

**CENTER FOR DRUG EVALUATION AND
RESEARCH**

APPLICATION NUMBER:

208032Orig1s000

**ADMINISTRATIVE and CORRESPONDENCE
DOCUMENTS**

EXCLUSIVITY SUMMARY

NDA # 208032

SUPPL #

HFD # 170

Trade Name Kovanaze

Generic Name Tetracaine HCl & Oxymetazoline HCl

Applicant Name St. Renatus, LLC

Approval Date, If Known 6/29/2016

PART I IS AN EXCLUSIVITY DETERMINATION NEEDED?

1. An exclusivity determination will be made for all original applications, and all efficacy supplements. Complete PARTS II and III of this Exclusivity Summary only if you answer "yes" to one or more of the following questions about the submission.

a) Is it a 505(b)(1), 505(b)(2) or efficacy supplement?

YES NO

If yes, what type? Specify 505(b)(1), 505(b)(2), SE1, SE2, SE3,SE4, SE5, SE6, SE7, SE8

505(b)(2)

b) Did it require the review of clinical data other than to support a safety claim or change in labeling related to safety? (If it required review only of bioavailability or bioequivalence data, answer "no.")

YES NO

If your answer is "no" because you believe the study is a bioavailability study and, therefore, not eligible for exclusivity, EXPLAIN why it is a bioavailability study, including your reasons for disagreeing with any arguments made by the applicant that the study was not simply a bioavailability study.

If it is a supplement requiring the review of clinical data but it is not an effectiveness supplement, describe the change or claim that is supported by the clinical data:

c) Did the applicant request exclusivity?

YES NO

If the answer to (d) is "yes," how many years of exclusivity did the applicant request?

Three

d) Has pediatric exclusivity been granted for this Active Moiety?

YES NO

If the answer to the above question in YES, is this approval a result of the studies submitted in response to the Pediatric Written Request?

IF YOU HAVE ANSWERED "NO" TO ALL OF THE ABOVE QUESTIONS, GO DIRECTLY TO THE SIGNATURE BLOCKS AT THE END OF THIS DOCUMENT.

2. Is this drug product or indication a DESI upgrade?

YES NO

IF THE ANSWER TO QUESTION 2 IS "YES," GO DIRECTLY TO THE SIGNATURE BLOCKS ON PAGE 8 (even if a study was required for the upgrade).

PART II FIVE-YEAR EXCLUSIVITY FOR NEW CHEMICAL ENTITIES

(Answer either #1 or #2 as appropriate)

1. Single active ingredient product.

Has FDA previously approved under section 505 of the Act any drug product containing the same active moiety as the drug under consideration? Answer "yes" if the active moiety (including other esterified forms, salts, complexes, chelates or clathrates) has been previously approved, but this particular form of the active moiety, e.g., this particular ester or salt (including salts with hydrogen or coordination bonding) or other non-covalent derivative (such as a complex, chelate, or clathrate) has not been approved. Answer "no" if the compound requires metabolic conversion (other than deesterification of an esterified form of the drug) to produce an already approved active moiety.

YES NO

If "yes," identify the approved drug product(s) containing the active moiety, and, if known, the NDA #(s).

NDA#

NDA#

NDA#

2. Combination product.

If the product contains more than one active moiety(as defined in Part II, #1), has FDA previously approved an application under section 505 containing any one of the active moieties in the drug product? If, for example, the combination contains one never-before-approved active moiety and one previously approved active moiety, answer "yes." (An active moiety that is marketed under an OTC monograph, but that was never approved under an NDA, is considered not previously approved.)

YES NO

If "yes," identify the approved drug product(s) containing the active moiety, and, if known, the NDA #(s).

NDA# 021623

Synera (lidocaine and tetracaine topical patch)

NDA#

NDA#

IF THE ANSWER TO QUESTION 1 OR 2 UNDER PART II IS "NO," GO DIRECTLY TO THE SIGNATURE BLOCKS ON PAGE 8. (Caution: The questions in part II of the summary should only be answered "NO" for original approvals of new molecular entities.)
IF "YES," GO TO PART III.

PART III THREE-YEAR EXCLUSIVITY FOR NDAs AND SUPPLEMENTS

To qualify for three years of exclusivity, an application or supplement must contain "reports of new clinical investigations (other than bioavailability studies) essential to the approval of the application and conducted or sponsored by the applicant." This section should be completed only if the answer to PART II, Question 1 or 2 was "yes."

1. Does the application contain reports of clinical investigations? (The Agency interprets "clinical investigations" to mean investigations conducted on humans other than bioavailability studies.) If the application contains clinical investigations only by virtue of a right of reference

to clinical investigations in another application, answer "yes," then skip to question 3(a). If the answer to 3(a) is "yes" for any investigation referred to in another application, do not complete remainder of summary for that investigation.

YES NO

IF "NO," GO DIRECTLY TO THE SIGNATURE BLOCKS ON PAGE 8.

2. A clinical investigation is "essential to the approval" if the Agency could not have approved the application or supplement without relying on that investigation. Thus, the investigation is not essential to the approval if 1) no clinical investigation is necessary to support the supplement or application in light of previously approved applications (i.e., information other than clinical trials, such as bioavailability data, would be sufficient to provide a basis for approval as an ANDA or 505(b)(2) application because of what is already known about a previously approved product), or 2) there are published reports of studies (other than those conducted or sponsored by the applicant) or other publicly available data that independently would have been sufficient to support approval of the application, without reference to the clinical investigation submitted in the application.

(a) In light of previously approved applications, is a clinical investigation (either conducted by the applicant or available from some other source, including the published literature) necessary to support approval of the application or supplement?

YES NO

If "no," state the basis for your conclusion that a clinical trial is not necessary for approval AND GO DIRECTLY TO SIGNATURE BLOCK ON PAGE 8:

(b) Did the applicant submit a list of published studies relevant to the safety and effectiveness of this drug product and a statement that the publicly available data would not independently support approval of the application?

YES NO

(1) If the answer to 2(b) is "yes," do you personally know of any reason to disagree with the applicant's conclusion? If not applicable, answer NO.

YES NO

If yes, explain:

(2) If the answer to 2(b) is "no," are you aware of published studies not conducted or sponsored by the applicant or other publicly available data that could independently demonstrate the safety and effectiveness of this drug product?

YES NO

If yes, explain:

- (c) If the answers to (b)(1) and (b)(2) were both "no," identify the clinical investigations submitted in the application that are essential to the approval:

SR3-02, *A Phase III, Multi-Center, Randomized, Double-Blind, Parallel-Groups Clinical Trial Comparing the Efficacy and Safety of Intranasally Administered Kovacaine Mist to Tetracaine Alone and to Placebo for Anesthetizing Maxillary Teeth in Adults*

SR3-03, *A Phase 3, Multi-Center, Randomized, Double-Blind, Parallel-Groups Clinical Trial Comparing the Efficacy and Safety of Intranasally Administered Kovacaine Mist to Placebo for Anesthetizing Maxillary Teeth in Adults*

SR3-04, *A Phase 3, Multi-Center, Randomized, Double-Blind, Parallel-Groups Clinical Trial Comparing the Efficacy and Safety of Intranasally Administered K305 to Placebo for Anesthetizing Maxillary Teeth in Pediatric Patients*

Studies comparing two products with the same ingredient(s) are considered to be bioavailability studies for the purpose of this section.

3. In addition to being essential, investigations must be "new" to support exclusivity. The agency interprets "new clinical investigation" to mean an investigation that 1) has not been relied on by the agency to demonstrate the effectiveness of a previously approved drug for any indication and 2) does not duplicate the results of another investigation that was relied on by the agency to demonstrate the effectiveness of a previously approved drug product, i.e., does not redemonstrate something the agency considers to have been demonstrated in an already approved application.

- a) For each investigation identified as "essential to the approval," has the investigation been relied on by the agency to demonstrate the effectiveness of a previously approved drug product? (If the investigation was relied on only to support the safety of a previously approved drug, answer "no.")

Investigation #1 YES NO

Investigation #2 YES NO

Investigation #3 YES NO

If you have answered "yes" for one or more investigations, identify each such investigation and the NDA in which each was relied upon:

b) For each investigation identified as "essential to the approval", does the investigation duplicate the results of another investigation that was relied on by the agency to support the effectiveness of a previously approved drug product?

Investigation #1 YES NO

Investigation #2 YES NO

Investigation #3 YES NO

If you have answered "yes" for one or more investigation, identify the NDA in which a similar investigation was relied on:

c) If the answers to 3(a) and 3(b) are no, identify each "new" investigation in the application or supplement that is essential to the approval (i.e., the investigations listed in #2(c), less any that are not "new"):

SR3-02
SR3-03
SR3-04

4. To be eligible for exclusivity, a new investigation that is essential to approval must also have been conducted or sponsored by the applicant. An investigation was "conducted or sponsored by" the applicant if, before or during the conduct of the investigation, 1) the applicant was the sponsor of the IND named in the form FDA 1571 filed with the Agency, or 2) the applicant (or its predecessor in interest) provided substantial support for the study. Ordinarily, substantial support will mean providing 50 percent or more of the cost of the study.

a) For each investigation identified in response to question 3(c): if the investigation was carried out under an IND, was the applicant identified on the FDA 1571 as the sponsor?

Investigation #1
IND #70868 YES !
! ! NO
! Explain:

Investigation #2
IND #70868 YES !
! ! NO
! Explain:

Investigation #3
IND #70868 YES !
! ! NO
! Explain:

(b) For each investigation not carried out under an IND or for which the applicant was not identified as the sponsor, did the applicant certify that it or the applicant's predecessor in interest provided substantial support for the study?

Investigation #1
YES !
! ! NO
Explain: ! Explain:

Investigation #2
YES !
! ! NO
Explain: ! Explain:

(c) Notwithstanding an answer of "yes" to (a) or (b), are there other reasons to believe that the applicant should not be credited with having "conducted or sponsored" the study? (Purchased studies may not be used as the basis for exclusivity. However, if all rights to

the drug are purchased (not just studies on the drug), the applicant may be considered to have sponsored or conducted the studies sponsored or conducted by its predecessor in interest.)

YES NO

If yes, explain:

=====
Name of person completing form: Mavis Darkwah, PharmD
Title: RPM, DAAAP
Date: 06/29/2016

Name of Office/Division Director signing form: Rigoberto Roca, MD
Title: Deputy Division Director, DAAAP

Form OGD-011347; Revised 05/10/2004; formatted 2/15/05; removed hidden data 8/22/12

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

/s/

MAVIS Y DARKWAH
06/29/2016

RIGOBERTO A ROCA
06/29/2016

ACTION PACKAGE CHECKLIST

APPLICATION INFORMATION ¹		
NDA # 208032 BLA #	NDA Supplement # BLA Supplement #	If NDA, Efficacy Supplement Type: <i>(an action package is not required for SE8 or SE9 supplements)</i>
Proprietary Name: Kovanaze Established/Proper Name: Tetracaine HCl & Oxymetazoline HCl Dosage Form: nasal spray		Applicant: St. Renatus, LLC Agent for Applicant (if applicable):
RPM: Mavis Darkwah		Division: Division of Anesthesia, Analgesia, and Addiction Products (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)		For ALL 505(b)(2) applications, two months prior to EVERY action: 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 <i>(notify CDER OND IO)</i> Date of check: <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 March 29, 2016; Extended to June 29, 2016		☒ 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):
(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 <i>(approvals only)</i>	☐ Yes ☐ No
❖ Public communications <i>(approvals only)</i>	
• 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)? • If so, specify the type	☒ No ☐ Yes
❖ 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 <i>(approvals only)</i>	☒ Included
Documentation of consent/non-consent by officers/employees	☒ Included

Action Letters	
❖ Copies of all action letters <i>(including approval letter with final labeling)</i>	Action(s) and date(s) AP/ 06/29/2016
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
Original applicant-proposed labeling	☒ 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
Original applicant-proposed labeling	☒ 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>	08/21/2015 08/06/2015
❖ Labeling reviews <i>(indicate dates of reviews)</i>	RPM: ☐ None 08/14/2015 DMEPA: ☐ None 11/23/2015, 06/27/2016, 06/29/2016 DMPP/PLT (DRISK): ☒ None OPDP: ☐ None 06/08/2016, 06/24/2016 SEALD: ☒ None CSS: ☒ None Product Quality ☒ None Other: ☐ None
Administrative / Regulatory Documents	
❖ RPM Filing Review ⁴ /Memo of Filing Meeting <i>(indicate date of each review)</i>	07/22/2015
❖ All NDA 505(b)(2) Actions: Date each action cleared by 505(b)(2) Clearance Committee	☐ Not a (b)(2) 06/20/2015
❖ NDAs/NDA supplements only: Exclusivity Summary <i>(signed by Division Director)</i>	☒ Included
❖ Application Integrity Policy (AIP) Status and Related Documents http://www.fda.gov/ICECI/EnforcementActions/ApplicationIntegrityPolicy/default.htm	
Applicant is on the AIP	☐ Yes ☒ No

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

- This application is on the AIP - 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>)	☐ Yes ☒ No ☐ Not an AP action
❖ Pediatrics (<i>approvals only</i>) - Date reviewed by PeRC 01/13/2016 - If PeRC review not necessary, explain: _____	
❖ 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>)	
❖ 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)	
❖ 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 09/23/2014
EOP2 meeting (<i>indicate date of mtg</i>)	☐ No mtg 04/01/2011
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>)	
❖ 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
Cross-Discipline Team Leader Review (<i>indicate date for each review</i>)	☐ None 06/29/2016
PMR/PMC Development Templates (<i>indicate total number</i>)	☒ None
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>)		06/28/2016
• 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>)		Reviewed in clinical review 06/28/2016
❖ Clinical reviews from immunology and other clinical areas/divisions/Centers (<i>indicate date of each review</i>) ⁵		☐ None CDRH 04/29/16 DDDP, 03/14/2016 Office of Pediatric Therapeutics, OC, 03/03/2016, 03/04/2016
❖ Controlled Substance Staff review(s) and Scheduling Recommendation (<i>indicate date of each review</i>)		☒ N/A
❖ 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>)		☐ None
❖ OSI Clinical Inspection Review Summary(ies) (<i>include copies of OSI letters to investigators</i>)		☐ None requested 03/09/2016
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 02/22/2016
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 02/22/2016
❖ OSI Clinical Pharmacology Inspection Review Summary (<i>include copies of OSI letters</i>)		☒ None requested

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).

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 06/17/2016
• Pharm/tox review(s), including referenced IND reviews (<i>indicate date for each review</i>)	☐ None 06/17/2016
❖ Review(s) by other disciplines/divisions/Centers requested by P/T reviewer (<i>indicate date for each review</i>)	☐ None DPMH 05/26/16
❖ 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 06/20/2016
❖ 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</i>)(<i>all original applications and all efficacy supplements that could increase the patient population</i>)	07/06/2016
☐ Review & FONSI (<i>indicate date of review</i>)	
☐ Review & Environmental Impact Statement (<i>indicate date of each review</i>)	
❖ Facilities Review/Inspection	
☐ Facilities inspections (<i>action must be taken prior to the re-evaluation date</i>) (<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 Re-evaluation date: ☐ Withhold recommendation ☐ Not applicable

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

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 (<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
❖ 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

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

/s/

MAVIS Y DARKWAH
07/06/2016

From: [Nick Diel](#)
To: [Darkwah, Mavis](#); [Jim Mulvahill](#)
Subject: RE: NDA 208032 Labeling
Date: Wednesday, June 29, 2016 2:39:34 PM
Attachments: [kovanaze-pi-29June16-clean.docx](#)
[kovanaze-pi-29June16-clean.docx](#)
[St.Renatus_Kovanaze_IFU_v15_20160629.pdf](#)

Hi Mavis,

We have accepted all of the new changes and have no new redlines. I have attached a clean version of the label. I have also attached the updated IFU with FDA's recommend language on duration.

Thanks and let me know if you need anything else,
Nick

From: Darkwah, Mavis [mailto:Mavis.Darkwah@fda.hhs.gov]
Sent: Wednesday, June 29, 2016 12:14 PM
To: Nick Diel <ndiel@St-Renatus.com>; Jim Mulvahill <jmulvahill@St-Renatus.com>
Subject: RE: NDA 208032 Labeling
Importance: High

Dear Nick,

We've additional minor edits to the PI. Please return a version of the label with our changes accepted and with your proposed changes tracked. Also provide a clean copy of the word version. In addition we have the following comment and recommendation for the IFU:

Modify the statement in the IFU under **How long will the patient will feel numb? to read:**

In a clinical trial with KOVANAZE, the median duration of a dental procedure successfully completed with KOVANAZE was 11 minutes, although one successfully completed dental procedure was as long as 43 minutes.

We request a response as soon as possible, preferably by **3:30pm (Eastern), today, June 29, 2016.**

Regards,

Mavis

From: Nick Diel [<mailto:ndiel@St-Renatus.com>]
Sent: Wednesday, June 29, 2016 10:26 AM
To: Darkwah, Mavis; Jim Mulvahill
Subject: RE: NDA 208032 Labeling

Hi Mavis,

We have accepted all of the FDA's purposed changes in the label. Attached is a clean version along with a redline version. In the redline version you can see where we made a couple of minor cleanup edits. The edits include correcting some word spacing once the redlines were accepted, and made a few of the purposed changes consistent throughout the label.

We also updated the carton drawing and the IFU based on the FDA's purposed changes. In the carton we updated the indication along with removing the trailing 0 in 6.0. In the IFU we updated the indication, removed the question in the FAQ about (b) (4) and updated the language on duration in the FAQ.

Let me know if you have any questions,
Nick

Nick Diel
Project Director

EMAIL ndiel@st-renatus.com | OFFICE 970.449.4455
FAX 970.449.4456 | WEB www.St-Renatus.com
St. Renatus, LLC | 1000 Centre Avenue | Fort Collins, CO 80526
[St.Renatus](#)



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From: Darkwah, Mavis [<mailto:Mavis.Darkwah@fda.hhs.gov>]
Sent: Tuesday, June 28, 2016 6:17 PM
To: Nick Diel <ndiel@St-Renatus.com>; Jim Mulvahill <jmulvahill@St-Renatus.com>
Subject: RE: NDA 208032 Labeling
Importance: High

Dear Nick,

Thank you for the response. Find attached the word version of the label with our proposed changes.

We have accepted your proposed changes we agree with, and rejected the proposed changes we do not agree with. We have also added information to the labeling. Please return a version of the label with our changes accepted and with your proposed changes tracked. Also provide a clean copy of the word version. In addition we have the following comments and recommendation for the IFU:

Remove the following language from the product packaging:

(b) (4)

Because the proposed changes affect other labeling, please submit revised Instruction For Use, packaging, and carton labeling, as applicable, to reflect the revised changes.

We request a response as soon as possible, preferably by 10:30am (Eastern), June 29, 2016. Note that additional changes may be made, but in the interest of getting you time to review, I am sending this tonight.

Regards,

Mavis

From: Nick Diel [<mailto:ndiel@St-Renatus.com>]
Sent: Tuesday, June 28, 2016 4:05 PM
To: Darkwah, Mavis; Jim Mulvahill
Subject: RE: NDA 208032 Labeling

Hi Mavis,

Attached is the updated IFU, Sprayer Label, Outer Shipper Label, and Carton based on the FDA's comments.

Please let me know if you have any questions,
Nick

From: Darkwah, Mavis [<mailto:Mavis.Darkwah@fda.hhs.gov>]
Sent: Tuesday, June 28, 2016 7:49 AM
To: Nick Diel <ndiel@St-Renatus.com>; Jim Mulvahill <jmulvahill@St-Renatus.com>
Subject: RE: NDA 208032 Labeling
Importance: High

Dear Nick,

Attached and below are the comments and recommendations we have for the IFU, and carton and container labeling:

A. Instructions for Use

1. As a reference to dental professionals, add brief dosing instructions in table format at the beginning of the IFU, (i.e., 2 sprays with an optional third dose for adults, and 2 sprays for children [REDACTED] (b) (4) who weigh 40 kg or more). This information is a helpful reference to dental professionals, and the addition of this information would not require further validation testing.
2. Revise the following statements in the instructions for the spray positions located just before step 1a from “[REDACTED] (b) (4) [REDACTED])...” to read “Spray Position for First Spray (Approximately Horizontal)...” and “Spray position for second spray (Approximately 45 Degree Angle)...” This revision may provide clarity for dental professionals and would not require further validation testing.

B. Carton Labeling and Outer Shipping Box Labeling

1. Revise the storage statement and bold it as follows: “**Must be refrigerated, store at 2°C to 8°C (36°C to 46°F)**”. We recommend this to increase the prominence of this important information and minimize the risk of the storage information being overlooked.

Please submit the revised versions as soon as possible, preferably by **4pm (Eastern), today, June 28, 2016.**

Regards,

Mavis

From: Nick Diel [<mailto:ndiel@St-Renatus.com>]
Sent: Thursday, June 23, 2016 11:10 AM
To: Darkwah, Mavis; Jim Mulvahill
Subject: RE: NDA 208032 Labeling

Hi Mavis,

The following changes have been made to the Kovanaze labeling to reflect the proposed changes to the Prescribing Information:

Carton:

- Removed concentration from established name
- Updated indication

Barrel label:

- Removed concentration from established name

Finger Grip label:

- Removed concentration from established name
- Revised company contact information
- Updated layout

Outer Shipping Label:

- Updated format to reflect Contract Manufacturer's capabilities

Let me know if you have any questions,
Nick

Nick Diel

Project Director

EMAIL ndiel@st-renatus.com | OFFICE 970.449.4455

FAX 970.449.4456 | WEB www.St-Renatus.com

St. Renatus, LLC | 1000 Centre Avenue | Fort Collins, CO 80526



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Enhancing Patient Comfort Through Innovation

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From: Darkwah, Mavis [<mailto:Mavis.Darkwah@fda.hhs.gov>]

Sent: Tuesday, June 21, 2016 1:59 PM

To: Nick Diel <ndiel@St-Renatus.com>; Jim Mulvahill <jmulvahill@St-Renatus.com>

Subject: RE: NDA 208032 Labeling

Importance: High

Dear Nick,

Thank you for the response; the review team is currently reviewing your proposals for the PI. Please submit revised Instruction For Use, packaging, and carton labeling, as applicable, to reflect the revised changes as soon as possible, latest by 12PM (Eastern), June 23, 2016.

Regards,

Mavis

From: Nick Diel [<mailto:ndiel@St-Renatus.com>]
Sent: Tuesday, June 21, 2016 12:59 PM
To: Darkwah, Mavis; Jim Mulvahill
Subject: RE: NDA 208032 Labeling

Hi Mavis,

Attached is an additional table that may be of use to the reviewer when reviewing our request about nasal ulcerations. I apologize that it was not finalized in time for my earlier email.

Let me know if you have any questions,
Nick

Nick Diel
Project Director

EMAIL ndiel@st-renatus.com | OFFICE 970.449.4455
FAX 970.449.4456 | WEB www.St-Renatus.com
St. Renatus, LLC | 1000 Centre Avenue | Fort Collins, CO 80526



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From: Nick Diel

Sent: Tuesday, June 21, 2016 10:19 AM

To: Darkwah, Mavis <Mavis.Darkwah@fda.hhs.gov>; Jim Mulvahill <jmulvahill@St-Renatus.com>

Subject: RE: NDA 208032 Labeling

Hi Mavis,

Attached, please find the draft label for Kovanaze. I have included one version with St. Renatus' proposed changes tracked, as well as a clean version. I have also included a justification document for some of St. Renatus' proposed changes.

Please let me know if you have any questions.

Thank you,
Nick

Nick Diel

Project Director

EMAIL ndiel@st-renatus.com | OFFICE 970.449.4455

FAX 970.449.4456 | WEB www.St-Renatus.com

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From: Darkwah, Mavis [<mailto:Mavis.Darkwah@fda.hhs.gov>]

Sent: Friday, June 17, 2016 9:06 AM
To: Jim Mulvahill <jmulvahill@St-Renatus.com>
Cc: Nick Diel <ndiel@St-Renatus.com>
Subject: NDA 208032 Labeling
Importance: High

Dear Jim and Nick,

Please refer to you NDA 208032 for Kovanaze. Find attached the word version of the label with our proposed changes. We have accepted your proposed changes we agree with, and rejected the proposed changes we do not agree with. We have also added information to the labeling. Please return a version of the label with our changes accepted and with your proposed changes tracked. Also provide a clean copy of the word version. The comments and recommendations for the carton and container will be forthcoming.

We request a response as soon as possible, preferably by 12pm (Eastern), June 21, 2016 .

Regards,

Mavis

*Mavis Y. Darkwah, PharmD
LT, USPHS Commissioned Corps
Regulatory Health Project Manager
Division of Anesthesia, Analgesia, and Addiction Products (DAAAP)
FDA/CDER/OND/ODE II
Ph: (240) 402-3158
Email: Mavis.Darkwah@fda.hhs.gov*

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

/s/

MAVIS Y DARKWAH
06/29/2016

PeRC Meeting Minutes
January 13, 2016

PeRC Members Attending:

Lynne Yao
Hari Cheryl Sachs
Linda Lewis
Gil Burckart
Andrew Mulberg
Thomas Smith
Daiva Shetty
Gettie Audain
Meshaun Payne
George Greeley
Gregory Reaman
Dianne Murphy
Michelle Roth-Kline
Rosemary Addy
Gerrie Baer
Maura Oleary
Wiley Chambers
Rachel Witten
Shrikant Pagay

Agenda

NON-RESPONSIVE					

10:35	NDA 208032	Kovanaze (tetracaine HCL/oxymetazoline HCL) Partial Waiver/Assessment	DAAAP	Mavis Darkwah	Treatment for regional anesthesia when performing a restorative procedure on teeth 4-13 and A-J

NON-RESPONSIVE					

2 Pages have been Withheld in Full as NON-RESPONSIVE immediately following this page

NON-RESPONSIVE

Kovanaze (tetracaine HCL/oxymetazoline HCL) Partial Waiver/Assessment

- Indication: Treatment for regional anesthesia when performing a restorative procedure on teeth 4-13 and A-J
- PDUFA goal date is March 29, 2015.
- The plan for this application is a partial waiver in patients ages birth to less than 3 years of age (b) (4)
- (b) (4)
- *PeRC Recommendations:*
 - The PeRC agreed with the division to grant a partial waiver in patient's birth to less than 3 years because studies are impossible or highly impractical (b) (4)

NON-RESPONSIVE

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

/s/

GETTIE AUDAIN
02/02/2016



DEPARTMENT OF HEALTH & HUMAN SERVICES

Food and Drug Administration
Silver Spring, MD 20993

NDA 208032

**PROPRIETARY NAME REQUEST
CONDITIONALLY ACCEPTABLE**

St. Renatus, LLC
1000 Centre Avenue
Fort Collins, CO 80526

ATTENTION: James P. Mulvahill
Project Manager

Dear Mr. Mulvahill:

Please refer to your New Drug Application (NDA) dated and received May 29, 2015, submitted under section 505(b)(2) of the Federal Food, Drug, and Cosmetic Act for Tetracaine HCl and Oxymetazoline HCl Nasal Spray, 3%/0.05%.

We also refer to your correspondence, dated and received May 29, 2015, requesting review of your proposed proprietary name, Kovanaze.

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

If any of the proposed product characteristics as stated in your May 29, 2015, submission are altered prior to approval of the marketing application, the proprietary name should be resubmitted for review.

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 Lisa Skarupa, Safety Regulatory Project Manager in the Office of Surveillance and Epidemiology, at (301) 796-2219. For any other information regarding this application, contact Mavis Y. Darkwah, Regulatory Project Manager in the Office of New Drugs, at (240) 402-3158.

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/

TODD D BRIDGES
08/21/2015



DEPARTMENT OF HEALTH AND HUMAN SERVICES

Food and Drug Administration
Silver Spring MD 20993

IND 070868

MEETING MINUTES

St. Renatus, LLC
1000 Centre Avenue, Suite 120
Fort Collins, CO 80526

Attention: James P. Mulvahill
Project Manager

Dear Mr. Mulvahill:

Please refer to your Investigational New Drug Application (IND) submitted under Section 505(i) of the Federal Food, Drug, and Cosmetic Act for K305 (tetracaine HCl/oxymetazoline HCl) nasal spray.

We also refer to the meeting between representatives of your firm and the FDA on August 21, 2014. The purpose of the meeting was to discuss the proposed structure and content of the CMC, non-clinical, and clinical sections of the upcoming NDA for K305.

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) 796-4085.

Sincerely,

{See appended electronic signature page}

Swati Patwardhan
Regulatory 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: Type B
Meeting Category: Pre-NDA

Meeting Date and Time: August 21, 2014, 3:00 to 4:00 pm
Meeting Location: 10903 New Hampshire Avenue, White Oak Building 22,
Conference Room 1315, Silver Spring, Maryland 20903

Application Number: IND 070868
Product Name: K305 (tetracaine HCl/oxymetazoline HCl) nasal spray,
6.0 mg/0.10 mg per spray

Indication: Topical anesthetic producing anesthesia of the maxillary teeth after
intranasal application

Sponsor/Applicant Name: St. Renatus, LLC.

Meeting Chair: Rigoberto Roca, MD, Deputy Director, Division of Anesthesia,
Analgesia, and Addiction Products (DAAAP)

Meeting Recorder: Swati Patwardhan, Regulatory Project Manager, DAAAP

ATTENDEES:

FDA Attendees	Title
Bob A. Rappaport, MD	Director, DAAAP
Rigoberto Roca, MD	Deputy Director, DAAAP
Mary Luckett, MD	Medical Officer, DAAAP
Dan Mellon, PhD	Supervisory Pharmacology/Toxicology, DAAAP
Zengjun Xu, PhD	Pharmacology/Toxicology Reviewer, DAAAP
David Lee, PhD	Clinical Pharmacology Reviewer, Office of Clinical Pharmacology (OCP)
Yun Xu, PhD	Clinical Pharmacology Team Leader, OCP
Janice Derr, PhD	Biostatistics Team Leader, Division of Biometrics II (DBII)
Eugenia Nashed, PhD	CMC Reviewer, Office of New Drug Quality Assessment
Frederick Hyman, DDS, MPH	Dental Officer, Division of Dermal and Dental Products
Irene Chan, Pharm D, BCPS	Associate Director, Division of Medication Error and Prevention Analysis (DMEPA)
James Schlick, RPh, MBA	Safety Evaluator, DMEPA
Swati Patwardhan, MS	Regulatory Project Manager, DAAAP

St. Renatus	Title
Steve Merrick	Chief Executive Officer
Sandra Brown, PhD	Director of Technical Affairs
Paul Sletten, DDS	Director of Clinical & Scientific Affairs
Mark Kollar, DDS	Co-founder, Senior Advisor
Jim Mulvahill	Co-founder, Senior Advisor
Nicholas Diel	Technical Information Specialist
Jill Shoemaker	Director of Finance
Stephen Snyder	Board Director

(b) (4)

BACKGROUND

St. Renatus submitted a Pre-NDA meeting request on May 29, 2014, to discuss the proposed structure and content of the CMC, non-clinical, and clinical sections of the upcoming New Drug Application for their K305 drug-device combination product. K305 is a fixed combination of tetracaine HCl (3% w/v) and oxymetazoline HCl (0.05% w/v), administered as a nasal spray. The combination solution is prefilled (0.2 mL) into glass syringes equipped with a spray valve (Accuspray device). Each spray delivers 6.0 mg of tetracaine HCl and 0.10 mg of oxymetazoline HCl in 0.2 mL solution volume. The Sponsor intends to submit a 505(b)(2) application that will rely on published literature, reliance on the OTC monograph for oxymetazoline, the Agency's previous findings of the safety for Synera (lidocaine and tetracaine) Patch (NDA 021623), as well as non-clinical studies conducted by St. Renatus.

A Pre-IND meeting was held on June 6, 2005, and an End-of-Phase 2 (EOP2) meeting was held on March 3, 2011.

The Pre-NDA meeting request was granted, and the briefing package was received on July 14, 2014.

DISCUSSION

Below are the Division's responses to the questions from the July 14, 2014, briefing package. Questions submitted in the briefing package reproduced below are in italics, the Division's responses are in bolded text, and the meeting discussion is in regular font.

After initial introduction, the discussion was focused on Questions, 2, 3, Additional Comment 7 under Questions 5, 6, and 13.

Questions

Chemistry, Manufacturing, and Controls

Question 1

Both tetracaine hydrochloride and oxymetazoline hydrochloride have been included in marketed products in the U.S. for over 50 years using drug content labeling expressed in terms of the salt strength equivalent. We propose that the label declaration for drug content of K305 be exempted from the USP policy to use the name and strength of the active moiety rather than presented in terms of the salt strength equivalent. The policy stated in the recent FDA MAPP 5021.1, Naming of Drug Products Containing Salt Drug Substances, Section C.2.a provides for the possibility of such an exemption "when retention of the name of the salt is appropriate for safety or historical reasons" to maintain consistency with existing products.

Does the Agency agree to grant an exemption to allow statement of the drug content of K305 as tetracaine HCl 3% w/v and oxymetazoline HCl 0.05% w/v?

FDA Response

Your proposal to use salt names, tetracaine hydrochloride and oxymetazoline hydrochloride, (instead of tetracaine and oxymetazoline) in the drug product name is acceptable based on the history of both drug substances. Consider expressing the strength of the dose in milligrams rather than w/v.

Meeting Discussion

No discussion occurred during the meeting. The preliminary responses were found to be adequate.

Question 2

Test results for one batch each of K305 manufactured by drug product manufacturers (b) (4) are provided to show comparability of the products to the development lots manufactured by (b) (4) that have been used throughout the K305 clinical program. [A request for regulatory guidance on this topic was submitted as SN 0030 December 6, 2012; FDA responded April 4, 2013].

Does the Agency agree that these results will be sufficient to support a request for approval of both (b) (4) as equivalent suppliers in addition to (b) (4)?

FDA Response

No, we do not agree. To qualify a new supplier, comparative data on at least three batches of drug product from each supplier should be provided. Further, the manufacturing process and equipment used by all suppliers should be comparable. All manufacturing facilities must be ready for inspection at the time of NDA submission.

Meeting Discussion:

The Sponsor stated that the advice received in the preliminary response was different from the comments received previously in Advice letter date April 4, 2013, specifically regarding number of batches required for the comparative data. The Division responded that it is unclear how some of the old development batches will be used commercially and establishing comparability, between three manufacturers, with just one batch from each manufacturer is difficult. In addition, during the NDA review, the emphasis will be placed on the product representative of marketing and an adequate amount of data is needed to establish control specifications. The Sponsor stated that, at this time, four development batches were manufactured by (b) (4) and 24 months of stability have been completed on those batches. However, only one batch of K305 has been manufactured at (b) (4), with six months of stability data available. In addition, the data from the three validation batches manufactured at (b) (4) will be provided post-approval. The Division noted that submission of the validated commercial drug product batches are not necessary for the NDA. However, the Sponsor will not be able to market their product until the validation of commercial process is complete. The Sponsor should submit their strategy and provide all the data available from the (b) (4) batches, even if they are not fully validated. The submission should include a list of all batches manufactured to date with manufacturing date, manufacturing site and scale, validation status, and stability information. If the submission is received in a timely manner, a response may be included as a post-meeting note. The Sponsor acknowledged the "validation before marketing" cGMP requirement during the meeting and requested a timely feedback from the Division on the acceptability of the incoming post-meeting amendment regarding the NDA strategy submission for CMC data.

Post-Meeting Note:

In the amendment dated September 3, 2014, and received September 4, 2014, the Sponsor submitted their NDA submission strategy for the supporting CMC data. The Sponsor requested clarification on acceptability of the proposed plan in the final meeting minutes if possible. Refer to Table 1, reproduced below from the IND amendment dated September 3, 2014:

TABLE 1 – STRATEGY FOR QUALIFICATION OF MANUFACTURING SITES

Stage	(b) (4)
Phase 1-2 production	
Phase 3 production	
Process transfer – lab scale and engineering batch	
Registration stability batches (primary stability)	
Additional development studies	
Scale-up plan	
Process validation (and product launch supplies)	
Available batch test data for inclusion in NDA submission	

Considering the relatively simple manufacturing process (developed by the Sponsor) and the good comparability of the drug product manufactured at alternate sites (refer to data presented in pre-NDA meeting package dated July 11, 2014, Tables 5.12 and 5.13), the proposed submission strategy, as outlined in the amendment dated September 3, 2014, and summarized in Table 1, above, is acceptable. The Applicant agreed to submit for NDA review all available release data from the three alternate manufacturing sites. Data from 4 stability batches (24 months) and one supporting stability batch (24 months) manufactured at the (b) (4) site will be submitted to the NDA. Also, at least one engineering and one pilot scale batch, with a minimum of 9-12 months of stability data will be submitted from the (b) (4) sites.

Question 3

Extensive data have been collected on multiple lots of K305 during development to characterize its spray properties. The variability for some of the spray parameters, especially spray pattern, presents a challenge for setting meaningful product specifications for routine product control. Despite the observed variability in laboratory data collected under controlled conditions, the product has performed consistently in the clinical program.

In light of the excellent clinical efficacy obtained using drug product lots with variable spray pattern characteristics, and considering anatomical features of the nose that facilitate dose delivery, we view the future use of spray pattern testing primarily as a quality control tool without direct relevance to in vivo performance. If it is necessary to include spray pattern control as part of future product specifications, will the Agency accept (a) an acceptance criterion based on production of a spray without quantitative limits, or alternatively, (b) parametric release criteria based on the variability observed, following the recommendations of

IPAC-RS working group or other similar approach, in setting specifications for routine product testing?

FDA Response

We encourage you to investigate the cause of the variability in the spray pattern data, and to provide a full report with the NDA submission. Determination of the acceptability of the spray pattern controls will be made upon review of the data. Further, adequate controls should be in place for droplet size distribution, plume geometry, and dose uniformity.

Meeting Discussion

The Sponsor concurred about the variability in the spray pattern. However, they noted that the variability has not impacted the clinical efficacy. Therefore, even if the spray pattern is not consistent, it is not affecting the dose delivered. Nonetheless, they are challenged by the specification requirement for the spray pattern. They further explained that the only differentiation identified by the device manufacturer is spray vs. liquid dribble. The Division responded that the K305 is treated as a nasal spray product, hence the quality of the product performance should be established accordingly with adequate (quantitative rather than qualitative) controls and specifications. The Agency guidance on the nasal sprays is a good reference for recommendations on characterization studies and product controls (guidance for industry: *Nasal Spray and Inhalation Solution, Suspension, and Spray Drug Products — Chemistry, Manufacturing, and Controls Documentation*, <http://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/ucm070575.pdf>).

The Division further advised that a control of the spray pattern with size and shape will be adequate for this spray product and controls for plume geometry are not necessary. Additionally, the Sponsor can collaborate with the DMF holder (b)(4) manufacturer) regarding the performance controls for the spray. In response to the Sponsor's proposal to submit parametric release data for spray pattern, the Division advised the Sponsor to develop quantitative controls for the spray pattern. While the parametric release controls could be developed, the data and proposed controls should not be statistically inferior to the quantitative controls for the spray pattern. The Sponsor should submit data and actual images of the spray patterns in the submission and propose data-based acceptance criteria. Further, the Division responded that three point acceptance criteria for control of droplet size distribution (e.g., D₁₀, D₅₀ and D₉₀) are recommended and are typically used for nasal spray products. Also, tightening of the acceptance criteria for pH is recommended, to be consistent with the data from the representative drug product batches. For the fill volume specification, a range should be established for the acceptance criteria rather than using a single limit of NMT (b)(4) mL. The Sponsor agreed to provide the requested info.

Post-Meeting Note:

We recommend that you also consider including controls for the osmolality and viscosity of the solution into the drug product specifications.

Question 4

Reference will be made in the NDA to a drug master file submitted by BD for all supporting information to describe the manufacture and control of the Accuspray delivery system.

Does the Agency agree that it is sufficient to reference the DMF submitted by BD for the Accuspray delivery system to provide the descriptive container closure information required for approval? Can preliminary feedback be provided concerning completeness of the contents of the DMF for this purpose?

FDA Response

It is acceptable to reference the DMF to support the device. The DMF for the Accuspray delivery system will be reviewed concurrently with the review of your NDA.

Additional CMC Comments

- 1. Analytical methods for determination of impurities in the drug substances should be by HPLC methods. Provide validated HPLC methods for impurity determination together with the validation reports in your NDA.**
- 2. We note that the data for impurities in the data tables is reported as 'complies' or 'n/a' or '<0.1' when the specification is NMT 0.1%. Actual data should be reported in all batch analysis and stability tables.**

Meeting Discussion

The Agency noted that a letter of authorization (LOA) to a drug master file (DMF) controlling the manufacturing and release of the spray valve should be submitted, if these information and data are not covered by the DMF controlling the Accuspray device.

Nonclinical**Question 5**

At the EOP2 meeting in 2011, FDA suggested that St. Renatus perform several nonclinical studies with the combination product for the NDA. The suggested studies included a 14-day intranasal dog study and a rat embryo fetal study (supported by a dose finding study in rats), with TK analysis. St. Renatus has completed these studies and submitted the study reports to the IND on June 24, 2014. Two studies are ongoing: a rat peri- and post-natal study, and a rat fertility study. Study reports for the two ongoing in vivo studies will be included in the NDA submission. In addition, two mutagenicity studies to qualify impurities containing structural alerts were completed and are negative. The mutagenicity studies were also submitted to the IND on June 24, 2014. No additional studies beyond the 5 in vivo and 2 in vitro studies in progress or already completed are planned for the NDA filing. As further support, St. Renatus will be providing a right of reference obtained from the NDA holder to safety information contained in NDA 21-623 for Synera.

Does the Division agree that the nonclinical data package described above is sufficient to support filing the NDA for K305?

FDA Response

Yes, we agree. The nonclinical development program that includes the studies we previously recommended and reference to the Agency's previous finding to FDA approved drug products as described in this meeting package appears sufficient to support NDA filing for your drug product.

We have the following additional nonclinical comments to assist you in the preparation of your NDA.

- 1. You must submit a letter of authorization granting the Agency permission to use the data in NDA 021632 (Synera) to support your drug product. If you have right of reference to these data, you must submit the documentation of this right to the Agency.**
- 2. We note that you currently do not have genetic toxicology data for oxymetazoline. Although we will not require these data for a 505(b)(2) NDA, in the interest of public health, we encourage you to obtain genotoxicity information for oxymetazoline to appropriately inform your drug product labeling.**
- 3. For the NDA submission, 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.**
 - 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 duration should be completed.**
 - c. 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.****
- 4. We note that your oxymetazoline drug substance contains Impurity A ^{(b) (4)} [REDACTED] which**

contains a structural alert for mutagenicity. Genotoxic impurities, carcinogenic impurities, or impurities that contain a structural alert for genotoxicity must be adequately controlled during drug development. Drug substance manufacturing often creates the potential for introduction of compounds with structural alerts for genotoxicity through use of reagents, catalysts and other processing aids or the interaction of these with starting materials or intermediates during the stages of chemical synthesis. You should refer to ICH M7 guidance document titled: *Assessment and Control of DNA Reactive (Mutagenic) Impurities in Pharmaceuticals to Limit Potential Carcinogenic Risk* for the appropriate framework for identifying, categorizing, qualifying, or controlling these impurities. This draft guidance is available at:

http://www.ich.org/fileadmin/Public_Web_Site/ICH_Products/Guidelines/Multidisciplinary/M7/M7_Step_4.pdf. Actual and potential impurities likely to arise during synthesis and storage of a new drug substance and manufacture and storage of a new drug product should be identified for assessment, briefly. A hazard assessment should be undertaken to categorize these impurities with respect to mutagenic and carcinogenic potential and risk characterization applied to derive acceptable intakes during clinical development. Finally, a control strategy should be proposed and enacted where this is determined to be necessary to ensure levels are within the accepted limits established for the stage of drug development in order to mitigate risk.

5. The 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 the 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, consult the FDA guidance documents: *Container Closure Systems for Packaging Human Drugs and Biologics*, available at, <http://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/>

Guidances/UCM070551.pdf and *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>. For your toxicological risk assessment, any leachable that contains a structural alert for mutagenicity should not exceed 1.5 mcg/day total daily exposure for a chronic indication or be adequately qualified for safety. From a genetic toxicology perspective, we will allow up to 120 mcg/day for an acute indication for most potentially genotoxic impurities. A toxicological risk assessment should be provided for any non-genotoxic leachable that exceeds 5 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.

- 6. 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.**
- 7. 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 the Agency's previous finding of safety for an approved product, the exposure margins provided in the referenced label must be updated to reflect exposures from your product. 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.**

Meeting Discussion

The Sponsor wanted to know if it would be acceptable to provide a letter of authorization (LOA) from Galen Specialty, the Synera NDA holder, for the Agency's review. The Division responded that this is appropriate. The adequacy of the information in the referenced NDA to support the proposed NDA for this drug product will be based on a review of the content and specifics of the LOA from Galen and the referenced data in the NDA. The Division encouraged the Sponsor to provide appropriate bridging data to justify why the referenced data supports their NDA. The Sponsor agreed to submit the LOA in the NDA submission.

- 8. We may refuse to file your application if your NDA submission does not contain adequate safety qualification data for any identified drug substance impurity or drug product degradant that exceeds the ICH qualification thresholds or extractable leachable that exceeds the qualification thresholds outlined above.**

Meeting Discussion

No discussion occurred for other aspects of Question 5 responses during the meeting. The preliminary responses were found to be adequate.

Clinical Pharmacology

Question 6

The Clinical Pharmacology section of the NDA will include a summary of relevant human absorption, distribution, metabolism, excretion (ADME), and related data extracted from the scientific literature; detailed summaries of three human pharmacokinetic studies conducted by St. Renatus (two studies in adults; one in pediatric subjects); and a population pharmacokinetic analysis based on data from the St. Renatus pharmacokinetic studies.

Does the Division agree that the clinical pharmacology data to be provided are sufficient to enable filing and review of the K305 NDA?

FDA Response

We note that you propose to submit your application using the 505(b)(2) pathway. As previously discussed in the EOP2 meeting, for a 505(b)(2) submission, you should establish a scientific bridge (e.g., via a comparative bioavailability study) between your product and the listed approved NDA products. However, it appears that you do not plan to conduct a relative bioavailability study for your NDA submission.

For the tetracaine component, you indicated that you will obtain a right of reference to the safety information contained in NDA 021623, Synera Patch. If you can obtain all the original study reports to support your application without referring to the Agency's previous findings of Synera Patch, then a comparative bioavailability study may not be needed. We recommend that you draft the product labeling by using your own study reports or the study reports for which you have a right of reference, without referring to the labeling of Synera Patch. If you still need to reference the labeling of Synera Patch for any safety information, clinical or preclinical, then you will need to conduct a relative BA study to establish a scientific bridge.

For the oxymetazoline component, you plan to rely on the OTC monograph for oxymetazoline. However, your product contains tetracaine and has a different indication compared to the oxymetazoline monograph. You have not specified in the meeting package which part of the monograph findings you plan to rely upon. In your NDA submission, clearly identify which monograph findings you will rely on, and provide adequate justification as to why these findings can be used to support your NDA considering the differences mentioned above.

Meeting Discussion

The Sponsor stated that they would be providing an LOA to review the data from Synera NDA. The Division responded that with authorization to review the application in entirety in support of St. Renatus application, a comparative bioavailability study will not be required. However, the

Sponsor will have to create their own label without referencing the Synera label and they cannot rely on the Agency's previous finding on safety and efficacy. Alternatively, if a 505(b)(2) application is submitted referring Synera, then a scientific bridge should be established.

With regard to the oxymetazoline monograph, the Sponsor responded that they intend to rely on the labeling and the literature referenced in the monograph. The Division stated that the Sponsor should provide justification for why the literature references in monograph can be used to support the new product. The application should clearly identify what part of monograph is being relied on and the reason for the reliance, as the proposed drug indication is different from the one in the monograph.

The Division inquired if the Sponsor had obtained the actual toxicology studies for the original oxymetazoline NDA. The Sponsor responded that the pharmacology and toxicology reviews were requested from the Agency under the Freedom of Information Act (FOIA). The Division clarified that those reviews are interpretation of data and not actual study reports; therefore, they cannot be referenced to support their application. In this case, they must rely upon the Agency's previous finding of safety and efficacy of the product or the final monograph.

The Sponsor was also reminded to evaluate drug-drug interactions (DDI) as the K305 drug product is a combination product. If the systemic exposure of oxymetazoline in the new combination is different from the oxymetazoline monograph product due to DDI, then the monograph findings may no longer apply to the combination product.

The Sponsor was also reminded to utilize the to-be-marketed formulation in their PK and clinical studies.

Question 7

A specific drug-drug interaction study was not carried out; however, all concomitant medications taken by patients during the course of the clinical trials were recorded, including medications administered for seasonal and allergic rhinitis. The safety profiles for subjects receiving investigational product along with these specific medications will be specifically evaluated for potential drug-drug interactions within each of the Phase 3 clinical study reports.

Does the Division agree that the safety evaluations of concomitant medications in the Phase 3 studies will be sufficient to enable an assessment of potential drug-drug interactions?

FDA Response

We agree with your proposal. In addition, conduct a literature search and submit any drug interaction information from the literature.

Meeting Discussion

No discussion occurred during the meeting. The preliminary responses were found to be adequate.

Clinical**Efficacy: Adequacy of Phase 3 Program****Question 8**

St. Renatus is proposing to submit an NDA to support approval of K305 for (b) (4) (b) (4) anesthesia (b) (4) restorative (b) (4) procedure on teeth #4- (b) (4) 13 (b) (4) in adults and (b) (4) based on data obtained in the completed studies that will be summarized in the briefing package.

Does the Agency agree that the studies designed and sponsored by St. Renatus for K305 as a dental anesthetic are sufficient to demonstrate safety and efficacy in adult and (b) (4) dental patients requiring an anesthetic for an (b) (4) restorative dental procedure?

FDA Response

Based on your meeting package, your efficacy findings in adults and adolescents, if submitted in the required format, appear adequate for review.

The safety data from your Phase 3 studies package may not be adequate to support a determination of safety of K305. Determination of this will be a matter of application review. We are concerned about the lack of vital signs assessment during the actual dental procedures in the Phase 3 studies. However, it appears that some of your Phase 2 studies did obtain vital signs immediately after administration of study drug. These data may be used to support the safety of your drug product. Provide a rationale that the subjects whose data you would like to use to support your safety profile, the doses, and procedures may be generalized to the population proposed in your labeling.

Also, provide a rationale as to why electrocardiogram monitoring was not performed and how you evaluated subjects for the risk and incidence of arrhythmias in your clinical trials.

You did not present adverse events (AEs) "...associated with dental pain and/or the desired effect of anesthesia." To adequately evaluate your safety database, information on all untoward medical occurrences associated with the use of K305 is required, whether or not it was considered drug-related.

In your documents, you acknowledged the risk of developing methemoglobinemia, but we were unable to locate evidence that patients were evaluated for methemoglobinemia. If you did evaluate subjects for methemoglobinemia, provide the location of your data. If you did not evaluate for methemoglobinemia, please explain your rationale for not doing so.

Meeting Discussion

No discussion occurred during the meeting. The preliminary responses were found to be adequate.

Question 9

St. Renatus has conducted a Phase 3 Pediatric safety and efficacy study that enrolled 90 total patients (60 received K305 and 30 received placebo spray). The study was designed to evaluate the overall response rate across all patients who received K305 vs patients who received placebo. Secondary analysis determined that the response rate for adolescents aged 12 or older was equivalent to the adult response rate. As documented in dental publications, this response in adolescents is common in dental pain studies. However, in pediatrics 11 years and younger, the response was variable with a high placebo response rate. The rationale to explain the differences in response rates is discussed in Section 8.2.3.3 of this information package.

- a. *St. Renatus proposes to analyze the pediatric efficacy data for the (b) (4) as a separate group in study SR 3-04 and plans to submit this data to support the intended use in adults and (b) (4) restorative (b) (4) procedure on teeth #4-#8 or #9-#13 (b) (4). Does the Agency agree with this plan?*

FDA Response

The results of study SR 3-04 appear to demonstrate overall efficacy for subjects aged 3 to 17 years of age. In the subgroup of subjects aged 12 to 17 years, 15 out of 16 subjects in the K305 group and 2 out of 5 subjects in the placebo group were rated as a success on the primary efficacy endpoint. However, we believe that the statistical support for efficacy in this age subgroup of Study SR 3-04 may be limited by the following considerations: (a) The protocol did not pre-specify a separate analysis for each age subgroup with control of Type I error; and (b) the number of subjects in the age 12-17 subgroup is fairly small (b) (4)

- b. *St. Renatus believes we have met the requirements discussed with FDA regarding evaluation of K305 in the pediatric population and that no additional studies are required for the NDA submission. Does the Agency agree?*

FDA Response

You may submit your NDA with your available pediatric data but a determination of whether the studies are adequate will be a matter of review.

Meeting Discussion

No discussion occurred during the meeting. The preliminary responses were found to be adequate.

Question 10

For the Integrated Summary of Efficacy (ISE), St. Renatus does not plan to pool the efficacy results for the two pivotal studies in adult dental patients, but will instead present results in a single table comparing the Phase 3 results for each study side-by-side.

Does the Agency agree with this approach?

FDA Response

Yes, we agree that the efficacy results should be analyzed and presented by individual study in the ISE.

Meeting Discussion

No discussion occurred during the meeting. The preliminary responses were found to be adequate.

Safety

Question 11

St. Renatus has conducted thirteen (13) clinical studies, of which eleven (11) studies are proposed for integration into a single database for characterizing demographics, exposure, deaths, study discontinuations and serious adverse events in the Integrated Summary of Safety (ISS). Two early Phase 1 studies (AP 1-01 and AP 1-02) using different formulations and combinations of tetracaine and/or oxymetazoline will be separately summarized in the ISS. Included in the eleven studies are 8 studies in adult subjects: 5 in dental patients and 3 in healthy volunteers. Three studies in pediatric subjects have been completed: 2 in dental patients and 1 in healthy volunteers. The proposed integrated population includes 424 healthy volunteers and dental patients administered a variety of K305 dosing regimens involving unilateral and bilateral nasal spray dosing, differing spray volumes, and different instructions for administering the spray. The comparator population includes 180 subjects receiving either placebo, tetracaine or lidocaine.

ISS safety tables will display comparisons based on treatment (all active doses versus controls). Safety parameters will include AEs, vital signs, naris examinations, and clinical safety laboratory results (as applicable). In addition to the "all exposure dataset," safety data will be combined for two additional subgroups:

- *Group 1: subjects who received K305 and had a dental procedure*
- *Group 2: subjects who received K305 and did not have a dental procedure (healthy volunteers).*

In addition, safety data for the "all exposure dataset," as well as Group 1 and Group 2 sub-populations, will be evaluated for each safety parameter by gender, race, and age (pediatric age groups specified within the study protocols, and adults greater than age 50 versus less than age 50).

Does the Agency agree with this approach?

FDA Response

We agree with pooling based on having had a dental procedure or not having had a dental procedure. It will be informative to also pool adult and pediatric patients separately given

their differences in demographics, safety considerations, and dosing. When you pool subjects, you should provide a rationale to explain why they are appropriate for pooling.

Meeting Discussion

No discussion occurred during the meeting. The preliminary responses were found to be adequate.

Question 12

The studies contributing to the All Adult Phase 3 Controlled Studies dataset used a treatment emergent adverse events (TEAEs) approach to collecting adverse event information. This resulted in the reporting of events associated with the procedure (e.g., pain) and events associated with anesthesia that are expected (e.g., numbness, tingling). We intend to separate reporting and discussion of the procedural and expected anesthetic events within the individual clinical study reports (CSR) and in the ISS from the reporting and discussion of other TEAEs.

Numbness and tingling associated with use of a local anesthetic during a dental procedure are not coded with sufficient anatomical specificity using MedDRA. During the Phase 3 clinical studies of K305, investigators were instructed to specify the anatomical location for numbness or tingling; however, during MedDRA coding this information was not captured based on the available coding options. The sponsor proposes to develop an auxiliary dictionary for the MedDRA codes of INTRANASAL HYPOESTHESIA, INTRANASAL PARAESTHESIA, HYPOESTHESIA ORAL, HYPOESTHESIA TEETH, PARAESTHESIA, HYPOESTHESIA, PARAESTHESIA ORAL that would specify ipsilateral or contralateral or bilateral with respect to the nostril sprayed with K305 and that would specify facial location (e.g., cheek, tongue, lip, etc.) numbness and/or tingling. The codes included in the auxiliary dictionary would only be applied to the All Adult Phase 3 Controlled Studies data set and reported as part of the ISS.

Does the Agency agree with this approach?

FDA Response

If you believe the existing MedDRA coding does not capture sufficient information, such as anatomical specificity, you can submit additional adverse event datasets with your more specific terminology. However, we would like you to submit the adverse event data with existing MedDRA terminology, as well, and not just based on the auxiliary dictionary.

Meeting Discussion

No discussion occurred during the meeting. The preliminary responses were found to be adequate.

Human Factors

Question 13

The Agency recommended in 2011 at the EOP2 meeting for K305 that human factor testing be performed to demonstrate safe use of the product under simulated-use conditions. St. Renatus will submit a plan for review by DMEPA to address this concern. Timing for any agreed upon study may delay availability of results until after the planned target for NDA submission, and therefore, St. Renatus plans to submit these study results as an amendment to the NDA.

Will the Agency accept results of human factor testing after NDA submission during the review period?

FDA Response

Human factors study data are necessary for the review of the application and should be included in the initial NDA submission. However, if you expect that the human factors study data can be submitted within 30 days of the initial submission, we would also accept the data at that time. We acknowledge the July 24, 2014 submission of your human factors study plan. We will review this submission and provide comments as soon as our resources allow.

Meeting Discussion

The Sponsor wanted to know that if they submit the human factors validation study results data within 30 days of their initial NDA submission whether it will affect the review clock. The Agency clarified that if the results are submitted within 30 days of submitting the initial NDA the review clock will not be extended.

The Sponsor further informed the Division that they plan to conduct a labeling comprehension study to evaluate how well the instructions are interpreted. The Agency indicated that labeling comprehension should be completed prior to validation as part of the formative evaluation. The Agency also cautioned that labeling comprehension data gathered under a clinical trial, which is a more controlled environment, and may not allow for translation to real-world use.

Post-meeting Note

Please note the following correction. In order to meet the current PDUFA timelines, all studies and data required for approval must be submitted with the initial application in order for the application to be filed. Data submitted during the review, will be reviewed as resources permit and could result in a clock extension.

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. As you develop your proposed PI, we encourage you to review the labeling review resources on the PLR Requirements for Prescribing Information website including:

- The Final Rule (Physician Labeling Rule) on the content and format of 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.

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

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.				

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.

ISSUES REQUIRING FURTHER DISCUSSION

There were no issues requiring further discussion.

ACTION ITEMS

1. The Sponsor agreed to provide strategy for characterizing spray pattern in a submission for the Division's review and input.
2. The Sponsor agreed to provide a LOA from Galen Specialty to authorize review of data from the Synera NDA.

ATTACHMENTS AND HANDOUTS

There were no attachments or handouts for the meeting minutes.

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

/s/

SWATI A PATWARDHAN
09/23/2014



IND 070868

MEETING MINUTES

St. Renatus, LLC
1000 Centre Avenue
Fort Collins, CO 80526

Attention: James Mulvahill

Dear Mr. Mulvahill:

Please refer to your Investigational New Drug Application (IND) submitted under section 505(i) of the Federal Food, Drug, and Cosmetic Act for (b) (4) (tetracaine HCl and oxymetazoline) (b) (4)

We also refer to the meeting between representatives of your firm and the FDA on March 3, 2011. The purpose of the meeting was to provide you with feedback on the questions in your January 19, 2011, meeting package, which were related to preparations for conducting Phase 3 studies with your product.

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

If you have any questions, call me at 301-796-1191.

Sincerely,

{See appended electronic signature page}

Kimberly Compton, R.Ph.
Regulatory Project Manager
Division of Anesthesia, Analgesia, and
Addiction Products
Office of Drug Evaluation II
Center for Drug Evaluation and Research

Enclosure

INDUSTRY MEETING



Meeting Date: March 3, 2011

Time: 12:00 PM EST

Location: White Oak Conference Room 1313

Application: IND 070868

Regulatory Status: Active

Investigational Product: (b) (4) (Tetracaine HCl and oxymetazoline) (b) (4)

Proposed Indication: anesthesia (b) (4) for peds and adults who require (b) (4) restorative procedures on teeth numbers 4-13

Sponsor: St. Renatus, LLC

Type of Meeting: Type B, EOP2

Meeting Chair: Rigoberto Roca, M.D., Deputy Director

Division of Anesthesia, Analgesia and Addiction Products (DAAAP)

Minutes Recorder: Kimberly Compton, Senior Regulatory Project Manager, DAAAP

Industry Representatives	Title
Chaline Brown, Pharm.D.	Clinical/Regulatory Consultant
Sandra Brown, Ph.D.	Director of Technical Affairs, St. Renatus
(b) (6)	Clinical Consultant
(b) (6)	Statistical Consultant
Mark Kollar, D.D.S.	Senior Advisor, St. Renatus
(b) (6)	Regulatory Consultant
Steve Merrick	CEO, St. Renatus
Paul Moore, D.D.S., Ph.D.	Principal Investigator, University of Pittsburgh
James Mulvahill	Project Manager, St. Renatus
Hilary Sheevers, Ph.D.	Toxicology Consultant
Paul Sletten, D.D.S.	Director of Clinical and Scientific Affairs, St. Renatus
FDA	Title
Bob A. Rappaport, M.D.	Director, DAAAP
Rigoberto Roca, M.D.	Deputy Director, DAAAP
Arthur Simone, M.D., Ph.D.	Medical Officer, DAAAP
Alex Xu, Ph.D.	Pharmacology/Toxicology Reviewer, DAAAP
Dan Mellon, Ph.D.	Supervisory Pharmacologist, DAAAP
David Lee, Ph.D.	Clinical Pharmacology Reviewer, Office of Clinical Pharmacology (OCP)
Ramesh Raghavachari, Ph.D.	CMC Lead, Office of New Drug Quality Assessment (ONDQA)
Frederick Hyman, D.D.S.	Clinical Reviewer, Division of Dermatology and Dental Products (DDDP)
David Petullo, M.S.	Biometrics Reviewer, Division of Biostatistics II (DBII), Office of Biostatistics (OB)
Dionne Price, Ph.D.	Biometrics Team Leader, DBII, OB
Kim Compton	Senior Regulatory Project Manager, DAAAP
Martin Pollock, Pharm.D.	Safety Evaluator, Office of Surveillance and Epidemiology (OSE)
Meredith Moy, Pharm.D.	Pharmacy Extern, DAAAP
Candidate	

Meeting Objective:

To provide the Sponsor with feedback on the questions in their January 19, 2011, meeting package, which were related to preparations for conducting Phase 3 studies with their product.

Background:

On March 1, 2011 (prior to the March 3, 2011, meeting) the Agency forwarded to the firm the Agency's comments and responses to the questions posed by the Sponsor in their January 19, 2011, meeting package.

The meeting entailed further discussion of Questions 9, 12, 17, 26, 27, 31, 33, and 34, as well as Chemistry Comments, Clinical Comments 3, 4, and 5, and Clinical Pharmacology Comments.

Presented below are the Agency's March 1, 2011, comments and responses to questions in the background meeting package, followed by a summary of relevant discussion that took place at the meeting itself. The Sponsor's questions are listed in *italics*, with Agency responses and comments in **bold**. Discussion that took place at the meeting is captured in normal text following the question to which it pertains.

Meeting:

Chemistry Questions

Question 1

The specifications for both drug substances consist of current USP requirements supplemented by requirements for related substance impurities that have been developed by the manufacturer of each drug substance and adopted by St. Renatus. Do the proposed drug substance specifications satisfy regulatory requirements for NDA review?

FDA Response

Based on the limited information provided, it appears to be acceptable for an NDA review.

Discussion

There was no further discussion on this point.

Question 2

For clinical purposes, St. Renatus considers one therapeutic dosage unit to consist of two sprays (one spray per nostril), which would represent the full content of one Accuspray unit delivered as two sprays. We are collecting spray characterization data on the individual sprays during development but propose that product specifications for delivered dose uniformity be applied on the basis of two sprays from a single bi-spray unit. Please comment on our understanding of the applicability of the definition of one therapeutic dosage unit for this purpose.

FDA Response

Your proposal for using one dose as two sprays is acceptable from the CMC perspective. It is expected that the single spray results will be provided as a characterization study in the NDA.

Discussion

There was no further discussion on this point.

Question 3

Drug product testing requirements for control of spray properties are being implemented for the Phase 3 and registration stability batches. Does the planned testing included in the drug product specifications satisfy the regulatory expectations for NDA approval of this type of product? Please also comment on the other proposed product specifications, and specifically the toxicological qualification of the main degradation product

(b) (4)

(b) (4)

FDA Response

- Based on the limited information provided, the proposed drug product specification appears to be acceptable.
- We recommend you follow the ICH guidelines for the qualification of the impurities as stated in the response to Question 12.

(b) (4)

Discussion

There was no further discussion on this point.

Question 4

St. Renatus manufactured registration stability batches in September and October 2010. We plan to include results obtained for these three primary stability batches, each covering 6 months of long-term and accelerated storage, in the initial NDA submission as well as data for one supporting stability batch covering 9 months of long-term storage. We accept that this may result in the initial assignment of an expiration dating period of only 6 months for the commercial product. With that understanding, will the proposed stability package be acceptable for NDA filing in spite of the usual regulatory expectations to have 12-month data available for three lots at the time of submission? Also, is the plan to perform studies for the product stored in the described combination of horizontal and upright orientations acceptable?

FDA Response

Your proposal appears to be acceptable. It will be evaluated during the review and the expiry dating will be assigned based upon the trends for the stability indicating parameters as per ICH Q1E. We recommend the stability studies be conducted with the product stored in all possible orientations, including inverted.

Discussion

The Sponsor stated that they will follow the nasal spray guidance that recommends upright and horizontal orientation testing, and inquired if they will also need to conduct inverted testing. The Division stated that the Sponsor should submit a rationale for why they do not believe such orientation testing is needed.

Question 5

Do the plans described for stability studies to include stoppers from the same manufacturer having the same composition and dimensions but produced with different mold markings (see Section 10.3.5) satisfy requirements to support use of either type for future commercial production?

FDA Response

Your proposal is acceptable.

Discussion

There was no further discussion on this point.

Question 6

The NDA will contain a stability protocol for post-approval extension of the expiration dating period. Does the Division agree that approval of this protocol will allow future extensions of the expiration dating period by annual report submission if the defined criteria are met?

FDA Response

Your strategy seems reasonable and the actual protocol will be evaluated in your proposed NDA submission in conjunction with the available stability data.

Discussion

There was no further discussion on this point.

Question 7

Extractable profile data were provided by (b) (4) for the stopper type being used, showing only small amounts of potential extractables produced under various test conditions (see Section 10.3.5). Are the (b) (4) study results sufficient to address the issue of leachables/extractables for this product (with consideration of the route of administration and the likelihood of even lower levels being produced during more realistic conditions of actual product use)?

FDA Response

The extractable/leachable data should be evaluated with the proposed formulation for this drug product.

Discussion

There was no further discussion on this point.

Question 8

Please comment on any additional issues that may not have been considered related to approvability of the Accuspray delivery system used to package the product.

FDA Response

We will discuss this information internally and communicate additional comments as applicable as post meeting notes. It is likely that we may consult with CDRH with respect to human factors studies and communicate those comments when available.

Discussion

There was no further discussion on this point.

Question 9

Please comment on the completeness of the proposed CMC development plan to address issues related to review of a (b) (4) NDA for a product containing a combination of two active ingredients.

FDA Response

Provide complete in vitro compatibility data between tetracaine and oxymetazoline in the drug product.

Discussion

The Division clarified that the requested data is to ensure that nothing unexpected is likely to happen, such as side reactions, etc.

Question 10

Because of the short anticipated shelf life that may be assigned with the initial product approval, timing for performing process validation may be scheduled to allow use of validation lots for commercial product launch, by delaying process validation until after approval or very near to expected approval. Given that validation must be completed prior to commercial introduction of the product, will this delay be acceptable?

FDA Response

It is not anticipated that full process validation on commercial lots be performed prior to approval. Additional comments will be forthcoming from CDER, DMPQ.

Discussion

There was no further discussion on this point.

*****Post-Meeting Note-**(the following information is provided by the Division of Manufacturing and Product Quality (DMPQ) as indicated in the preliminary response above)

FDA does not specify or require completed full-scale process validation studies before the approval of the application. However, full-scale process validation studies

are required to be completed prior to distribution of the commercial product. The Current Good Manufacturing Practice regulations at 21 CFR 211.100(a) and 211.110(a) require that drug manufacturers validate their manufacturing processes, but FDA does not prescribe how that is to be accomplished as it will depend on multiple factors, some of which are specific to the complexity of the product and process. The validation lots can be released for commercial distribution if all requirements in the process validation study are met.

Prior to marketed product distribution, it is necessary for firms to justify and confirm earlier process design and development work for their proposed scale up to commercial scale. Firms need to have justification for their process parameters, component characteristics, and how these relate to the final product attributes, demonstrated at commercial scale.

Please find more information in the Guidance for Industry, *Process Validation: General Principles and Practices* (January 2011).

<http://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/UCM070336.pdf>

Chemistry Comments

We have noted two impurities, (b) (4), that form during stability studies. These impurities are structural alert compounds and potential genotoxic molecules.

We suggest you refer to the following guidance documents as you develop your NDA.

- a. **Guidance for Industry ICH Q3A (R) Impurities in New Drug Substances** available at <http://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/ucm073385.pdf>.
- c. **Guidance for Industry ICH Q3B (R2) Impurities in New Drug Products** available at <http://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/ucm073389.pdf>
- d. **Guidance on 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 Text on validation of Analytical Procedures** available at

<http://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/ucm073381.pdf>.

- g. **Guidance for Industry Validation of Analytical Procedures: methodology available at <http://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/ucm073384.pdf>.**
- h. **Guidance for Industry Genotoxic and Carcinogenic Impurities in Drug Substances and Products: Recommended Approaches available at <http://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/ucm079235.pdf>**
- i. **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>.**
- j. **Guidance for Industry Process Validation: General Principles and Practices available at <http://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/UCM070336.pdf>.**

Discussion

The Sponsor stated that all the structural alerts were present in the reference product Synera and noted that they are using the same sources for their API. The Sponsor inquired why a 505(b)(2) reference would not be adequate justification for the safety of the drug product impurities. The Division clarified that, for a 505(b)(2) application, the Agency is not permitted to look at the data from another application, nor can they refer to the Summary Basis of Approval or any particular review or any data in the label without a right of reference or letter of authorization. The Agency is only permitted to use the information in the label of the referenced product. In order for the Division to use toxicology studies submitted to the referenced NDA submission, the Sponsor must submit either a letter of authorization from the NDA holder granting the Agency permission to review the data in the NDA or obtain right of reference to the study reports.

The Division stated that the Sponsor may provide data to show that the exposure to the referenced drug product impurities is equal to or higher than the exposure to the drug product impurities via their intranasal drug product. Actual exposure data would be required since the reference product is a patch and the patient exposures for the two products could be very different. However, it should be noted that policies with regard to genotoxic impurities have evolved since the Synera action, and therefore these data alone may not be adequate to support the lack of a safety concern based on current standards.

(b) (4)



[REDACTED] (b) (4)

The Sponsor indicated that [REDACTED] (b) (4). The Division recommended that the Sponsor provide a risk assessment based on the potential for added toxicity due to the presence of the impurity [REDACTED] (b) (4).

[REDACTED] However, [REDACTED] (b) (4) therefore, the Sponsor understood that further data would be needed to justify the safety of the proposed level of [REDACTED] (b) (4).

The Division stated that the most definitive means to justify a lack of genotoxicity concern for [REDACTED] (b) (4) would be to conduct an Ames assay with the isolated impurity. As per the draft *Guidance for Industry - Genotoxic and Carcinogenic Impurities in Drug Substances and Products: Recommended Approaches*, the Agency will also currently accept for review data from a Qualitative Structure Activity Relationship (QSAR) assessment; however, it was noted that the Agency would run an independent analysis to confirm any findings submitted. The QSAR approach is currently being debated both within CDER as well as ICH with respect to the utility of the results. Although a positive QSAR would require either reduction to NMT [REDACTED] (b) (4) mcg/day or actual negative Ames Assay result; a negative QSAR result may be due to lack of adequate representative samples in the QSAR database. As such, a negative Ames test is the strongest argument to support the safety of this impurity in terms of mutagenic potential. The Sponsor will consider the existing options for [REDACTED] (b) (4) and provide their justification in the NDA.

Nonclinical Questions

Question 11

At the pre-IND meeting (June 6, 2005), DAAP specified that a 14-day intranasal study was required for the NDA. The proposed design for that toxicology study is provided in Section 11.0. To evaluate local neurotoxicity, histopathology of the olfactory bulb and epithelium will be performed. The study design includes 4 doses over a 2-week period, which we believe is adequate for a single-dose product. Does the Division have any comments on the current study design?

FDA Response

Based on the protocol submitted, the study design of the 2-week dog toxicity study appears to be adequate with the following modifications:

- **Provide a sufficient rationale for the dosing regimen proposed. You must specifically explain why a more frequent regimen (such as daily dosing) would not be feasible or appropriate.**

- Incorporate specific staining methods such as silver and/or Fluro-Jade to examine the potential damage to local nerves in the nasal cavity.

Discussion

The Sponsor indicated the response was acceptable to them.

Question 12

We plan to submit a [REDACTED] (b) (4) in the NDA to support approval of [REDACTED] (b) (4). As oxymetazoline is an approved OTC drug, and the doses to be used in the [REDACTED] (b) (4) formulation do not exceed the OTC doses, [REDACTED] (b) (4). We also plan to submit the toxicology study report for the single dog study using the [REDACTED] (b) (4) formulation. [REDACTED] (b) (4). Does the Division agree with this approach?

FDA Response

No. We do not agree the approach you proposed is sufficient.

You have indicated you intend to submit a 505(b)(2) NDA referencing Synera® to address the safety of tetracaine. We have the following general 505(b)(2) comments:

We recommend 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 October 1999 Draft Guidance for Industry "Applications Covered by Section 505(b)(2)" 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 challenging the Agency's interpretation of this statutory provision (see Dockets 2001P-0323, 2002P-0447, and 2003P-0408 (available at <http://www.fda.gov/ohrms/dockets/dailys/03/oct03/102303/02p-0447-pdn0001-voll.pdf>)).

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 must 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 is scientifically appropriate.

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 the Agency's previous finding of safety for an approved product, the exposure margins provided in the referenced label must be updated to reflect exposures from your product. 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.

You are not required to submit literature review or studies to support the safety of oxymetazoline for the NDA submission. However, available information regarding genotoxicity and reproductive toxicity of oxymetazoline should be provided to enable appropriate labeling.

In addition, as a combination drug, an embryo-fetal development toxicity study must be provided to evaluate the potential effects of this combination unless available information indicates significant risk for developmental toxicity of tetracaine or oxymetazoline. You may refer the FDA guidance for nonclinical safety evaluation of drug or biologic combinations for more details at (<http://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/ucm079243.pdf>).

Any impurity or degradation product that exceeds ICH thresholds may need to be adequately qualified for safety as per (ICH Q3A(R2), ICH Q3B(R2)) at the time of NDA submission.

Adequate qualification would 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

We may refuse to file your application if your NDA submission does not contain adequate safety qualification data for any identified impurity that exceeds the ICH qualification thresholds.

We note two impurities bearing structural alerts for mutagenicity have been identified on stability. Potentially genotoxic impurities or degradation products pose an additional risk; therefore, a specification of NMT 1.5 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 1.5 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. We may refuse to file your application if your NDA submission does not contain adequate safety qualification data for any identified impurity containing a structural alert for mutagenicity that exceeds 1.5 mcg/day.

The 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. Certain drug products are considered to present a high concern for risk, for example, liquid formulations or drugs in patches or other devices employed for parenteral delivery. The evaluation of extractables and leachables from the drug container closure system or device 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, drug product formulation, dosage form, route of administration, and dose regimen (i.e., duration of use). 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. You may refer to Ball et al., *Toxicological Sciences* 97(2), 226-236, 2007 for a general discussion of issues and concepts regarding leachable qualification.

Discussion

The Sponsor planned to rely on the previous findings of tetracaine reproductive and developmental studies in the label of Synera for the labeling of their product and inquired whether they could use a mg/m^2 basis to extrapolate the dosage in these studies (subcutaneous administration) to the human dosage of their drug product (intranasal administration). The Sponsor further indicated that information on tetracaine plasma exposure in these studies does not exist and direct extrapolation using the mg/m^2 basis from rat subcutaneous administration to human dermal application was utilized for the information in the Synera label. The Division acknowledged these facts and stated that the mg/m^2 extrapolation approach is acceptable.

*** Post-Meeting Note

Upon further discussion, the Division is less confident that extrapolation by mg/m^2 is appropriate unless systemic tetracaine exposure in clinical studies is shown to be negligible. The Division notes that the Synera label indicates clinical use is associated with little tetracaine absorption (1.6 mg) which produces systemic exposures that are below the limit of detection (0.9 ng/mL). Although large margins may be present, in the absence of nonclinical exposure levels, mg/m^2 extrapolation was used as the most conservative approach for calculating safety margins. In contrast, intranasal administration of 18 mg of tetracaine in (b) (4) may produce significantly greater absorption of tetracaine with higher plasma tetracaine exposure to tetracaine as compared to the dermal application of Synera.

Therefore, in the event of demonstrated systemic tetracaine exposure in clinical studies, safety margin calculations will be required to be based on plasma exposure comparisons in the (b) (4) label. The Sponsor will need to conduct a bridging toxicokinetic (TK) study in rats with subcutaneous tetracaine injection in order to compare the plasma exposure of tetracaine in this animal model to human exposure with use of this drug product unless sufficient toxicokinetic information can be obtained from the combination tetracaine/oxymetazoline embryofetal development toxicity study to allow appropriate labeling.

The Sponsor stated that they believe information on the use of oxymetazoline during pregnancy is available and noted that they plan to submit it with the NDA and put that information in their label. The Division stated that a study with the combination of tetracaine and oxymetazoline would provide the best information and recommended that the firm conduct such a study. Such a study is usually done with increasing ratios of the two drugs and the subcutaneous route of administration would be acceptable for obtaining the information. A single species is acceptable. The Division noted that the Sponsor should use the most appropriate species. They should also collect exposure data from this study and provide exposure margins for the product labeling based on a comparison of the exposure levels obtained in the animals to the maximum daily human intranasal exposures.

The Sponsor stated that they would look into available reproductive toxicity data on oxymetazoline and provide it in the NDA. They will provide their search strategy as well. The Division cautioned the Sponsor that some pregnancy databases list pregnancy category information that may not be an actual FDA determination. The Sponsor should submit copies of all literature cited and any data they have on this issue.

The Division confirmed that, despite the product being an aqueous solution with no organic component, information on extractables and leachables would still need to be provided.

Clinical Questions—Adult Phase 3 Program

Question 13

The total planned safety database for the product is a minimum of 305 subjects with 239 to receive the maximum to be marketed dose (and with 12 of these 239 receiving twice the maximum dose). The source of these exposures is: 10 healthy subjects in AP 1-02 (5 of whom received the highest to-be-marketed dose); 10 healthy subjects in AP 1-02 who received a half "ipsilateral" dose; 30 dental patients in SR 2-01 (all receiving maximum dose); 12 healthy volunteers in SR 2-02 (receiving twice the maximum dose); 192 adult dental patients; 96 in Phase 3 studies (across 2 studies and all receiving maximum dose); and a minimum of 51 pediatric dental patients (across 2 studies). Does the Division confirm that the size of this safety database is adequate to support marketing approval as was agreed in the pre-IND meeting June 6, 2005?

FDA Response

A safety database this size could be adequate, given the widespread use of these products for many years. However, should a safety signal be noted in your database, additional information may be required to adequately characterize the safety profile of

(b) (4)

Discussion

There was no further discussion on this point.

Question 14

St Renatus believes the described populations for the two Phase 3 adult studies (protocol for one of the two identical studies is provided as Appendix 2) and the Phase 2 pediatric study (protocol synopsis is provided as Appendix 3) are appropriate. Does the Division agree?

FDA Response

The pivotal trials should be designed such that all patients and procedures for which Kovacaine is likely to be used in the clinical setting will be evaluated. Any limitations for either of these parameters would likely be reflected in the label.

Discussion

There was no further discussion on this point.

Question 15

The two multicenter Phase 3 adult studies are planned as randomized, placebo-controlled studies with subjects randomized in an imbalanced pattern to receive either Kovacaine Mist (n=96) or saline placebo spray (n=24). The efficacy analysis is based on the percentage of Kovacaine Mist subjects who are able to complete the dental procedure without rescue medication. Does the Division agree with the selection and use of the control arm?

FDA Response

This is acceptable.

Be aware that any claims you wish to make with your product compared to standard of care (i.e., injected local anesthetics) need to be substantiated with data obtained from appropriately designed and adequately powered studies.

Discussion

There was no further discussion on this point.

Question 16

The primary endpoint in the two Phase 3 adult studies is the number of subjects who received Kovacaine Mist and did not require rescue anesthesia to complete the first 60 minutes of the dental procedure. The secondary endpoints are: the proportion of subjects receiving Kovacaine Mist with a global discomfort assessment of no more than mild pain measured at completion of an operative

dental procedure, the proportion of subjects who report either no or mild pain from the pulpal anesthesia assessment points (after 2 bi-lateral sprays and after 3 bi-lateral sprays), the incidence of subjects with changes in vital signs after receiving Kovacaine Mist exceeding $\pm 25\%$ of preoperative values, characterization of the effects of Kovacaine Mist on soft tissue anesthesia of the incisive papilla (including determination of time of onset and duration), the incidence of minor expected drug reactions after administration of Kovacaine Mist, and the incidence of unexpected drug reactions after administration of Kovacaine Mist. Does the Division agree with these endpoints?

FDA Response

Your proposal to study the endpoints identified above is acceptable, as is your choice for the primary endpoint. However, you should carefully note three points:

1. If you intend to seek label claims for any secondary efficacy endpoints, your analyses should incorporate an appropriate adjustment for multiplicity.
2. No claim will be permitted for a secondary safety endpoint.
3. Claims for a secondary efficacy endpoint will require that a validated metric be used for the assessment and that the endpoint is clinically relevant.

Discussion

There was no further discussion on this point.

Question 17

To ensure that target populations are included in the safety and efficacy database, the Phase 3 protocols specify randomization of at least 25% patients who are older than 50 and at least 25% of patients with multiple medical conditions. The recruitment criteria will be site-based to avoid an imbalance of recruitment that could complicate overall efficacy analyses. Does the Division agree with this approach?

FDA Response

The proposed approach is well-intentioned but not consistent with the inclusion and exclusion criteria.

Inclusion criterion #1 limits the age of enrollees to ≤ 75 years old; this restriction needs to be eliminated. Also, patients with dental interventions for which (b) (4) might be efficacious should be included in the study.

Exclusion Criterion #1 eliminates subjects with uncontrolled GI, renal, hepatic, hematologic, cardiovascular, neurologic, thyroid, musculoskeletal, prostate, dermatologic and connective tissue diseases among others. It is not clear what is meant by "uncontrolled," and the implication is that dentists will assess their patients for each of these conditions prior to administering the drug. Such exclusions might be appropriate for Phase 1 and 2 studies, but to include them in Phase 3 suggests that the

drug poses substantial risk to these patients. If this is indeed the case, then they should be excluded and the label, if the product is approved, would have to reflect this fact.

Discussion

The Division expressed concern that without evaluating safety for many of the patients excluded from the study by Criterion #1, dentists would need to carefully screen their patients prior to using the drug if it were approved, and that the population of patients in whom the product could be used would be severely restricted by evaluating it only in healthy individuals. The Sponsor stated that they would try to expose as many types of patients to the product in their clinical trials as possible, including patients greater than age 75 and cardiac patients as possible. They also plan to look carefully at the blood pressure changes of patients with hypertension.

Additional Clinical Comments

Several issues need to be considered as you finalize the protocols for your pivotal studies and conclude your clinical development program:

1. Only the to-be-marketed formulation of (b) (4) and the delivery device should be used in the pivotal studies. If they are not, justification needs to be provided for doing otherwise, and bridging studies may be required prior to NDA submission.
2. Safety assessments in the pivotal studies need to include inspection of the nares for reactions to the study drug, protocol-specified assessments for neurotoxicity related to tetracaine (e.g., lethargy, tinnitus), and evaluations for anosmia.
3. The potential for drug-drug interactions with medications used to treat seasonal and allergic rhinitis needs to be evaluated.

Discussion

The Sponsor stated that they will carefully examine blood pressure changes of greater than 25% but wondered if the Division had any other specific concerns. The Division indicated that the use of topical allergy products may affect efficacy, as well as safety, due to vasoconstrictive properties that may limit the extent to which (b) (4) can anesthetize the nerves necessary to provide adequate dental anesthesia. By evaluating a substantial number of subjects who are using inhaled allergy products, it is possible to assess for alterations to efficacy or the safety profile and label (b) (4) accordingly.

4. There is concern regarding the failure rate for (b) (4) observed in studies AP 1-02 and SR 2-01. While these studies were not designed to determine efficacy, they suggest that a means of assessing the adequacy of anesthesia prior to starting the dental procedure may be needed for proper use of the product. Incorporating these assessments into the protocols may help in the labeling of (b) (4) if it is approved.

Discussion

The Sponsor noted that any challenge to test if the area is anesthetized will be painful if the area is not anesthetized, so they chose to employ the standard of care most dentists

use in clinical settings (to start to drill if they believe the area is anesthetized based on surface probes) and then give rescue medication if there is pain. The Division stated that this approach is most useful and could readily be incorporated in the label if (b) (4) is approved.

The Division stated that it will be important to include in the product labeling any differences from the usual clinical practice that are necessary to use (b) (4) safely and effectively (e.g., lip numbness cannot be used as a marker for adequate anesthesia))

5. The failure rate noted above, in Item 4, suggests that a comparator arm, in which the standard of care is utilized for the procedure, could be useful. While not required for approval, such information could be useful for dentists in determining how best to utilize (b) (4) in their practice. If a claim were to be sought, based on this type of comparison, the study would need to be designed and powered to assess the endpoint(s) used.

Discussion

The Division noted that a reasonable sample of patients who present with these dental issues should help ensure that these are properly addressed in the labeling.

6. The primary endpoint proposed in your pivotal trials is acceptable. The use of a patient-reported global assessment is also considered useful for a product such as (b) (4). It is recommended that you refer to the FDA guidance on such outcomes, if you wish them to be the basis of a claim.
<http://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/UCM193282.pdf>

The use of a patient-reported outcome for a claim would likely require input from the Study Endpoints and Labeling Development (SEALD) team at FDA prior to the start of the study.

7. You are strongly urged to request a Pre-NDA meeting to discuss the findings and adequacy of your clinical studies and how you addressed the issues above, as well as issues related to the other disciplines as well.

Statistical Questions—Adult Phase 3 Program

Question 18

The primary endpoint determines if the proportion of subjects receiving Kovacaine Mist (3 bilateral sprays) who do not require rescue anesthesia to complete an operative dental procedure is statistically superior to the proportion of subjects receiving placebo. The null hypothesis is the success rate for Kovacaine Mist is equal to the success rate for placebo.

$$H_0: p_{\text{Kovacaine}} = p_{\text{Placebo}}$$

$$H_A: p_{\text{Kovacaine}} > p_{\text{Placebo}} \text{ (superiority)}$$

A one-tailed Fisher's exact test ($\alpha = 0.05/2 = 0.025$) will be used to compare the proportion of anesthetic success of Kovacaine Mist to placebo. Does the Division agree?

FDA Response

A Fisher's exact test is appropriate for testing proportions.

Discussion

There was no further discussion on this point.

Question 19

Previous studies have shown the Kovacaine Mist anesthetic success rate to be 83.3%. The placebo success rate is expected to be 20%. Type I (alpha) error is set at 5% with one-sided tests set at 2.5% and Type II (beta) is set at 10%. The power of the test is $1.00 - 0.10 = 0.90$ or 90%. The sample size in this study consisting of 96 subjects in the Kovacaine Mist treatment group and 24 subjects in the placebo group is large enough for the superiority test based on a one-sided Fisher's exact test of success rate for Kovacaine Mist compared to placebo. Does the Division agree?

FDA Response

Based on the specified parameters, your sample size calculation is acceptable.

Discussion

There was no further discussion on this point.

Question 20

The secondary endpoint determines if the proportion of subjects receiving Kovacaine Mist with a global discomfort assessment of no more than mild pain measured at completion of an operative dental procedure (or immediately prior to receiving the rescue anesthetic) is statistically superior to the proportion of subjects receiving placebo. The null hypothesis is the success rate for Kovacaine Mist is equal to the success rate for placebo.

$$H_0: p_{\text{Kovacaine}} = p_{\text{Placebo}}$$

$$H_A: p_{\text{Kovacaine}} > p_{\text{Placebo}} \text{ (superiority)}$$

A one-tailed Fisher's exact test ($\alpha = 0.05/2 = 0.025$) will be used to compare the proportion of no more than mild pain of Kovacaine Mist to placebo. Does the Division agree?

FDA Response

A Fisher's exact test is appropriate for testing proportions.

Discussion

There was no further discussion on this point.

Question 21

There are secondary endpoints characterizing pulpal anesthesia on a 4-point scale and characterizing soft tissue anesthesia, onset and duration. Descriptive tables and proportions or means, standard deviations, etc., by treatment will be provided. No inferential statistical comparisons of the treatments are planned. Does the Division agree?

FDA Response

This information is useful for describing the pharmacodynamic effects of the drug, to the extent that the techniques for evaluating pulpal anesthesia correlate with the ability to perform the dental procedure.

The proposed method for presenting the data is acceptable.

Note that the pharmacodynamic information provided will be incorporated into the Clinical Pharmacology section of the product label and cannot be used as the basis of a claim.

Discussion

There was no further discussion on this point.

Question 22

For the secondary endpoint comparing the two treatments with respect to the number of adverse events or vital sign measurements (blood pressure, heart rate) that exceed predetermined limits, descriptive tables and proportions by treatment will be provided. No inferential statistical comparisons of the treatments are planned. Does the Division agree?

FDA Response

This approach is acceptable; however, it should be noted that these comparisons alone will not be sufficient to substitute for a full characterization of the safety profile. They may be incorporated into the clinical assessment of safety within the NDA.

Furthermore, no claims will be supported by these secondary endpoints as they are proposed to be assessed (see clinical comments above).

Discussion

There was no further discussion on this point.

Question 23

The Phase 3 program will recruit adult patients who have a history of requiring local anesthesia for dental procedures on teeth #4-13. We intend to conduct formal statistical analyses on the complete population (not taking tooth number into account as we are not examining teeth #1, 2, 3, 14, 15, or 16). However, an ad-hoc presentation of the efficacy by tooth number will be provided. Does the Division agree with this approach?

FDA Response

Recruiting patients who have historically required local anesthesia for dental procedures on teeth #4 – 13, constitutes an enriched population. A rationale would be needed to approve the product for use in patients that have not required such treatments in the past.

Analyzing efficacy for procedures on all teeth is acceptable. Assessing whether efficacy differs for some teeth versus others is important and should be undertaken. If the analysis suggests that the product is substantially less effective for some teeth compared to others, it may be necessary to conduct further studies to evaluate whether that is indeed the case. Such a finding would likely be reflected in the label if the product is approved.

Discussion

There was no further discussion on this point.

Question 24

The Phase 3 program will recruit across three sites with at least 25% patients who are older than 50 and at least 25% of patients with multiple medical conditions. We intend to conduct formal statistical analyses on the complete population (as these conditions satisfy the safety profile and do not have an impact on efficacy). However, an ad-hoc presentation of the efficacy by site, age group, and medical conditions will be provided. Does the Division agree?

FDA Response

While the proposed analyses are acceptable, they should be incorporated into the statistical analysis plan and not performed ad hoc. As indicated in the response to Question 23, the analysis suggests that the product is substantially less effective for some age groups or in patients with some medical conditions compared to others, it may be necessary to conduct further studies to evaluate whether the differences are real. Such a finding would likely be reflected in the label if the product is approved.

Discussion

There was no further discussion on this point.

Question 25

Does the Division have other comments on the statistical components of the adult protocol?

FDA Response

Your primary analysis should be conducted on all randomized patients that receive at least one dose of study drug. You should not exclude or replace any randomized and/or treated patients.

The protocol defines the primary endpoint as the proportion of patients “not requiring rescue during the first 60 minutes of the procedure.” The primary endpoint should be defined as the proportion of patients not requiring rescue medication during the dental procedure.

You state that missing data will not be imputed, and analyses will use observed data. Although the amount of missing data should be minimal, you must propose a strategy to handle missing data. One such strategy for the proposed primary endpoint is to incorporate discontinuations or withdrawals into the definition of treatment failure.

Discussion

There was no further discussion on this point.

Clinical Questions—Pediatric Program

Question 26

(b) (4)

pediatric program is supported by the safety profile of the pharmacokinetic and Phase 2 adult efficacy studies and the two Phase 1 clinical studies. The Phase 2 pediatric study is a dose-finding study and will treat 15 to 30 pediatric patients with the to-be-marketed formulation. A synopsis of the pediatric protocol is provided as Appendix 3. Does the Division agree with this timing?

FDA Response

Pediatric patients should be exposed to (b) (4) only after its safety and efficacy have been evaluated in adults. If sufficient data are available at the time Phase 3 adult studies are scheduled to begin, it is possible to conduct pediatric studies in parallel with the adult trials.

Dividing the pediatric population into subgroups by age, as proposed, is appropriate. Safety and efficacy should be established in the older patients before proceeding to the next younger subgroup.

(b) (4) will need to be assessed in pediatric patients less than 6 years old as the product would likely be used in this group. The lowest age of patients to be evaluated should be based on the need for dental procedures on the teeth that would be affected by (b) (4)

Conducting open-label dose-ranging studies for each age group to determine the correct dose prior to conducting randomized, double-blinded, controlled studies for each group is appropriate.

Discussion

The Sponsor stated that they were planning to conduct the study as a non-placebo controlled study because of their concern for patient safety. They agreed to explore ages down to 3 years old as suggested in the dose de-escalation study and inquired if a double-blind structure was necessary in pediatric patients. The Division stated that the Sponsor will need to demonstrate that their product is safe and efficacious at the recommended dose(s) in pediatric patients. This is the purpose of the second study. A study that does not utilize a comparator will not provide adequate information on safety or efficacy. The Division recommended that the Sponsor use the adult studies and standard of care as a model, and assess pediatric patients the same as they are assessed in a clinical setting before drilling takes place, i.e., follow the standard of care used in

treating pediatric patients in the clinical setting. Otherwise, a risk:benefit analysis cannot be completed. The Division stated that the Sponsor should submit their proposed studies for review and comment.

The Division clarified that their recommendation is that the Sponsor conduct studies in older pediatric patients first, using the safety and efficacy information from the adults to select the initial dose for evaluation, then move on to studies in the younger pediatric patients using the findings from older patients to guide dose selection. The Sponsor stated that the proposed Phase 3 dosing comes from a Phase 2 study in 30 adults. Dr. Rappaport indicated that the Division would take this issue back for further discussion and share any additional feedback with the Sponsor via a Post-Meeting Note.

*****Post-Meeting Note**

After additional internal discussion, the Division concurs with the Sponsor that evaluating the safety and efficacy of (b) (4) in pediatric subjects in parallel with adult subjects is acceptable, provided the pediatric studies are conducted in a sequential, age-descending manner as proposed.

Question 27

For (b) (4) review of the NDA, while the adult efficacy studies are to be conducted as placebo-controlled studies, St. Renatus believes this is not ideal for the pediatric study, which is therefore designed as an open-label study. Does the Division agree that design is acceptable?

FDA Response

The Division concurs with your concern for conducting placebo-controlled studies in pediatric patients. However, controlled trials to assess efficacy and safety in this population are possible. At least two approaches may be possible:

- 1. Compare (b) (4) to current standard of care**
- 2. Assess adequacy of the dental block as is currently practiced and use that result to determine whether the test drug is efficacious enough to proceed or the treatment is a failure before the procedure begins.**

The second method would allow for the use of placebo as the comparator without raising ethical concerns.

Discussion

The Sponsor indicated that their IRB will have issues with the placebo control study design in pediatric patients.

*****Post-Meeting Note**

The Sponsor stated at the meeting that they believe their IRB will raise ethical issues with the clinical trials in pediatric patients being placebo-controlled. The Division notes that an active-control trial is an acceptable alternative approach. Additional

discussion may be necessary if the Sponsor encounters difficulties finding an acceptable approach with which to move forward.

Question 28

For [REDACTED] (b) (4) review of the NDA, the size of the Phase 2 pediatric study is planned to be 15 to 30 children ages 6 to 17 years in need of dental anesthesia for dental fillings. This study will be stratified with equal numbers of children in the 6 to 11 age group and the 12 to 17 age group. Does the Division agree with the size and definition of the pediatric study population?

FDA Response

The Phase 2 study should enroll a sufficient number of subjects in each age group to obtain a meaningful assessment of the appropriate dose of [REDACTED] (b) (4) to be used in the subsequent Phase 3 study.

Discussion

There was no further discussion on this point.

Question 29

For [REDACTED] (b) (4) review of the NDA, to adequately investigate [REDACTED] (b) (4)

[REDACTED]

Does the Division agree that this dosing approach is appropriate?

FDA Response

The Division concurs with your concerns with selecting an ineffective initial dose for pediatric subjects. It is recommended that the lowest efficacious dose for the adult population be the first evaluated in the older pediatric patients, barring any safety signals. The lowest effective dose in the oldest subgroup then can be used as the starting dose for the next younger group, and likewise for the youngest subgroup.

Discussion

There was no further discussion on this point.

Question 30

Does the Division have other comments on the design of the phase 2 pediatric protocol?

FDA Response

At this time, you are advised to take into consideration the comments provided regarding the adult studies and incorporate them into the pediatric protocols as appropriate. Further comments may be provided when full protocols are submitted under a Proposed Pediatric Study Request.

Discussion

There was no further discussion on this point.

Clinical Questions--Dose Definition

Question 31

We are defining a single dosage unit as two sprays (one spray per nostril), and the total dose according to the number of units administered. Is this acceptable to the Division?

FDA Response

The proposed terminology is potentially confusing for both the investigators conducting the studies and for clinicians who will be using the product if it is approved. Particularly the use of the word "unit," which sounds more like a reference to the spray device itself than to the dosage. Alternative wording may need to be employed.

The following advice is provided from the Division of Medication Error Prevention and Analysis (DMEPA).

- 1. Explain the clinical consequences of a patient that receives one full dose (2 sprays) in one nostril and of a patient that receives two full doses (2 sprays) per nostril.**
- 2. Although you state that the device is the [REDACTED] ^{(b) (4)}, we remind you of the need to perform human factor testing. The purpose of a human factors study is to demonstrate that the device can be used by representative users under simulated-use conditions without producing patterns of failures that could result in negative clinical impact to patients or injury to device users.**
 - a. Tasks included in the study should be those identified through completion of a risk assessment of hazards that may be associated with use-related problems and represent greater than minimal risk to users.**
 - b. The study should collect sufficient and appropriate data to facilitate identification and understanding of the root causes of any use failures or problems that do occur. The causes may be related to the design of the device, the device labeling (including instructions for use), and/or the training of test participants.**

- c. The test report should present a summary of your test results, data analysis, and conclusions, including whether any modifications are indicated; if they are, these modifications should be described and if significant, the modifications should also be validated.**

3. Your validation study protocol should include the items listed below.

a. Devices and Labeling Used

- i. For design validation, the devices used in your testing should represent the final design, including the labeling.**
- ii. Your participants should assess the clarity of the instructions for use and you should assess the extent to which the instructions support safe and effective use of your device. If any of the other labeling (e.g., packaging, inserts) is critical to use, include it in your validation testing as well. You may include these assessments in your validation testing or conduct them in a separate study.**

b. User Tasks and Training

- i. FDA expects to see a clear description of how you determined which user tasks would be included in the testing and how many trials each participant would complete.**
- ii. In order to adequately assess user performance and safety, the tasks selected for testing should be derived from the results of a comprehensive assessment of use-related hazards and risks that consider all functions of the device.**
- iii. The tasks should be prioritized to reflect the relative magnitude and severity of the potential impact of inadequate task performance on the safety of the device and the user.**
- iv. Please describe and provide a rationale for the tasks you include in your testing and their relative priority. Also describe all activities in which your test participants will engage during the test.**
- v. The training you provide to your test participants should approximate the training that your actual end users will receive.**
- vi. Describe the training you provide and how it corresponded to realistic training levels.**

c. Use Environment and Conditions

- i. Conduct your validation testing in an environment that includes, or simulates, all key aspects of the real-world environments in which you anticipate your device would be used.**

- ii. **Identification of potentially challenging use conditions should be derived through analyses of use hazards prior to conducting validation testing and aspects of use that can be reasonably anticipated, such as use with gloves or wet fingers, dim lighting, noisy situations, etc., should be included in your testing.**
 - iii. **Evaluate the use of your device under whatever conditions you identify as potentially occurring and hazardous.**
 - iv. **Describe the testing environment and realism of the simulated use in sufficient detail for the Agency to determine it they were appropriate for validation testing.**
- d. Study Participants**
- i. **FDA expects you to test a minimum of 15 participants from each major user group for validation of device use. Your test participants should be representative of your intended end-user populations, as described in your indications for use statement. If users with distinctly different characteristics (e.g., age ranges, skill sets, or experience levels) will use your device, you should include 15 from each group.**
 - ii. **Regardless of the number of groups you test, provide a rationale that the groups adequately represent the overall population of users for your device. Note that study participants should not be your own employees.**
- e. Data Collection**
- i. **Any data collected and analyzed in a validation study should be described in terms of how it supports the safety case claim that your device can be used safely and effectively by the indicated users. FDA expects you to collect both empirical and qualitative data in a design validation study.**
 - ii. **Empirical Data – Your test participants should be given an opportunity to use the device independently and in as realistic a manner as possible, without guidance, coaching, praise or critique from the test facilitator/moderator. Some data, such as successful or failed performance of key tasks or time taken to perform tasks – if time is a safety-critical criterion – should be measured directly rather than soliciting participant opinions. Observing participant behavior during the test is also important, in order to assess participants’ adherence to protocol and proper technique and especially to assess and understand the nature of any errors or problems that occur.**
 - iii. **Qualitative Data – The Agency expects you to ask open-ended questions of participants at the end of a usability validation, such**

as, "Did you have any difficulty using this device? [If so] can you tell me about that?" The questions should explore performance of each critical task involved in the use of the device and any problems encountered. Note that since the labeling and instructions for use are considered part of the user interface for your device, the questions should cover those components as well.

- iv. Please describe and provide a rationale for including each type of data you collect.

Discussion

The Sponsor stated that they wanted to use simulated saline spray in the device for the human factors studies and not the active device. The Division indicated that since no one from DMEPA was present at the meeting, the Division would forward this question to them and add a Post-Meeting Note to the meeting minutes with their reply.

***Post-Meeting Note

Human Factor studies should represent real life scenario and demonstrate that the device can be used with the proposed drug and by representative users. The use of active-product device is recommended in order to identify potential failure modes related to drug/device interaction.

Question 32

Previous studies have shown that the optimal concentration of (b) (4) is 3% tetracaine HCl with 0.05% oxymetazoline HCl, but that there is variable response. To avoid overdosing subjects with variable sensitivity (and to collect information useful for labeled dosing directions in a clinical setting), the Phase 3 program has been designed with an individual dose titration algorithm. Subjects will be subjectively evaluated for anesthesia efficacy after the second and third bilateral nasal spray. Does the Division agree with this approach to establish the lowest effective dose for (b) (4)?

FDA Response

Gradually increasing the number of sprays needed to achieve efficacy is an appropriate method for determining the lowest effective dose. While determining an effective dose is generally accomplished prior to the conduct of the pivotal study, which is typically used to confirm the correct dose was identified and that it is safe when used as proposed, your approach is acceptable.

If there are concerns that one dose will not work for a substantial percentage of the population, you are encouraged to either determine whether those patients in whom the proposed (b) (4) dose will likely be ineffective can be identified a priori or develop a dosing paradigm that will permit the product to be titrated to effect within a safe range of doses similar to the way local anesthetics are currently administered in dentistry.

Discussion

There was no further discussion on this point.

Question 33

We believe that the “ipsilateral dosing only” arm in the dose-ranging study AP 1-02 (data are summarized in Section 12.1.2) adequately established that bilateral dosing is required for effective anesthesia. Does the Division agree?

FDA Response

Study AP 1-02 was not designed and powered to compare ipsilateral and bilateral dosing; therefore, the results cannot be interpreted to answer the question posed.

Discussion

The Sponsor stated that they agreed that the numbers in this study were small and that the results were not statistically significant, but believed that the directional information gathered was useful and would like guidance on how to proceed. The Division observed that the study was designed primarily for testing the concept and noted that confirmatory data would come from the Phase 3 trial. The Division noted that the Sponsor could proceed based on their convictions from the data in Study AP 1-02, but that they did so at their own risk.

Regulatory Questions

Question 34

We believe the results of study AP1-01 established that tetracaine only (without oxymetazoline) does not provide effective pulpal anesthesia. As there is no plausible scenario by which oxymetazoline as monotherapy can be expected to provide pulpal anesthesia, we believe that further factorial design studies are not needed to support the approval of this combination drug product. Does the Division agree?

FDA Response

The Division recognizes that oxymetazoline does not stabilize membrane potentials by action on the sodium channels, and it is plausible that it does not affect nerve conduction. Therefore, a factorial design demonstrating oxymetazoline’s contribution to the anesthetic effect of the product is not necessary.

Discussion

The Division stated that the sponsor will need to study (b) (4) vs. tetracaine alone and demonstrate that the addition of oxymetazoline adds something to the product over a product with tetracaine alone. While the sponsor indicated that they demonstrated this in a Phase 1 study, the Division stated that it needs to be demonstrated in a Phase 3 trial. The design of such a study is up to the Sponsor but may involve a subset of the subjects who participate in the Phase 3 trials.

Question 35

The planned first indication for approval is the (b) (4) anesthesia for pediatric or adult patients (b) (4) procedure on adult teeth numbers 4-13 or pediatric teeth A-J." Does the Division agree with this labeling indication?

FDA Response

It is premature to determine whether the proposed indication is acceptable. Typically, the Agency would prefer to avoid such a restrictive indication; however, if safety or efficacy data warrant the inclusion of limitations of use in the indication, such an indication could be considered.

Discussion

There was no further discussion on this point.

Question 36

St. Renatus intends separately to request that the Agency grant "Priority Designation" for the NDA as set forth in Section 6020.3 of CDER's Manual of Policies and Procedures. In this Request, we will point out that (b) (4) would represent a major advance in treatment because it will prevent several different pathologies and adverse reactions that are associated with needle-based delivery of dental anesthetics, including the transmission of bloodborne pathogens, needle-related trauma and infection, and long term adverse reactions such as trismus, facial paralysis and paresthesia. Based on these grounds, would the Agency consider the product to be a suitable candidate for priority designation?

FDA Response

The decision to grant priority review will be made at the time of filing of the NDA submission. In your formal request for the priority review, you should include your justification and provide evidence to support it. Note that statements that (b) (4) will "prevent several different pathologies and adverse reactions that are associated with needle-based delivery of dental anesthetics, including the transmission of bloodborne pathogens, needle-related trauma and infection, and long term adverse reactions such as trismus, facial paralysis and paresthesia" are claims that would need to be supported with appropriately designed studies.

Discussion

There was no further discussion on this point.

Question 37

St. Renatus will also point out in its Request for Priority Designation that (b) (4) would further represent a major advance in treatment because it will contribute to enhanced patient willingness to visit the dentist and, if needed, undergo dental procedures that require the use of a local anesthetic. This is particularly the case with needle-phobic adult and pediatric patients and dental-phobic patients, and thus the use of the product would have a substantial positive effect on dental health. Based on these grounds, would the Agency consider the product to be a suitable candidate for priority designation?

FDA Response

See response to Question 36 above.

Discussion

There was no further discussion on this point.

NDA Formatting and Content Questions

Question 38

Does the Division require a CDISC-compliant data submission for the NDA?

FDA Response

Although you are highly encouraged to submit CDISC-compliant data, the Center does not currently require CDISC-compliant submissions.

Please see the CDER Data Standards Reference Guide/Checklist (Attachment 1) as well.

Discussion

There was no further discussion on this point.

Question 39

We plan to file a paper copy NDA upon completion of the Phase 3 clinical studies. The NDA will include the report of the single nonclinical study mentioned above. In addition, the nonclinical section will include a summary of published nonclinical pharmacology and toxicology data on tetracaine and oxymetazoline. Hard copies of the cited publications will be included in nonclinical Module 4 of the NDA. Does the Division agree with this approach for the nonclinical section of the NDA?

FDA Response

Refer to the following guidance for the location of documents in the CTD format <http://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/UCM072349.pdf>

Discussion

There was no further discussion on this point.

Question 40

The clinical section (Module 5) of the NDA will include summaries and full reports of all studies St. Renuis has conducted on tetracaine and (b) (4). In addition to reports of the two planned Phase 3 studies and the Phase 2 pediatric study that are mentioned above, these include two Phase 1 studies (AP 1-01 and AP 1-02), one Phase 2 study (SR 2-01), and one pharmacokinetic study (SR 2-02). In addition, the clinical section will include a summary of published clinical data

on tetracaine and oxymetazoline. Hard copies of the cited publications will be included in clinical Module 5 of the NDA. Does the Division agree with this approach for the clinical section of the NDA?

FDA Response

The proposed approach appears to be reasonable. The integrated summaries of efficacy and safety should include not only references to published literature but critiques and analyses of the data contained in those references and a discussion describing the relevance of those data to the safety and efficacy of (b) (4).

This matter may be revisited at the PreNDA meeting, if you have further questions at that time.

Discussion

There was no further discussion on this point.

Question 41

With respect to completed case report forms (CRFs) to be included in the NDA, we propose to include these for any subjects who experience a serious adverse event or who discontinue a study due to an adverse event. Does the Division agree with this approach for inclusion of CRFs in the NDA?

FDA Response

CRFs must be included with the NDA submission in accordance with the regulations. See 21 CFR §314.50 (f) (2). In addition, the Division requires that CRFs for all subjects who discontinued the study, regardless of whether is was related to an adverse event.

Discussion

There was no further discussion on this point.

Clinical Pharmacology Comments

- 1. For Study SR 2-02, please clarify if blood samples were collected for only up to 2 hours. Sample collection for only 2 hours may not permit accurate calculation of the PK parameters.**
- 2. As part of your pediatric program, you need to submit pharmacokinetic information in pediatric patients as well.**
- 3. For an eventual 505(b)(2) NDA, you need to submit a relative bioavailability information comparing your product to referenced product(s).**

Discussion

The Sponsor indicated that they would provide PK data on the tetracaine, its major metabolite, and the oxymetazoline, noting that the PK studies were designed around the

tetracaine, which has a short half-life. At 2 hours after administration, tetracaine levels were not measurable and the oxymetazoline levels were on the decline. Since this will be a single-dose product, the sponsor inquired what the clinical significance of further PK information might be.

The Division stated that the Sponsor will need to demonstrate that, after administration of the single-dose, levels of tetracaine, its major metabolite, etc., return to baseline. Usually blood samples are collected up to 4 to 5 half-lives of the drug (or its metabolites). A 24-hour blood sample collection after drug administration may be acceptable (taking half-life into consideration). The Sponsor should propose the blood collection time points and number of subjects to be studied to the Division for review comments. The Division also recommended that the Sponsor refer to the Bioavailability/Bioequivalence Guidance for further guidance on designing these studies.

The Sponsor summarized their understanding of the meeting as follows (includes action items)

1. The Sponsor will provide justification for the safety of (b) (4) by providing (b) (4).
2. The Sponsor will provide safety justification for (b) (4) either by providing QSAR data indicating a lack of mutagenic potential which may be deemed adequate upon review or will provide a definitive negative Ames assay demonstrating a lack of mutagenic potential.
3. The Sponsor understands that they may construct their label based on mg/m².

[*Please refer to the "Post-Meeting Note" above which clarifies conditions under which this will be accepted.]
4. The Sponsor understands that they may conduct a literature search to determine what reproductive toxicology information is available on oxymetazoline and include any adequate data in the proposed product labeling, if available. In addition, they will complete an embryo-fetal developmental study in a single species with the drug product combination that includes pharmacokinetic data to establish exposure margins.
5. The Sponsor understands the comments provided on leachables and extractables.
6. The Sponsor understands that clinical trial eligibility criteria should reflect how the product will be used clinically.
7. The Sponsor agrees that the plans for the additional safety measures as outlined in Clinical Comment 2 are acceptable.

8. The sponsor will attempt not to limit patient enrollment in an effort to get reasonable patient representation and will carefully monitor blood pressure levels of those in the trials.
9. The Sponsor plans to follow the standard of care when the patient is evaluated for anesthetic effectiveness before the provider begins the procedure.
10. The Sponsor understands that the Division recommends that they follow study designs for the pediatrics studies similar to those in adults.
11. The Sponsor understands that they should follow the Bioequivalence/Bioavailability Guidance and that the Division is requesting 24-hour PK blood sampling (or adequate blood sampling).
12. The Sponsor understands that the selection of 1 dose instead of 2 doses in the study design is their own choice and at their own risk.
13. The Sponsor understands that they will need to study tetracaine alone vs. Kovacaine in Phase 3 trials.
14. The Sponsor understands that the question of conducting placebo-controlled studies in pediatric patients will be presented in a Post-Meeting note, as will follow-up on the discussion of human factors studies.
15. The Sponsor noted that they believe their IRB will have an issue with the ethics of a placebo-controlled trial in pediatric patients. (See Post-Meeting note after Question 27)
16. The Sponsor understands that conducting studies in patients down to age 3 years will be necessary.
17. The Sponsor confirmed that they plan to request a Pre-NDA meeting when the timing is appropriate.

Attachment 1**CDER Data Standards Reference Guide/Checklist**

(Version 1.0/December, 2010)

CDER is encouraging sponsors to submit data in standard form as a key part of its efforts to continue with advancement of review efficiency and quality. CDER has been collaborating with CDISC, a standards development organization (SDO), in the development of standards to represent study data submitted in support of regulatory application. CDISC standards are vendor-neutral, platform-independent and freely available via the CDISC website (www.CDISC.org). CDISC study data standards include SDTM for representation of clinical trial tabulations, ADaM for clinical trial analysis files, and SEND for representation of nonclinical animal toxicology studies tabulations.

CDER has accepted SDTM since 2004, however, due to differences in sponsor implementation of the standard, CDER has observed significant variability in submissions containing “standardized” electronic clinical trial data. CDER has received numerous “SDTM-like” applications over the past several years in which sponsors have not followed the SDTM implementation guide. Furthermore, aspects of particular sponsor implementations have actually resulted in increased review difficulty for CDER reviewers. The goal of this document is to communicate general CDER preferences and experiences regarding the submission of standardized data to aid sponsors in the creation of standardized datasets.

This document is not intended to replace the need for sponsors to communicate with review divisions regarding data standards implementation approaches or issues, but instead, it is designed to compliment and facilitate the interaction between sponsors and divisions. Because of specialized needs in different divisions, it is likely that divisions may have additional requests or preferences. When uncertainty exists regarding a particular data standards implementation or submission issue, the sponsor should contact the review division to discuss further.

This document will be **updated regularly** (every 6-12 months) based on division/reviewer feedback and experience. Therefore, it is important that reviewers refer to the CSC website to ensure that they are using the most up-to-date version.

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GENERAL CONSIDERATIONS

INTRODUCTION:

Sponsors should refer to <http://www.cdisc.org> for the latest version of the SDTM IG, SEND IG and ADaM IG in addition to other documentation related to the study data standards.

It is understood that CDISC data standards are evolving and that there may be instances in which the current implementation guides do not provide specific instruction as to how certain study data should be represented. In this instance, sponsors should discuss their proposed solution with the review division and submit supporting documentation at the time of submission that describes these decisions/solutions.

Additionally, sponsors should refer to the following webpage on the CDISC.org site (XXXXX) where proposed draft changes to CDISC standard are located. These represent CDER-desired changes that sponsors should account for. It is expected that these changes will proceed through the usual CDISC data standards development process for evaluation and finalization.

A properly functioning define.xml file is an important part of the submission of electronic datasets and should not be considered optional. As a transition step, CDER prefers that sponsors submit both the define.pdf and define.xml formats. CDER will advise when it is ready to only receive define.xml.

Additionally, sponsors should make certain that every data variable's codelists, origin, and derivation is clearly and easily accessible from the define file. An insufficiently documented define file is a common deficiency that reviewers have noted.

Please include the variables EPOCH, ELEMENT, and ETCD (element code) for every subject-level observation (e.g. adverse events, laboratory, concomitant medications, exposure, vital signs). This will allow the reviewer to easily determine during which phase of the trial the observation occurred (e.g., screening, on-therapy, follow-up), as well as actual intervention the subject experienced during that phase. In the case where an event duration spans multiple epochs and elements, the entry should contain the epoch and element at the onset of the event.

SDTM:

The ideal time to implement SDTM standards for representation of clinical trial tabulation is prior to the conduct of the study. Use of case report forms that incorporate SDTM-standard data elements (such as with CDASH-style case report forms) allows for a simplified process for creation of SDTM domains. This approach is preferred to the alternative of collecting data in non-standard format and then converting to SDTM format after the trial (legacy data conversion). Legacy data conversion is often complex and difficult, and CDER has received submissions in which reviewers have occasionally encountered difficulties while reviewing converted data that were submitted in support of a product application.

It is very important that analysis data be traceable back to the original data elements as they were collected in the case report form and represented in the SDTM data sets. Datasets created via a

legacy conversion must be able to replicate the results presented in the Study Report, although it is understood that some analyses rely on derived data elements found in ADaM that are not contained in SDTM. Such derived data elements must be reproducible through use of the SDTM data elements used in the derivation.

If a sponsor decides to convert trial data to SDTM that was originally collected in non-SDTM format, it is important to note that the resulting SDTM data should support the accompanying analysis data sets and sponsors' reports (study reports, etc.). CDER has received applications in which the converted SDTM data sets were not consistent with the submitted analysis datasets and study report analyses, thus causing confusion during application review.

The **SDTM Implementation Guide (SDTMIG)** (CDISC.org) should be followed carefully. Section 3.2.2 of the SDTMIG provides general criteria conformance with the SDTM data model. These criteria should not be interpreted as the sole indication of the adequacy of submitted data. However, they should be followed unless otherwise indicated. If there is uncertainty with regards to implementation, the sponsor should discuss with the division.

Efficacy Flags: Efficacy observations should be placed in the corresponding SDTM domain for that type of data, if possible. For example, a laboratory finding used in an efficacy analysis should be placed in the LB domain; a blood pressure finding in a hypertension trial should be placed in the VS domain. CDER often sees efficacy variables placed in custom domains. Although this makes it easy to locate the data, it makes data validation processes more challenging as current processes are optimized to work with existing SDTM domains. To make it easy to identify the efficacy data, each domain that contains efficacy data should contain a new variable called --EFF and the entry should be "1" to flag the observation as one that was used in an efficacy analysis.

ADAM

For **analysis datasets**, sponsors should refer to the published ADaM Implementation Guide (CDISC.org) as well as the CDER Study Data Specifications Document. It is expected that significant discussion between the sponsor and CDER reviewers will be necessary to appropriately determine which analysis datasets and associated content are needed to support application review.

Dataset label names should not be identical for ADaM and SDTM datasets. For example, the AE and ADAE domains should not both share a single label of "Adverse Events."

The label names of analysis data sets should not be identical to those of the SDTM datasets. For example: the SDTM adverse event dataset (AE) and the analysis adverse event dataset (ADAE) should not share the exact same label, such as "adverse events".

SEND

CDER currently accepts regulatory submissions of tabulated nonclinical toxicology data in electronic format provided that a complete study report is also submitted. If a sponsor elects to submit datasets in the SEND format, they should clearly note in the define file what version of the data standard was used in addition to definitions of variables and data submitted. Sponsors should continue to consult the Study Data Specifications for information regarding submission of tumor datasets from rodent carcinogenicity studies

(<http://www.fda.gov/downloads/Drugs/DevelopmentApprovalProcess/FormsSubmissionRequirements/ElectronicSubmissions/UCM163561.pdf>). Sponsors should contact the appropriate division with any additional questions. CDER is currently piloting SEND as a potential standard for submission of nonclinical data for general toxicology and carcinogenicity studies.

TERMINOLOGY

CDISC CONTROLLED TERMINOLOGY

Field entries for CDISC standards-specified variables should use the CDISC Controlled Terminology which can be found at the NCI Enterprise Vocabulary Services (<http://www.cancer.gov/cancertopics/terminologyresources/page6>).

NO STANDARD TERMINOLOGY EXISTS

For variables/field entries for which no standard terminology exists or if the available terminology is insufficient and needs to be extended, the sponsor may propose their own terminology. Please provide supporting documentation that describes the non-standard terminology that is used. The define.xml is the preferred mechanism for documenting such terminology issues.

CONSISTENT DRUG DICTIONARY

It is strongly preferred that a consistent drug dictionary (for example, the WHO-Drug Dictionary) terminology be used for the concomitant medications domain. The generic preferred term for a drug should be used for the SDTM standardized medication name variable. The SDTM medication class variable (CMCLAS) should be used to represent a grouping term to allow for rapid identification of drugs in a particular class or pharmacologic sub-group.

MEDDRA

When using MedDRA for adverse events and medical history terms, sponsors should exactly follow the spelling and case of the MedDRA terms. A common error that has been seen is a misspelling of a System Organ Class term or other MedDRA term. Sometimes trials are conducted at different times during the development cycle which results in the use of different versions of MedDRA from one study to the next. It is expected that the Adverse Event data set for the Integrated Summary of Safety include MedDRA preferred terms from a single version of MedDRA. The reason for this request is that reviewers often want to analyze adverse events across trials, including the use of Standardized MedDRA Queries. If different dictionaries are used for data included in the same analysis, there is the potential for confusion or incorrect results.

Generally, no numerically **CODED VARIABLES** should be submitted as part of the SDTM datasets. Numeric values generated from validated scoring instruments or questionnaires do not represent codes, and so have no relevance for this issue. There may be special instances where codes are preferred, so sponsors should refer to the Division for direction, if there is any question. CDER is currently exploring the potential use of codes for particular variables (example: UNI codes for concomitant medications or MedDRA codes for adverse events), possibly as a pilot.

COMMON DICTIONARIES

It is expected that common dictionaries are used across all trials and throughout the submission for each the following: adverse events, concomitant medications, procedures, indications, study drug names, and medical history. Implementation of such dictionaries should be careful to exactly follow

the terminology conventions (e.g., spelling and case) specified by the dictionary or according to a single consistent sponsor specification if no pre-existing terminology exists. CDER has frequently received data in which terminology conventions were not followed, for example, misspelling of MedDRA or WHO Drug terms or lack of conformance to upper/lower case or the use of hyphens. This makes it difficult to use or develop tools to analyze this data in an automated fashion. Again, the use of a standard dictionary that is sponsor defined or extended, should be documented using the define.xml.

SDTM DOMAINS

SUPPQUAL DOMAIN

Suppqual is a dataset domain in both SDTM and SEND. It is intended to include data variables that are not specified in SDTM. SUPPQUAL datasets are often used as a “waste-basket” for data elements that the sponsor is not sure how to allocate. Discussion needs to occur if the sponsor intends to include important variables (that support key analyses) in the SUPPQUAL domains. For clinical trial data in SDTM, one way to deal with this issue for important data elements that are likely to be needed to support review work, is to ensure that analysis datasets include these and other relevant data elements. However, these data elements should not then be excluded from suppqual, because there is a need to maintain traceability from ADaM back to SDTM..

DM DOMAIN

In the DM domain (Demographics), uncertainty exists in the situation that a subject was randomized, however, did not receive treatment for other reasons or if the patient were randomized to one arm, but was actually treated under another arm. In this situation, for ARMCD, the arm entry should be equal to the therapy the patient was randomized to, even if they mistakenly were treated under a different arm. However, there is no current variable included in the DM domain that denotes actual therapy received which can be used to determine the safety population. For example, if a subject were randomized to one arm, but then actually received therapy in accordance with a different arm, there is no variable in the DM dataset that captures this. The recommended solution for this is to include in the DM dataset a new variable called ACTARM or “description of actual arm” and ACTARMCD or “code of actual arm.” If a patient were randomized to receive treatment but did not actually receive therapy, then the field entry should be “NOTTXD”. Terminology for this variable should include the name of the arm that the patient was treated under (consistent with the terminology used for the ARM and ARMCD variables) and patients must have received at least one dose of drug in order to have a treatment arm entry for this variable.

Variable	SDTM Definition
ACTARMCD	Code of actual Arm. May of may not be present in Trial Arms unless TA rules are changed.
ACTARM	Description of actual Arm. May of may not be present in Trial Arms unless TA rules are changed.

In DM, there is uncertainty and inconsistency with regard to the use of the reference start and end dates. Some sponsors are using these variables to denote start and end dates of study drug exposure while others are using them to represent date of informed consent and last date of contact. To

address this, sponsors should use the following variables:

Variable	SDTM Definition
RFXSTDTC	First date of exposure, corresponding to the earliest EXSTDTC.
RFXENDTC	Last date of exposure, corresponding to the latest EXSTDTC.
RFPSDTC	Date/time of informed consent in ISO 8601 character format. This will be the same as the date of informed consent in the Disposition domain, if that protocol milestone is documented.
RPEDTC	Date/time when subject ended participation or follow-up in a trial, in ISO 8601 character format. Should correspond to the last known date of contact. Examples include completion date, withdrawal date, last follow-up, date recorded for lost to follow up, or death date.

In the DM domain, each subject should have only one single record.

A critical review activity involves accounting for all deaths that occur at any time during subject contact. Some implementations of SDTM have resulted in difficulty for reviewers in completing this review activity. There has been some uncertainty regarding how sponsors should represent deaths, particularly, for example, deaths that occurred during the actual treatment, or ones that occurred after enrollment but before drug exposure or ones that occurred after final scheduled visit. Regardless of when a death occurred, reviewers need to easily and quickly be able to identify all deaths associated in any way with the conduct of a study. For this reason, CDER would like sponsors to include two death variables in DM defined as follows:

Variable	SDTM Definition
DTHDTC	Date of death for any subject who died to the sponsor's knowledge, regardless of how or when the death occurred, in ISO 8601 format. Will be null for all subjects who did not die.
DTHFL	Indicates the subject died. Should be Y or null.

This variable should include the date of death for any subject who died, regardless of when the death occurred or whether the death was determined to be related or not related to study drug. All deaths contained in the clinical trial database should be represented here.

DS DOMAIN:

When there is more than one disposition event the EPOCH variable should be used to distinguish between them so that if the death occurred during the treatment period EPOCH='TREATMENT' and if the death occurred during the follow-up period EPOCH='FOLLOW-UP'. Other values may be used for epoch depending upon the terminology used in the trial design model datasets. It is expected that EPOCH variable values (e.g., "FOLLOW-UP" or "TREATMENT") will often be determined based on the trial design and should be defined clearly and documented in the define.xml.

AE DOMAIN (ADVERSE EVENTS):

There is currently no variable in the AE domain that indicates if a variable was “treatment emergent.” CDER would like the AE domain to include all adverse events recorded in any way in the patients’ case report forms, regardless of whether the sponsor has determined that particular events were non-treatment emergent. Since judgment is often used to make a determination of whether an event is treatment-emergent, reviewers need to be able to easily identify all reported adverse events to allow for an evaluation of the sponsor’s assessment. It is not acceptable that the AE domain only include those adverse events that a sponsor has decided are “treatment-emergent.” A treatment-emergent flag should be included in AE to indicate if the event was or was not treatment emergent, as determined by the sponsor and as used in the sponsor’s primary adverse event analyses. For example, depending on the study design, one definition of treatment-emergence might be all adverse events (new events and worsening of pre-existing events/conditions) that occurred after the first dose of study drug exposure and within a certain amount of time following final dose.

In addition, the currently defined AE domain does not include variables for levels of the MedDRA hierarchy other than the preferred term or system organ class levels. This has created challenges for reviewers who typically perform analyses at the different MedDRA levels as a method of safety signal detection and who currently do not have the ability to easily populate these other MedDRA term levels.

The following table represents new variables that include a treatment-emergent flag and MedDRA hierarchy terms.

Variable Name	Variable Label	Type	Controlled Terms, Codelist or Format	Role	CDISC Notes	Core	References
AETRTEM	Treatment Emergent Flag	Char	(NY)	Record Qualifier	Indicates if the event was treatment emergent for any treatment, as defined by the protocol, determined by the sponsor, and used in the sponsor’s adverse event analyses. Should be Y or null.	Exp	DSTU 1.2.1 Section 1.1
AELLT	Lowest Level Term	Char	MedDRA	Variable Qualifier	Dictionary-derived text description of the lowest level term. (MedDRA	Exp	DSTU 1.2.1 Section 1.1

					defined).		
AELLTCD	Lowest Level Term Code	Num	MedDRA	Variable Qualifier	Dictionary-derived code for the lowest level term. (MedDRA defined).	Exp	DSTU 1.2.1 Section 1.1
AEPTCD	Preferred Term Code	Num	MedDRA	Variable Qualifier	Dictionary-derived code for the preferred term. (MedDRA defined).	Exp	
AEHLT	High Level Term	Char	MedDRA	Variable Qualifier	Dictionary-derived text description of the high level term. (MedDRA defined) for the primary System Organ Class.	Exp	DSTU 1.2.1 Section 1.1
AEHLTCD	High Level Term Code	Num	MedDRA	Variable Qualifier	Dictionary-derived code for the high-level term (MedDRA defined) for the primary System Organ Class.	Exp	DSTU 1.2.1 Section 1.1
AEHLGT	High Level Group Term	Char	MedDRA	Variable Qualifier	Dictionary-derived text description of the high level group term. (MedDRA defined) for the primary System Organ Class.	Exp	DSTU 1.2.1 Section 1.1
AEHLGTCD	High Level Group Term Code	Num	MedDRA	Variable Qualifier	Dictionary-derived code for the high level group term. (MedDRA defined) for the primary System Organ Class.	Exp	DSTU 1.2.1 Section 1.1
AESOC	Primary System Organ Class	Char	MedDRA	Variable Qualifier	Dictionary-derived text description of the primary system organ class	Exp	DSTU 1.2.1 Section 1.1

					(MedDRA defined). Will be the same as AEBODSYS if the primary SOC was used for analysis.		
AESOCCD	System Organ Class Code	Num	MedDRA	Variable Qualifier	Dictionary-derived code for the primary system organ class. Will be the same as AEBDSYCD if the primary SOC was used for analysis.	Exp	
AEBDSYCD	System Organ Class Code		MedDRA	Variable Qualifier	Dictionary derived. Code for the body system or organ class used by the sponsor (MedDRA defined). When using a multi-axial dictionary such as MedDRA, this should contain the SOC used for the sponsor's analyses and summary tables, which may not necessarily be the primary SOC.	Exp	DSTU 1.2.1 Section 1.1

The SOC (System Organ Class) variable entry should represent the MedDRA-defined, primary mapped SOC. The SDTM Implementation Guide states that sponsors have the choice to use secondary mapped SOC in place of primary mapped SOC as they wish, however, CDER generally does not agree with this. The SOC variable entry should contain the MedDRA-defined, primary mapped SOC. If the sponsor used a secondary SOC for a subsequent analysis, then the AE domain should contain a second variable called AESOCA (AE SOC for Analysis) that contains the secondary SOC used for analysis. The inclusion of both AESOC and AESOCA allows reviewers to easily determine whether the use of a secondary SOC for analysis was appropriate.

CUSTOM DOMAINS:

Both the SDTM and SEND Implementation Guides allow for the creation of custom domains if the data do not fit into an existing domain. Prior to creating a custom domain, sponsors should confirm that the data do not fit an existing domain and also check the CDISC website for domains added after the most recent published implementation guide. If necessary, sponsors should follow the recommendations in the Implementation guides for how to create a custom domain.

LB DOMAIN (LABORATORY):

The size of the LB domain is often quite large and can exceed the reviewers' ability to open the file using standard-issue computers. This issue can be addressed by splitting the large LB dataset into smaller data sets according to LBCAT and LABSCAT. Using LBCAT as initial splitting. If size is still too large, then use LBSCAT for further splitting. For example: chemistry (named "LBC"), hematology (named "LBH"), UA (LBU), serology (LBS), etc. Splitting it other ways (by subject or file size, etc) makes the data less useable. Sponsors should submit these smaller files **in addition to** the larger non-split standard LB domain file. Individual file size up to 400 megabytes is usually fine, however, it is recommended to confirm this with the review division.

ADAM DOMAINS (ANALYSIS DATASETS)**GENERAL COMMENTS:**

In determining how to create ADaM analysis datasets for submission to CDER, sponsors should refer to **three documents**: the ADaM Implementation Guide, the FDA Data Specifications Document, and the CDER Analysis Data Submission Document. Close adherence to the ADaMIG is expected and any specific questions that result from attempts to adhere to these documents should be discussed with the review division.

A careful assessment of **which analysis datasets** will be needed should occur. Sponsors must submit analysis datasets with their application to support key efficacy and safety analyses. Additionally, it is important to remember that SDTM datasets do not have core variables (such as demographic and population variables) repeated across the different domains. The need for such duplication of core variables across various domains can be fulfilled through their inclusion in the corresponding analysis datasets. This need is sufficient for the purposes of justifying a request for analysis datasets. For example, the SDTM adverse event dataset does not allow for the inclusion of variables such as treatment arm, sex, age, or race. These and other variables may be included in an adverse event analysis dataset.

ADSL

ADSL is the subject level analysis dataset for ADaM. CDER expects this ADaM-defined dataset along with the other supporting analysis datasets. **All CDISC submissions are expected to contain an ADSL file.** In addition to the variables specified for ADSL in the ADaM Implementation Guide, it is expected that the sponsor will include multiple additional variables representing various important baseline patient characteristics. A few examples could include: disease severity scores such as APACHE scores or FINE scores; baseline organ function measurements such as calculated creatinine clearance or FEV1; range categories for continuous variables; numeric date variables in non-ISO format such as SAS or Oracle.

VARIABLES

REQUIRED VS. EXPECTED VS. PERMISSIBLE

CDISC data standards categorize SDTM and SEND variables as being Required, Expected, and Permissible. Some sponsors have interpreted Permissible variables as being optional. However, for the purposes of SDTM and SEND submission to CDER, all permissible variables for which data were collected or for which derivations are possible should be submitted. **Examples** of some of the permissible variables in SDTM that CDER expects to see include:

- Baseline flags for Laboratory results, Vital Signs, ECG, Pharmacokinetic Concentrations, Microbiology results
- EPOCH designators. An extensible code list for EPOCH will be developed. Please follow C-DISC guidance for terminology.
- STDY variables in SE or other findings domains. STDY should be calculated based on first treatment date.

NAMING CONVENTIONS

Naming conventions (variable name and label) and variable formats should be followed as specified in the implementation guides.

DATES:

Dates in SDTM and SEND domains should conform to the ISO 8601 format. Examples of how to implement this are included in the IGs. If no time measurements are available, the sponsor should only keep ISO 8601 date, not date and time.

USUBJID:

Each individual patient must be assigned a single unique identifier (USUBJID) across the entire submission. An individual subject should have the exact same unique identifier across all datasets including SDTM and ADaM. Do not add leading or trailing spaces in any dataset. This is a common error that is seen with applications.

IMPUTED DATA:

SDTM should not include any imputed data. If there is a need for data imputation, this should occur in an analysis dataset and the relevant supporting documentation must be provided.

COMMON ERRORS

In this section, this document includes some of the most common data errors that CDER finds when performing conformance checking.

Each error listed in this section lists the name of the actual error as the title and then provides some brief comment and/or description.

It is expected that as CDER increases the scope of its data checking activities, this section will be updated based on which errors are seen most frequently. The purpose of this section is to bring attention to common errors.

DEFINE DOESN'T VALIDATE

Please refer to www.cdisc.org/define-xml for instructions. Here sponsors can find the white paper for XML Schema Validation for Define.xml which provides guidance on validating define.xml version 1.0 documents against the define.xml XML schemas. Prior to submission, a sponsor may submit their define.xml for testing to determine whether it validates. The submission of a define.xml is expected with all CDISC applications. If sponsors would like to also include a define.pdf document additionally, this would be ok.

INVALID ISO 8601 DATE FORMAT

All dates in the SDTM domains must conform to the ISO 8601 format.

BEGIN DATE MUST BE ≤ END DATE

This is a common error. Examples include a concomitant medication or adverse event begin date that is after the end date.

REQUIRED VARIABLE NOT FOUND.

Required variable not found. A Required variable is any variable that is basic to the identification of a data record (such as the unique subject identifier) or is necessary to make the record meaningful. Required variables must always be included in the dataset and cannot be null for any record.

INCONSISTENT VALUE FOR STANDARD UNITS.

INVALID VALUE FOR MEDDRA TERM

This occurs when the sponsor has not accurately represented the MedDRA term as it appears in the MedDRA terminology. This seems to be more common with the System Organ Class terms which are commonly longer and more prone to misspellings.

NARRATIVES:

In addition to narratives provided in .pdf format, CDER would strongly desire that narratives are also provided in a format that is a computer \-readable textual description of the patient's events and patient's care. The narrative text should integrate the information on all serious events, outcomes of serious adverse events, withdrawals, deaths, and causes of death, autopsy reports, concomitant conditions and procedures, etc. into a single narrative text. The narrative text should describe all the information mentioned above and any other additional information as review needed.

Narrative text files should be named as narrative.txt. Text File format should be plain ASCII text (txt) files. Each row of the file has two fields delimited by tab characters.

The first field is the unique subject ID (USUBJID) that is used in the submission. The USUBJID should be *identical* to the USUBJID used in all SDTM submission data sets. The second field is the text of the narrative. The narrative must not contain TABS, HARD RETURNS, non-printing characters, or hidden “funny” or formatted characters. See example for narrative template.

Narrative template format Example:

USUBJID	Narrative
330111009	A 46-year old female subject was enrolled in a Phase 3, Multicenter, Ra.....
Etc.	

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

/s/

KIMBERLY A COMPTON
04/01/2011