Drug Evaluation and Research

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/s/

DAVIS MATHEW
07/07/2017



DEPARTMENT OF HEALTH AND HUMAN SERVICES

Food and Drug Administration
Silver Spring MD 20993

NDA 209963

INFORMATION REQUEST

Genus Lifesciences, Inc.
Attention: Melissa L. Goodhead
Authorized US Agent
11705 Boyette Road, Suite 171
Riverview, FL 33569

Dear Ms. Goodhead:

Please refer to your New Drug Application (NDA) dated November 23, 2016, submitted under section 505(b) (2) of the Federal Food, Drug, and Cosmetic Act for Cocaine Hydrochloride Topical Solution, 4%.

We are reviewing the Chemistry, Manufacturing and Controls section of your submission and have the following comments and information requests. We request a written response by **Tuesday, July 11, 2017**, in order to continue our evaluation of your NDA.

1. The certificates of analysis provided in Module 3.2.P.5.4 Batch Analysis do not contain Related Substances testing. Related Substances testing must be performed at release and on stability. Resubmit the batch analysis data and certificate of analyses with Related Substances results.
2. According to AS-MVR-CH-TS-078 "Assay, Related Substances, Preservative Content, Identification A: HPLC and Identification B: HPLC (PDA)" method validation, it appears as though Accuracy and Precision (repeatability, intermediate precision) data are not provided for cocaine hydrochloride at the concentration used in the related substances method. This data is required as part of the validation for this method. Update the validation report to include this data.
3. Methods AS-TM-CH-TS-014 Assay, Related Substances and (b) (4) content and AS-TM-CH-TS-061 PDA Spectrum Identification Test include in the Equipment section a requirement for an HPLC with a solvent delivery system, detector and autosampler. Considering which manufacturer (b) (4) was used in the method validation of the individual method, provide the specific HPLC instrument used in all HPLC methods.

If you have any questions, please contact Dr. Steven Kinsley, Regulatory Business Process Manager, at (240) 402-2773, or LCDR Luz E Rivera at (301) 796-4013.

Sincerely,

{See appended electronic signature page}

(LCDR Rivera for)
Steven Kinsley, Ph.D.
Regulatory Business Process Manager
Office of Program and Regulatory Operations
Office of Pharmaceutical Quality
Center for Drug Evaluation and Research



Luz
Rivera

Digitally signed by Luz Rivera
Date: 6/28/2017 10:57:05AM
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DEPARTMENT OF HEALTH & HUMAN SERVICES

Food and Drug Administration
Silver Spring, MD 20993

Sent: 06/28/2017 03:37:42 PM

To: [REDACTED] (b) (4)

CC: luz.e.rivera@fda.hhs.gov; Steven.Kinsley@fda.hhs.gov

BCC:

Subject: INFORMATION REQUEST NDA 209963

NDA 209963

INFORMATION REQUEST

Genus Lifesciences, Inc.
Attention: Melissa L. Goodhead
Authorized US Agent
11705 Boyette Road, Suite 171
Riverview, FL 33569

Dear Ms. Goodhead:

Please refer to your New Drug Application (NDA) dated November 23, 2016, submitted pursuant to section 505(b)(2) of the Federal Food, Drug, and Cosmetic Act for Cocaine Hydrochloride Topical Solution, 4%.

Please find attached the Product Quality team information requests.

We request a written response by July 11, 2017. Please provide your response via email followed by an official submission to the NDA.

We request that you acknowledge this communication upon receipt.

Best regards,
LCDR Luz E Rivera, Psy.D.
Quality Assessment Lead (Acting), Div. I, Branch I
Office of Program and Regulatory Operations
Office of Pharmaceutical Quality

Center for Drug Evaluation and Research

APPEARS THIS WAY ON ORIGINAL

From: [Walker, Diana](#)
To: [Melissa Goodhead](#)
Subject: NDA 209963 Statistics Information Request 02Jun17
Date: Friday, June 02, 2017 1:17:46 PM

Dear Melissa,

I have received the following information request from our statistics review team. Please respond with a submission to your NDA as soon as possible.

According to the document submitted on May 1, 2017, (sequence 0014) and the dataset “time.xpt” submitted on May 9, 2017, (sequence 0016), some subjects in Study 2013011 were unblinded before the Von Frey filament test and for many subjects, the time of unblinding was at the same as the time of Von Frey filament test. Explain why this occurred and address its impact on the subsequent study conduct.

Warm regards,

Diana

Diana L. Walker, Ph.D.
Sr. Regulatory Health Project Manager
FDA/CDER/ODE II/DAAAP
Tel: 301-796-4029
Email: Diana.Walker@fda.hhs.gov

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DIANA L WALKER
06/02/2017

From: [Walker, Diana](#)
To: [Melissa Goodhead](#) (b) (4)
Subject: NDA 209963 Clinical Information Request 17May17
Date: Wednesday, May 17, 2017 9:24:57 AM
Importance: High

Dear Melissa,

I have received the following information request from our Clinical review team. Please respond with an email by the requested date, followed by a submission to your NDA as soon as possible.

It appears that the clinical summaries submitted to your NDA on May 1, 2017, contain several unprompted text additions and deletions that have not been adequately explained and cannot be assumed to be related to the data transposition error that was discovered on April 4, 2017. Four examples of such changes are as follows:

- 1. On page 17 of the PDF version of Clinical Overview – Tracked Changes, section 4.2 Efficacy Endpoint, second bullet, you have deleted the following text (red) without explanation:**

Had no need for further medication (with the exception of antibiotics or cardiac medications) during the diagnostic procedure or surgery ~~as determined by the investigator/physician based upon his/her clinical impressions of the presence of pain or excessive bleeding~~

- 2. On page 33 of the PDF version of Clinical Safety – Tracked Changes, section 2.2 Frequent Adverse Events, you have deleted the following text without explanation:**

... no subjects in the placebo group; ~~anxiety by 0.5% of subjects in the 4% RX0041-002 group and no subjects in the placebo group;~~

- 3. On page 51 of the PDF version of Clinical Safety – Tracked Changes, section 7.3 Drug Interactions, you have added the following text without explanation:**

In addition, it has been demonstrated that cocaine does not inhibit P-gp or BCRP in vitro at concentrations up to 100 µM [Tournier et al, 2010].

- 4. On page 10 of the PDF version of Clinical Efficacy – Tracked Changes, section 1.5 Efficacy Assessments, you have added the following text without explanation:**

Evaluation of procedural medications confirmed that, for almost all subjects, the pain control attained with cocaine allowed for completion of the surgical procedures without additional medication.

We request that you submit annotated documents, including explanations, for all text

edits that have been made but are unrelated to the data transposition error. We request these documents by the close of business on Monday, June 5, 2017.

Kindly acknowledge receipt of this email.

Warm regards,

Diana

Diana L. Walker, Ph.D.
Sr. Regulatory Health Project Manager
FDA/CDER/ODE II/DAAAP
Tel: 301-796-4029
Email: Diana.Walker@fda.hhs.gov

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DIANA L WALKER
05/17/2017

From: [Walker, Diana](#)
To: [Melissa Goodhead](#) (b) (4)
Subject: NDA 209963 Carton and Container comments 12May17
Date: Friday, May 12, 2017 8:55:02 AM

Dear Melissa,

I have received the following comments from our DMEPA labeling review team. Please respond to these comments with a submission to your NDA of revised carton and container labels.

A. Container Label and Carton Labeling

- 1. Revise the statement 'Not for Injection or Ophthalmic Use' on the principal display panel to 'For Topical Use Only. Not for Injection or Ophthalmic Use'. We have received post-marketing reports that negative statements (e.g. Not for) without a preceding positive statement may be read accidentally as the opposite of the intended meaning. The reader can overlook the word 'not', and interpret the statement as an affirmative statement.**
- 2. We recommend you include the package type 'single-use' on the principal display panel to inform users the bottle is for a single administration.**

B. Carton Labeling

- 1. Revise the font size of the dosage form statement 'Topical Solution' on the principal display panel to a larger font. A larger font size will increase the prominence of this important information.**

In addition, I wanted to remind you to submit updated package insert labeling to reflect your revised data tables and results due to the data transposition.

Warm regards,

Diana

Diana L. Walker, Ph.D.
Sr. Regulatory Health Project Manager
FDA/CDER/ODE II/DAAAP
Tel: 301-796-4029
Email: Diana.Walker@fda.hhs.gov

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/s/

DIANA L WALKER
05/17/2017



DEPARTMENT OF HEALTH AND HUMAN SERVICES

Food and Drug Administration
Silver Spring MD 20993

NDA 209963

**ACKNOWLEDGE CORPORATE
NAME CHANGE**

Genus Lifesciences, Inc.
514 North 12th Street
Allentown, PA 18102

Attention: William Reightler
Vice President of Regulatory Affairs

Dear Mr. Reightler:

We acknowledge your correspondence dated and received May 10, 2017, notifying the Food and Drug Administration (FDA) that the corporate name and/or address has been changed from



Genus Lifesciences, Inc.
514 North 12th Street
Allentown, PA 18102

for the following new drug application:
NDA 209963 for Cocaine Hydrochloride Topical Solution, 4%.

We have revised our records to reflect this change.

If your NDA references any Drug Master Files (DMF), we request that you notify your suppliers and contractors who have DMFs referenced by your NDA of the change so that they can submit a new letter of authorization (LOA) to their DMFs and send you a copy of the new LOAs. Please submit these copies of the LOAs to this NDA.

Please cite the NDA number listed above at the top of the first page of all submissions to this application. Send all submissions, electronic or paper, including those sent by overnight mail or courier, to the following address:

Food and Drug Administration
Center for Drug Evaluation and Research
Division of Anesthesia, Analgesia, and Addiction Products
5901-B Ammendale Road
Beltsville, MD 20705-1266

If you have any questions, call me at (301) 796-4029.

Sincerely,

{See appended electronic signature page}

Diana L. Walker, PhD
Sr. Regulatory Health Project Manager
Division of Anesthesia, Analgesia, and
Addiction Products
Office of Drug Evaluation II
Center for Drug Evaluation and Research

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/s/

DIANA L WALKER

05/11/2017

From: [Walker, Diana](#)
To: [Melissa Goodhead](#)
Subject: Response to request for feedback: Follow-up to Nonclinical Call 05May17
Date: Friday, May 05, 2017 9:28:35 AM

Dear Melissa,

I have received the following response for feedback regarding dose selection:

The Division agrees with your proposal (b) (4)

Warm regards,

Diana

From: Melissa Goodhead (b) (4)
Sent: Tuesday, May 02, 2017 2:47 PM
To: Walker, Diana
Subject: Follow-up to Nonclinical Call

Hi Diana:

As a follow-up to the teleconference on April 18, 2017 between (b) (4) and the Division where the study designs for the (b) (4) rat studies were discussed, we are providing preliminary data from the 2-week intranasal vehicle study, data from solubility/stability testing with different formulations that was ongoing at that time, and a request for feedback on the dose selection for the upcoming 2-week intranasal qualification study in rats (b) (4)

Briefly, the study design for the (b) (4) rat study contains both a single- and a repeat-dose arm. For the single-dose portion of the study, half of the animals will be necropsied 24-hours after the dose while the other half of the animals will be necropsied after a 14-day postdose period. For the repeat-dose phase of the study, half of the animals will be evaluated after 14 days of dosing while the other half of animals will be evaluated following a 14-day postdose period. The study includes clinical pathology evaluations and histologic evaluation limited to the nasal turbinates (6 cross sections/rat). Dose selection will be as described below.

1. Preliminary data from the 2-week intranasal vehicle study in rats demonstrates the following:

Vehicle	Findings
Deionized (DI) water	Unilateral foreign body in lumen nasal level II and associated minimal neutrophilic infiltrate in the squamous epithelium of 1 animal; likely an incidental finding related to treatment procedure and not water.

10% ethanol (14 days)	No findings
20% ethanol (14 days)	Nasal Level II: 1 animal with bilateral minimal squamous metaplasia
40% ethanol (14 days)	Nasal Level II: minimal to moderate squamous metaplasia, moderate degeneration of respiratory epithelium (1 animal), minimal neutrophilic infiltrate (1 animal). Nasal Level III: minimal to mild degeneration of the respiratory epithelium and minimal to mild infiltrates of the squamous or respiratory epithelium; and findings in single animals included: moderate ulceration of respiratory epithelium, minimal degeneration of the transitional epithelium, minimal atrophy of olfactory epithelium, mild transitional metaplasia of epithelium, and minimal mucous cell hyperplasia. Nasal Level IV: minimal to marked degeneration of respiratory epithelium and mild degeneration of olfactory epithelium (1 animal). Nasal Level V: minimal degeneration of respiratory epithelium (1 animal).
20% ethanol (single dose)	Day 2 Necropsy: minimal unilateral neutrophilic infiltrate of the respiratory epithelium (1 animal; nasal level III). Day 15 Necropsy: minimal degeneration of olfactory epithelium (1 animal; nasal level IV).

2. Solubility Information:

A series of studies were conducted to determine the maximum feasible concentration that could be prepared using (b) (4) in different diluents. These studies were designed to generate supersaturated solutions (data not shown); results pertinent to the (b) (4) dose selection are summarized below.

Diluent	Conditions	(b) (4) Solubility by HPLC analysis (mg/mL)
Deionized (DI) water	25°C with 30 minute shaking at 200 rpm	(b) (4)
5% ethanol in DI water		
10% ethanol in DI water		
20% ethanol in DI water		

(b) (4)

Thus, (b) (4) proposes the use of DI water as the diluent for the (b) (4) study. Using a (b) (4) mg/mL

concentration of (b) (4) in DI water in the upcoming 2-week qualification study would result in a dose of (b) (4) mg/kg (which provides an approximate (b) (4) multiple of the anticipated dose of (b) (4)).

Question: Does the agency agree that a dose of (b) (4) mg/kg in DI water is acceptable to support the qualification of the (b) (4) impurity? We would appreciate comments no later than close of business on 08-May-2017.

Please do not hesitate to reach out to me if you require anything further as it relates to this request.
Thank you.

Best Regards,
Melissa

Melissa L. Goodhead, MSc, RAC
President

(b) (4)
(813) 671-8570 Office
(813) 927-9302 Cell

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/s/

DIANA L WALKER
05/09/2017

From: [Walker, Diana](#)
To: [Melissa Goodhead](#) (b) (4)
Subject: NDA 209963 Statistics Information Request 05May17
Date: Friday, May 05, 2017 9:33:09 AM
Importance: High

Dear Melissa,

I have received the following information request from our statistics review team. Please respond with a submission to your NDA as soon as possible, or by May 19, 2017.

In your submission dated May 1, 2017, you submitted a listing that contained the time of unblinding for 16 subjects in Study 2013011. Submit the unblinding time for all subjects in this study along with the corresponding SAS dataset.

Warm regards,

Diana

Diana L. Walker, Ph.D.
Sr. Regulatory Health Project Manager
FDA/CDER/ODE II/DAAAP
Tel: 301-796-4029
Email: Diana.Walker@fda.hhs.gov

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/s/

DIANA L WALKER
05/09/2017

From: Steven Kinsley
To: (b) (4)
Cc: Diana Walker
Subject: NDA 209963 CMC Information Request 4-28-17
Date: April 28, 2017

Dear Melissa,

I have received the following information request from our CMC review team. Please respond to the following with a submission to your NDA by Friday, May 5, 2017.

1. We acknowledge the response received 27 April 2017 to the information request dated 18 April 2017. Please confirm that the stability testing of Weight Loss test (MOC-17-118) will include samples stored both upright and inverted.

If you have any questions, contact me. Also, please verify receipt of this Information Request via return e-mail.

Best Regards,
Steve

Steven Kinsley, Ph.D.
Regulatory Business Process Manager

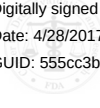
Office of Program and Regulatory Operations
U.S. Food and Drug Administration
Tel: 240-402-2773
Steven.Kinsley@fda.hhs.gov





Steven
Kinsley

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DEPARTMENT OF HEALTH AND HUMAN
SERVICES Public Health Service
Food and Drug
Administration
Center for Drug Evaluation and Research

Memorandum

Date: April 25, 2017
From: Steven Kinsley, Regulatory Business Process Manager, OPQ/OPRO/B1
Subject: NDA 209963 – (b) (4)
Clarification of Information Request from April 18, 2017

Date and Time of Teleconference: April 24, 2017 3:00-3:10 PM

FDA Participants:

Julia Pinto, Ph.D., Acting Branch Chief, OPQ/ONDPII/BIV
Valerie Amspacher, Drug Product Reviewer, OPQ/ONDPII/BIV
Steve Kinsley, Regulatory Business Process Manager, OPQ/OPRO/B1

(b) (4)

Sponsor requested clarification of Information Request of April 18, 2017.

Background:

On April 18, 2017, Melissa Goodhead sent an e-mail stating: "Our CMC group would like to request a very short clarification call with your team regarding the below request:

1. We acknowledge your response dated 17 Apr 2017 to the information request dated 5 Apr 2017 and your agreement to include USP <698> Deliverable Volume to the release and stability specification FPS-CH-TS. We are still concerned about possible leakage and do not agree that testing for deliverable volume alone is sufficient. In addition to USP <698> Deliverable Volume, include weight loss in the release and stability specification FPS-CH-TS. If the product is approved, you may submit a PAS to remove the additional testing from commercial batches after you have supporting data on a sufficient number of batches."

Summary of the Tcon:

The sponsor proposed

(b) (4)

FDA accepted the sponsor proposal.

The FDA noted that batches S35900113 and S35900213 both had 3 bottles that were found to have slightly leaked under accelerated stability conditions, yet the stability tables submitted to

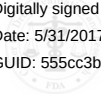
the application show all samples for all batches as conforms. During the meeting FDA asked the sponsor why the stability tables state “conform” for “Container/Closure” if there were leaks observed. The sponsor stated that the policy of not assessing leaks as failures was in effect at the time the leaks were found. The sponsor stated that their previous response to the April 4, 2017 Information Request stated the policy has been changed to assess leaks as failures. The sponsor clarified that the leakage was observed prior to the policy change. FDA verified that the method was changed so that leaks would be assessed as failures for “Container/Closure.”

The FDA agreed that the sponsor could submit their response to the April 18, 2017 Information Request by Friday, April 28, 2017.



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Kinsley

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From: Steven Kinsley
To: (b) (4)
Cc: Diana Walker
Subject: NDA 209963 CMC Information Request 4-18-17
Date: April 18, 2017

Dear Melissa,

I have received the following information request from our CMC review team. Please respond to the following with a submission to your NDA by Tuesday, April 25, 2017.

1. We acknowledge your response dated 17 Apr 2017 to the information request dated 5 Apr 2017 and your agreement to include USP <698> Deliverable Volume to the release and stability specification FPS-CH-TS. We are still concerned about possible leakage and do not agree that testing for deliverable volume alone is sufficient. In addition to USP <698> Deliverable Volume, include weight loss in the release and stability specification FPS-CH-TS. If the product is approved, you may submit a PAS to remove the additional testing from commercial batches after you have supporting data on a sufficient number of batches.

If you have any questions, contact me. Also, please verify receipt of this Information Request via return e-mail.

Best Regards,
Steve

Steven Kinsley, Ph.D.
Regulatory Business Process Manager

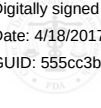
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U.S. Food and Drug Administration
Tel: 240-402-2773
Steven.Kinsley@fda.hhs.gov





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Kinsley

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From: Steven Kinsley
To: (b) (4)
Cc: Diana Walker
Subject: NDA 209963 CMC Information Request 4-4-17
Date: April 4, 2017

Dear Melissa,

I have received the following information requests from our CMC review team. Please respond to the following with a submission to your NDA by Tuesday, April 18, 2017.

1. We acknowledge your response dated 23 Mar 2017 to question 6 sent on 2 Mar 2017. Given the leaking examples discussed for batches S35900113 and S35900213, provide the volume of leakage and the root cause for the leaking.
2. Add the following tests of the container closure system to specification FPS-CH-TS: weight loss, fill volume, torque test.

If you have any questions, contact me. Also, please verify receipt of this Information Request via return e-mail.

Best Regards,
Steve

Steven Kinsley, Ph.D.
Regulatory Business Process Manager

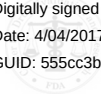
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Tel: 240-402-2773
Steven.Kinsley@fda.hhs.gov





Steven
Kinsley

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From: Walker, Diana
To: [Melissa Goodhead](#) (b) (4)
Subject: NDA 209963 Request for teleconference - Nonclinical issue 07Apr17
Date: Friday, April 07, 2017 10:18:00 AM
Importance: High

Dear Melissa,

I received the following request to schedule a teleconference with your team. Here is the request:

Upon preliminary review of study (b) (4) 256501, the 14-day rat intranasal toxicology study to qualify the impurities (b) (4) does not provide a NOAEL for local tissue effects (b) (4). Although the local tissue effects of the two impurities are not clearly worse than the vehicle, the vehicle effects preclude the ability to conclude that there are no adverse effects from these impurities. We would like to discuss with you options for adequately qualifying these impurities.

I have also been informed that if any CMC issues come up or need discussion, they may combine the teleconference. Right now I have not received any CMC issues for discussion however, but I will keep you posted.

Next week is completely booked, but I have been able to find two times the week after. Please let me know if one of the times works for you, and please send a call-in number.

Tuesday April 18 – 9:00 am (eastern)

Thursday April 20 - 3:30 pm (eastern)

Please let me know as soon as possible so that I can block the appropriate time and that it doesn't get filled up – thanks!

Warm regards,

Diana

Diana L. Walker, Ph.D.
Sr. Regulatory Health Project Manager
FDA/CDER/ODE II/DAAAP
Tel: 301-796-4029
Email: Diana.Walker@fda.hhs.gov

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/s/

DIANA L WALKER
04/20/2017

From: [Walker, Diana](#)
To: [Melissa Goodhead](#) (b) (4)
Subject: NDA 209963 Clinical Information Request 30Mar17
Date: Thursday, March 30, 2017 3:32:10 PM
Importance: High

Dear Melissa,

I have received the following information request from our Clinical review team. Please respond with an email by the requested date, followed by a submission to your NDA as soon as possible.

During review of your NDA 209963 submission, we have identified two issues that need to be addressed further: additional medication administered to placebo subjects and adverse event listings with corresponding vital sign data. Please provide the following additional information by the close of business Friday, April 7, 2017:

1. Provide the name and dose of the additional anesthetic or analgesic medication(s) used for treatment for each of the 55 placebo subjects who reported a greater than zero pain score on the VNRS during von Frey filament testing in your Phase 3 study, 2013011. We request that you provide this data in a single summary table including USUBJID, additional medication administered, and the procedure performed. Based upon the data you submitted, it appears that 40 of the 95 subjects in the placebo group completed their diagnostic or surgical procedure without additional medications. Clarify that our interpretation of this data is correct.

2. Provide a summary table of all the subjects who experienced an adverse event in your Phase 3 study, 2013011, and their vital sign data during the entire recorded time of the adverse event. Include heart rate, systolic blood pressure, diastolic blood pressure, and mean arterial pressure measurements in the summary table. Include columns for the USUBJID, the treatment group, the adverse event, the procedure performed, and all vital signs as described above (including baseline and screening values).

Kindly acknowledge receipt of this email.

Warm regards,

Diana

Diana L. Walker, Ph.D.
Sr. Regulatory Health Project Manager
FDA/CDER/ODE II/DAAAP
Tel: 301-796-4029
Email: Diana.Walker@fda.hhs.gov

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/s/

DIANA L WALKER
03/30/2017



NDA 209963

**PROPRIETARY NAME REQUEST
UNACCEPTABLE**

(b) (4)

Dear (b) (4)

Please refer to your New Drug Application (NDA) dated and received November 23, 2016, submitted under section 505(b)(2) of the Federal Food, Drug, and Cosmetic Act for Cocaine Hydrochloride Topical Solution, 4%.

We also refer to your correspondence dated and received December 20, 2016, requesting review of your proposed proprietary name, (b) (4)

We have completed our review of this proposed proprietary name and have concluded that this name is unacceptable for the following reasons:

The proposed proprietary name, (b) (4) may be confused with the product, (b) (4)

(b) (4)
they contain a similar number of letters (8 letters vs. 9 letters), and are similar in shape when scripted. Additionally, (b) (4)
These similarities are further supported by the FDA Phonetic and Orthographic Computer Analysis (POCA) which calculates a combined score of 79% for this name pair (orthographic only score of 88%), indicating that this name pair is highly similar.¹ (b) (4)

¹POCA search conducted on January 5, 2017, POCA tool updated to incorporate a revised orthographic algorithm.

In addition to their orthographic similarity, (b) (4) shares similar product characteristics with (b) (4). Both products are single strength, which may be omitted from a prescription, and there also can be a numerical overlap in dose, (b) (4).

We acknowledge that (b) (4) is not currently marketed; however, there are generic equivalents available.² We have postmarketing experience where a brand name or product is discontinued, but the name is still used in prescriptions if generic equivalents are available.³

We acknowledge that our conclusion differs from that of the external study presented in your December 20, 2016, proprietary name submission. However, the study conducted by (b) (4) did not include a safety analysis of the name, (b) (4) hence the reason our conclusions differ. Thus, considering the totality of evidence cited above, we determine that the name pair, (b) (4) cannot safely co-exist on the market.

We note that you have not proposed an alternate proprietary name for review. If you intend to have a proprietary name for this product, we recommend that you submit a new request for a proposed proprietary name review.

If you require additional information on developing proprietary names for drugs, proposing alternative proprietary names for consideration, or requesting reconsideration of our decision, we refer you to the following:

- Draft Guidance for Industry Best Practices in Developing Proprietary Names for Drugs, (<http://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/UCM398997.pdf>)
- Guidance for Industry Contents of a Complete Submission for the Evaluation of Proprietary Names (<http://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/UCM075068.pdf>)
- PDUFA Reauthorization Performance Goals and Procedures Fiscal Years 2013 through 2017, (<http://www.fda.gov/downloads/ForIndustry/UserFees/PrescriptionDrugUserFee/UCM270412.pdf>)

² Orange Book: approved Drug Products with Therapeutic Equivalent evaluations. Available at http://www.accessdata.fda.gov/scripts/cder/ob/search_product.cfm . Accessed March 1, 2017.

³ Tu, CM, Taylor, K, and Chai, G. Use of Proprietary Names by Prescribers for Discontinued Brand Drug Products With Existing Generic Equivalents. Drug Information Journal, published online August 21, 2012, available at <http://dij.sagepub.com/content/early/2012/08/21/0092861512456282.full.pdf+html>

If you have any questions regarding the contents of this letter or any other aspects of the proprietary name review process, contact Davis Mathew, Safety Regulatory Project Manager in the Office of Surveillance and Epidemiology, at (240) 402-4559. For any other information regarding this application, contact Diana L. Walker, Regulatory Project Manager in the Office of New Drugs, at (301) 796-4029.

Sincerely,

{See appended electronic signature page}

Todd Bridges, RPh
Director
Division of Medication Error Prevention and Analysis
Office of Medication Error Prevention and Risk Management
Office of Surveillance and Epidemiology
Center for Drug Evaluation and Research

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/s/

DANIELLE M HARRIS on behalf of TODD D BRIDGES
03/15/2017

From: Steven Kinsley
To: (b) (4)
Cc: Diana Walker
Subject: NDA 209963 CMC Information Request 3-14-17
Date: March 14, 2017

Dear Melissa,

I have received the following information requests from our CMC review team. Please respond to the following with a submission to your NDA by Tuesday, March 21, 2017.

1. The drug substance DMF (b) (4) is currently inadequate. Be advised that the NDA cannot be approved until the DMF deficiencies are addressed satisfactorily.
2. In your list of organic impurities in the drug substance in Module 3.2.S.3.2, the structure of (b) (4) Correct the structure of this impurity.
3. You have not discussed your justification for the limit of (b) (4) in the drug substance in Module 3.2.S.4.5 (Justification of Specification). Revise this module with the needed justification, as your limit is above the ICH Q3A qualification threshold.

If you have any questions, contact me. Also, please verify receipt of this Information Request via return e-mail.

Best Regards,
Steve

Steven Kinsley, Ph.D.
Regulatory Business Process Manager

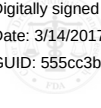
Office of Program and Regulatory Operations
U.S. Food and Drug Administration
Tel: 240-402-2773
Steven.Kinsley@fda.hhs.gov





Steven
Kinsley

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Date: 3/14/2017 08:29:41AM
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From: Steven Kinsley
To: (b) (4)
Cc: Diana Walker
Subject: NDA 209963 CMC Information Request 3-2-17
Date: March 2, 2017

Dear Melissa,

I have received the following information requests from our CMC review team. Please respond to the following with a submission to your NDA by Thursday, March 23, 2017.

1. Method validation report AS-MVR-CH-TS-078 includes a forced degradation study in which the (b) (4) peak in the drug product grows significantly when stored at the thermal condition (Table 32). What does the "NA" mean in the % of Degradation against Control? Does the "NA" signify that the peak grew? Provide information on the % growth of the (b) (4) peak in the degradation studies. Provide a possible mechanism for the growth.
2. In module 3.2.P.5.3 Validation of Analytical Procedures, Method Validation Report AS-MVR-CH-TS 078 describes forced degradation testing. In figures 4-15 UV spectra are provided visually showing peak purity for cocaine hydrochloride (b) (4). Provide calculations of peak purity based on UV spectra for cocaine hydrochloride, (b) (4).
3. Module 3.2.P.5.3 Validation of Analytical Procedures, Method Validation Report AS-MVR-CH-TS 078 states the forced degradation study included placing samples under long wavelength ultraviolet light and fluorescent light for a period of at least 7 days. It appears as though separate samples were prepared for storage under ultraviolet light and fluorescent light which would not meet the requirements of ICH Q1B Stability Testing: Photostability. Clarify if the photostability conditions described in the method validation report meet the requirements of ICH Q1B Stability Testing: Photostability. For example, does the study meet the requirement of exposing samples to "light providing an overall illumination of not less than 1.2 million lux hours and an integrated near ultraviolet energy of not less than 200 watt hours/square meter," as stated in the ICH guidance?
4. In module 3.2.P.2 Pharmaceutical Development "Formulation Development Report" section 3.2.P.2.2.6 Bulk Hold Study two different sets of results are listed for batch S35900113 and no results are listed for batch S35900213. Please clarify which set of results belongs to batch S35900113 and report results for batch S35900213.
5. The assay, related substances, (b) (4) AS-TM-CH-TS-014 states that related substances will be run but not reported for drug product release. Additionally, notes on specification FPS-CH-TS appear to suggest that description, assay, pH, preservative contents, microbial limits and container closure system are not performed at release. This is not acceptable. All tests listed on the specification must be performed and reported at release.

6. The change history of method AS-TM-000-073 (Appearance, Container Closure Description) states, "Containers stored inverted on stability is not manufacturers recommended storage condition and are therefore subjected to leaks and should not be assessed as failure." Clarify this statement. A leak could be concerning for the stability of the product. Were any leaks found for any of the batches on stability?
7. In module 3.2.P.5.2 Analytical Procedures, method AS-TM-CH-TS-014 system suitability requirements include:
- The %RSD between multiple injections of the assay standard solution of Std 1 must be NMT (b) (4) %;
 - The % difference between assay Std 1 and assay Std 2 must be NMT (b) (4) %;
 - The %RSD of multiple injections of the Working Related Substances and (b) (4) standard must be NMT (b) (4) % for cocaine and (b) (4) % for (b) (4);
 - The % difference between the Working Related Substances and (b) (4) Std 1 and Std 2 must be NMT (b) (4) % for cocaine and (b) (4) % for (b) (4).

The validation data reported in AS-MVR-CH-TS 078 for precision and repeatability in the drug product matrix does not support these wide limits. These wide system suitability criteria do not provide confidence that the methods are suitable. Tighten these criteria to offer more certainty around values determined by these methods.

8. For the gas chromatography method to determine methanol content (AS-TM-CH-TS-065) the %RSD between standard injections is NMT (b) (4) %. The validation data reported in AS-MVR-CH-TS-083 for precision and repeatability does not support these wide limits. These wide system suitability criteria do not provide confidence that the methods are suitable. Tighten these criteria to offer more certainty around values determined by these methods.
9. For the gas chromatography method to determine (b) (4) the %RSD between standard injections is NMT (b) (4) %. The validation data reported in AS-MVR-CH-124 for precision and repeatability does not support these wide limits. These wide system suitability criteria do not provide confidence that the methods are suitable. Tighten these criteria to offer more certainty around values determined by these methods.
10. In module 3.2.P.5.3 Validation of Analytical Procedures, Method Validation Report AS-MVR-CH-TS 078 describes robustness testing. In the robustness section reference is made to "corrected results." Provide an explanation of what corrected results are and provide an example calculation for one of the samples reported in the robustness study.
11. Module 3.2.P.6 Reference Standards and Materials references DMF (b) (4) for reference standards. Provide Certificates of Analysis for reference standards used in methods (b) (4)

12. We note the Environmental Analysis included with the application. Provide a calculation of expected introduction concentration of the active moiety as described in FDA "Guidance for Industry Environmental Assessment of Human Drug and Biologics Applications." Provide an explicit statement that no extraordinary circumstances exist, as required at 21 CFR 25.15 (a) and (d). Extraordinary circumstances are discussed at 21 CFR 25.21.
13. We note a freeze thaw/temperature cycling study was not performed. Justify the absence of such study.

If you have any questions, contact me. Also, please verify receipt of this Information Request via return e-mail.

Best Regards,
Steve

Steven Kinsley, Ph.D.
Regulatory Business Process Manager

Office of Program and Regulatory Operations
U.S. Food and Drug Administration
Tel: 240-402-2773
Steven.Kinsley@fda.hhs.gov





Steven
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Date: 3/02/2017 12:22:15PM
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From: Steven Kinsley
To: (b) (4)
Cc: Diana Walker
Subject: NDA 209963 CMC Information Request 2-13-17
Date: February 13, 2017

Dear Melissa,

I have received the following information requests from our CMC review team. Please respond to the following with a submission to your NDA by Monday, March 06, 2017.

- 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:

- 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 materials 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 environment (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 of 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 numbers of BCC. Your submission should describe the preconditioning 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.

- 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).

If you have any questions, contact me. Also, please verify receipt of this Information Request via return e-mail.

Best Regards,

Steve

Steven Kinsley, Ph.D.
Regulatory Business Process Manager

Office of Program and Regulatory Operations
U.S. Food and Drug Administration
Tel: 240-402-2773
Steven.Kinsley@fda.hhs.gov





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NDA 209963

**FILING COMMUNICATION -
FILING REVIEW ISSUES IDENTIFIED**



Dear (b) (4)

Please refer to your New Drug Application (NDA) dated and received November 23, 2016, submitted pursuant to section 505(b)(2) of the Federal Food, Drug, and Cosmetic Act (FDCA), for Cocaine Hydrochloride Topical Solution, 4%.

We also refer to your amendments dated December 12, 14, and 20, 2016, and January 27, 2017.

We have completed our filing review and have determined that your application is sufficiently complete to permit a substantive review. Therefore, in accordance with 21 CFR 314.101(a), this application is considered filed 60 days after the date we received your application. The review classification for this application is **Standard**. Therefore, the user fee goal date is September 23, 2017.

We are reviewing your application according to the processes described in the Guidance for Review Staff and Industry: Good Review Management Principles and Practices for PDUFA Products. Therefore, we have established internal review timelines as described in the guidance, which includes the timeframes for FDA internal milestone meetings (e.g., filing, planning, mid-cycle, team and wrap-up meetings). Please be aware that the timelines described in the guidance are flexible and subject to change based on workload and other potential review issues (e.g., submission of amendments). We will inform you of any necessary information requests or status updates following the milestone meetings or at other times, as needed, during the process. If major deficiencies are not identified during the review, we plan to communicate proposed labeling and, if necessary, any postmarketing commitment requests by August 26, 2017.

During our filing review of your application, we identified the following potential review issues:

Clinical

1. Safety database concerns

- a. In prior communications with the Agency, you indicated that you would be relying on safety information in the published literature in support of your application and would incorporate summaries of your findings into the NDA submission. In your response dated January 27, 2017, to an Information Request sent on January 6, 2017, inquiring about the location of this information, however, you stated that (b) (4) "...no longer was relying on referenced literature to support this NDA, but on (b) (4) own data, and therefore, although referenced, where applicable throughout our NDA, a comprehensive critical evaluation of the relevant literature data was not provided". Whether the data collected from your studies provide adequate support for the safety of this product can only be determined after review of the data. Therefore, it is recommended that you submit referenced summaries from the published literature in support of the safety profile of this product.

2. Phase 3 trial concerns

- a. The Phase 3 trial was conducted using a 6.10 Von Frey Filament for assessment of anesthetic/analgesic efficacy prior to initiation of the diagnostic or surgical procedure. During a prior correspondence, Pre-IND meeting, Written Responses Only, in August 2013, we requested justification for filament selection as a means of assessing efficacy. You have not provided any justification.
- b. We previously expressed concerns about revealing treatment assignment to subjects and investigators. The impact of the unblinding on the conclusions regarding safety and efficacy will be determined after review of the data.
- c. Whether the increases blood pressure and heart rate are considered acceptable and associated with cocaine administration or whether they are considered adverse events and expressed as such in the labeling of the final marketed product will be determined after review of the data.
- d. Preliminary review of the data suggests a lower success rate in the 8% topical cocaine treatment arm when compared to the 4% cocaine treatment arm. Additionally, preliminary review of the heart rate and blood pressure data suggests a higher percentage of subjects in the 4% cocaine treatment arm experienced higher systolic and diastolic blood pressure and heart rate readings when compared to those subjects in the 8% cocaine treatment arm. Provide an explanation for these findings.
- e. During previous correspondence with the Agency regarding the accuracy of the cocaine topical dose, advice was provided regarding measurement of residual cocaine solution not fully absorbed when applied to the cotton pledgets. Preliminary review of the submission did not reveal such an assessment. As a result, there may concerns about incorrect determination of doses delivered in addition to potentially becoming an inventory documentation concern.

3. Missing data

There appears to be large numbers of subjects with incomplete vital sign data; e.g., only 75.5% of scheduled heart rate data are recorded for the 4% cocaine treatment arm during the 0 to 15 minutes time interval after application. Preliminary review of the NDA submission did not find adequate explanations for all of these missing data in the protocol deviation summaries. This could impact the conclusions about the overall safety of the product.

4. Labeling concerns

- a. The proposed indication for use of this product is "...for the induction of local anesthesia when performing diagnostic procedures and surgeries on or through the mucous membranes of the nasal cavities in adults" may not be adequately supported by the data. Preliminary analysis of the surgical procedures performed using the proposed marketing dose of 4% cocaine topical solution has revealed that 164 subjects (59.6%) had nasal endoscopy alone, which does not typically cause significant discomfort and generally requires minimal anesthetic for successful completion. Safety and efficacy of 4% cocaine topical solution for invasive procedures may need to be confirmed with future adequate and well-controlled studies in order to support a broad indication.
- b. Some published literature reports the safety of cocaine dosing of 1-3 mg/kg or a maximum dose of 400 mg during a single application. The proposed marketing dose for this product is 160 mg, which for a small adult patient, <53 kg, would be greater than 3 mg/kg and could result in a higher incidence of adverse events. The labeling of the final product may need to reflect this body weight restriction.

Statistics

5. In the Clinical Study Report for Study 2013011, a subject was considered an analgesic success if the subject both reported a score of 0 on visual numeric rating scale (VNRS) based on a Von Frey Filament Test prior to the diagnostic procedure or surgery, and had no need for additional nasal analgesic medication during the diagnostic procedure or surgery. However, this definition of analgesic success is different from what was pre-specified in the study protocol and Statistical Analysis Plan (SAP). According to the protocol and SAP, a placebo subject would be an analgesic success if the subject reported a score of 0 on VNRS based on the Von Frey Filament Test. Clarify this discrepancy.
6. At the pre-NDA meeting held on July 14, 2015, we requested that the time of unblinding for each subject be reported in the clinical study report. However, this information could not be located. If this information was submitted, indicate the location in the current submission otherwise provide this information.

We are providing the above comments to give you preliminary notice of potential review issues. Our filing review is only a preliminary evaluation of the application and is not indicative of deficiencies that may be identified during our review. Issues may be added, deleted, expanded upon, or modified as we review the application. If you respond to these issues during this review cycle, we may not consider your response before we take an action on your application.

In addition, we have the following comments:

1. We note that you are requesting 5 years of exclusivity based on your assertion that cocaine hydrochloride is considered a New Chemical Entity (NCE). As a reminder, please note that NCE determination (and associated eligibility for exclusivity) will not be carried out until or following the time of approval.
2. We note that, in the pre-NDA meeting minutes dated August 14, 2015, the Agency initially informed you that Cocaine Hydrochloride Topical Solution, 4% meets the definition of New Molecular Entity (NME), but that whether this product will be reviewed as an NME may change prior to NDA submission based on pending revisions to the relevant Manual of Policies and Procedures (MAPP). Based on the NME definition in MAPP 5018.2, your product is not classified as an NME: *“An NME is an active ingredient that contains no active moiety that has been previously approved by the Agency in an application submitted under section 505 of the Act3 or has been previously marketed as a drug in the United States. A pure enantiomer or a racemic mixture is an NME only when neither has been previously approved or marketed.”*

The MAPP can be found at the following link:

<http://www.fda.gov/downloads/AboutFDA/CentersOffices/OfficeofMedicalProductsandTobacco/CDER/ManualofPoliciesProcedures/UCM470773.pdf>

PRESCRIBING INFORMATION

Your proposed prescribing information (PI) must conform to the content and format regulations found at 21 [CFR 201.56\(a\) and \(d\)](#) and [201.57](#). As you develop your proposed PI, we encourage you to review the labeling review resources on the [PLR Requirements for Prescribing Information](#) and [Pregnancy and Lactation Labeling Final Rule](#) websites, which include:

- The Final Rule (Physician Labeling Rule) on the content and format of the PI for human drug and biological products
- The Final Rule (Pregnancy and Lactation Labeling Rule) on the content and format of information in the PI on pregnancy, lactation, and females and males of reproductive potential
- Regulations and related guidance documents
- A sample tool illustrating the format for Highlights and Contents
- The Selected Requirements for Prescribing Information (SRPI) – a checklist of important format items from labeling regulations and guidances, and
- FDA’s established pharmacologic class (EPC) text phrases for inclusion in the Highlights Indications and Usage heading.

Please respond only to the above requests for information. While we anticipate that any response submitted in a timely manner will be reviewed during this review cycle, such review decisions will be made on a case-by-case basis at the time of receipt of the submission.

PROMOTIONAL MATERIAL

You may request advisory comments on proposed introductory advertising and promotional labeling. Please submit, in triplicate, a detailed cover letter requesting advisory comments (list each proposed promotional piece in the cover letter along with the material type and material identification code, if applicable), the proposed promotional materials in draft or mock-up form with annotated references, and the proposed package insert (PI). Submit consumer-directed, professional-directed, and television advertisement materials separately and send each submission to:

OPDP Regulatory Project Manager
Food and Drug Administration
Center for Drug Evaluation and Research
Office of Prescription Drug Promotion (OPDP)
5901-B Ammendale Road
Beltsville, MD 20705-1266

Alternatively, you may submit a request for advisory comments electronically in eCTD format. For more information about submitting promotional materials in eCTD format, see the draft Guidance for Industry (available at: <http://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/UCM443702.pdf>).

Do not submit launch materials until you have received our proposed revisions to the package insert (PI), and you believe the labeling is close to the final version.

For more information regarding OPDP submissions, please see <http://www.fda.gov/AboutFDA/CentersOffices/CDER/ucm090142.htm>. If you have any questions, call OPDP at 301-796-1200.

REQUIRED PEDIATRIC ASSESSMENTS

Under the Pediatric Research Equity Act (PREA) (21 U.S.C. 355c), all applications for new active ingredients, new indications, new dosage forms, new dosing regimens, or new routes of administration are required to contain an assessment of the safety and effectiveness of the product for the claimed indication(s) in pediatric patients unless this requirement is waived, deferred, or inapplicable.

We acknowledge receipt of your request for a full deferral of pediatric studies for this application. Once we have reviewed your request, we will notify you if the full deferral request is denied.

If you have any questions, call Diana L. Walker, PhD, Regulatory Project Manager, at (301) 796-4029.

Sincerely,

{See appended electronic signature page}

Sharon Hertz, MD
Director
Division of Anesthesia, Analgesia, and
Addiction Products
Office of Drug Evaluation II
Center for Drug Evaluation and Research

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/s/

SHARON H HERTZ
02/06/2017

From: [Walker, Diana](#)
To: [Melissa Goodhead](#) (b) (4)
Subject: NDA 209963 Clinical Pharmacology Information Request 13Jan17
Date: Friday, January 13, 2017 10:21:56 AM
Importance: High

Dear Melissa,

I have received the following information request from our Clinical Pharmacology review team. Please respond with a submission to your NDA by March 13, 2017.

For all human PK studies you cited and summarized from literature, we are unable to locate the bioanalytical validation/performance data and raw PK data in your NDA submission. Contact the authors to obtain these data and submit it. Due diligence is required to acquire such information about the studies, otherwise you must provide adequate justification that the required information is not obtainable and why the results from the literature can still be used to support your proposed product.

Warm regards,

Diana

Diana L. Walker, Ph.D.
Sr. Regulatory Health Project Manager
FDA/CDER/ODE II/DAAAP
Tel: 301-796-4029
Email: Diana.Walker@fda.hhs.gov

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/s/

DIANA L WALKER
01/25/2017

From: [Walker, Diana](#)
To: [Melissa Goodhead](#) (b) (4)
Subject: NDA 209963 Clinical Information Request 06Jan17
Date: Friday, January 06, 2017 9:23:20 AM
Importance: High

Dear Melissa,

I have received the following information request from our Clinical review team. Please respond with a submission to your NDA by close of business on January 10, 2017.

- 1. Provide the location in your NDA submission for the Clinical Executive Literature Review/Summary, which was discussed during the Pre-IND Meeting, Written Responses Only dated August 20, 2013.**
- 2. Provide the Case Report Form or Narrative Summary for Subject 901-0015. This subject was described as having an adverse event of arrhythmia and uncontrolled hypertension 3 days after treatment with 8% topical cocaine solution.**

Warm regards,

Diana

Diana L. Walker, Ph.D.
Sr. Regulatory Health Project Manager
FDA/CDER/ODE II/DAAAP
Tel: 301-796-4029
Email: Diana.Walker@fda.hhs.gov

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/s/

DIANA L WALKER
01/10/2017



NDA 209963

NDA ACKNOWLEDGMENT



Dear (b) (4)

We have received your New Drug Application (NDA) submitted pursuant to section 505(b)(2) of the Federal Food, Drug, and Cosmetic Act (FDCA) for the following:

Name of Drug Product: Cocaine Hydrochloride Topical Solution, 4%

Date of Application: November 23, 2016

Date of Receipt: November 23, 2016

Our Reference Number: NDA 209963

Unless we notify you within 60 days of the receipt date that the application is not sufficiently complete to permit a substantive review, we will file the application on January 22, 2017, in accordance with 21 CFR 314.101(a).

If you have not already done so, promptly submit the content of labeling [21 CFR 314.50(l)(1)(i)] in structured product labeling (SPL) format as described at <http://www.fda.gov/ForIndustry/DataStandards/StructuredProductLabeling/default.htm>. Failure to submit the content of labeling in SPL format may result in a refusal-to-file action under 21 CFR 314.101(d)(3). The content of labeling must conform to the content and format requirements of revised 21 CFR 201.56-57.

You are also responsible for complying with the applicable provisions of sections 402(i) and 402(j) of the Public Health Service Act (PHS Act) [42 USC §§ 282 (i) and (j)], which was amended by Title VIII of the Food and Drug Administration Amendments Act of 2007 (FDAAA) (Public Law No. 110-85, 121 Stat. 904).

The NDA number provided above should be cited at the top of the first page of all submissions to this application. Send all submissions (if not submitting via the Gateway), electronic or paper, including those sent by overnight mail or courier, to the following address:

Food and Drug Administration
Center for Drug Evaluation and Research
Division of Anesthesia, Analgesia, and Addiction Products
5901-B Ammendale Road
Beltsville, MD 20705-1266

Secure email between CDER and applicants is useful for informal communications when confidential information may be included in the message (for example, trade secrets or patient information). If you have not already established secure email with the FDA and would like to set it up, send an email request to SecureEmail@fda.hhs.gov. Please note that secure email may not be used for formal regulatory submissions to applications.

If you have any questions, call me at (301) 796-4029.

Sincerely,

{See appended electronic signature page}

Diana L. Walker, PhD
Sr. Regulatory Health Project Manager
Division of Anesthesia, Analgesia, and
Addiction Products
Office of Drug Evaluation II
Center for Drug Evaluation and Research

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/s/

DIANA L WALKER
11/29/2016

From: [Walker, Diana](#)
To: [Melissa Goodhead](#) (b) (4)
Subject: NDA 209963 Nonclinical PMR information Request 08Nov17
Date: Wednesday, November 08, 2017 11:48:42 AM
Importance: High

Dear Melissa,

Please see below for the two (2) PREA Nonclinical PMRs and 5 additional Nonclinical PMRs that will be required for Goprelto. Please review these PMRs and respond with concurrence to the PMRs and proposed dates for the 5 studies that you have not proposed dates for previously (the proposed dates for the two PREA studies were previously received).

PREA #1

Conduct a juvenile animal study to characterize the impact of cocaine on brain development and male reproductive tissue and development to support pediatric dosing in children under 3 years of age.

Draft Protocol Submission: 12/2017
Final Protocol Submission: 06/2018
Study Completion: 11/2018
Final Report Submission: 02/2019

PREA #2

Conduct a juvenile animal study to characterize the impact of cocaine on brain development and male reproductive tissue and development to support pediatric dosing in children 3 years of age to less than 17 years of age.

Draft Protocol Submission: 12/2017
Final Protocol Submission: 06/2018
Study Completion: 11/2018
Final Report Submission: 02/2019

PMR #3

Conduct a female fertility and early embryonic development study in the rat model to adequately characterize the effect of cocaine on female fertility and early embryonic development.

Draft Protocol Submission: MM/YYYY
Final Protocol Submission: MM/YYYY
Study Completion: MM/YYYY
Final Report Submission: MM/YYYY

PMR #4

Conduct an embryo-fetal development study in the rat model to characterize the teratogenic potential of cocaine.

Draft Protocol Submission: MM/YYYY
Final Protocol Submission: MM/YYYY
Study Completion: MM/YYYY

Final Report Submission: MM/YYYY

PMR #5

Conduct an embryo-fetal development study in the rabbit model to characterize the teratogenic potential of cocaine.

Draft Protocol Submission: MM/YYYY
Final Protocol Submission: MM/YYYY
Study Completion: MM/YYYY
Final Report Submission: MM/YYYY

PMR #6

Conduct a pre- and post-natal development study in the rat model to characterize the impact of cocaine on development, including exposure during lactation to weaning, growth and development, functional assessments, and reproductive capacity of the offspring.

Draft Protocol Submission: MM/YYYY
Final Protocol Submission: MM/YYYY
Study Completion: MM/YYYY
Final Report Submission: MM/YYYY

PMR #7

Submit a complete histopathological assessment from the 14-day rat intranasal toxicology study testing (b) (4) (Study Number 256501 or 558503) and revise the final study report accordingly.

Draft Protocol Submission: MM/YYYY
Final Protocol Submission: MM/YYYY
Study Completion: MM/YYYY
Final Report Submission: MM/YYYY

Feel free to contact me with any questions.

Warm regards,

Diana

Diana L. Walker, Ph.D.
Sr. Regulatory Health Project Manager
FDA/CDER/ODE II/DAAAP
Tel: 301-796-4029
Email: Diana.Walker@fda.hhs.gov

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/s/

DIANA L WALKER
11/17/2017



NDA 209963

**PROPRIETARY NAME
ACKNOWLEDGEMENT**



Dear (b) (4)

Please refer to your New Drug Application (NDA) dated and received November 23, 2016, submitted under section 505(b)(2) of the Federal Food, Drug, and Cosmetic Act for Cocaine Hydrochloride Topical Solution, 4%.

We acknowledge receipt of your correspondence, dated and received December 20, 2016, requesting a review of your proposed proprietary name, (b) (4)

If the application is filed, the user fee goal date will be March 20, 2017.

If you have any questions regarding the contents of this letter or any other aspects of the proprietary name review process, contact Davis Mathew, Safety Regulatory Project Manager in the Office of Surveillance and Epidemiology, at (240) 402-4559. For any other information regarding this application, contact Diana L. Walker, Regulatory Project Manager, in the Office of New Drugs at (301) 796-4029.

Sincerely,

{See appended electronic signature page}

Davis Mathew, PharmD, RPh
Safety Regulatory Project Manager
Office of Surveillance and Epidemiology
Center for Drug Evaluation and Research

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/s/

DAVIS MATHEW
12/30/2016

From: [Walker, Diana](#)
To: [Melissa Goodhead](#) (b) (4)
Subject: NDA 209963 Maternal Health Information Request 08dec16
Date: Thursday, December 08, 2016 3:13:11 PM
Importance: High

Dear Melissa,

I have received the following information request from our Maternal Health review team. Please respond with a submission to your NDA by December 29, 2016.

Topical cocaine solution is currently a marketed, unapproved product. Confirm whether or not exposures during pregnancy or exposures during lactation have been reported during unapproved marketing of your proposed product, cocaine 4% solution. If pregnancies have been reported, provide any known details about these pregnancies, including gestational age at the time of drug exposure, pregnancy outcomes (gestational age at type of birth, type of delivery, spontaneous abortion, stillbirth, etc) and fetal outcomes (fetal malformations, small-for-gestational age, etc.).

Warm regards,

Diana

Diana L. Walker, Ph.D.
Sr. Regulatory Health Project Manager
FDA/CDER/ODE II/DAAAP
Tel: 301-796-4029
Email: Diana.Walker@fda.hhs.gov

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DIANA L WALKER
01/05/2017

Mathew, Davis

From: Mathew, Davis
Sent: Wednesday, December 07, 2016 12:36 PM
To: (b) (4)
Cc: Walker, Diana; Flowers, Louis
Subject: Request for Proprietary Name Review for NDA 209963

Dear (b) (4)

Please refer to your NDA 209963 for Cocaine Hydrochloride Topical Solution, 4% received on November 23, 2016.

If you intend to have a proprietary name for the above referenced product, you should submit a new request for proprietary name review within 14 days of this communication.

To request review of a new proprietary name for consideration; please submit a new, complete, request. Include the statement **"REQUEST FOR PROPRIETARY NAME REVIEW"** in bold capital letters, at the top of your cover letter and on the first page of the main submission document (please refer to the complete submission guidance link below). The review of this name will be initiated when the new submission is received.

If you require additional information on developing proprietary names for drugs or proposing alternative proprietary names for consideration, we refer you to the following:

- Draft Guidance for Industry Best Practices in Developing Proprietary Names for Drugs, (<http://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/UCM398997.pdf>)
- Guidance for Industry Contents of a Complete Submission for the Evaluation of Proprietary Names (<http://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/UCM075068.pdf>)
- PDUFA Reauthorization Performance Goals and Procedures Fiscal Years 2013 through 2017, (<http://www.fda.gov/downloads/ForIndustry/UserFees/PrescriptionDrugUserFee/UCM270412.pdf>)

If you have any further questions regarding any other aspects of the proprietary name review process, please feel free to contact me directly. Thanks

Davis Mathew, PharmD, RPh
FDA/CDER/OSE/SRPM
WO22 RM4443
10903 New Hampshire Avenue
Silver Spring, MD 20993
Ph: 240-402-4559
E-mail: Davis.Mathew@fda.hhs.gov

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/s/

DAVIS MATHEW
12/07/2016



FACSIMILE TRANSMITTAL SHEET

DATE: December 6, 2016

To: Melissa Goodhead
President

From: Steven Kinsley
Office of Program and Regulatory Operations
Office of Pharmaceutical Quality

Company:

(b) (4)

Fax number: (b) (4)

Fax number: 301-595-5093

Phone number: (b) (4)

Phone number: 240-402-2773

Subject: NDA 209963 Information Request

Total # of pages including cover: 2

Comments: Please verify receipt of this fax via phone at 240-402-2773.

Original document to be mailed:

☐

Yes

☒

No

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From: Steven Kinsley
To: Ms. Melissa Goodhead MSc, RAC
Cc: Diana Walker
Subject: NDA 209963 CMC Information Request 12-6-16
Date: December 6, 2016

Dear Ms. Goodhead,

I have received the following information request from our CMC review team. Please respond to the following with a submission to your NDA Tuesday, December 13, 2016

1. Update your submission with all facilities responsible for manufacturing or testing the drug substance and critical intermediates.

If you have any questions, contact me. Also, please verify receipt of this Information Request to steven.kinsley@fda.hhs.gov.

Best Regards,

Steve

Steven Kinsley, Ph.D.
Regulatory Business Process Manager
Office of Program and Regulatory Operations
Office of Pharmaceutical Quality
CDER/FDA
240-402-2773



Steven
Kinsley

Digitally signed by Steven Kinsley
Date: 12/06/2016 02:44 36PM
GUID: 555cc3bc000836e194b17e8bf695ce5f





DEPARTMENT OF HEALTH AND HUMAN SERVICES

Food and Drug Administration
Silver Spring, MD 20993

IND 118527

MEETING MINUTES

(b) (4)

Attention:

(b) (4)

Dear

(b) (4)

Please refer to your Investigational New Drug Application (IND) submitted under Section 505(i) of the Federal Food, Drug, and Cosmetic Act for Cocaine hydrochloride topical solution 4%.

We also refer to the meeting between representatives of your firm and the FDA on July 14, 2015. The purpose of the meeting was to discuss the plan for a 505(b)(2) NDA submission for Cocaine hydrochloride topical solution 4%.

A copy of the official minutes of the meeting is enclosed for your information. Please notify us of any significant differences in understanding regarding the meeting outcomes.

If you have any questions, call me at (301) 796-4029.

Sincerely,

{See appended electronic signature page}

Diana L. Walker, PhD
Sr. Regulatory Health Project Manager
Division of Anesthesia, Analgesia, and
Addiction Products
Office of Drug Evaluation II
Center for Drug Evaluation and Research

ENCLOSURE:
Meeting Minutes



FOOD AND DRUG ADMINISTRATION
CENTER FOR DRUG EVALUATION AND RESEARCH

MEMORANDUM OF MEETING MINUTES

Meeting Type: B
Meeting Category: Pre-NDA

Meeting Date and Time: July 14, 2015, 4:00 p.m. - 5:00 p.m. (Eastern)
Meeting Location: 10903 New Hampshire Avenue
White Oak Building 22, Conference Room: 1419
Silver Spring, Maryland 20903

Application Number: IND 118527
Product Name: Cocaine hydrochloride topical solution 4%
Indication: Diagnostic procedures and surgeries on or through the accessible mucous membranes of the nasal cavities
Sponsor/Applicant Name: (b) (4)

Meeting Chair: Rigoberto Roca, MD, Deputy Director, DAAAP
Meeting Recorder: Diana Walker, PhD, Sr. Regulatory Project Manager, DAAAP

FDA Attendees	Title
Sharon Hertz, MD	Division Director, DAAAP
Rigoberto Roca, MD	Deputy Director, DAAAP
Amelia Luckett, MD	Medical Officer, DAAAP
Daniel Mellon, PhD	Pharmacology-Toxicology Supervisor
Belinda Hayes, PhD	Pharmacology-Toxicology Reviewer
Julia Pinto, PhD	Branch Chief, Branch IV, Division of New Drug Products II (DNDPII), Office of New Drug Products (ONDP), Office of Product Quality (OPQ)
Ciby Abraham, PhD	Acting Pharmaceutical Assessment Lead, ONDP/OPQ
Freda Cooner, PhD	Biometrics Team Leader
Feng Li, PhD	Biometrics Reviewer
Yun Xu, PhD	Clinical Pharmacology Team Leader
Wei Qiu, PhD	Clinical Pharmacology Reviewer
Diana Walker, PhD	Sr. Regulatory Project Manager, DAAAP

EASTERN RESEARCH GROUP ATTENDEES

Christopher Sese, Independent Assessor

1.0 BACKGROUND

- a. (b) (4) plans to submit a 505(b)(2) NDA for Cocaine hydrochloride topical solution 4%, indicated for diagnostic procedures and surgeries on or through the accessible mucous membranes of the nasal cavities. The purpose of this meeting is to discuss the Sponsor's proposed plan for the NDA submission.
- b. The Sponsor received the Division's preliminary responses to the meeting questions on June 15, 2015, via email. The Sponsor requested that the meeting be delayed and converted into a face-to-face meeting and the Agency agreed.
- c. The Sponsor sent a response to the Agency via email on July 13, 2015, containing additional clarification information and questions for the Agency.
- d. The Sponsor's original questions are incorporated below in *italics* followed by the FDA Response in **bold** font. Discussion that took place during the meeting is captured following the question to which it pertains in normal text.

2. DISCUSSION

Question 1. A proposed NDA Content Plan is provided in Appendix 1 for your review and agreement. (b) (4) requests the Agency's agreement with the proposed content of complete application as provided.

Agency Response:

From the CMC perspective, we are unable to agree with the outline provided because it is unclear. However, we recommend you refer to the guidance documents listed below for the required CMC information to support your NDA. In addition, the following is required at the time of filing.

1. **Include a well-documented Pharmaceutical Development Report per the ICH-Q8 guideline and highlight how critical quality attributes and critical process parameters are identified and controlled. Refer to guidance for industry: Q8(R2) *Pharmaceutical Development*, available at <http://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/UCM073507.pdf>.**

Discussion:

The Sponsor provided the following response: (b) (4) *has reviewed the referenced Guidance and will provide a Pharmaceutical -Development Report at the time of filing. No further discussion required.*

- 2. Include at least 12 months of real time stability data and 6 months of accelerated stability data for the drug product stored in both the upright and inverted orientations. In order to be able to grant a viable expiry, data must be provided for at least three batches of drug product, on a production scale.**

Discussion:

The Sponsor provided the following response: (b) (4) *will provide stability, on three production scale batches of drug product, demonstrating at least 12 months real time, 6 months accelerated data and 12 months data on the intermediate stability conditions in both upright and inverted orientations. No further discussion required.*

- 3. Provide a list of all manufacturing and testing facilities and their complete addresses, and a statement about their cGMP status. For all sites, provide a name contact and address with telephone number and facsimile number at the site. Clearly specify the responsibilities (e.g., manufacturer, packager, release tester, stability tester etc.) of each facility, the site CFN numbers and designate which sites are intended to be primary or alternate sites. Note that facilities with unacceptable cGMP compliance may risk approvability of the NDA. Ensure that all of the facilities are ready for inspection by the day the application is submitted, and include a statement confirming to this in the NDA cover letter.**

Discussion:

The Sponsor provided the following response: (b) (4) *will provide a full listing of all manufacturing and testing facilities with complete facility information. No further discussion required.*

- 4. Particularly, refer to the Nasal Guidance for the required testing for nasal sprays. *Nasal Spray and Inhalation Solution, Suspension, and Spray Drug Products – Chemistry, Manufacturing, and Controls Documentation*, available at, <http://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/UCM070575.pdf>.**

Additional Guidance documents:

- a. Guidance for industry: *INDs for Phase 2 and Phase 3 Studies Chemistry, Manufacturing, and Controls Information*,” available at <http://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/ucm070567.pdf> and the 21 CFR 312.23**

- b. **Guidance for industry: *Q3A Impurities in New Drug Substances***, available at <http://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/ucm073385.pdf>
- c. **Guidance for industry: *Q3B (R2) Impurities in New Drug Products***, available at <http://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/ucm073389.pdf>
- d. **Guidance for industry: *Q6A Specifications: Test Procedures and Acceptance Criteria for New Drug Substances and New Drug Products: Chemical Substances***,” available at <http://www.fda.gov/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/ucm134966.htm>
- e. **Guidance for industry: *Container Closure Systems for Packaging Human Drugs and Biologics Chemistry, Manufacturing and Controls Documentation***,” available at <http://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/ucm070551.pdf>
- f. **Guidance for industry: *Q2A Text on Validation of Analytical Procedures***, available at <http://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/ucm073381.pdf>
- g. **Guidance for industry: *Q2B Validation of Analytical Procedures: Methodology***, available at <http://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/ucm073384.pdf>
- h. **Guidance for industry: *Q1A (R2) Stability Testing for New Drug Substances and Products***, available at <http://www.fda.gov/downloads/drugs/guidancecomplianceregulatoryinformation/guidances/ucm073369.pdf>
- i. **Guideline for Elemental Impurities *Q3D*** <http://www.fda.gov/downloads/drugs/guidancecomplianceregulatoryinformation/guidances/ucm371025.pdf>

Discussion:

The Sponsor provided the following response: *It should be noted that this is not a nasal spray product, but a pledget that is saturated with drug product in a practitioner’s office, and then placed in the nasal cavity by a practitioner. We do not believe the nasal spray guidance is applicable to this drug product as administered. Pledgets are commercially available devices commonly used with intranasal products.*

(b) (4) would like the Division's agreement that the nasal spray guidance, as referenced, is not applicable to this drug product.

The Agency clarified that the guidance citation was provided in case the Sponsor elects to change the method of product delivery in the future. The Sponsor stated that they understood the clarification.

Clinical Comments:

We are unable to agree with the proposed content of your application as provided because the outline you have submitted is difficult to understand and not enough information is presented. If you would like additional information on eCTD specifications, refer to guidance for industry: *Providing Regulatory Submissions in Electronic Format — Certain Human Pharmaceutical Product Applications and Related Submissions Using the eCTD Specifications*, available at <http://www.fda.gov/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/ucm064994.htm>. If you follow this guidance, as well as the documents to which this guidance refers, the content of your application will likely be acceptable.

Discussion:

The Sponsor provided the following response: (b) (4) will refer to and follow the Guidance and referenced documents when compiling the content of the application. No further discussion required.

Question 2. A Statistical Analysis Plan with proposed data listings and tables and a proposed Table of Contents of the Clinical Study Report are provided in Appendix 2. (b) (4) requests the Agency's agreement with the proposed analysis plan to include presentation of the data listings, tables and clinical study report.

Agency Response:

We do not agree with your Statistical Analysis Plan (SAP) and have the following comments:

- a. It appears that each strength of the active treatments (cocaine 4% or 8%) will be compared with placebo separately at a two-sided significance level of 0.05. If you only intend to demonstrate the superiority of the 4% strength over placebo, you must state so clearly in your SAP and the comparison between the 8% strength and placebo will be considered exploratory. Otherwise, you must propose a strategy for multiplicity adjustment to control the study-wise type I error rate.

Discussion:

The Sponsor provided the following response: (b) (4) intends to demonstrate the superiority of the 4% strength over placebo and will edit the SAP to clearly state this. Additionally, the SAP will indicate the 8% strength against placebo is for exploratory purpose only. No further discussion required.

- b. Clarify whether taking additional medications of any type (including antibiotics and/or cardiac-related medications) during the procedure or surgery will be considered as analgesic treatment failure in the efficacy analyses. The pages 11 and 14 of your SAP are not consistent in this regard.**

Discussion:

The Sponsor provided the following response: *Page 14, second bullet has been corrected to read the following:*

- *During the procedure or surgery, no further medication (with the exception of antibiotics and/or cardiac-related medications) is required (4% or 8% RX0041-002).*

No further discussion required.

- c. Report the timing of unblinding for each subject in the study report.**

Additionally, subgroup analyses by gender, race and age must be conducted and presented in your NDA submission.

Discussion:

The Sponsor provided the following response: *Unblinding in each subject occurred following the removal of the pledgets and the Von Frey Filament Test (pain assessment). A listing of individual time of unblinding will be including in the Clinical Study Report. The strength of Cocaine HCl remained unblinded throughout the procedure. Subgroup analyses by gender, race and age will also be presented in the NDA. No further discussion required.*

Clarify if you intend to embed the Clinical Study Report in the Statistical Analysis Plan. This is acceptable as long as all the necessary information is present in the Clinical Study Report. Clinical information that would be desirable in the Clinical Study Report that does not appear to exist in the Statistical Analysis Plan you outlined include:

- **Table of efficacy by subject weight**
- **Table of adverse events by subject weight**
- **BMI included in demographic table**
- **ECG, blood pressure, heart rate, respiratory rate, and temperature shift tables that detail the respective changes in ECG, blood pressure, heart rate, respiratory rate and temperature of subjects in the 90 minutes following topical cocaine administration**
- **Table of the percentage of treatment-emergent adverse events by preferred term and concentration of cocaine received compared to placebo**
- **Table of laboratory-related adverse events by concentration of cocaine received compared to placebo**
- **Table describing time to onset and duration of adverse events by concentration of cocaine received**

- **Analysis of past medical history as it pertains to adverse events from cocaine. For example, analyze whether those with a history of hypertension are more likely to experience high blood pressure from cocaine.**
- **Analysis of concomitant medications as they pertain to adverse events from cocaine**

Discussion:

The Sponsor provided the following response: *It is not our intent to embed the Clinical Study Report in the Statistical Analysis Plan. (b) (4) will include the referenced tables as requested in the filing. No further discussion required.*

Question 3. At this time, (b) (4) does not propose any minor components to be submitted within 30 days after the original submission. (b) (4) requests the Agency's agreement that no minor components will be submitted following the original submission of the NDA.

Agency Response:

We advise that you read the FDA comments present in this document and then decide whether this question is still applicable.

Discussion:

The Sponsor provided the following response: *At this time, (b) (4) does not foresee any minor components to be submitted within 30 days after the original submission. However, based on discussions during our meeting, (b) (4) may identify information requiring the post submission phase.*

There was no further discussion of this point.

Question 4. Cocaine Hydrochloride Topical Solution 4% is administered in the office or operating suite by the healthcare practitioner or medical staff. At no time is the drug product prescribed for home use or self-administered by the patient. (b) (4)
(b) (4) As such, this product does not pose any risk of abuse at the patient level and does not require a REMS program.
(b) (4) requests the Agency's agreement that a REMS program is not required with this New Drug Application.

Agency Response:

It does not appear at this time that your NDA would require a REMS program. However, a REMS program may be necessary if FDA becomes aware of new safety information.

Discussion:

There was no further discussion of this question.

Question 5. (b) (4) submitted a Pediatric Study Plan on March 24, 2015 (Serial Number 0006) to IND 118527. (b) (4) requests the Agency's agreement on the proposed Pediatric Study Plan as submitted.

Agency Response:

Protocols are in place to ensure appropriate review of your Pediatric Study Plan.

Comments on your Pediatric Study Plan are due to you on June 23, 2015.

Discussion:

The Sponsor provided the following response: (b) (4) received the Division's June 19, 2015, Information Request on the submitted Pediatric Study Plan and will respond to this Information Request in a separate response document by the recommended response time. No further discussion required at this meeting.

Question 6. (b) (4) is not aware of any FDA approval of a marketing application for a drug product containing cocaine. As such, cocaine is considered a New Chemical Entity (NCE) as defined in 21 CFR § 314.108(a) to mean "a drug that contains no active moiety that has been approved by FDA in any other application submitted under section 505(b) of the act.

(b) (4) requests the Agency's agreement that Cocaine Hydrochloride Topical Solution, 4% qualifies as a NCE.

Agency Response:

At this time, Cocaine Hydrochloride Topical Solution, 4% is considered a new chemical entity. It also meets the definition of a New Molecular Entity.

Discussion:

There was no further discussion of these comments requested by the Sponsor; however, the Agency reminded the Sponsor that determination of exclusivity is made after an NDA is approved, and that the Sponsor should refer to CFR 314.50j for a description of the information they should include in their NDA submission regarding exclusivity.

Additionally, the Division informed the Sponsor that the determination of whether this product will be reviewed as an NME may change prior to NDA submission, based on pending revisions to the relevant MAPP. The Sponsor will be informed of this change occurs, and how this change might impact their application.

Question 7. As a NCE, the statute, FDA Act §§ 505(o)(3)(E)(ii) and 505(j)(5)(F)(ii) provides that the first approval of a drug product containing cocaine as an active ingredient will result in FDA granting a period of 5 year exclusivity to that application sponsor, and that such exclusivity prevents the submission and

approval of an ANDA or a 505(b)(2) NDA for a drug product containing cocaine until the exclusivity period has expired.

(b) (4) *requests the Agency's agreement that the first company to obtain approval of a NDA for cocaine will be granted 5 year NCE exclusivity.*

Agency Response:

We agree that the first company to obtain approval of an NDA for cocaine is eligible for 5-year NCE exclusivity. However, the Agency does not make exclusivity determinations pursuant to Sections 505(c)(3)(E) and (j)(5)(F) of the Federal Food Drug and Cosmetic Act, and 21 CFR 314.108, until after approval of an NDA. As described at 314.50(j), an applicant should include in its NDA a description of the exclusivity to which the applicant believes it is entitled. FDA will consider the applicant's assertions regarding exclusivity in the review of the application. See additional information below under "Additional Comments/Exclusivity Determination".

Discussion:

There was no further discussion of this question.

Question 8. Cocaine Hydrochloride Topical Solution is a schedule II narcotic intended for the introduction of local (topical) anesthesia for diagnostic procedures and surgeries on or through the accessible mucous membranes of the nasal cavities that is currently marketed without FDA approval of a marketing application. To prevent further distribution of an addictive drug product without appropriate FDA controls, to encourage companies to seek approval of marketed unapproved drug products, and consistent with FDA policy on expedited review (and precedent in the context of morphine sulfate), FDA should grant priority review to (b) (4) application for Cocaine Hydrochloride Topical Solution.

(b) (4) *requests the Agency's agreement that (b) (4) Cocaine Hydrochloride Topical Solution meets the criteria for granting priority review and that the company's 505(b)(2) NDA will be designated as such after submission.*

Agency Response:

Whether or not priority review will be granted will be determined at the time of NDA submission.

Discussion:

There was no further discussion of this question.

ADDITIONAL COMMENTS

Nonclinical Comments:

Based on the information submitted to date, you do not appear to have adequately addressed the concerns raised in the PreIND meeting comments provided in 2013. Specifically, in 2013, we indicated that a full standard battery of genetic toxicology studies will be required to support your NDA submission. Based on preliminary review of the literature submitted to date, you appear to have submitted literature references for an incomplete Ames assay, a positive in vitro chromosomal aberrations assay, and a negative in vivo micronucleus assay. Final determination of the adequacy of the published literature to address this requirement has not yet been completed. However, based on preliminary review, the Ames assay is not adequate and the positive results in the in vitro chromosomal aberrations assay should be further evaluated either via a repeat of the in vitro study, mechanistic studies to show that the result is not relevant to humans or via a fourth assay, as described in the FDA guidance to industry titled: *Recommended Approaches to Integration of Genetic Toxicology Study Results*, available at <http://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/UCM079257.pdf> .

Discussion:

The Sponsor provided the following response: (b) (4) *believes the in vivo micronucleus assay (negative result) and the in vitro chromosomal aberration assay (positive result) that are reported in the scientific literature are adequate to support this 505(b)(2) application. (b) (4) plans to perform a complete AMES assay under GLP, (b) (4) also recognizes that a forth assay is needed to address the positive in vitro chromosomal aberration assay. We propose to perform a GLP Comet assay in liver tissue (the primary target organ for cocaine metabolism) from rats dosed via IP dosing at an experienced contract GLP laboratory. Does the Agency agree that the genotoxicity potential of cocaine will be adequately addressed for labeling and safety evaluation with summaries of the existing published cocaine genotoxicity data, a GLP Ames assay, and a GLP comet assay in liver tissue?*

The Division agreed that the proposal is acceptable. The Agency also agreed that the use of liver tissue is acceptable, as it is commonly used in this type of assay.

In addition, based upon review of your drug product formulation, there are technically three excipients that are not present in FDA-approved intra-nasal drug products and are therefore defined as new excipients via this route of administration: sodium benzoate, D&C Yellow No. 10, and FD&C Green No. 3. As noted in the PreIND meeting minutes, your NDA must include adequate safety justification for these excipients used for this route of administration as per the guidance for industry: *Nonclinical Studies for the Safety Evaluation of Pharmaceutical Excipients*, available at, <http://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/UCM079250.pdf>.

Discussion:

The Sponsor provided the following response: (b) (4) *notes that the 3 excipients are used extensively in other drug products, and that this is a single use product that has been in use for 50 years, as well as in a phase 3 clinical trial where human nasal tissue was evaluated in each*

patient. We realize that histopathology data are not collected in humans. (b) (4) however, does not understand what at this time could be learned in an animal qualification study that would be useful or relevant to human safety when there is an incredibly large amount of clinical experience with these excipients. Please note that we have read and understand the guidance document cited, as well as the guidance for drugs on route of administration changes. We understand the general approach for safety evaluation of excipients. We note, however, that these are guidances, and seem to not be applicable to excipients that are so very well known and utilized in so many drug products, and for a single-dose intranasal topical drug product that has been marketed for 50 years. (b) (4) would like the Agency's agreement that no additional qualification of the 3 excipients is needed.

The Division stated that this rationale is not acceptable and did not agree, as the excipients are new to the intranasal route of administration. The Agency suggested that one option would be to provide available human data to justify the safety of the excipients. Any clinical safety justification will be reviewed for adequacy, and if found to be inadequate, there could be potential approval or post-marketing requirement implications. As topical cocaine is a marketed, unapproved product and the formulation is currently being used, the Sponsor could leverage the existing data and provide rationale for the excipient qualification. The adequacy of this submission would be a review issue, and not a refuse-to-file issue.

The Sponsor asked whether, if they were to provide a clinical assessment of abnormal/normal from their Phase 3 study in which nasal passages were examined after product administration, would this be sufficient to justify the intranasal route safety of the excipients. The Division stated that using only an "abnormal/normal" assessment is not sufficient, and additional information is required. The Sponsor should provide detailed information on both what was observed and what was expected in order for the Division to make a safety assessment based on these data.

The Division stated that, if the Sponsor does plan to conduct a local toxicity study, a 14-day study duration would be acceptable. The concentrations and doses tested should be adequately justified as per ICH M3(R2).

Your drug substance specifications include two (b) (4) that are not addressed in ICH Q3C(R5), specifically, (b) (4). Your NDA must include justification for the proposed specifications. Refer to guidance for industry: Q3C Impurities: (b) (4) available at <http://www.fda.gov/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/ucm065005.htm>

and

Q3C Tables and List, available at <http://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/UCM073395.pdf>.

Discussion:

The Sponsor provided the following response:

(b) (4) has determined there is an error in the DMF which is being addressed with the drug substance manufacturer. (b) (4)

(b) (4) should be limited under the guidance ICH Q3A, Impurities in New drug substance. (b) (4) intends to set the specification limit for this impurity as per this guidance. Details of this information will be included in the NDA. No further comments needed at meeting.

(b) (4) will provide available literature to establish and justify the specification for the (b) (4), in the Cocaine Hydrochloride drug substance.

No further discussion required.

The NDA must also specifically define the maximum daily dose of cocaine in order to fully evaluate the drug substance specifications, drug product specifications, excipient safety, and extractable/leachables. Submit clinical use data to support the worst-case daily use and evaluate the safety of the product accordingly.

Discussion:

The Sponsor provided the following response: *This product is for physician's office use only, and will not be available as an Rx prescription product to consumers. For labeling and where calculations are needed we will assume that patients are exposed to the full 4 ml of the 4% cocaine solution. Does the Division agree with this approach?*

The Division stated that, in their NDA submission, the Sponsor must provide justification for the number chosen for the MDD based on clinical use data, and that the MDD should be based on a theoretical "worst case" scenario. The Division also stated that, if an assessment is presented and during the course of the NDA and literature review the Division does not find evidence contradictory to the justification, the number chosen for the MDD will likely be acceptable.

The Sponsor should assume 100% of the MDD for excipient qualification.

We remind you of the following nonclinical comments that have been provided to assist you in the development of you NDA submission:

- 1. Your NDA submission must contain information on potential leachables and extractables from the drug container closure system and/or drug product formulation, unless specifically waived by the Division. The evaluation of extractables and leachables from the drug container closure system or device should include specific assessments for residual monomers, solvents, polymerizers, etc. The choice of solvents and conditions for the extraction studies should be justified. The results of the extraction studies should be used to assure that you are adequately monitoring the drug product stability samples for potential leachables. Although a**

toxicological risk assessment based on the results of the extraction studies may be adequate to support the safety assessment during development, you should still evaluate at least three batches of your drug product over the course of your stability studies and base the final safety assessment on the levels of leachables identified to determine the safe level of exposure via the label-specified route of administration. The approach for toxicological evaluation of the safety of leachables must be based on good scientific principles and take into account the specific container closure system or patch, drug product formulation, dosage form, route of administration, and dose regimen (chronic or short-term dosing). As many residual monomers are known genotoxic agents, your safety assessment must take into account the potential that these leachables may either be known or suspected highly reactive and/or genotoxic compounds. The safety assessment should be specifically discussed in Module 2.6.6.8 (Toxicology Written Summary/Other Toxicity) of the NDA submission. For additional guidance on extractables and leachables testing, refer to the FDA guidance for industry: *Container Closure Systems for Packaging Human Drugs and Biologics*, available at, <http://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/UCM070551.pdf> and the FDA guidance for industry: *Nasal Spray and Inhalation Solution, Suspension, and Spray Drug Products – Chemistry, Manufacturing, and Controls Documentation*, available at, <http://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/UCM070575.pdf>. From a genetic toxicology perspective, we will allow up to 120 mcg/day for an acute indication for most potentially genotoxic impurities. However, a toxicological risk assessment should be provided for any non-genotoxic leachable that exceeds (b) (4) mcg/day. The risk assessment should be based on the levels of leachables detected in long-term stability samples that include any intended secondary container closure system(s) unless otherwise justified.

Discussion:

The Sponsor provided the following response: (b) (4) plans to address extractables and leachables of the container closure system as per the applicable guidances' and the USP general chapters' requirements. (b) (4)

. Does the Division agree with this approach?

The Sponsor clarified (b) (4)

The Agency clarified that information (b) (4) is required. (b) (4) they can obtain an LOA from the DMF holder. If the DMF has appropriate extractable/leachable data to support the proposed product then the Sponsor does not need to conduct the study.

Regarding the extraction study solvent, the Agency stated that the extraction studies should use multiple solvents and that the container-closure materials should be exposed to harsh environments so that the compounds that will be assayed for on long-term stability can be identified. It was also recommended that the Sponsor include high temperature as part of the extraction studies.

The toxicology assessment will be based on what is found in the leachables, ideally over long-term stability. The Sponsor should test for leachables in 3 batches over multiple timepoints throughout the expiry.

- 2. Your NDA submission should include a detailed discussion of the nonclinical information in the published literature and should specifically address how the information within the published domain impacts the safety assessment of your drug product. This discussion should be included in Module 2 of the submission. Copies of all referenced citations should be included in the NDA submission in Module 4. Journal articles that are not in English must be translated into English.**

Discussion:

The Sponsor provided the following response: *We will submit a detailed discussion of the published literature in the NDA. No further discussion required.*

- 3. The nonclinical information in your proposed drug product labeling must include relevant exposure margins with adequate justification for how these margins were obtained. As you intend to rely upon literature to support the pregnancy and fertility sections of the labeling, if the referenced studies employ a different route of administration or lack adequate information to allow scientifically justified extrapolation to your product, you may need to conduct additional pharmacokinetic studies in animals in order to adequately bridge your product to the referenced product labeling.**

Discussion:

The Sponsor provided the following response: *We intend to calculate exposure margins utilized Body Surface Area (BSA) comparisons. No bridging PK studies are planned for this 505(b)(2) submission. We understand that literature will include various routes of administration, and not just intra-nasal administration. However, we believe the BSA comparison will be a very conservative comparison, given that the drug product is intended to be a local, single dose product with limited systemic exposure by design.*

The Agency stated that, while a BSA comparison is acceptable, exposure data are better. Exposure data would assist in providing a more accurate label for this specific product. One suggestion is to conduct an animal pharmacokinetic bridging study across various doses and exposures. Then, likely exposures from all other studies can be extrapolated to provide a more biologically meaningful safety or exposure margin. This is the same recommendation provided to the Sponsor to assist in the interpretation of the juvenile animal data from the published literature, as noted in our response to their pediatric study plan.

- 4. We note that all NDA applications filed after June 30, 2015, must submit labeling consistent with the Final Pregnancy Labeling and Lactation Rule (PLLR). In order**

to prepare for this new labeling format, you should conduct a thorough review of the existing clinical and nonclinical literature for each drug substance in your drug product and propose a risk summary statement and text for Section 8 of the labeling. Refer to

<http://www.fda.gov/drugs/developmentapprovalprocess/developmentresources/ucm093307.htm>

Discussion:

The Sponsor provided the following response: *Proposed labeling consistent with the PLLR will be submitted within the filing. In animal studies, dose levels will be compared using BSA multiples. No further discussion required.*

5. **We recognize that you have already submitted a literature-based safety assessment for drug product degradants and drug substance impurities. This will be reviewed at the time of the NDA submission. However, we remind you that if these data are not deemed adequate or if other impurities or degradants are identified during the course of the NDA review, any impurity or degradation product that exceeds ICH thresholds must be adequately qualified for safety as per ICH Q3A(R2), ICH Q3B(R2) or be demonstrated to be within the specifications of the referenced drug used for approval through the 505(b)(2) pathway. In order to provide adequate qualification:**
 - a. **You must complete a minimal genetic toxicology screen (two *in vitro* genetic toxicology studies, e.g., one point mutation assay and one chromosome aberration assay) with the isolated impurity, tested up to the limit dose for the assay.**

Discussion:

The Sponsor provided the following response:

1. (b) (4) will provide data from two *in vitro* genetic toxicology studies needed for drug substance impurity, (b) (4)
 - a. Ames assay and chromosomal aberration assay *in vitro* in reporting stage. Similar to cocaine, (b) (4) in the chromosomal aberration assay.
 - b. Plan to perform *in vivo* micronucleus assay and *in vivo* rat liver Comet assay.
2. In the FDA's June 25, 2015 Preliminary Comments Letter, under the CMC comments, the limit for (b) (4) impurity is stated to be above ICH Q3B limits. (b) (4) a qualified impurity per the ICH guidance Q3b, "Impurities in new drug products with a permissible level up to (b) (4) %." (b) (4) has established the specification of (b) (4) at NMT (b) (4) %.

Does the Division agree with justification of the specification for this impurity?

The Agency stated that the acceptability depends on the context of the (b) (4) levels. A (b) (4) specification level is very high and may have clinical implications. The NDA should include justification for the safety of the degradant at this level. The NDA application should address whether this specification level has clinical implications for local or systemic exposure, and should also address the relationship of these levels to the levels that were present during the clinical trials when the local tissue assessments were performed. If justification for the specification is submitted, it will be considered a review issue and not a filing issue. If no justification is provided, it could be considered a refuse-to-file issue.

The Sponsor clarified that the assay range is (b) (4)%, and that they could potentially tighten the specification for the assay and for the major impurity.

- a. In addition, you must conduct a repeat-dose toxicology study of appropriate duration to support the proposed indication. In this case, a study of 14-days duration should be completed.**

Discussion:

The Sponsor provided the following response: (b) (4) *plans to conduct a repeat-dose toxicology study for (b) (4) would like the Division's guidance on the design of the:*

- a. Rat study*
- b. Intranasal study*
- c. Vary dose by volume*
- d. Saline control, 3 treated groups*
- e. Histopathology of nasal cavity and respiratory track only*

The Agency stated that the proposed approach appears to be logical. Varying the volume instead of the concentration is acceptable, but there may be practical issues surrounding volume limits in a rat nose. The Agency noted that the Sponsor may need to increase volume to push the dose with a target of a (b) (4)-fold higher dose than planned for clinical use, but the dose should at least mirror the clinical maximum. It was also suggested that including both placebo- and vehicle-controlled arms in the study would be useful. The Agency stated that the Sponsor should provide full histopathology in this study.

- 6. In Module 2 of your NDA (2.6.6.8 Toxicology Written Summary/Other Toxicity), include a table listing the drug substance and drug product impurity specifications, the maximum daily exposure to these impurities based on the maximum daily dose of the product, how these levels compare to ICHQ3A(R2) and Q3B(R2) qualification thresholds, and if the impurity contains a structural alert for mutagenicity. Any proposed specification that exceeds the qualification thresholds should be adequately justified for safety from a toxicological perspective.**

Discussion:

The Sponsor provided the following response: *Impurity data will be tabulated as requested. No further discussion required.*

7. **We may refuse to file your application if your NDA submission does not contain adequate safety qualification data for any identified impurity or degradant that exceeds the ICH qualification thresholds, if the submission lacks adequate safety information for any novel excipient, or if the submission lacks an adequate extractable/leachable risk assessment.**

Discussion:

The Sponsor provided the following response: *We have read your statement about reasons for a refuse to file. Please note in our meeting minutes of 3/2/15, it was specifically noted that not including a 14 day study for impurities would NOT be a refuse to file issue. Does the Agency still agree with this statement made on 3/2/2015?*

The Agency stated that this is an incorrect interpretation of the comment in the meeting minutes, in that it is not applicable to every situation. The statement in the meeting minutes was true in the context of the (b) (4) impurity and should not be generalized across the board. Additionally, the statement only holds true if justification for not including the study is provided. If justification is not provided, it could be a refuse-to-file issue.

8. **For general toxicology, supporting nonclinical toxicokinetic and carcinogenicity studies we encourage you to both use Standards for the Exchange of Nonclinical Data (SEND) for regulatory submissions and to submit sample or test data sets before implementation becomes required. Sponsors will be provided feedback on the suitability of these test data sets. Information about submitting a test submission can be found here:**
<http://www.fda.gov/Drugs/DevelopmentApprovalProcess/FormsSubmissionRequirements/ElectronicSubmissions/ucm174459.htm>.

Discussion:

The Sponsor provided the following response: (b) (4) *will submit SEND data if they are available from the selected GLP contract laboratories. No further discussion required.*

Clinical Pharmacology Comments:

We remind you that a complete clinical pharmacology package is expected at the time of NDA submission. You must address all pertinent clinical pharmacology information related to the following aspects of the drug and the pharmacokinetics of the drug in special populations including but not limited to: (1) absorption, (2) distribution (e.g., in vivo study with radiolabeled product), (3) metabolism (e.g., in vitro study using human microsomes/hepatocytes and/or analyze plasma samples from in vivo studies for assessment of potential metabolites), (4) elimination (e.g., collect urine and feces samples in Phase 1 studies to determine elimination pathways), (5) PK and dosing in special populations (e.g., effect of age, gender, hepatic and renal impairment), (6) drug interaction potential (e.g., in vitro enzyme and transporter induction and inhibition properties of your drug and in vivo

studies if warranted), and (7) QT prolongation potential. This information can be obtained from dedicated studies or sub-population analyses in Phase 3 studies) or from the public domain (if information of adequate quality is available in the published literature). If literature articles are used for obtaining this information, full articles must be included in the NDA.

Discussion:

The Sponsor provided the following response: (b) (4) believes that sufficient data will be available in the literature to address all pertinent clinical pharmacology and pharmacokinetic information. We are also aware of the literature addressing the potential for cardiovascular problems (QTc prolongation; hypertension etc) with cocaine, when administered by systemic routes (i.v.; intranasal; pulmonary inhalation). We have not observed cardiovascular safety problems in our clinical trial; however, we will provide a thorough discussion of this dose-related topic in the NDA submission. Additionally, we also believe that this is primarily a topical product designed to have minor systemic exposure, and thus special population studies are not relevant as they would be for a systemic drug product. Finally, we are considering a dedicated pharmacokinetic study, if necessary, to bridge the pharmacokinetics of our 4% topical Cocaine HCl formulation with the literature values and to support the pharmacokinetic safety during routine procedures and/or surgeries conducted in the nasal cavity. Does the Division agree that studies conducted in special populations are not relevant with this drug product and do not need to be conducted?

The Agency stated that the Sponsor must provide justification as to why special population studies are not relevant to their product. The Sponsor must provide evidence of low systemic exposure levels using data from the PK study. The PK study must be of adequate sample size, and include validated analytical assays for cocaine and its metabolites. The Agency also recommended that the Sponsor attempt to obtain analytical reports cited in literature sources and submit these as additional evidence.

ABUSE POTENTIAL ASSESSMENT

Drugs that affect the central nervous system, are chemically or pharmacologically similar to other drugs with known abuse potential, or produce psychoactive effects such as mood or cognitive changes (e.g., euphoria, hallucinations) need to be evaluated for their abuse potential and a proposal for scheduling will be required at the time of the NDA submission [21 CFR 314.50(d)(5)(vii)]. For information on the abuse potential evaluation and information required at the time of your NDA submission, see the draft guidance for industry, "Guidance for Industry Assessment of Abuse Potential of Drugs", available at: <http://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/UCM198650.pdf>.

Discussion:

The Sponsor provided the following response: (b) (4) *is somewhat perplexed by the citation of guidance for abuse potential for our single use 4% cocaine solution product. Given the controlled distribution of the drug product, (b) (4) believes we have limited the possibility of abuse. That said, the harmful and addictive effects of repetitive use of cocaine are well known, and additional studies would not make this risk better understood. Clear labeling warning against repeated use is planned for the drug product. Does the Division agree that abuse potential evaluations are not required with this product as the abuse potential is known and will be fully described within the prescribing label?*

The Division stated that a post-meeting note from the Controlled Substances Staff clarifying the Abuse Potential advice would be added to the meeting minutes.

Post Meeting Note: Your NDA submission will need to include a proposal for the scheduling of your drug product under the Controlled Substances Act (CSA), and the basis for the proposal, per 21 CFR 314.50,(d),(5), (vii). You should comply with advice in the draft guidance for abuse potential assessment of your drug. If you will not be conducting abuse-related studies with your proposed topical cocaine HCl formulation, which might support the scheduling of your product in a schedule other than Schedule II, your product will necessarily be placed in Schedule II under the CSA. Your NDA submission must also include summaries of abuse potential- and dependence-related studies to include in Sections 9.2 and 9.3, respectively, of product labeling. Some or all of the necessary information to reference may be in the public domain. Other data in the NDA that relates to scheduling should include abuse and diversion information collected from the clinical studies conducted with your product.

DISCUSSION OF THE CONTENT OF A COMPLETE APPLICATION:

Post Meeting Comments

- All applications are expected to include a comprehensive and readily located list of all clinical sites and manufacturing facilities included or referenced in the application.
- Major components of the application are expected to be submitted with the original application and are not subject to agreement for late submission. You stated you intend to submit a complete application and therefore, there are no agreements for late submission of application components.

3. ACTION ITEMS

- a) The Agency agreed to provide a post-meeting note addressing the Sponsor's question concerning the Abuse Potential Assessment.

4. ATTACHMENTS AND HANDOUTS

None.

5. GENERAL Pre-NDA COMMENTS

DISCUSSION OF THE CONTENT OF A COMPLETE APPLICATION

As stated in our April 10, 2015, communication granting this meeting, if, at the time of submission, the application that is the subject of this meeting is for a new molecular entity or an original biologic, the application will be subject to “the Program” under PDUFA V. Therefore, at this meeting be prepared to discuss and reach agreement with FDA on the content of a complete application, including preliminary discussions on the need for risk evaluation and mitigation strategies (REMS) or other risk management actions. You and FDA may also reach agreement on submission of a limited number of minor application components to be submitted not later than 30 days after the submission of the original application. These submissions must be of a type that would not be expected to materially impact the ability of the review team to begin its review. All major components of the application are expected to be included in the original application and are not subject to agreement for late submission.

Discussions and agreements will be summarized at the conclusion of the meeting and reflected in FDA’s meeting minutes. If you decide to cancel this meeting and do not have agreement with FDA on the content of a complete application or late submission of any minor application components, your application is expected to be complete at the time of original submission.

In addition, we remind you that the application is expected to include a comprehensive and readily located list of all clinical sites and manufacturing facilities.

Finally, in accordance with the PDUFA V agreement, FDA has contracted with an independent contractor, Eastern Research Group, Inc. (ERG), to conduct an assessment of the Program. ERG will be in attendance at this meeting as silent observers to evaluate the meeting and will not participate in the discussion. Please note that ERG has signed a non-disclosure agreement.

Information on PDUFA V and the Program is available at
<http://www.fda.gov/ForIndustry/UserFees/PrescriptionDrugUserFee/ucm272170.htm>.

Discussion:

There was no further discussion of these comments.

PREA REQUIREMENTS

Under the Pediatric Research Equity Act (PREA) (21 U.S.C. 355c), all applications for new active ingredients, new indications, new dosage forms, new dosing regimens, or new routes of administration are required to contain an assessment of the safety and effectiveness of the product for the claimed indication(s) in pediatric patients unless this requirement is waived, deferred, or inapplicable.

Please be advised that under the Food and Drug Administration Safety and Innovation Act (FDASIA), you must submit an Initial Pediatric Study Plan (PSP) within 60 days of an End of

Phase (EOP2) meeting. The PSP must contain an outline of the pediatric study or studies that you plan to conduct (including, to the extent practicable study objectives and design, age groups, relevant endpoints, and statistical approach); any request for a deferral, partial waiver, or waiver, if applicable, along with any supporting documentation, and any previously negotiated pediatric plans with other regulatory authorities. In addition, your iPSP should specifically provide your justification why you believe that nonclinical juvenile animal studies are or are not needed to support your pediatric drug development taking into consideration the specific age ranges to be studied. The justification should be based on a comprehensive literature search focusing on the specific toxicological concerns related to the drug substance and each individual excipient in your drug product and any data you have generated suggesting a unique vulnerability to toxicological insult for the proposed age range to be tested. This risk assessment should take into consideration the expected maximum daily dose of the drug product for the intended patient population and include rationale for your proposed maximum daily dose. In addition, your risk assessment should address how the drug substance and excipients are absorbed, distributed, metabolized, and excreted by the ages of the children you will be studying. You must include copies of all referenced citations. If you conclude that a juvenile animal study is necessary, provide a detailed outline of the specific study you propose to conduct, including what toxicological endpoints you will include in the study design to address any specific questions, and justification for your selection of species and the age of the animal to be tested. We recommend that you refer to the FDA guidance for industry, *Nonclinical Safety Evaluation of Pediatric Drug Products*, available at, <http://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/UCM079247.pdf>. The PSP should be submitted in PDF and Word format.

For additional guidance on the timing, content, and submission of the PSP, including a PSP Template, please refer to the draft guidance for industry, *Pediatric Study Plans: Content of and Process for Submitting Initial Pediatric Study Plans and Amended Pediatric Study Plans* at: <http://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/UCM360507.pdf>. In addition, you may contact the Division of Pediatric and Maternal Health at 301-796-2200 or email pdit@fda.hhs.gov. For further guidance on pediatric product development, please refer to: <http://www.fda.gov/Drugs/DevelopmentApprovalProcess/DevelopmentResources/ucm049867.htm>.

Discussion:

There was no further discussion of these comments.

PRESCRIBING INFORMATION

In your application, you must submit proposed prescribing information (PI) that conforms to the content and format regulations found at 21 [CFR 201.56\(a\) and \(d\)](#) and [201.57](#) including the Pregnancy and Lactation Labeling Rule (PLLR) (for applications submitted on or after June 30, 2015). As you develop your proposed PI, we encourage you to review the labeling review resources on the [PLR Requirements for Prescribing Information](#) and [PLLR Requirements for Prescribing Information](#) websites including:

- The Final Rule (Physician Labeling Rule) on the content and format of the PI for human drug and biological products
- The Final Rule (Pregnancy and Lactation Labeling Rule) on the content and format of information related to pregnancy, lactation, and females and males of reproductive potential in the PI for human drug and biological products
- Regulations and related guidance documents
- A sample tool illustrating the format for Highlights and Contents, and
- The Selected Requirements for Prescribing Information (SRPI) – a checklist of 42 important format items from labeling regulations and guidances.
- FDA’s established pharmacologic class (EPC) text phrases for inclusion in the Highlights Indications and Usage heading.

Prior to submission of your proposed PI, use the SRPI checklist to ensure conformance with the format items in regulations and guidances.

Discussion:

There was no further discussion of these comments.

DATA STANDARDS FOR STUDIES

CDER strongly encourages IND sponsors to consider the implementation and use of data standards for the submission of applications for investigational new drugs and product registration. Such implementation should occur as early as possible in the product development lifecycle, so that data standards are accounted for in the design, conduct, and analysis of clinical and nonclinical studies. CDER has produced a web page that provides specifications for sponsors regarding implementation and submission of clinical and nonclinical study data in a standardized format. This web page will be updated regularly to reflect CDER's growing experience in order to meet the needs of its reviewers. The web page may be found at: <http://www.fda.gov/Drugs/DevelopmentApprovalProcess/FormsSubmissionRequirements/ElectronicSubmissions/ucm248635.htm>

Discussion:

There was no further discussion of these comments.

MANUFACTURING FACILITIES

To facilitate our inspectional process, we request that you clearly identify *in a single location*, either on the Form FDA 356h, or an attachment to the form, all manufacturing facilities associated with your application. Include the full corporate name of the facility and address where the manufacturing function is performed, with the FEI number, and specific manufacturing responsibilities for each facility.

Also provide the name and title of an onsite contact person, including their phone number, fax number, and email address. Provide a brief description of the manufacturing operation conducted at each facility, including the type of testing and DMF number (if applicable). Each facility should be ready for GMP inspection at the time of submission.

Consider using a table similar to the one below as an attachment to Form FDA 356h. Indicate under Establishment Information on page 1 of Form FDA 356h that the information is provided in the attachment titled, "Product name, NDA/BLA 012345, Establishment Information for Form 356h."

Site Name	Site Address	Federal Establishment Indicator (FEI) or Registration Number (CFN)	Drug Master File Number (if applicable)	Manufacturing Step(s) or Type of Testing [Establishment function]
1.				
2.				

Corresponding names and titles of onsite contact:

Site Name	Site Address	Onsite Contact (Person, Title)	Phone and Fax number	Email address
1.				
2.				

Discussion:

There was no further discussion of these comments.

505(b)(2) REGULATORY PATHWAY

The Division recommends that sponsors considering the submission of an application through the 505(b)(2) pathway consult the Agency's regulations at 21 CFR 314.54, and the draft guidance for industry *Applications Covered by Section 505(b)(2)* (October 1999), available at <http://www.fda.gov/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/default.htm>.

In addition, FDA has explained the background and applicability of section 505(b)(2) in its October 14, 2003, response to a number of citizen petitions that had challenged the Agency's interpretation of this statutory provision (see Docket FDA-2003-P-0274-0015, available at <http://www.regulations.gov>).

If you intend to submit a 505(b)(2) application that relies for approval, in part, on FDA's finding of safety and/or effectiveness for one or more listed drugs, you must establish that such reliance is scientifically appropriate, and must submit data necessary to support any aspects of the proposed drug product that represent modifications to the listed drug(s). You should establish a "bridge" (e.g., via comparative bioavailability data) between your proposed drug product and each listed drug upon which you propose to rely to demonstrate that such reliance is scientifically justified.

If you intend to rely, in part, on literature or other studies for which you have no right of reference but that are necessary for approval, you also must establish that reliance on the studies described in the literature or on the other studies is scientifically appropriate. You should include a copy of such published literature in the 505(b)(2) application and identify any listed drug(s) described in the published literature (e.g., trade name(s)).

If you intend to rely, in part, on the Agency's finding of safety and/or effectiveness for a listed drug(s) or published literature describing a listed drug(s) (which is considered to be reliance on FDA's finding of safety and/or effectiveness for the listed drug(s)), you should identify the listed drug(s) in accordance with the Agency's regulations at 21 CFR 314.54. It should be noted that 21 CFR 314.54 requires identification of the "listed drug for which FDA has made a finding of safety and effectiveness," and thus an applicant may only rely upon a listed drug that was approved in an NDA under section 505(c) of the FD&C Act. The regulatory requirements for a 505(b)(2) application (including, but not limited to, an appropriate patent certification or statement) apply to each listed drug upon which a sponsor relies.

If you propose to rely on FDA's finding of safety and/or effectiveness for a listed drug that has been discontinued from marketing, the acceptability of this approach will be contingent on FDA's consideration of whether the drug was discontinued for reasons of safety or effectiveness.

We encourage you to identify each section of your proposed 505(b)(2) application that relies on FDA's finding of safety and/or effectiveness for a listed drug(s) or on published literature. In your 505(b)(2) application, we encourage you to clearly identify (for each section of the application, including the labeling): (1) the information for the proposed drug product that is provided by reliance on FDA's finding of safety and/or effectiveness for the listed drug or by reliance on published literature; (2) the "bridge" that supports the scientific appropriateness of such reliance; and (3) the specific name (e.g., proprietary name) of each listed drug named in any published literature on which your marketing application relies for approval. If you are proposing to rely on published literature, include copies of the article(s) in your submission.

In addition to identifying in your annotated labeling the source(s) of information essential to the approval of your proposed drug that is provided by reliance on FDA's previous finding of safety and efficacy for a listed drug or by reliance on published literature, we encourage you to also

include that information in the cover letter for your marketing application in a table similar to the one below.

List the information essential to the approval of the proposed drug that is provided by reliance on the FDA’s previous finding of safety and efficacy for a listed drug or by reliance on published literature	
Source of information (e.g., published literature, name of listed drug)	Information Provided (e.g., specific sections of the 505(b)(2) application or labeling)
<i>1. Example: Published literature</i>	<i>Nonclinical toxicology</i>
<i>2. Example: NDA XXXXXX “TRADENAME”</i>	<i>Previous finding of effectiveness for indication X</i>
<i>3. Example: NDA YYYYYY “TRADENAME”</i>	<i>Previous finding of safety for Carcinogenicity, labeling section XXX</i>
<i>4.</i>	

Please be advised that circumstances could change that would render a 505(b)(2) application for this product no longer appropriate. For example, if a pharmaceutically equivalent product were approved before your application is submitted, such that your proposed product would be a “duplicate” of a listed drug and eligible for approval under section 505(j) of the FD&C Act, then it is FDA’s policy to refuse to file your application as a 505(b)(2) application (21 CFR 314.101(d)(9)). In such a case, the appropriate submission would be an Abbreviated New Drug Application (ANDA) that cites the duplicate product as the reference listed drug.

Discussion:

There was no further discussion of these comments.

EXCLUSIVITY DETERMINATION

Please be advised that the Agency does not make exclusivity determinations pursuant to sections 505(c)(3)(E) and (j)(5)(F) of the Federal Food Drug and Cosmetic Act, and 21 CFR 314.108, until after approval of an NDA. As described at 314.50(j), an applicant should include in its NDA a description of the exclusivity to which the applicant believes it is entitled. FDA will consider the applicant’s assertions regarding exclusivity in the review of the application. Please also note that the New Molecular Entity (NME) determination for an application is distinct from and independent of the New Chemical Entity (NCE) determination and any related exclusivity determinations.

Discussion:

There was no further discussion of these comments.

NEW MOLECULAR ENTITY (NME) DETERMINATION

FDA has made a preliminary determination that the application for this product would be reviewed as a new molecular entity (NME) and therefore subject to the Program, under PDUFA V. Please note that this is a preliminary determination, based on information available to FDA at this time, and will be re-evaluated at the time your application is submitted. This determination is based on our understanding of the active moiety (21 CFR 314.108(a)) and whether another marketing application containing the same active moiety is approved or marketed. Please also note that the NME determination for an application is distinct from and independent of the new chemical entity (NCE) determination and any related exclusivity determinations, which are made after approval of an NDA.

Discussion:

There was no further discussion of these comments; however, the Agency informed the Sponsor that the determination of whether this product will be reviewed as an NME may change prior to NDA submission, based on pending revisions to the relevant MAPP. The Sponsor will be informed when this change occurs.

OFFICE OF SCIENTIFIC INVESTIGATIONS (OSI) REQUESTS

The Office of Scientific Investigations (OSI) requests that the following items be provided to facilitate development of clinical investigator and sponsor/monitor/CRO inspection assignments, and the background packages that are sent with those assignments to the FDA field investigators who conduct those inspections (Item I and II). This information is requested for all major trials used to support safety and efficacy in the application (i.e., phase 2/3 pivotal trials). Please note that if the requested items are provided elsewhere in submission in the format described, the Applicant can describe location or provide a link to the requested information.

The dataset that is requested in Item III below is for use in a clinical site selection model that is being piloted in CDER. Electronic submission of the site level dataset is voluntary and is intended to facilitate the timely selection of appropriate clinical sites for FDA inspection as part of the application and/or supplement review process.

This request also provides instructions for where OSI requested items should be placed within an eCTD submission (Attachment 1, Technical Instructions: Submitting Bioresearch Monitoring (BIMO) Clinical Data in eCTD Format).

I. Request for general study related information and comprehensive clinical investigator information (if items are provided elsewhere in submission, describe location or provide link to requested information).

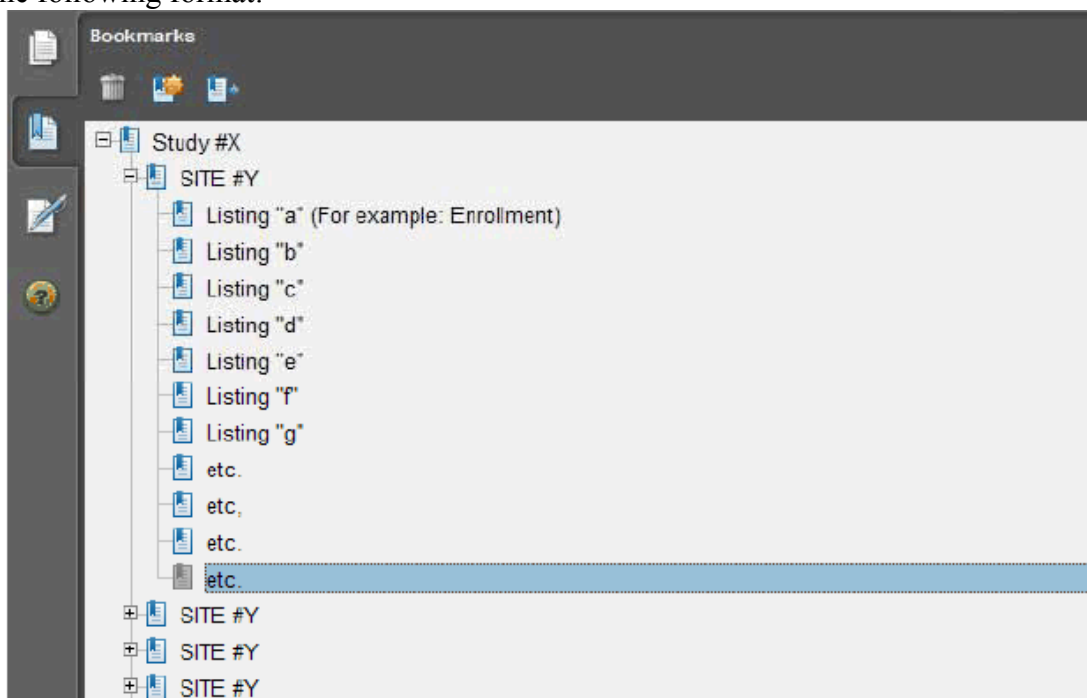
1. Please include the following information in a tabular format in the original NDA for each of the completed pivotal clinical trials:

- a. Site number
 - b. Principal investigator
 - c. Site Location: Address (e.g., Street, City, State, Country) and contact information (i.e., phone, fax, email)
 - d. Location of Principal Investigator: Address (e.g., Street, City, State, and Country) and contact information (i.e., phone, fax, email). If the Applicant is aware of changes to a clinical investigator's site address or contact information since the time of the clinical investigator's participation in the study, we request that this updated information also be provided.
2. Please include the following information in a tabular format, *by site*, in the original NDA for each of the completed pivotal clinical trials:
 - a. Number of subjects screened at each site
 - b. Number of subjects randomized at each site
 - c. Number of subjects treated who prematurely discontinued for each site by site
3. Please include the following information in a tabular format in the NDA for each of the completed pivotal clinical trials:
 - a. Location at which sponsor trial documentation is maintained (e.g., , monitoring plans and reports, training records, data management plans, drug accountability records, IND safety reports, or other sponsor records as described ICH E6, Section 8). This is the actual physical site(s) where documents are maintained and would be available for inspection
 - b. Name, address and contact information of all Contract Research Organization (CROs) used in the conduct of the clinical trials and brief statement of trial related functions transferred to them. If this information has been submitted in eCTD format previously (e.g., as an addendum to a Form FDA 1571, you may identify the location(s) and/or provide link(s) to information previously provided.
 - c. The location at which trial documentation and records generated by the CROs with respect to their roles and responsibilities in conduct of respective studies is maintained. As above, this is the actual physical site where documents would be available for inspection.
4. For each pivotal trial, provide a sample annotated Case Report Form (or identify the location and/or provide a link if provided elsewhere in the submission).
5. For each pivotal trial provide original protocol and all amendments ((or identify the location and/or provide a link if provided elsewhere in the submission).

II. Request for Subject Level Data Listings by Site

1. For each pivotal trial: Site-specific individual subject data listings (hereafter referred to as "line listings"). For each site, provide line listings for:
 - a. Listing for each subject consented/enrolled; for subjects who were not randomized to treatment and/or treated with study therapy, include reason not randomized and/or treated

- b. Subject listing for treatment assignment (randomization)
 - c. Listing of subjects that discontinued from study treatment and subjects that discontinued from the study completely (i.e., withdrew consent) with date and reason discontinued
 - d. Listing of per protocol subjects/ non-per protocol subjects and reason not per protocol
 - e. By subject listing of eligibility determination (i.e., inclusion and exclusion criteria)
 - f. By subject listing, of AEs, SAEs, deaths and dates
 - g. By subject listing of protocol violations and/or deviations reported in the NDA, including a description of the deviation/violation
 - h. By subject listing of the primary and secondary endpoint efficacy parameters or events. For derived or calculated endpoints, provide the raw data listings used to generate the derived/calculated endpoint.
 - i. By subject listing of concomitant medications (as appropriate to the pivotal clinical trials)
 - j. By subject listing, of testing (e.g., laboratory, ECG) performed for safety monitoring
2. We request that one PDF file be created for each pivotal Phase 2 and Phase 3 study using the following format:



III. Request for Site Level Dataset:

OSI is piloting a risk based model for site selection. Voluntary electronic submission of site level datasets is intended to facilitate the timely selection of appropriate clinical sites for FDA inspection as part of the application and/or supplement review process. If you wish to voluntarily provide a dataset, please refer to the draft “Guidance for Industry Providing

Submissions in Electronic Format – Summary Level Clinical Site Data for CDER’s Inspection Planning” (available at the following link <http://www.fda.gov/downloads/Drugs/DevelopmentApprovalProcess/FormsSubmissionRequirements/UCM332468.pdf>) for the structure and format of this data set.

Discussion:

There was no further discussion of these comments.

I. Attachment 1

Technical Instructions:

Submitting Bioresearch Monitoring (BIMO) Clinical Data in eCTD Format

- A. Data submitted for OSI review belongs in Module 5 of the eCTD. For items I and II in the chart below, the files should be linked into the Study Tagging File (STF) for each study. Leaf titles for this data should be named “BIMO [list study ID, followed by brief description of file being submitted].” In addition, a BIMO STF should be constructed and placed in Module 5.3.5.4, Other Study reports and related information. The study ID for this STF should be “bimo.” Files for items I, II and III below should be linked into this BIMO STF, using file tags indicated below. The item III site-level dataset filename should be “clinsite.xpt.”

DSI Pre-NDA Request Item ¹	STF File Tag	Used For	Allowable File Formats
I	data-listing-dataset	Data listings, by study	.pdf
I	annotated-crf	Sample annotated case report form, by study	.pdf
II	data-listing-dataset	Data listings, by study (Line listings, by site)	.pdf
III	data-listing-dataset	Site-level datasets, across studies	.xpt
III	data-listing-data-definition	Define file	.pdf

- B. In addition, within the directory structure, the item III site-level dataset should be placed in the M5 folder as follows:



- C. It is recommended, but not required, that a Reviewer’s Guide in PDF format be included. If this Guide is included, it should be included in the BIMO STF. The leaf title should be “BIMO Reviewer Guide.” The guide should contain a description of the BIMO elements being submitted with hyperlinks to those elements in Module 5.

¹ Please see the OSI Pre-NDA/BLA Request document for a full description of requested data files

References:

eCTD Backbone Specification for Study Tagging Files v. 2.6.1
(<http://www.fda.gov/downloads/Drugs/DevelopmentApprovalProcess/FormsSubmissionRequirements/ElectronicSubmissions/UCM163560.pdf>)

FDA eCTD web page
(<http://www.fda.gov/Drugs/DevelopmentApprovalProcess/FormsSubmissionRequirements/ElectronicSubmissions/ucm153574.htm>)

For general help with eCTD submissions: ESUB@fda.hhs.gov

Discussion:

There was no further discussion of these comments.

This is a representation of an electronic record that was signed electronically and this page is the manifestation of the electronic signature.

/s/

DIANA L WALKER
08/14/2015



DEPARTMENT OF HEALTH AND HUMAN SERVICES

Food and Drug Administration
Silver Spring, MD 20993

IND 118527

MEETING MINUTES



(b) (4)

Dear (b) (4)

Please refer to your Investigational New Drug Application (IND) submitted under Section 505(i) of the Federal Food, Drug, and Cosmetic Act for Cocaine hydrochloride topical solution 4%.

We also refer to the meeting between representatives of your firm and the FDA on January 29, 2015. The purpose of the meeting was to discuss the qualification of (b) (4) with the Division of Anesthesia, Analgesia, and Addiction Products (DAAAP).

A copy of the official minutes of the meeting is enclosed for your information. Please notify us of any significant differences in understanding regarding the meeting outcomes.

If you have any questions, call me at (301) 796-4029.

Sincerely,

{See appended electronic signature page}

Diana L. Walker, PhD
Sr. Regulatory Health Project Manager
Division of Anesthesia, Analgesia, and
Addiction Products
Office of Drug Evaluation II
Center for Drug Evaluation and Research

ENCLOSURE:
Meeting Minutes

MEMORANDUM OF MEETING MINUTES

Meeting Type: Type C
Meeting Category: Guidance

Meeting Date and Time: January 29, 2015, 4:00 p.m. – 4:30 p.m. (Eastern)
Meeting Location: Teleconference

Application Number: IND 118527
Product Name: Cocaine hydrochloride topical solution 4%
Indication: Diagnostic procedures and surgeries on or through the accessible mucous membranes of the nasal cavities

Sponsor/Applicant Name: (b) (4)

Meeting Chair: Rigoberto Roca, MD, Deputy Director, DAAAP
Meeting Recorder: Diana Walker, PhD, Sr. Regulatory Project Manager, DAAAP

Industry Representatives	Title
(b) (4)	
FDA	Title
Rigoberto Roca, MD	Deputy Director, DAAAP
Daniel Mellon, PhD	Pharmacology-Toxicology Supervisor
BeLinda Hayes, PhD	Pharmacology-Toxicology Reviewer
Diana Walker, PhD	Sr. Regulatory Project Manager, DAAAP

1.0 BACKGROUND

- a. (b) (4) plans to submit an 505(b)(2) NDA for Cocaine hydrochloride topical solution 4%, indicated for diagnostic procedures and surgeries on or through the accessible mucous membranes of the nasal cavities. The purpose of this teleconference is to discuss the proposed approach regarding the qualification of (b) (4)
- b. The Sponsor received the Division's preliminary responses to the meeting questions on January 23, 2015, via email.
- c. The Sponsor sent a response to the Agency via email on January 28, 2015, containing additional data supporting their position. Due to the limited time prior to the meeting that this response was received, the data was not reviewed by the Division.

- d. The Sponsor's original questions are incorporated below in *italics* followed by the FDA Response in **bold** font. Discussion that took place during the meeting is captured following the question to which it pertains in normal text.

2.0 DISCUSSION

Question 1. Does the Division agree that the expert rule-based method (Derek Nexus) and the statistical-based (Q)SAR method (Leadscope Model Applier Study) testing performed meets the requirements for the qualification of (b) (4)? Also, as no structural alerts were found from this testing (b) (4) can be classified as (b) (4) impurity with no alerting mutagenic features and can be qualified as an ordinary (non-mutagenic) impurity, without the need for a minimal genetic toxicology screen (two in vitro genetic toxicology studies, e.g. one point mutation assay and one chromosome aberration assay) with the isolated impurity, tested up to the limit dose for the assay and repeat-dose toxicology of appropriate duration to support the proposed indication? If not, please comment.

Agency Response:

No, we do not agree. Your proposal to address the safety of this drug substance impurity and drug product degradant via the use of a QSAR analysis, as discussed in the ICH M7 document (titled *Assessment and Control of DNA Reactive (Mutagenic) Impurities in Pharmaceuticals to Limit Potential Carcinogenic Risk*, available at http://www.ich.org/fileadmin/Public_Web_Site/ICH_Products/Guidelines/Multidisciplinary/M7/M7_Step_4.pdf) is not acceptable. ICH M7 is applicable only for the assessment of DNA reactive (mutagenic) impurities and this document does not supersede ICH Q3A(R2) or ICH Q3B(R2). Although the impurity (b) (4) does not contain a structural alert for mutagenicity, your proposed specification of NMT (b) (4) % for (b) (4) in both the drug substance and drug product exceeds the qualification thresholds outlined in ICH Q3A(R2) and ICH Q3B(R2). Therefore, the safety of (b) (4) must be adequately qualified as previously mentioned during the pre-IND meeting. In order to provide adequate qualification:

- a. You must complete a minimal genetic toxicology screen (two *in vitro* genetic toxicology studies, e.g., one point mutation assay and one chromosome aberration assay) with the isolated impurity, tested up to the limit dose for the assay.**
- b. In addition, you must conduct a repeat-dose toxicology study of appropriate duration to support the proposed indication. In this case, a study of 14 days must be completed.**

Refer to

Guidance for Industry: *Q3A Impurities in New Drug Substances* available at <http://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/ucm073385.pdf>

and

Guidance for Industry: *Q3B (R2) Impurities in New Drug Products* available at <http://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/ucm073389.pdf>

Discussion:

The Sponsor stated that they are committed to conducting two in vitro genetic toxicology studies – one point mutation and one chromosomal aberration assay. These studies will be submitted with the NDA for this product.

The Sponsor stated that they believe they do not need to conduct the 14-day repeat-dose toxicology study required by the Division, and can support their position with the data that they submitted via email the day before, on January 28, 2015. The Division stated that we cannot commit to agreeing with this proposal, as we have not reviewed the material that was just received prior to the telecon. The Division recommended that the Sponsor submit the information formally to the IND as “Nonclinical Information” with a question(s) included, and that, although we cannot commit to a timeframe, the material will be reviewed in as timely a manner as allowed by workload and we will send an advice letter containing responses to the question(s). The Sponsor agreed to submit the information to their IND, along with referenced publications.

The Division stated, as a point of procedure that, if the Sponsor were to submit their NDA along with scientific rationale for not conducting the 14-day repeat dose toxicology study, it would not constitute a filing issue. However, determination of the adequacy of the safety qualification for the impurity would be part of the review process. Possible outcomes based on review of the submitted data and justification could include approval, Complete Response, or approval with additional studies as a Postmarketing Requirement (PMR).

Additionally, the Division stated that the Sponsor is still encouraged to conduct the 14-day repeat dose toxicology study because the proposed specifications for (b) (4) are above ICH guidelines.

General Meeting Discussion

The Sponsor stated that they plan to file an NDA within the timeframe of the end of the 3rd quarter or the beginning of the 4th quarter of 2015. The Division reminded the Sponsor that the iPSP must be submitted at least 210 days prior to the NDA submission. The Sponsor stated that they understand this time requirement, and will be submitting the iPSP to the Agency soon.

Post Meeting Note: Given the complexity of any drug development program, the Division strongly recommends that you request a preNDA meeting that includes background plans for all disciplines prior to submission of your NDA in order to avoid a potentially costly “refuse-to-file” determination.

Additional General Comments

PREA REQUIREMENTS

Under the Pediatric Research Equity Act (PREA) (21 U.S.C. 355c), all applications for new active ingredients, new indications, new dosage forms, new dosing regimens, or new routes of administration are required to contain an assessment of the safety and effectiveness of the product for the claimed indication(s) in pediatric patients unless this requirement is waived, deferred, or inapplicable.

Please be advised that under the Food and Drug Administration Safety and Innovation Act (FDASIA), you must submit an Initial Pediatric Study Plan (PSP) within 60 days of an End of Phase (EOP2) meeting. The PSP must contain an outline of the pediatric study or studies that you plan to conduct (including, to the extent practicable study objectives and design, age groups, relevant endpoints, and statistical approach); any request for a deferral, partial waiver, or waiver, if applicable, along with any supporting documentation, and any previously negotiated pediatric plans with other regulatory authorities. In addition, your iPSP should specifically provide your justification why you believe that nonclinical juvenile animal studies are or are not needed to support your pediatric drug development taking into consideration the specific age ranges to be studied. The justification should be based on a comprehensive literature search focusing on the specific toxicological concerns related to the drug substance and each individual excipient in your drug product and any data you have generated suggesting a unique vulnerability to toxicological insult for the proposed age range to be tested. This risk assessment should take into consideration the expected maximum daily dose of the drug product for the intended patient population and include rationale for your proposed maximum daily dose. In addition, your risk assessment should address how the drug substance and excipients are absorbed, distributed, metabolized, and excreted by the ages of the children you will be studying. You must include copies of all referenced citations. If you conclude that a juvenile animal study is necessary, provide a detailed outline of the specific study you propose to conduct, including what toxicological endpoints you will include in the study design to address any specific questions, and justification for your selection of species and the age of the animal to be tested. We recommend that you refer to the FDA guidance for industry, *Nonclinical Safety Evaluation of Pediatric Drug Products*, available at, <http://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/UCM079247.pdf>. The PSP should be submitted in PDF and Word format.

For additional guidance on the timing, content, and submission of the PSP, including a PSP Template, please refer to the draft guidance for industry, *Pediatric Study Plans: Content of and Process for Submitting Initial Pediatric Study Plans and Amended Pediatric Study Plans* at: <http://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/UCM079247.pdf>

[CM360507.pdf](#). In addition, you may contact the Pediatric and Maternal Health Staff at 301-796-2200 or email pdit@fda.hhs.gov. For further guidance on pediatric product development, please refer to:
<http://www.fda.gov/Drugs/DevelopmentApprovalProcess/DevelopmentResources/ucm049867.htm>.

DATA STANDARDS FOR STUDIES

CDER strongly encourages IND sponsors to consider the implementation and use of data standards for the submission of applications for investigational new drugs and product registration. Such implementation should occur as early as possible in the product development lifecycle, so that data standards are accounted for in the design, conduct, and analysis of clinical and nonclinical studies. CDER has produced a web page that provides specifications for sponsors regarding implementation and submission of clinical and nonclinical study data in a standardized format. This web page will be updated regularly to reflect CDER's growing experience in order to meet the needs of its reviewers. The web page may be found at:
<http://www.fda.gov/Drugs/DevelopmentApprovalProcess/FormsSubmissionRequirements/ElectronicSubmissions/ucm248635.htm>

LABORATORY TEST UNITS FOR CLINICAL TRIALS

CDER strongly encourages IND sponsors to identify the laboratory test units that will be reported in clinical trials that support applications for investigational new drugs and product registration. Although Système International (SI) units may be the standard reporting mechanism globally, dual reporting of a reasonable subset of laboratory tests in U.S. conventional units and SI units might be necessary to minimize conversion needs during review. Identification of units to be used for laboratory tests in clinical trials and solicitation of input from the review divisions should occur as early as possible in the development process. For more information, please see [CDER/CBER Position on Use of SI Units for Lab Tests](http://www.fda.gov/ForIndustry/DataStandards/StudyDataStandards/default.htm) (<http://www.fda.gov/ForIndustry/DataStandards/StudyDataStandards/default.htm>).

505(b)(2) REGULATORY PATHWAY

The Division recommends that Sponsors considering the submission of an application through the 505(b)(2) pathway consult the Agency's regulations at 21 CFR 314.54, and the draft guidance for industry *Applications Covered by Section 505(b)(2)* (October 1999), available at <http://www.fda.gov/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/default.htm>. In addition, FDA has explained the background and applicability of section 505(b)(2) in its October 14, 2003, response to a number of citizen petitions that had challenged the Agency's interpretation of this statutory provision (see Docket FDA-2003-P-0274-0015, available at <http://www.regulations.gov>).

If you intend to submit a 505(b)(2) application that relies for approval, in part, on FDA's finding of safety and/or effectiveness for one or more listed drugs, you must establish that such reliance is scientifically appropriate, and must submit data necessary to support any aspects of the proposed drug product that represent modifications to the listed drug(s). You should establish a

“bridge” (e.g., via comparative bioavailability data) between your proposed drug product and each listed drug upon which you propose to rely to demonstrate that such reliance is scientifically justified.

If you intend to rely, in part, on literature or other studies for which you have no right of reference but that are necessary for approval, you also must establish that reliance on the studies described in the literature or on the other studies is scientifically appropriate. You should include a copy of such published literature in the 505(b)(2) application and identify any listed drug(s) described in the published literature (e.g. trade name(s)).

If you intend to rely, in part, on the Agency’s finding of safety and/or effectiveness for a listed drug(s) or published literature describing a listed drug(s) (which is considered to be reliance on FDA’s finding of safety and/or effectiveness for the listed drug(s)), you should identify the listed drug(s) in accordance with the Agency’s regulations at 21 CFR 314.54. It should be noted that 21 CFR 314.54 requires identification of the “listed drug for which FDA has made a finding of safety and effectiveness,” and thus an applicant may only rely upon a listed drug that was approved in an NDA under section 505(c) of the FD&C Act. The regulatory requirements for a 505(b)(2) application (including, but not limited to, an appropriate patent certification or statement) apply to each listed drug upon which a sponsor relies.

If you propose to rely on FDA’s finding of safety and/or effectiveness for a listed drug that has been discontinued from marketing, the acceptability of this approach will be contingent on FDA’s consideration of whether the drug was discontinued for reasons of safety or effectiveness.

We encourage you to identify each section of your proposed 505(b)(2) application that relies on FDA’s finding of safety and/or effectiveness for a listed drug(s) or on published literature. In your 505(b)(2) application, we encourage you to clearly identify (for each section of the application, including the labeling): (1) the information for the proposed drug product that is provided by reliance on FDA’s finding of safety and/or effectiveness for the listed drug or by reliance on published literature; (2) the “bridge” that supports the scientific appropriateness of such reliance; and (3) the specific name (e.g., proprietary name) of each listed drug named in any published literature on which your marketing application relies for approval. If you are proposing to rely on published literature, include copies of the article(s) in your submission.

In addition to identifying in your annotated labeling the source(s) of information essential to the approval of your proposed drug that is provided by reliance on FDA’s previous finding of safety and efficacy for a listed drug or by reliance on published literature, we encourage you to also include that information in the cover letter for your marketing application in a table similar to the one below.

List the information essential to the approval of the proposed drug that is provided by reliance on the FDA’s previous finding of safety and efficacy for a listed drug or by reliance on published literature
--

Source of information (e.g., published literature, name of listed drug)	Information Provided (e.g., specific sections of the 505(b)(2) application or labeling)
<i>1. Example: Published literature</i>	<i>Nonclinical toxicology</i>
<i>2. Example: NDA XXXXXX “TRADENAME”</i>	<i>Previous finding of effectiveness for indication X</i>
<i>3. Example: NDA YYYYYY “TRADENAME”</i>	<i>Previous finding of safety for Carcinogenicity, labeling section XXX</i>
<i>4.</i>	

Please be advised that circumstances could change that would render a 505(b)(2) application for this product no longer appropriate. For example, if a pharmaceutically equivalent product were approved before your application is submitted, such that your proposed product would be a “duplicate” of a listed drug and eligible for approval under section 505(j) of the FD&C Act, then it is FDA’s policy to refuse to file your application as a 505(b)(2) application (21 CFR 314.101(d)(9)). In such a case, the appropriate submission would be an Abbreviated New Drug Application (ANDA) that cites the duplicate product as the reference listed drug.

3.0 ACTION ITEMS

- a) The Sponsor agreed to submit their data and scientific rationale for not conducting the 14-day repeat-dose toxicology study to their IND, along with referenced publications.
- b) The Agency agreed to review the information and provide an advice letter.

4.0 ATTACHMENTS/HANDOUTs

None.

This is a representation of an electronic record that was signed electronically and this page is the manifestation of the electronic signature.

/s/

DIANA L WALKER
03/02/2015



PIND 118527

**MEETING REQUEST-
WRITTEN RESPONSES**

(b) (4)

Dear (b) (4)

Please refer to your Pre-Investigational New Drug Application (PIND) file for Cocaine Hydrochloride Topical Solution.

We also refer to your submission dated May 13, 2013, containing a pre-IND meeting request. The purpose of the requested meeting was to discuss the development program for Cocaine Hydrochloride Topical Solution, (b) (4)

Further reference is made to our Meeting Granted letter dated June 3, 2013, wherein we stated that written responses to your questions would be provided in lieu of a meeting.

The enclosed document constitutes our written responses to the questions contained in your April 30, 2013, background package.

If you have any questions, call me at (301) 796-1183.

Sincerely,

{See appended electronic signature page}

Dominic Chiapperino, Ph.D.
Senior Regulatory Health Project Manager
Division of Anesthesia, Analgesia, and
Addiction Products
Office of Drug Evaluation II
Center for Drug Evaluation and Research

Enclosure:
Written Responses



FOOD AND DRUG ADMINISTRATION
CENTER FOR DRUG EVALUATION AND RESEARCH

WRITTEN RESPONSES

Meeting Type: Type B
Meeting Category: Pre-IND
Application Number: PIND 118527
Product Name: Cocaine Hydrochloride Topical Solution
Indication: (b) (4)
Sponsor/Applicant Name: (b) (4)
Regulatory Pathway: 505(b)(2)

1.0 BACKGROUND

(b) (4) requested a meeting to discuss their clinical development program and planned NDA submission for Cocaine Hydrochloride Topical Solution, (b) (4)

(b) (4) submitted a meeting request and briefing package, dated May 13, 2013, containing a description of their clinical development program, a proposed Phase 3 protocol, and questions to DAAAP, shown below in Section 2 in italic font. DAAAP and (b) (4) agreed that responses to these questions could be provided in writing in lieu of a face-to-face meeting or teleconference. DAAAP's responses to the questions in the May 13, 2013, briefing package are provided in Section 2 in bold font.

2.0 QUESTIONS AND RESPONSES

Question 1. Is the proposed sample size of 90 patients (30 per arm), as described in the draft protocol (Appendix 1) of this document, agreeable to the Agency?

FDA Response:

No. Your proposed sample size was based on the findings from *Adriani et al.* However, this study examines the potency of topical anesthetics to the stimulation from a Burdick Muscle Stimulator, which is a different paradigm from that proposed in your study. Your sample size calculation should be based on a primary endpoint similar to that proposed in your study, i.e., the anticipated success of the two cocaine arms relative to placebo. Information on the expected success rates should come from studies in the literature that are more closely related to your proposed study. Alternatively, you could conduct a Phase 2 study to generate this information.

Additionally, you must enroll an adequate number of subjects in each procedure and dose group to support a reasonable assessment of the overall efficacy and safety of your product. Further, your safety database needs to include at least 500 subjects, evenly distributed between the dose strengths of 4% and 8%. Therefore, if Study 2013CST001 plans to treat fewer than 500 subjects with the active product, an additional study should be considered, which could be an open-label study. We note that, depending on the findings from your studies, the safety data base may need to be expanded in terms of the size and/or duration of observation. Acknowledging that the following guidance is intended for patient populations that are undergoing long-term treatment, you may nonetheless find it useful: *The Extent of Population Exposure to Assess Clinical Safety: For Drugs Intended for Longterm Treatment of Non-Life-Threatening Conditions*; <http://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/ucm073083.pdf> .

As the placebo arm is only included in the first phase of the study (the evaluation with Von Frey filaments), we have the following suggestions that may help optimize the allocation of subjects in Study 2013CST001.

- 1. Use an unequal allocation to placebo and active arms, such as 1:3:3 or 1:4:4, for the placebo:4%:8% treatment groups. The unequal allocation supports the different needs of the two stages of the study. For example, if 80 patients are allocated to the placebo arm, then a 1:3:3 allocation would result in 480 patients treated with the active product, and a 1:4:4 allocation would result in 640 patients treated with the active product. This could enable the collection of all, or nearly all, of the needed efficacy and safety information within the context of one clinical study. We note that, while we have used 1:3:3 and 1:4:4 as examples, other allocation ratios are also feasible. Further, we note that an equal, 1:1:1 allocation ratio is also acceptable. We recognize that efficacy and safety information may be obtained from other sources, such as another study.**
- 2. To ensure an adequate number of subjects are evaluated for each procedure, stratify randomization by type of procedure.**

Question 2. Does the Agency agree with the efficacy assessment as described in the draft protocol (Appendix 1) of this document?

FDA Response:

Your proposed primary endpoint is comprised of an initial placebo-controlled sensory assessment followed by a surgical or diagnostic procedure using cocaine hydrochloride 4% or 8% for topical anesthesia. While your proposal is generally acceptable, there are a number of details regarding the assessment and statistical analysis of this endpoint that are either missing or unclear.

- 1. Clearly define treatment success for patients in the placebo arm versus treatment success for patients in the cocaine arms. A decision tree or a table might be useful**

for demonstrating the sequence of drug application and the assessment that leads to treatment success or failure.

- a. The protocol is unclear as to whether a treatment success results when no further analgesic treatment is needed (Section 11.1), or when, more narrowly, no further cocaine is administered (Section 12.3.3).**
 - b. Your primary endpoint also includes a statement about “...duration of time to second and third [cocaine HCl] applications,” which we agree may provide useful information if recorded and analyzed. However, because second or third cocaine HCl doses equate to treatment failure, the duration to additional cocaine application should not factor into your primary outcome measure of analgesic success sustained throughout the diagnostic procedure or surgery.**
- 2. The use of Von Frey monofilaments for assessing the initial clinical effect is acceptable. However, you have not provided a rationale for your choice of Von Frey monofilament sizes for screening and assessment of study drug effect. In addition to providing an acceptable rationale for your choice of monofilament size, you must indicate the circumstance that would necessitate assessment with the (b) (4) monofilament.**
- 3. The protocol indicates that the study solution will be “applied using a cotton pledget for 20 minutes prior to the diagnostic procedure or surgery.” In your protocol, you should describe a standardized technique for administration, to include duration that the pledget remains in the study solution, so that the product labeling can appropriately describe how the product should be applied to the nasal mucous membranes.**
- 4. The protocol indicates that each “dose” of study drug will be up to 4 mL in volume. If less than 4 mL of study drug will be contained in the pledget, the actual volume absorbed must be captured in order to more precisely determine the dose administered.**
- 5. You have proposed, as an inclusion criterion, a predetermined need for a diagnostic procedure or surgery on or through the nasal membranes of either one or two nostrils. If you intend to include bilateral nasal procedures in your study, you must describe how study drug will be applied, i.e., to one or both sides, sequentially or simultaneously, and with a total volume of up to 4 mL per side or a combined total volume of up to 4 mL between the two sides. Likewise, for bilateral procedures, you must clearly describe the process for conducting efficacy assessments and the definition of a treatment success.**
- 6. A statistical analysis plan is missing from the submission.**
- 7. We have noted that your briefing package states that the purpose of your trial is to show efficacy for oral, laryngeal, and nasal anesthesia. (b) (4)**

Question 3. Does the Agency agree with the Nonclinical and Clinical Executive Literature Review to further support the demonstration of Safety and Efficacy for this New Drug Application as outlined in this document?

FDA Response:

No, we are not able to agree at this time. You have proposed to develop a literature-based Executive Summary based on all published literature on Cocaine HCl from 1980 through 2013 and you have submitted an outline that may be reasonable for summarizing the literature. However, you have not included any content for us to evaluate.

Your critical evaluation of the relevant literature data upon which you intend to rely for this application should be comprehensive, including published studies on cocaine HCl with either positive or negative outcomes. The studies should be individually assessed, and a discussion of their strength and weakness or deficiency, including comparability of the study drug to your proposed cocaine HCl solution, should be included in your submission. If such drug information is unavailable, you must provide justification for why data from cited literature are acceptable as a source of information to support your submission.

You will need to both provide a synopsis of each study from the literature and critically review the literature with respect to the efficacy and safety of cocaine for topical anesthesia, providing a summary that, in addition to the evidence from your trial, supports each element of your proposed labeling.

Additional literature on the use of cocaine for other indications, or administered by other routes, may be included in your clinical review, as it may inform about safety. You should provide your rationale as to why this literature may be relevant. Similarly, if there is a body of literature on the use of cocaine for other indications or administered by other routes that you do not include, you should provide your rationale as to why it would not be informative about the safety of your product.

Considering that you propose to use information referenced from the literature, refer also to Section 3.4 below for information pertaining to 505(b)(2) application requirements.

Comments on the Nonclinical Development Program:

- 1. Based upon review of clinical use data available to the Agency at this time, the use of the currently marketed 10% solutions appears to have limited sales and this product may be diluted prior to use, suggesting limited clinical experience with the 10% solution. Therefore, your IND should specifically discuss the known local tolerability of the marketed 10% cocaine solutions to support your conclusion that there are adequate clinical data to support the use of the proposed novel 8% concentration without the need for nonclinical local toxicology studies. Assuming**

there are adequate clinical data to justify the safety of both the 4% and the 8% solutions, based on the long history of clinical use of topical cocaine, general toxicology studies and reproductive and developmental toxicology studies will not be required to be submitted in support of your NDA. However, approval of an NDA for cocaine will require a comprehensive assessment of its genotoxic potential. The genotoxic potential is characterized in a battery of in vitro and in vivo tests for genotoxicity. The standard battery of tests include the following:

- A test for gene mutation in bacteria (Ames assay)
- An in vitro chromosomal assay
- An in vivo assay to detect chromosomal damage

Refer to the Guidance for Industry: *S2(R1) Genotoxicity Testing and Data Interpretation for Pharmaceuticals Intended for Human Use*

<http://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/UCM074931.pdf>.

2. For all other aspects of the NDA, your proposal to submit literature references to address the nonclinical requirements for an NDA submission is acceptable. However, you must conduct a comprehensive and critical review of the literature and specifically address what studies identified provide the most relevant data with respect to current ICH M3(R2) requirements. Please refer to the Guidance for Industry: *M3(R2) Nonclinical Safety Studies for the Conduct of Human Clinical Trials and Marketing Authorization for Pharmaceuticals*
<http://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/UCM073246.pdf>
3. Your proposed nonclinical safety and efficacy outline only discusses nonclinical pharmacology and ADME. Your NDA must also review and analyze the existing toxicology data for cocaine, including general and local toxicology, genetic toxicology and reproductive and developmental toxicology (fertility and early embryonic development, embryofetal development, and pre- and postnatal development).
4. Your NDA must include annotated proposed drug product labeling that specifically proposes language to address the Pregnancy Section of the label, including reproductive and developmental effects of cocaine based on existing human and animal data. An overall risk summary statement, consistent with the proposed Pregnancy Labeling and Lactation Rule will be required for your product labeling.
5. Your NDA submission should include a detailed discussion of the nonclinical information in the published literature and should specifically address how the information within the published domain impacts the safety assessment of your drug product. This discussion should be included in Module 2 of the submission. Copies of all referenced citations should be included in the NDA submission in Module 4. Journal articles that are not in English must be translated into English.

6. For the NDA submission, any impurity or degradation product that exceeds ICH thresholds must be adequately qualified for safety as per (ICHQ3A(R), ICHQ3B(R)). Adequate qualification must include:
- Minimal genetic toxicology screen (two *in vitro* genetic toxicology studies, e.g., one point mutation assay and one chromosome aberration assay) with the isolated impurity, tested up to the limit dose for the assay.
 - Repeat dose toxicology of appropriate duration to support the proposed indication.
7. In Module 2 of your NDA (2.6.6.8 Toxicology Written Summary/Other Toxicity), include a table listing the drug substance and drug product impurity specifications, the maximum daily exposure to these impurities based on the maximum daily dose of the product and how these levels compare to ICH Q3A and Q3B qualification thresholds and determination if the impurity contains a structural alert for mutagenicity. Any proposed specification that exceeds the qualification thresholds should be adequately justified for safety from a toxicological perspective. NOTE: An NDA submission that does not contain adequate safety qualification data for any proposed impurity/degradant specification that exceeds ICH qualification thresholds may not be filed.
8. Potentially genotoxic impurities or degradation products pose an additional risk; therefore, a specification of NMT (b) (4) mcg/day must be set for genotoxic or potentially genotoxic impurities in the drug substance and drug product unless otherwise adequately justified. Adequate safety qualification for any potential genotoxic impurities identified via a structural alert for mutagenicity must be provided with the NDA submission and must include and *in vitro* bacterial reverse mutation assay (Ames assay) with the isolated impurity, tested up to the limit dose for the assay. Should this qualification produce positive or equivocal results, the impurity specification must be set at NMT (b) (4) mcg/day, or otherwise justified. Justification may require an assessment for carcinogenic potential in either a standard 2-year rodent bioassay or in an appropriate transgenic mouse model. NOTE: An NDA submission that does not contain adequate safety qualification data for any identified impurity containing a structural alert for mutagenicity that exceeds (b) (4) mcg/day may not be filed.
9. Any novel excipients must be adequately qualified for safety. Studies must be submitted to the IND in accordance with the FDA Guidance for Industry: *Nonclinical Studies for the Safety Evaluation of Pharmaceutical Excipients* <http://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/UCM079250.pdf>. As noted in the document cited above, “the phrase *new excipients* means any ingredients that are intentionally added to therapeutic and diagnostic products but which: (1) we believe are not intended to exert therapeutic effects at the intended dosage (although they may act to improve product delivery,

e.g., enhancing absorption or controlling release of the drug substance); and (2) are not fully qualified by existing safety data with respect to the currently proposed level of exposure, duration of exposure, or route of administration.” (emphasis added)

- 10. The NDA submission must contain information on potential leachables and extractables from the drug container closure system, unless specifically waived by the Division. The evaluation of extractables and leachables from the drug container closure system should include specific assessments for residual monomers, solvents, polymerizers, etc.). Based on identified leachables you will need to provide a toxicological evaluation to determine the safe level of exposure via the label-specified route of administration. The approach for toxicological evaluation of the safety of leachables must be based on good scientific principles and take into account the specific container closure system or patch, drug product formulation, dosage form, route of administration, and dose regimen (chronic or short-term dosing). As many residual monomers are known genotoxic agents, your safety assessment must take into account the potential that these leachables may either be known or suspected highly reactive and/or genotoxic compounds. The safety assessment should be specifically discussed in Module 2.6.6.8 (Toxicology Written Summary/Other Toxicity) of the NDA submission. For additional guidance on extractables and leachables testing, consult the FDA Guidance documents “Container Closure Systems for Packaging Human Drugs and Biologics” and “Nasal Spray and Inhalation Solution, Suspension, and Spray Drug Products – Chemistry, Manufacturing, and Controls Documentation.” For your toxicological risk assessment, any leachable that contains a structural alert for mutagenicity should not exceed (b) (4) mcg/day total daily exposure or be adequately qualified for safety. A toxicological risk assessment should be provided for any non-genotoxic leachable that exceeds (b) (4) mcg/day. The risk assessment should be based on the levels of leachables detected in long-term stability samples.**

Clinical Pharmacology Comments:

We note that you plan to provide published reports of cocaine systemic exposure/PK. Ensure that such reports are based on relevant formulations, routes of administration, and durations of administration compared to your proposed product use. Specifically, provide information on systemic exposure of cocaine following single-dose topical exposure from various proposed application sites, such as nasal, laryngeal or oral routes. Indicate if the publications describe similar use of cotton applicators/pledgets to that which you propose to use. Alternatively, it is acceptable if you propose plasma sampling in a limited number of patients in the proposed clinical efficacy trial.

Question 4. Does the Agency agree that successful completion of the above described study protocol and further demonstration of the safety and efficacy of this product, as supported by available literature, would gain approval for (b) (4) Cocaine HCl?

FDA Response:

Whether a single clinical trial and your critical review of the available clinical literature will be sufficient evidence for approval of your marketing application will be a matter of

review. The guidance for industry *Providing Clinical Evidence of Effectiveness for Human Drug and Biological Products*, available at <http://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/ucm078749.pdf>, represents the Agency's current thinking on providing evidence of effectiveness in different clinical development scenarios, including your proposed scenario of one clinical study supported by contributory evidence from the published literature.

The following points should help guide you in how to plan and compile your NDA submission:

1. Data from well-designed, double-blinded, randomized, controlled clinical trials carry the most weight in determinations of safety and efficacy.
2. Only data that are in the public domain or for which you have right of access can be considered.
3. Agency access to original protocols and original data should be provided where possible. Lack of such access precludes assessment of data integrity and limits the evaluation of the adequacy of the trial design and conduct of the study.
4. Each published study should be critically reviewed and its data organized to allow an assessment of efficacy and safety.
5. Safety data should be integrated, to the extent possible, to create a safety database that can be analyzed according to subject demographics and the dose of cocaine used.
6. Published studies with outcomes that are favorable as well as those with outcomes that are not favorable for safety or efficacy must be included.

Question 5. (b) (4) intends to develop labeling from the proposed safety and efficacy study as well as from the data retrieved from the proposed literature review and FDA Safety Database for Cocaine HCl 4% (b) (4) (topical solution). Does the Agency agree with the above proposal for developing the prescribing information for this New Drug Application?

FDA Response:

You have proposed to develop labeling from the proposed study, data retrieved from the literature, and the "...FDA Safety Database" for Cocaine HCl 4% (b) (4) topical solution. We are not clear what you are referring to by the phrase "FDA Safety Database." You cannot reference an FDA finding of safety for cocaine, since there are no FDA-approved products containing cocaine. If you mean to analyze the postmarketing safety data found in the AERS database and incorporate a summary of this into the appropriate section of your labeling, we agree with this approach provided it is adequately described, analyzed, and sourced in your NDA.

Per 21 CFR 314.50, your application must provide annotations to the information in the summary and technical sections of the application that support the inclusion of each statement in the labeling.

The labeling must be in the currently required format, as described in the Structured Product Labeling and the Physicians Labeling Rule

<http://www.fda.gov/Drugs/GuidanceComplianceRegulatoryInformation/LawsActsandRules/ucm084159.htm>.

In addition to identifying the source of supporting information in your annotated labeling within your NDA, we encourage you to include in your marketing application a summary of the information that supports the application in a table similar to the one below.

List the information essential to the approval of the proposed drug that is provided by reliance on the FDA's previous finding of safety and efficacy for a listed drug or by reliance on published literature	
Source of information (e.g., published literature, name of listed drug)	Information Provided (e.g., specific sections of the 505(b)(2) application or labeling)
<i>1. Example: Published literature</i>	<i>Nonclinical toxicology</i>
<i>2. Example: NDA XXXXXX "TRADENAME"</i>	<i>Previous finding of effectiveness for indication X</i>
<i>3. Example: NDA YYYYYY "TRADENAME"</i>	<i>Previous finding of safety for Carcinogenicity, labeling section XXX</i>

Currently, the proposed prescribing information does not include the appropriate information related to the abuse potential of cocaine. The drug label for cocaine should include: 1) a symbol that cocaine is a Schedule II substance under the Controlled Substances Act (CSA); and 2) Section 9.0 Drug Abuse and Dependence (with subsections 9.1 Controlled substance, 9.2 Abuse and 9.3 Dependence), with appropriate information in each subsection, based on available data.

Additional Comments from Controlled Substance Staff (CSS):

1. Since cocaine is a Schedule II drug under the CSA, all Schedule II regulations and procedures regarding manufacture, distribution, dispensing, storage, recordkeeping, and disposal of study drug should be in place and strictly followed.
2. You should monitor subjects for abuse, misuse, diversion and overdose and submit all related information to the Agency. Specifically, you should submit descriptions of all reports and details, including narratives, of an incident of abuse, overuse, or overdose (intentional or unintentional), or drug that is lost, stolen, missing or unaccounted for in all clinical studies.

Additional Clinical Comments:

- 1. Your study needs to include the most commonly performed procedures as well as procedures that would be expected to require only the 4% formulation or only the 8% formulation. Then, comparing the success rates of the two cocaine formulations for each individual procedure will allow you, in conjunction with the safety data, to make labeling recommendations as to which formulation is more appropriate for each procedure.**
- 2. The maximum cocaine HCl dose that subjects might receive and sufficient evidence for the safety of that total dose should be clearly described in your protocol. You must take into account cocaine HCl that might be administered as rescue if, in the absence of sustained analgesia, subjects receive additional applications of cocaine HCl.**
- 3. You must clarify whether study subjects are eligible to receive sedative medications or parenteral analgesics for their procedures, and, if so, whether a subject who receives sedatives or analgesics but no additional cocaine HCl is considered a treatment success. If you do plan to allow for sedation in your protocol, the sedation medications, dosing regimens, and guidelines for use should be standardized to allow for interpretation of your study results.**
- 4. You have indicated that placebo subjects will have their procedure after receiving proper anesthesia. However, you have not defined the timing of the procedure nor what is meant by “proper anesthesia.” Regarding procedure timing, as these subjects provide a background adverse event rate, they will ideally complete the study on approximately Study Day 8, and thereafter have their procedure. However, subjects randomized to placebo may not receive cocaine HCl during the 8-day study period and, therefore, if they are to have their procedure performed during the 8-day study period, cocaine HCl may not be used.**
- 5. You have proposed to measure blood pressure (BP), heart rate (HR), respiratory rate (RR), and oral temperature (OT). You should also monitor cardiac rhythm (EKG) and pulse oximetry, in addition to the vital signs mentioned in your protocol. EKG and pulse oximetry should be monitored continuously, BP and HR at least every 5 minutes, and RR and OT every 15 minutes throughout the procedure. Because of the potential for significant autonomic changes in the period immediately after cocaine administration, you should consider performing HR and BP assessments as frequently as every 2 to 3 minutes immediately prior to administration until the time of cocaine’s peak exposure. A baseline recording should be obtained for each vital sign. Vitals may be conducted every one hour after the diagnostic procedure or surgery is completed.**
- 6. If you are to exclude subjects with “uncontrolled hypertension,” and thereby include subjects with controlled hypertension, you must also do the following:**
 - a. Define uncontrolled hypertension that would warrant exclusion from the study.**

- b. Define acceptable “controlled” hypertensive inclusion criteria, and provide an acceptable rationale for the study of cocaine in the above defined “controlled” hypertensive population.**

Additional CMC Comments:

As you prepare your IND for submission, we refer you to the Guidance for Industry: *INDs for Phase 2 and Phase 3 Studies (Chemistry, Manufacturing, and Controls Information)*, available at

<http://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/UCM070567.pdf>

3.0 OTHER IMPORTANT PRE-IND ADVICE

3.1 PREA REQUIREMENTS

Please be advised that under the Food and Drug Administration Safety and Innovation Act (FDASIA), you must submit an Initial Pediatric Study Plan (PSP). The PSP must contain an outline of the pediatric study or studies that you plan to conduct (including, to the extent practicable study objectives and design, age groups, relevant endpoints, and statistical approach); any request for a deferral, partial waiver, or waiver, if applicable, along with any supporting documentation, and any previously negotiated pediatric plans with other regulatory authorities. The PSP should be submitted in PDF and Word format.

For additional guidance on the timing, content, and submission of the PSP, including a PSP Template, please refer to the draft guidance for industry, *Pediatric Study Plans: Content of and Process for Submitting Initial Pediatric Study Plans and Amended Pediatric Study Plans* at: <http://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/UCM360507.pdf>. In addition, you may contact the Pediatric and Maternal Health Staff at 301-796-2200 or email pdit@fda.hhs.gov. For further guidance on pediatric product development, please refer to: <http://www.fda.gov/Drugs/DevelopmentApprovalProcess/DevelopmentResources/ucm049867.htm>.

3.2 DATA STANDARDS FOR STUDIES

CDER strongly encourages IND sponsors to consider the implementation and use of data standards for the submission of applications for investigational new drugs and product registration. Such implementation should occur as early as possible in the product development lifecycle, so that data standards are accounted for in the design, conduct, and analysis of clinical and nonclinical studies. CDER has produced a web page that provides specifications for sponsors regarding implementation and submission of clinical and nonclinical study data in a standardized format. This web page will be updated regularly to reflect CDER's growing experience in order to meet the needs of its reviewers. The web page may be found at: <http://www.fda.gov/Drugs/DevelopmentApprovalProcess/FormsSubmissionRequirements/ElectronicSubmissions/ucm248635.htm>

3.3 ABUSE POTENTIAL ASSESSMENT

Drugs that affect the central nervous system, are chemically or pharmacologically similar to other drugs with known abuse potential, or produce psychoactive effects such as mood or cognitive changes (e.g., euphoria, hallucinations) need to be evaluated for their abuse potential and a proposal for scheduling will be required at the time of the NDA submission [21 CFR 314.50(d)(5)(vii)]. For information on the abuse potential evaluation and information required at the time of your NDA submission, see the draft guidance for industry, “Guidance for Industry Assessment of Abuse Potential of Drugs”, available at:

<http://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/UCM198650.pdf>.

3.4 505(b)(2) REGULATORY PATHWAY

A 505(b)(2) application would be an acceptable approach at this time based on the information provided. The Division recommends that sponsors considering the submission of an application through the 505(b)(2) pathway consult the Agency’s regulations at 21 CFR 314.54, and the draft guidance for industry *Applications Covered by Section 505(b)(2)* (October 1999), available at <http://www.fda.gov/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/default.htm>. In addition, FDA has explained the background and applicability of section 505(b)(2) in its October 14, 2003, response to a number of citizen petitions that had challenged the Agency’s interpretation of this statutory provision (see Docket FDA-2003-P-0274-0015, available at <http://www.regulations.gov>).

If you intend to submit a 505(b)(2) application that relies for approval on FDA’s finding of safety and/or effectiveness for one or more listed drugs, you must establish that such reliance is scientifically appropriate, and must submit data necessary to support any aspects of the proposed drug product that represent modifications to the listed drug(s). You should establish a “bridge” (e.g., via comparative bioavailability data) between your proposed drug product and each listed drug upon which you propose to rely to demonstrate that such reliance is scientifically justified.

If you intend to rely on literature or other studies for which you have no right of reference but that are necessary for approval, you also must establish that reliance on the studies described in the literature or on the other studies is scientifically appropriate. You should include a copy of such published literature in the 505(b)(2) application and identify any listed drug(s) described in the published literature (e.g. trade name(s)).

If you intend to rely on the Agency’s finding of safety and/or effectiveness for a listed drug(s) or published literature describing a listed drug(s) (which is considered to be reliance on FDA’s finding of safety and/or effectiveness for the listed drug(s)), you should identify the listed drug(s) in accordance with the Agency’s regulations at 21 CFR 314.54. It should be noted that 21 CFR 314.54 requires identification of the “listed drug for which FDA has made a finding of safety and effectiveness,” and thus an applicant may only rely upon a listed drug that was approved in an NDA under section 505(c) of the FD&C Act. The regulatory requirements for a 505(b)(2)

application (including, but not limited to, an appropriate patent certification or statement) apply to each listed drug upon which a sponsor relies.

If you propose to rely on FDA's finding of safety and/or effectiveness for a listed drug that has been discontinued from marketing, the acceptability of this approach will be contingent on FDA's consideration of whether the drug was discontinued for reasons of safety or effectiveness.

We encourage you to identify each section of your proposed 505(b)(2) application that is supported by reliance on FDA's finding of safety and/or effectiveness for a listed drug(s) or on published literature. In your 505(b)(2) application, we encourage you to clearly identify (for each section of the application, including the labeling): (1) the information for the proposed drug product that is provided by reliance on FDA's finding of safety and/or effectiveness for the listed drug or by reliance on published literature; (2) the "bridge" that supports the scientific appropriateness of such reliance; and (3) the specific name (e.g., proprietary name) of each listed drug named in any published literature on which your marketing application relies for approval. If you are proposing to rely on published literature, include copies of the article(s) in your submission.

Please be advised that circumstances could change that would render a 505(b)(2) application for this product no longer appropriate. For example, if a pharmaceutically equivalent product were approved before your application is submitted, such that your proposed product would be a "duplicate" of a listed drug and eligible for approval under section 505(j) of the FD&C Act, then it is FDA's policy to refuse to file your application as a 505(b)(2) application (21 CFR 314.101(d)(9)). In such a case, the appropriate submission would be an Abbreviated New Drug Application (ANDA) that cites the duplicate product as the reference listed drug.

This is a representation of an electronic record that was signed electronically and this page is the manifestation of the electronic signature.

/s/

DOMINIC CHIAPPERINO
08/20/2013