CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

208791Orig1s000

ADMINISTRATIVE and CORRESPONDENCE DOCUMENTS
## ACTION PACKAGE CHECKLIST

### APPLICATION INFORMATION

<table>
<thead>
<tr>
<th>NDA #</th>
<th>NDA Supplement #</th>
<th>BLA #</th>
<th>BLA Supplement #</th>
<th>If NDA, Efficacy Supplement Type:</th>
</tr>
</thead>
<tbody>
<tr>
<td>208791</td>
<td></td>
<td></td>
<td></td>
<td>(an action package is not required for SE8 or SE9 supplements)</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Proprietary Name:</th>
<th>Clorotekal</th>
</tr>
</thead>
<tbody>
<tr>
<td>Established/Proper Name:</td>
<td>Chloroprocaine HCl 1% (10 mg/mL)</td>
</tr>
<tr>
<td>Dosage Form:</td>
<td>Injection</td>
</tr>
<tr>
<td>Applicant:</td>
<td>Sintetica SA</td>
</tr>
<tr>
<td>Agent for Applicant (if applicable):</td>
<td>VPCI, Inc</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>RPM:</th>
<th>Selma Kraft</th>
</tr>
</thead>
<tbody>
<tr>
<td>Division:</td>
<td>DAAAP</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>NDA Application Type:</th>
<th>□ 505(b)(1)</th>
<th>□ 505(b)(2)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Efficacy Supplement:</td>
<td>□ 505(b)(1)</td>
<td>□ 505(b)(2)</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>BLA Application Type:</th>
<th>□ 351(k)</th>
<th>□ 351(a)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Efficacy Supplement:</td>
<td>□ 351(k)</td>
<td>□ 351(a)</td>
</tr>
</tbody>
</table>

### Actions

- Proposed action
- User Fee Goal Date is 9/26/17

### 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](http://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/ucm069965.pdf)). If not submitted, explain ________

### Application Characteristics

- Received

---

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.

Reference ID: 4161289

Version: 05/09/17
Review priority: [ ] Standard [ ] Priority
Chemical classification (new NDAs only): Type 5
(confirm chemical classification at time of approval)
[ ] Fast Track [ ] Rx-to-OTC full switch
[ ] Rolling Review [ ] Rx-to-OTC partial switch
[ ] Orphan drug designation [ ] Direct-to-OTC
[ ] Breakthrough Therapy designation

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

NDAs: Subpart H
[ ] Accelerated approval (21 CFR 314.510)
[ ] Restricted distribution (21 CFR 314.520)
Subpart I
[ ] Approval based on animal studies
[ ] Submitted in response to a PMR
[ ] Submitted in response to a PMC
[ ] Submitted in response to a Pediatric Written Request

BLAs: Subpart E
[ ] Accelerated approval (21 CFR 601.41)
[ ] Restricted distribution (21 CFR 601.42)
Subpart H
[ ] Approval based on animal studies
[ ] REMS
[ ] MedGuide
[ ] Communication Plan
[ ] ETASU
[ ] MedGuide w/o REMS
[ ] REMS not required

Comments:

<table>
<thead>
<tr>
<th>BLAs only: Is the product subject to official FDA lot release per 21 CFR 610.2 (approvals only)</th>
<th>[ ] Yes [ ] No</th>
</tr>
</thead>
<tbody>
<tr>
<td>Public communications (approvals only)</td>
<td></td>
</tr>
<tr>
<td>• Office of Executive Programs (OEP) liaison has been notified of action</td>
<td>[ ] Yes [ ] No</td>
</tr>
<tr>
<td>• Indicate what types (if any) of information were issued</td>
<td>[ ] None</td>
</tr>
<tr>
<td>• FDA Press Release</td>
<td></td>
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<tr>
<td>• FDA Talk Paper</td>
<td></td>
</tr>
<tr>
<td>• CDER Q&amp;As</td>
<td></td>
</tr>
<tr>
<td>• Other</td>
<td></td>
</tr>
</tbody>
</table>

| Exclusivity                                                                                   | [ ] No [ ] Yes |
| Is approval of this application blocked by any type of exclusivity (orphan, 5-year NCE, 3-year, pediatric exclusivity)? |
| If so, specify the type                                                                       |

| Patent Information (NDAs only)                                                                |               |
| • Patent Information: Verify that form FDA-3542a was submitted for patents that claim the drug for which approval is sought. | [ ] Verified   |
| • Not applicable because drug is an old antibiotic.                                          |               |

**CONTENTS OF ACTION PACKAGE**

**Officer/Employee List**

| List of officers/employees who participated in the decision to approve this application and consented to be identified on this list (approvals only) | [ ] Included |
| Documentation of consent/non-consent by officers/employees                                 | [ ] Included |
### Action Letters

- Copies of all action letters *(including approval letter with final labeling)*
  - Action(s) and date(s) Approval, September 26, 2017

### Labeling

- Package Insert *(write submission/communication date at upper right of first page of Pl)*
  - Most recent draft labeling *(if it is division-proposed labeling, it should be in track-changes format)*
    - Included
  - Original applicant-proposed labeling
    - Included

- Medication Guide/Patient Package Insert/Instructions for Use/Device Labeling *(write submission/communication date at upper right of first page of each piece)*
  - Most-recent draft labeling *(if it is division-proposed labeling, it should be in track-changes format)*
    - Included
  - Original applicant-proposed labeling
    - Included

- Labels *(full color carton and immediate-container labels)* *(write submission/communication date on upper right of first page of each submission)*
  - Most-recent draft labeling
    - Included

- Proprietary Name
  - Acceptability/non-acceptability letter(s) *(indicate date(s))*
  - Review(s) *(indicate date(s))*
  - Acceptable (4/25/17)
    - 4/24/17

- Labeling reviews *(indicate dates of reviews)*
  - RPM: None 11/3/16
  - DMEPA: None 4/24/17, 4/26/17
  - DMPP/PLT (DRISK): None
  - OPDP: None 8/4/17
  - SEALD: None
  - CSS: None
  - Product Quality: None
  - Other: None

### Administrative / Regulatory Documents

- RPM Filing Review^4/Memo of Filing Meeting *(indicate date of each review)*
  - 11/3/16

- All NDA 505(b)(2) Actions: Date each action cleared by 505(b)(2) Clearance Committee
  - Not a (b)(2) 8/15/17

- NDAs/NDA supplements only: Exclusivity Summary *(signed by Division Director)*
  - Completed *(Do not include)*

- Application Integrity Policy (AIP) Status and Related Documents
  - [http://www.fda.gov/ICECI/EnforcementActions/ApplicationIntegrityPolicy/default.htm](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 *indicate date*
  - If yes, OC clearance for approval *indicate date of clearance communication*

- Pediatrics (approvals only)
  - Date reviewed by PeRC 3/15/17
  - If PeRC review not necessary, explain: _____

- Breakthrough Therapy Designation
  - N/A

- CDER Medical Policy Council Breakthrough Therapy Designation Determination Review Template(s) (include only the completed template(s) and not the meeting minutes)

- CDER Medical Policy Council Brief – Evaluating a Breakthrough Therapy Designation for Rescission Template(s) (include only the completed template(s) and not the meeting minutes)

(completed CDER MPC templates can be found in DARRTS as clinical reviews or on the MPC SharePoint Site)

- 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.) *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*

- 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 *indicate date of mtg*
  - Pre-NDA/BLA meeting *indicate date of mtg*
  - EOP2 meeting *indicate date of mtg*
  - Mid-cycle Communication *indicate date of mtg*
  - Late-cycle Meeting *indicate date of mtg*
  - Other milestone meetings (e.g., EOP2a, CMC focused milestone meetings) *indicate dates of mtgs*

- Advisory Committee Meeting(s)
  - No AC meeting

### Decisional and Summary Memos

- Office Director Decisional Memo *indicate date for each review*
  - None

- Division Director Summary Review *indicate date for each review*
  - None 09/26/17

- Cross-Discipline Team Leader Review *indicate date for each review*
  - None 9/22/17

- PMR/PMC Development Templates *indicate total number*
  - None 3

### Clinical

Reference ID: 4161289
<table>
<thead>
<tr>
<th>Section</th>
<th>Description</th>
<th>Date/Location</th>
<th>Notes</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Clinical Reviews</strong></td>
<td>Clinical Team Leader Review(s) (indicate date for each review)</td>
<td>8/10/17</td>
<td>No separate review</td>
</tr>
<tr>
<td></td>
<td>Clinical review(s) (indicate date for each review)</td>
<td>8/10/17</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Social scientist review(s) (if OTC drug) (indicate date for each review)</td>
<td></td>
<td>None</td>
</tr>
<tr>
<td></td>
<td>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 (indicate date of review/memo)</td>
<td>08/10/17</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Clinical reviews from immunology and other clinical areas/divisions/Centers (indicate date of each review)</td>
<td></td>
<td>None</td>
</tr>
<tr>
<td></td>
<td>Controlled Substance Staff review(s) and Scheduling Recommendation (indicate date of each review)</td>
<td></td>
<td>N/A</td>
</tr>
<tr>
<td></td>
<td>Risk Management</td>
<td></td>
<td></td>
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<tr>
<td></td>
<td>REMS Documents and REMS Supporting Document (indicate date(s) of submission(s))</td>
<td></td>
<td>None</td>
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<tr>
<td></td>
<td>REMS Memo(s) and letter(s) (indicate date(s))</td>
<td></td>
<td></td>
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<tr>
<td></td>
<td>Risk management review(s) and recommendations (including those by OSE and CSS) (indicate date of each review and indicate location/date if incorporated into another review)</td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>OSI Clinical Inspection Review Summary(ies) (include copies of OSI letters to investigators)</td>
<td></td>
<td>None requested 9/15/17</td>
</tr>
<tr>
<td><strong>Clinical Microbiology</strong></td>
<td></td>
<td></td>
<td>None</td>
</tr>
<tr>
<td></td>
<td>Clinical Microbiology Team Leader Review(s) (indicate date for each review)</td>
<td></td>
<td>No separate review</td>
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<td></td>
<td>Clinical Microbiology Review(s) (indicate date for each review)</td>
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<td>None</td>
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<tr>
<td><strong>Biostatistics</strong></td>
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<td>None</td>
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<tr>
<td></td>
<td>Statistical Division Director Review(s) (indicate date for each review)</td>
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<td>No separate review</td>
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<tr>
<td></td>
<td>Statistical Team Leader Review(s) (indicate date for each review)</td>
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<td>No separate review</td>
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<tr>
<td></td>
<td>Statistical Review(s) (indicate date for each review)</td>
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<td>None 7/28/17</td>
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<td><strong>Clinical Pharmacology</strong></td>
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<td></td>
<td>Clinical Pharmacology Division Director Review(s) (indicate date for each review)</td>
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<td>No separate review</td>
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<tr>
<td></td>
<td>Clinical Pharmacology Team Leader Review(s) (indicate date for each review)</td>
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<td>No separate review</td>
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<tr>
<td></td>
<td>Clinical Pharmacology review(s) (indicate date for each review)</td>
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<td>None 7/19/17</td>
</tr>
<tr>
<td></td>
<td>OSI Clinical Pharmacology Inspection Review Summary (include copies of OSI letters)</td>
<td></td>
<td>None requested</td>
</tr>
</tbody>
</table>

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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

<table>
<thead>
<tr>
<th>Event</th>
<th>Review Details</th>
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</thead>
<tbody>
<tr>
<td>Pharmacology/Toxicology Discipline Reviews</td>
<td>No separate review 7/31/17</td>
</tr>
<tr>
<td>ADP/T Review(s) <em>(indicate date for each review)</em></td>
<td>No separate review 7/31/17</td>
</tr>
<tr>
<td>Supervisory Review(s) <em>(indicate date for each review)</em></td>
<td>No separate review 7/31/17</td>
</tr>
<tr>
<td>Pharm/tox review(s), including referenced IND reviews <em>(indicate date for each review)</em></td>
<td>None 7/31/17</td>
</tr>
<tr>
<td>Review(s) by other disciplines/divisions/Centers requested by P/T reviewer <em>(indicate date for each review)</em></td>
<td>None</td>
</tr>
<tr>
<td>Statistical review(s) of carcinogenicity studies <em>(indicate date for each review)</em></td>
<td>No study</td>
</tr>
<tr>
<td>ECAC/CAC report/memo of meeting</td>
<td>Included in P/T review, page</td>
</tr>
<tr>
<td>OSI Nonclinical Inspection Review Summary <em>(include copies of OSI letters)</em></td>
<td>None requested</td>
</tr>
</tbody>
</table>

### Product Quality

<table>
<thead>
<tr>
<th>Event</th>
<th>Review Details</th>
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</thead>
<tbody>
<tr>
<td>Product Quality Discipline Reviews*</td>
<td>None</td>
</tr>
<tr>
<td>Tertiary review <em>(indicate date for each review)</em></td>
<td>None 8/1/17</td>
</tr>
<tr>
<td>Secondary review (e.g., Branch Chief) <em>(indicate date for each review)</em></td>
<td>None</td>
</tr>
<tr>
<td>Integrated Quality Assessment <em>(contains the Executive Summary and the primary reviews from each product quality review discipline)</em></td>
<td>Drug substance: 03/30/17</td>
</tr>
<tr>
<td></td>
<td>Drug Product: 07/21/17</td>
</tr>
<tr>
<td></td>
<td>Microbiology: 5/24/17</td>
</tr>
<tr>
<td></td>
<td>Facility: 5/11/17</td>
</tr>
<tr>
<td></td>
<td>Process: 6/9/17</td>
</tr>
<tr>
<td>Reviews by other disciplines/divisions/Centers requested by product quality review team <em>(indicate date of each review)</em></td>
<td>None</td>
</tr>
<tr>
<td>Environmental Assessment *(check one) <em>(original and supplemental applications)</em></td>
<td>None</td>
</tr>
<tr>
<td>Categorical Exclusion *(indicate review date) <em>(all original applications and all efficacy supplements that could increase the patient population)</em></td>
<td>8/1/17</td>
</tr>
<tr>
<td>Review &amp; FONSI <em>(indicate date of review)</em></td>
<td>8/1/17</td>
</tr>
<tr>
<td>Review &amp; Environmental Impact Statement <em>(indicate date of each review)</em></td>
<td>8/1/17</td>
</tr>
</tbody>
</table>

### Facilities Review/Inspection

<table>
<thead>
<tr>
<th>Event</th>
<th>Review Details</th>
</tr>
</thead>
<tbody>
<tr>
<td>Facilities inspections <em>(indicate date of recommendation; within one week of taking an approval action, confirm that there is an acceptable recommendation before issuing approval letter)</em> <em>(only original applications and efficacy supplements that require a manufacturing facility inspection (e.g., new strength, manufacturing process, or manufacturing site change)</em></td>
<td>Acceptable</td>
</tr>
</tbody>
</table>

---

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

<table>
<thead>
<tr>
<th>Activity</th>
<th>Status</th>
</tr>
</thead>
<tbody>
<tr>
<td>For all 505(b)(2) applications:</td>
<td>No changes</td>
</tr>
<tr>
<td>- Check Orange Book for newly listed patents and/or exclusivity (including pediatric exclusivity)</td>
<td></td>
</tr>
<tr>
<td>- Finalize 505(b)(2) assessment</td>
<td>Done</td>
</tr>
<tr>
<td>For Breakthrough Therapy (BT) Designated drugs:</td>
<td>Done</td>
</tr>
<tr>
<td>- Notify the CDER BT Program Manager</td>
<td></td>
</tr>
<tr>
<td>For products that need to be added to the flush list (generally opioids):</td>
<td></td>
</tr>
<tr>
<td>- Notify the Division of Online Communications, Office of Communications</td>
<td></td>
</tr>
<tr>
<td>Send a courtesy copy of approval letter and all attachments to applicant by fax or secure email</td>
<td>Done</td>
</tr>
<tr>
<td>If an FDA communication will issue, notify Press Office of approval action after confirming that applicant received courtesy copy of approval letter</td>
<td>Done</td>
</tr>
<tr>
<td>Ensure that proprietary name, if any, and established name are listed in the Application Product Names section of DARRTS, and that the proprietary name is identified as the “preferred” name</td>
<td>Done</td>
</tr>
<tr>
<td>Ensure Pediatric Record is accurate</td>
<td>Done</td>
</tr>
<tr>
<td>Send approval email within one business day to CDER-APPROVALS</td>
<td>Sent 9/26/17</td>
</tr>
<tr>
<td>Take Action Package (if in paper) down to Document Room for scanning within two business days</td>
<td></td>
</tr>
</tbody>
</table>
This is a representation of an electronic record that was signed electronically and this page is the manifestation of the electronic signature.

/s/

----------------------------------------------------

SELMA S KRAFT
10/02/2017
Dear Elisabetta,
We have the following labeling request:
   Add an equivalency statement for the chloroprocaine base to the labeling. Please submit revised carton and container labeling.

Please provide this information, via email initially is fine, by COB Tuesday August 22, 2017 so that we can expedite the review. I apologize for the short turn-around time. I appreciate your cooperation. Please follow up with an official submission to your NDA.

Kindly confirm receipt of this email. Let me know if you have any questions or concerns.

Sincerely,
Selma Kraft PharmD.
Regulatory Health Project Manager
Division of Anesthesia, Analgesia, and Addiction Products (DAAAP)
Food and Drug Administration
Phone: 240.402.9700
This is a representation of an electronic record that was signed electronically and this page is the manifestation of the electronic signature.

/s/

----------------------------------------
SELMA S KRAFT
08/18/2017
Hello,
We have the following information request:

Submit narrative summaries and Case Report Forms for the following subjects in Study CHL1/01-2012/M:

- Subject 03-001
- Subject 05-043

Provide rationale why neurologic symptoms experienced by Subjects 03-001 and 05-043 in Study CHL1/01-2012/M are not consistent with TNS.

Complete the following table with all adverse events recorded in Study CHL1/01-2012/M:

<table>
<thead>
<tr>
<th>System Organ Class</th>
<th>Preferred Term</th>
<th>CP 30 mg N=</th>
<th>CP &gt;30 to 40 mg N=</th>
<th>CP &gt;40 to &lt;50 mg N=</th>
<th>CP 50 mg N=</th>
<th>CP &gt;50 mg N=</th>
<th>CP Unknown N=</th>
<th>Overall N=</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td></td>
<td>n (%)</td>
<td>n (%)</td>
<td>n (%)</td>
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</tbody>
</table>

Please complete this as soon as possible, but no later than COB Thursday July 27, 2017. You may provide your responses via email to expedite review. Please follow up with an official submission to your NDA. Feel free to contact me with any questions.

Kindly confirm receipt of this. Thank you.

Sincerely,
Selma Kraft PharmD.
Regulatory Health Project Manager
Division of Anesthesia, Analgesia, and Addiction Products (DAAAP)
Food and Drug Administration
Phone: 240.402.9700
This is a representation of an electronic record that was signed electronically and this page is the manifestation of the electronic signature.

/s/

----------------------------------------------------
SELMA S KRAFT
07/24/2017
Hello,
We have the following recommendation for your carton container labeling:
   Add ‘store in carton” beside “protect from light” on the carton labeling.

Please update your carton label and re-submit to your NDA as soon as possible, but no later than Tuesday July 25, 2017. Let me know if you have any questions or concerns. Kindly acknowledge receipt of this email.

Thank you.

Sincerely,

Selma Kraft PharmD.
Regulatory Health Project Manager
Division of Anesthesia, Analgesia, and Addiction Products (DAAAP)
Food and Drug Administration
Phone: 240.402.9700
This is a representation of an electronic record that was signed electronically and this page is the manifestation of the electronic signature.

/s/

-----------------------------------------------
SELMA S KRAFT
07/20/2017
From: Steven Kinsley  
To: ckruman@vpcint.com  
Cc: Selma Kraft  
Subject: NDA 208791 CMC Information Request 7-10-17  
Date: July 10, 2017

Dear Craig,

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

1. We acknowledge the response dated 7 July 2017 to the information request dated 5 July 2017. The system suitability repeatability %RSD should be calculated based on the cumulative injections of all Std 1 and Std 2 injections throughout the HPLC run. Use validation data (precision repeatability and intermediate precision) as well as historical HPLC run data to determine an acceptable system suitability repeatability %RSD based on all Std 1 and Std 2 injections throughout the HPLC run (usually around \( \% \) for larger peaks and \( \% \) for impurity peaks). Update the method to state that system suitability repeatability %RSD will be determined using the cumulative injections of all Std 1 and Std 2 injections throughout the HPLC run.

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

Best Regards,

Steve

Steven Kinsley, Ph.D.
Regulatory Business Process Manager

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

I have received the following information request from our CMC review team. Please respond to the following with a submission to your NDA by Monday, July 10, 2017

1. The system suitability criteria appear to be inadequate in module 3.2.P.5.2.8 Chloroprocaine HCl and Related Substances Assay by HPLC because it only requires 3 injections of Std 1. According to USP <621> Chromatography, “Unless otherwise specified in the individual monograph, data from five replicate injections of the analyte are used to calculate the relative standard deviation, %RSD, if the requirement is 2.0% or less; data from six replicate injections are used if the relative standard deviation requirement is more than 2.0%.” State in the method that both Std 1 and Std 2 will be injected at least 5 times each and will bracket the beginning and the end of the HPLC run in addition to bracketing every 4 sample injections.

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

Best Regards,
Steve

Steven Kinsley, Ph.D.
Regulatory Business Process Manager

Office of Program and Regulatory Operations
U.S. Food and Drug Administration
Tel: 240-402-2773
Steven.Kinsley@fda.hhs.gov
Hello,
Is there a way for us to get the responses sooner than June 23? If not, we will anticipate responses by June 23.

We also have the following information request:

In addition to the previous Information Request from June 13, 2017, please provide the time of administration of all intraoperative breakthrough medications for the 42 subjects who required breakthrough medications for anxiety, analgesia, sedation, or anesthesia. Provide this data as soon as possible.

Thank you – Kindly acknowledge receipt of this request.

Regards,
Selma

---

Dear Selma,

thank you for your email. As anticipated in our response of last Friday by secure email, the Phase 4 study protocol did not capture the surgery duration. Therefore we need to gather this information from the OR forms. We have already contacted the concerned centers and we are waiting for their response. Please also consider that in Switzerland and Germany (two centers are German) June 15th 2017 is bank holiday. For these reasons we kindly ask you to wait till Monday June 19th 2017 for confirming you the due date of the response application. As a reasonable forecast we can give you June 23rd 2017.

Thanks for your comprehension and support.

Kindest regards

Elisabetta
Dear Craig,
We have an additional information request:
   With regard to the Phase 4 study, please provide surgical duration (in hours or minutes) for all 42 subjects that needed intraoperative rescue medications.

Please respond as soon as possible, but no later than COB June 15, 2017. Let me know if you have any questions or concerns. Kindly acknowledge receipt of this request. Thank you.

Sincerely,
Selma Kraft PharmD.
Regulatory Health Project Manager
Division of Anesthesia, Analgesia, and Addiction Products (DAAAP)
Food and Drug Administration
Phone: 240.402.9700
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/s/

SELMA S KRAFT
06/14/2017
Dear Craig,

We have an additional information request:

With regard to the Phase 4 study, please provide surgical duration (in hours or minutes) for all 42 subjects that needed intraoperative rescue medications.

Please respond as soon as possible, but no later than COB June 15, 2017. Let me know if you have any questions or concerns. Kindly acknowledge receipt of this request. Thank you.

Sincerely,
Selma Kraft PharmD.
Regulatory Health Project Manager
Division of Anesthesia, Analgesia, and Addiction Products (DAAAP)
Food and Drug Administration
Phone: 240.402.9700
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/s/

----------------------------------------------
SELMA S KRAFT
06/13/2017
Dear Craig,

We are currently in the process of reviewing the final study report for study CHL1/01-2012/M and have the following requests for information:

1. Table 10.6.1 in the CSR states that 42 (10.7%) subjects required additional intravenous analgesia and sedation in the operating room. Provide your assessment and conclusions to account for this unexpectedly high failure rate.

2. Provide a more detailed distribution of doses of chloroprocaine administered to all 393 subjects based on the following dose ranges:
   - 30 mg
   - 31 to < 40 mg
   - 40 mg
   - 41 to < 50 mg
   - 50 mg
   - > 50 mg

3. Provide the specific doses of chloroprocaine that were given to the 42 subjects who required additional intravenous analgesia and sedation in the operating room.

4. Provide the duration of surgical procedures, as well as time from intrathecal injection to the start of surgical procedures, for the 42 subjects who required additional intravenous analgesia and sedation in the operating room.

Please submit responses by COB Tuesday June 6, 2017. You may provide your responses via email, if possible, to expedite review. Please follow up with an official submission to your NDA. Feel free to contact me with any questions. Kindly confirm receipt of this request. Thank you.

Sincerely,

Selma Kraft PharmD.
Regulatory Health Project Manager
Division of Anesthesia, Analgesia, and Addiction Products (DAAAP)
Food and Drug Administration
Phone: 240.402.9700
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/s/

SELMA S KRAFT
06/01/2017
Dear Mr. Kruman:

Please refer to your New Drug Application (NDA) dated and received August 26, 2016, submitted under section 505(b)(2) of the Federal Food, Drug, and Cosmetic Act for Chlorprocaime HCl solution for injection, 1% [50 mg/5 mL (10 mg/mL)].

We also refer to your correspondence, dated and received February 14, 2017, requesting review of your proposed proprietary name, Clorotekal.

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

If any of the proposed product characteristics as stated in your February 14, 2017, submission are altered prior to approval of the marketing application, the proprietary name should be resubmitted for review. Additionally, if your application receives a complete response, a new request for name review for your proposed name should be submitted when you respond to the application deficiencies.

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

If you have any questions regarding the contents of this letter or any other aspects of the proprietary name review process, contact Davis Mathew, Safety Regulatory Project Manager in the Office of Surveillance and Epidemiology, at (240) 402-4559. For any other information regarding this application, contact Selma S. Kraft, Regulatory Project Manager in the Office of New Drugs, at (240) 402-9700.

Sincerely,

{See appended electronic signature page}

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

DANIELLE M HARRIS on behalf of TODD D BRIDGES
04/25/2017
Dear Craig,

We have the following information requests. The due dates are listed in red after each request.

Statistics:
1. In the submission dated February 17, 2017, you provided data regarding spinal duration, surgery duration, and analgesia, anesthesia and sedation adjuncts for Study CHL1/02-2014 (Table 1a, Table1b, Table 1c) and Study CHL1/02-2006/M (Table 2 and Table 3). To facilitate our review, provide .xpt files for these tables. The .xpt datasets should be provided no later than May 8, 2017.

Clinical:
2. Complete study report for study CHL1/01-2012/M. You should update appropriate sections of your NDA (i.e., Integrated Summary of Safety) with any new safety information learned about the drug that may reasonably affect the statement of contraindications, warnings, precautions, and adverse reactions in the draft labeling. If you do not choose to update your NDA with new safety information, provide rationale for why it is not necessary. Provide this information by May 11, 2017.

3. In-depth literature assessment for the incidence of transient neurologic syndrome and cauda equina syndrome with chloroprocaine in comparison to bupivacaine, which is currently the gold standard local anesthetic for intrathecal administration. Provide this information by May 11, 2017.

Please let me know if you have any questions or concerns. Kindly acknowledge receipt of this. Thank you.

Sincerely,
Selma Kraft PharmD.
Regulatory Health Project Manager
Division of Anesthesia, Analgesia, and Addiction Products (DAAAP)
Food and Drug Administration
Phone: 240.402.9700
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/s/

SELMA S KRAFT
04/21/2017
Dear Craig,

We have additional information request regarding NDA 208791 – Chloroprocaine 1% Injection:

Please submit the following:

1. An update on the status of your Phase 4 study (CHL1/01-2012/M), which should have been completed by September 2016, per your Clinical Overview included in the original NDA application.

2. Time of time of the following medications given in the OR to the following subjects in study CHL1/02-2006/M:
   - S203/203 (dipidolor, midazolam)
   - S205/205 (propofol, sevoflurane, sufentanil)
   - S211/211 (midazolam)
   - S202/202 (midazolam)
   - S212/212 (midazolam)
   - S120/121 (fentanest)
   - S110/107 (no information provided)
   - S204/204 (fentanyl, pantolax, propofol)
   - S206/206 (midazolam)
   - S210/210 (midazolam, fentanyl, propofol, suprane)
   - S220/220 (fentanyl, ketanest, propofol)
   - S403/304 (propofol, rapifen, sintenyl)

   If you do not have the exact times of rescue medications, you should attempt to estimate the times based on examining the operating room records, as you had done for study CHL1/02-2004.

3. Rationale for the difference in the incidence of rescue medications administration (including intraoperative doses of midazolam, opioids, propofol, ketamine, inhalational agents, neuromuscular blockers, etc.) at the Marburgo site, as compared to the other study sites in study CHL1/02-2006/M.

4. Case Report Form for subject 204 in study CHL1/02-2006/M.
Please submit responses by COB Friday April 14, 2017. You may provide your responses via email, if possible, to expedite review. Please follow up with an official submission to your NDA. Feel free to contact me with any questions.

Kindly confirm receipt of this. Thank you.

Sincerely,
Selma Kraft PharmD.
Regulatory Health Project Manager
Division of Anesthesia, Analgesia, and Addiction Products (DAAAP)
Food and Drug Administration
Phone: 240.402.9700
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/s/

SELMA S KRAFT
04/11/2017
Dear Craig,

Please see comments below regarding Chloroprocaine 1% injection’s proposed container label:

1. The linear barcode containing the National Drug Code (NDC) is missing on the revised container label. The drug barcode is often used as an additional verification before drug administration in the inpatient setting; therefore, it is an important safety feature that should be part of the label. Therefore, we request you add the drug barcode to each individual container label as required per 21CFR 201.25(c)(2). Ensure the drug barcode is surrounded by enough white space to allow scanners to read the barcode properly in accordance with 21 CFR 201.25(c)(1)(i). The barcode should be placed in an area where it will not be damaged because it appears at the point of label separation (e.g. perforation). We note the Quick Response Code appears on the revised container label. The presence of multiple barcodes is confusing to healthcare providers.\(^a\) Therefore, we recommend you move the barcode that does not contain the NDC number to the side or the back panel of the container label, away from the barcode containing the NDC number, and present it in a size that does not compete with, distract from the presentation of other required or recommended information on the label.\(^b\)

2. Add the statement, “Each ml contains: 10 mg Chloroprocaine Hydrochloride SodiumChloride, Hydrochloric Acid 1N, Water for Injection” to be consistent with the statement present on the carton labeling.

References:

Please provide responses by Tuesday April 18, 2017. Kindly confirm receipt of this information request.

Thank you. Let me know if you have any questions.

Sincerely,

Selma Kraft PharmD.
Regulatory Health Project Manager
Division of Anesthesia, Analgesia, and Addiction Products (DAAAP)
Food and Drug Administration
Phone: 240.402.9700
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/s/

SELMA S KRAFT
04/07/2017
Dear Craig,

We have the following information requests (2 parts):

In the study report for study CHL/02-2004, you have indicated that 14 subjects required supplemental analgesia/anesthesia for the surgical procedure (page 36 of clinical study report). Provide the following information for each of the 14 subjects that required supplemental analgesia:

1. Chloroprocaine dose received.
2. Time of chloroprocaine administration, particularly in relation to time of start of the surgical procedure.
3. Start and end time of the surgical procedure (total length of surgical procedure).
4. All analgesic/anesthetic medications given, their doses, and the time of administration in relationship to the surgical procedure (before, during, or after).
5. Possible etiologies that would explain the need for supplemental analgesia/anesthesia that are specific to each subject.

Provide this information by COB Friday, March 31, 2017.

In addition, provide translated Case Report Forms for each subject in study CHL/02-2004.

Provide this information by COB Friday, April 7, 2017.

Please provide responses as indicated in each information request. You may provide your responses via email, if possible, to expedite review. Please follow up with an official submission to your NDA. Feel free to contact me with any questions. Kindly confirm receipt of this. Thank you.

Sincerely,
Selma Kraft PharmD.
Regulatory Health Project Manager
Division of Anesthesia, Analgesia, and Addiction Products (DAAAP)
Food and Drug Administration
Phone: 240.402.9700
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/s/

SELMA S KRAFT
03/28/2017
From: Steven Kinsley
To: ckruman@vpcint.com
Cc: Selma Kraft
Subject: NDA 208791 CMC Information Request 3-23-17
Date: March 23, 2017

Dear Craig,

I have received the following information request from our CMC review team. Please respond to the following with a submission to your NDA by Thursday, March 30, 2017.

1. We acknowledge your response dated 10 Mar 2017 and acknowledge that the solution expiry of 24 hours has been added to 3.2.P.5.3.2.9 Stability of Solutions Validation Report. However, please also add the expiry to the “Preparation of Solutions” section of the HPLC Protocol 3.2.P.5.2.8 Chloroprocaine HCl and Related Substances Assay by HPLC.

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

Best Regards,
Steve

Steven Kinsley, Ph.D.
Regulatory Business Process Manager

Office of Program and Regulatory Operations
U.S. Food and Drug Administration
Tel: 240-402-2773
Steven.Kinsley@fda.hhs.gov
From: Steven Kinsley  
To: ckruman@vpcint.com  
Cc: Selma Kraft  
Subject: NDA 208791 CMC Information Request 3-2-17  
Date: March 2, 2017

Dear Craig,

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

1. Module 3.2.P.8.2 Post–Approval Stability Protocol and Stability Commitment lists stability test intervals to be 0 m, 12 m, 24 m. Commit to performing stability testing at 0, 3, 6, 9, 12, 18 and 24 months as stated in ICH Q1A (R2) Section 2.2.6. Testing Frequency, “For products with a proposed shelf life of at least 12 months, the frequency of testing at the long term storage condition should normally be every 3 months over the first year, every 6 months over the second year, and annually thereafter through the proposed shelf life.” Provide a table of planned post-approval stability testing with the following format specifying what testing will be performed at each timepoint:

<table>
<thead>
<tr>
<th></th>
<th>Initial</th>
<th>3 Month</th>
<th>6 Month</th>
<th>9 Month</th>
<th>12 month</th>
<th>18 month</th>
<th>24 month</th>
</tr>
</thead>
<tbody>
<tr>
<td>Test A</td>
<td>X</td>
<td>X</td>
<td>X</td>
<td>X</td>
<td>X</td>
<td>X</td>
<td>X</td>
</tr>
<tr>
<td>Test B</td>
<td>X</td>
<td>X</td>
<td>X</td>
<td>X</td>
<td>X</td>
<td>X</td>
<td>X</td>
</tr>
<tr>
<td>Additional tests in following rows</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

2. We note a freeze thaw/temperature cycling study was not performed. Justify the absence of such study.

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

Best Regards,
Steve

Steven Kinsley, Ph.D.  
Regulatory Business Process Manager

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

U.S. FOOD & DRUG ADMINISTRATION
From: Steven Kinsley
To: ckruman@vpcint.com
Cc: Selma Kraft
Subject: NDA 208791 CMC Information Request 2-21-17
Date: February 21, 2017

Dear Craig,

I have received the following information requests from our CMC review team. Please respond to the following with a submission to your NDA by Tuesday, March 14, 2017.

1. In module 3.2.P.5.3 Validation of Analytical Procedures a Specificity (Stress Test) is described. Provide a table showing quantification of impurities and chloroprocaine in the forced degradation samples. List the total % degradation for each of the conditions: heat, light, acid, alkali and oxidant.

2. Provide peak purity values for chloroprocaine at the forced degradation condition with the highest total % degradation.

3. In module 3.2.P.5.3 Validation of Analytical Procedures stability of solutions testing was performed hours. Based on this data, add an appropriate expiry to the method for the standard and sample solutions in “Chloroprocaine HCl and Related Substances Assay by HPLC.

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

Best Regards,
Steve

Steven Kinsley, Ph.D.
Regulatory Business Process Manager

Office of Program and Regulatory Operations
U.S. Food and Drug Administration
Tel: 240-402-2773
Steven.Kinsley@fda.hhs.gov
We have the following Information Requests from our review team regarding NDA 208791:

**Non-Clinical Information Request:**
In your extractables studies that were performed to assess the risk of chemical contamination from manufacturing equipment materials, you have identified several compounds, including those shown below, at concentrations that could potentially lead to greater than 0.15 mcg/day exposure to patients based on the maximum recommended daily dose of your 1% Chloroprocaine solution product.

Although these levels are below the acceptable daily intake level of individual genotoxic impurities per the ICH M7 guidance, the safety of these individual compounds with respect to potential local effects in the intrathecal space still needs to be addressed. Therefore, you will need to submit the following information as soon as possible so that it can be reviewed during this NDA review cycle:

1. Measure the concentration of all the compounds identified in the extractable studies in the drug product by analyzing at least 3 different registration batches on stability testing using an analytical evaluation threshold (AET) that can detect any leachable that is present in the product at [●●●] mcg per day or higher in order to permit an adequate toxicological risk assessment. Based on the maximum daily dose volume of 5 mL of 1% Chloroprocaine per day and a safety concern threshold of [●●●] mcg/day, the AET would be [●●●] mcg/mL or [●●●] ppm.

2. If any compounds are identified in the drug product at above the level of detection, you will need to provide an adequate toxicological risk assessment that justifies the local safety of the compound in the context of exposure to neural tissues. The approach for toxicological evaluation of the safety of leachables must be based on good scientific principles and the potential daily exposure must be based on the maximum level of each leachable detected in long-term stability samples. Include copies of all referenced studies upon which a safety assessment is based.

   a. If you employ a Permissible Daily Exposure (PDE) assessment as described in ICH Q3C, provide justification for all safety factors employed.

   b. Published literature to support the safety of any compound rarely provides adequate detail of the study design and study results to permit a thorough independent evaluation of the data. Summary reviews, (e.g., BIBRA, CIR, HERA), although potentially useful to identify original source material, are not acceptable as the source material is not provided and the conclusions cannot be independently verified. Submission of any published study reports must be accompanied by a detailed comparison to...
modern toxicology study endpoints and any shortcomings of the study must be discussed and justification must be provided to support your assertion that these data are adequate to support the safety of your drug product formulation.

c. Safety justifications based on analogous compounds are also not acceptable unless you can provide adequate data to support your conclusions that a risk assessment based on one compound can be logically interpolated to represent an adequate safety evaluation for your leachable/extractable. This should include a detailed understanding of the absorption, distribution, metabolism, and elimination of the compounds and an adequate scientific bridge to interpolate a NOAEL for the novel leachable.

**Clinical Information Requests:**

3. Provide operating room anesthesia records for all subjects in studies CHL1/02-2014 and CHL1/02-2006/M, as well as study CHL1/02/2004 (if available). Provide an analysis of the individual records citing surgical procedure length, as well as, analgesia, anesthesia, and sedation adjuncts given in the operating room, that supports your proposed indication.

4. Provide an evidence-based rationale as to why the efficacy results from the nearly identical phase 2 studies, CHL1/02/2004 and CHL1/02-2014, differ.

5. Revise your ISE to include justification that the data for the length of surgical procedures from studies CHL1/02-2014 and CHL1/02-2006/M is sufficient to support your proposed indication

6. Provide data on time of all concomitant medications administration, in addition to the date, for all subjects in study CHL1/02-2006/M. If this data was already provided, indicate where in the application it can be located.

7. Your ISE states “a total of 123 related cases of anesthesia insufficient (40 serious cases and 83 non serious) have been reported from European post-marketing experience.” Provide a comprehensive summary of these reports. Your summary should include an analysis of these reports, as well as, their relevance to the proposed drug indication.

8. Indicate whether you possess the original data in the form of Case Report Forms for study CHL1/02/2004.

9. The study report for study CHL1/02-2004 states “Intraoperative analgesic supplementation was required in 7 patients (50%) in group 30 mg, 5 patients (33%) in group 40 mg and 2 patients (13%) in 50 mg group. In 7 out of the total 14 patients, supplementation was required for completion of the procedure because of insufficient duration of the spinal block (p=0.014). The supplementation was required after 40 minutes and the spinal block was thus considered inadequate for the designed surgical procedure.” This data was not fully incorporated into your ISE. Revise your ISE to include more detailed efficacy data for study CHL1/02-2004. In particular, you should include explanation for all cases where supplementary analgesics/anesthetics/sedation medications were required, the length of surgical procedures, the time and dose of all concomitant medications, and the relevance of the concomitant medications in relation to the time-course of the surgical procedure.

10. Your most recent labeling submission on November 25, 2016, contains indication 50mg dose of 1% Chloroprocaine.
Please send in your responses by **COB Monday February 13, 2016**, initially via email is fine. Follow up with an official submission to your NDA. Let me know as soon as possible if you are not able to meet this deadline. Kindly confirm the receipt of this email. Feel free to contact me with any questions. Thank you.

Sincerely,
Selma Kraft PharmD.
Regulatory Health Project Manager
Division of Anesthesia, Analgesia, and Addiction Products (DAAAP)
Food and Drug Administration
Phone: 240.402.9700
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/s/

SELMA S KRAFT
01/30/2017
From: Steven Kinsley  
To: ckruman@vpcint.com  
Cc: Selma Kraft  
Subject: NDA 208791 CMC Information Request 1-27-17  
Date: January 27, 2017  

Dear Craig,

I have received the following information request from our CMC review team. Please respond to the following with a submission to your NDA by Friday, February 3, 2017.

1. In Section 3.2.R.1.P.1 Blank Manufacturing Batch Records, there is mention of checking (b)(4)

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

Best Regards,

Steve

Steven Kinsley, Ph.D.
Regulatory Business Process Manager

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

FDA U.S. Food & Drug Administration
Dear Craig,

I have received the following information requests from our CMC review team. Please respond to the following with a submission to your NDA by Thursday, January 19, 2017.

2. In module 2.3.P, the report titled “Drug Product,” section 2.3.P.5.4 Batch Analyses, drug product manufacturing info is provided in the first table for batches 12101, 12102, 12103. In the table below analytical results are provided for batches 13225, 13226, 13227. Are there 6 registration batches? If so, provide the analytical results for batches 12101, 12102, 12103 and the manufacturing info for batches 13225, 13226, 13227. Clarify which batches the provided information applies to.

3. Module 3.2.P.5.5 Characterisation of Impurities states, [b] (4)

4. In modules 3.2.P.5.2.6 Chloride Assay and 3.2.P.5.3.1 Validation of Chloride Assay Method one of the reagents is listed as [b] (4)

5. Module 3.2.P.5.3.1 Validation of Chloride Assay Method is missing the limit of detection and limit of quantitation. Please show the limit of detection and limit of quantitation.

6. In module 3.2.P.5.2.8 Chloroprocaine HCl and Related Substances Assay by HPLC the equation for calculation of [b] (4) content is included. The equations for calculation of [b] (4) content are not included. Add the equations for calculation of method. Clarify why [b] (4) content to the standard solutions are prepared by weighing a known amount of reference standard but then not used to calculate the amount of [b] (4) present in the chromatogram. Provide data
showing quantitation of using the appropriate reference standards.

7. In module 3.2.P.5.2.8 clarify why no response factor is listed.

8. In module 3.2.P.5.3.2 Validation of HPLC Method for Chloroprocaine HCl and Related Compounds Assay the

Provide a chromatogram showing a properly integrated baseline and clarify if that changes peak purity results.

9. In module 3.2.P.5.3.2 Validation of HPLC Method for Chloroprocaine HCl and Related Compounds Assay the accuracy section states that samples were run at these concentrations,

Are the percentages listed based on the working concentration of chloroprocaine at 1mg/mL? Or are the percentages listed based on the working concentrations of the individual impurities? List the 3 different concentrations measured in units of mg/mL or mcg/mL.

10. In module 3.2.P.5.3.2 Validation of HPLC Method for Chloroprocaine HCl and Related Compounds Assay the repeatability section states, List the actual concentrations of the solutions in units of mg/mL or mcg/mL. For the unknown related substances solution in this section – is that a solution of dilute chloroprocaine?

11. In module 3.2.P.5.3.2 Validation of HPLC Method for Chloroprocaine HCl and Related Compounds Assay the intermediate precision section does not list acceptance criteria.

12. In module 3.2.P.5.3.2 Validation of HPLC Method for Chloroprocaine HCl and Related Compounds Assay the section on detection and quantitation limit provides a chromatogram showing measurement of signal to noise ratio of chloroprocaine. The chromatogram provided shows a signal to noise ratio of for a solution concentration of mg/mL. It is not clear how a detection limit of mcg/mL
and a quantitation limit of mcg/mL were determined in relation to the provided chromatogram. Show chromatograms or provide calculations to show how the detection and quantitation limit were determined. This same question applies.

13. In module 3.2.P.5.3.2 Validation of HPLC Method for Chloroprocaine HCl and Related Compounds Assay the section on robustness lists a solution containing chloroprocaine, but only provides results for the chloroprocaine. Provide the results for the other components in the solution.

14. Provide data collected from any tests involving drug product critical quality attributes performed during the photostability study.

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

Best Regards,
Steve

Steven Kinsley, Ph.D.
Regulatory Business Process Manager

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

We have reviewed your submission dated December 22, 2016, received on December 23, 3016, and have the following follow-up information request:

Update Module 5 of your NDA submission to incorporate study CHL1/02-2004, EudraCT Number: 2004-004822-29. Include study CHL1/02-2004 study report, protocol, protocol amendments and deviations, case report forms, adverse event listings, and all data sets. In addition, revise your Integrated Summary of Effectiveness (ISE) and Integrated Summary of Safety (ISS) to integrate and evaluate the results of study CHL1/02-2004 in combination with your other clinical studies presented in the NDA. An alternative to revising the ISS and ISE would be to provide a rationale of why you believe this is unnecessary.

Please provide your responses as soon as possible but no later than COB Monday 1/23/17 via email (attachment is fine) initially so we can expedite the review and then followed by an official submission to the NDA. Let me know if you are unable to meet this deadline. Feel free to contact me with any questions.

Thank you.

Sincerely,
Selma

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From: Elisabetta Donati [mailto:edonati@sintetica.com]
Sent: Thursday, December 22, 2016 4:26 AM
To: Kraft, Selma
Subject: NDA # 208791 - Filing Communication and e-mail Dec 15 Answers

Dear Selma,

Enclosed answer to the FDA filing communication dated November 8, 2016 as per our previous agreement and supportive documentation. Included in this response also answer to your e-mail dated Dec. 15,2016 (please see cover letter for details).
E-CTD sequence 0008 will follow through ESG by the beginning of January.

Please confirm the receipt of this e-mail and the enclosed files.

Thanks for your kind collaboration and assistance.

Best regards,

Elisabetta Donati
Scientific Affairs
Corporate Director
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SELMA S KRAFT
01/03/2017
Dear Craig,

I have received the following information requests from our CMC review team. Please respond to the following with a submission to your NDA by Thursday, January 12, 2017.

1. Your executed batch record, BRF 176 03, instructs the operators to set the range for filling from \[\text{mL} \] with a target of \[\text{mL} \] mL. Section 3.2.P.3.3.4.3 Filling Stage, lists the target fill volume at \[\text{mL} \] mL and a range of \[\text{mL} \] mL; clarify the discrepancy and list your commercial fill volume target and ranges.

2. The batch numbers provided for the executed batch record vs. data in other sections of the submission are not consistent. For example, your executed batch record, BRF 176 03, specifies the batch # as 15007, while section 3.2.P.5.4 lists results for batch numbers 12101, 12102, and 12013. Section 2.3.P.5.4 lists the drug product batch numbers as 13225, 13226, and 13227. Clarify the discrepancy in batch numbers and provide results to date for all executed validation, commercial, and stability batches to date that supports your submission.

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

Best Regards,
Steve

Steven Kinsley, Ph.D.
Regulatory Business Process Manager

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

We have the following information request:

Your phase 2 study CHL1/02-2014 (EudraCT Number: 2014-003778-17) conducted in Bologna, Italy in 2015, appears identical your previously performed the Phase 2 study CHL1/02-2004 (EudraCT Number: 2004-004822-29) that was conducted in Parma, Italy in 2005. Provide your rationale for repeating the Phase 2 study in 2015 after the completion of the Phase 3 study. Provide rationale for conducting study CHL1/02-2014 at a different study center than study CHL1/02-2004. In addition, identify the differences between the two studies.

Please respond by COB December 22, 2016, via email initially is fine. Follow up with an official submission to the NDA. Feel free to contact me with any questions.

Thank you.

Sincerely,
Selma Kraft PharmD.
Regulatory Health Project Manager
Division of Anesthesia, Analgesia, and Addiction Products (DAAAP)
Food and Drug Administration
Phone: 240.402.9700
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SELMA S KRAFT
12/15/2016
Dear Craig,

We have some follow up comments and information requests pertaining to the articles Sintetica has provided:

We have looked at the English translated articles by Gao et al. We have also noted that the publication does not indicate the bioanalytical methods specificity, accuracy and precision in terms of validation.

Your product may be different from Nesacaine and also the product used by Gao et al. How do the chloroprocaine formulations and concomitant medications (epinephrine) used in Gao et al. publications relate to Nesacaine, and your own product?

Do you have publications documenting PK data following use of Nesacaine? If not, how can PK data from a different product used in Gao et al., be implied as Nesacaine.”

Please provide response via email by Friday October 14, 2016. Please confirm receipt of email.

Thank you.
Selma

From: Elisabetta Donati [mailto:edonati@sintetica.com]
Sent: Tuesday, October 11, 2016 10:08 AM
To: Kraft, Selma
Cc: 'Craig Kruman - VPCI'; Marta Pinter; Barbara Piccagli
Subject: I: IR for NDA 208791 Chloroprocaine 1% Injection

Dear Selma,

Please find in attachment:
- the two requested original full articles (Gao et al., 2006 and 2007) and the related translation in English
- the word document entitled ‘Bioanalytical methodology employed in Gao et al. 2006 and 2007 and correlation with bioanalytical method employed by the Applicant in study CHL.102-2014 in terms of sensitivity, specificity, accuracy and precision’

A duplicate copy to the NDA will follow soon.
I remain at disposal should you need any additional information.

Best regards
Elisabetta

Elisabetta Donati
Scientific Affairs
Corporate Director
Hello again. Please see another information request received from the FDA below.

Craig

Begin forwarded message:

From: "Kraft, Selma" <Selma.Kraft@fda.hhs.gov>
Date: October 6, 2016 at 9:14:19 PM GMT+2
To: 'Craig Kruman - VPCI' <ckruman@vpcint.com>
Subject: IR for NDA 208791 Chloroprocaine 1% Injection

Dear Craig,

We are currently reviewing NDA 208791. We have the following clinical pharmacology information request:


Provide full articles for citation The pharmacokinetics and pharmacodynamics of chloroprocaine in epidural blockade. The Journal of Clinical Anesthesiology. 2007 (CNKI:SUN:LCMZ.0.2007-05-009)
Pharmacokinetics and pharmacodynamics of chloroprocaine with or without epinephrine for epidural blockade Chinese Journal of Anesthesiology. 2006-05.

If these are foreign language articles, translation has to be provided. In addition, identify the bioanalytical methodology employed in these publications and indicate how they relate bioanalytical methods you have employed in terms of sensitivity, specificity, accuracy and precision.

Reference ID: 4001211
Please provide this information via return email (attachment is fine) by **Monday October 17, 2016.** Please follow up with a duplicate copy to the NDA. Please confirm receipt of this email.

Thank you.

Sincerely,
Selma Kraft PharmD.
Regulatory Health Project Manager
Division of Anesthesia, Analgesia, and Addiction Products (DAAAP)
Food and Drug Administration
Phone: 240.402.9700
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SELMA S KRAFT
10/19/2016
Dear Craig,

We are currently reviewing NDA 208791. We have the following clinical pharmacology information request:


Provide full articles for citation The pharmacokinetics and pharmacodynamics of chloroprocaine in epidural blockade. The Journal of Clinical Anesthesiology. 2007 (CNKI:SUN:LCMZ.0.2007-05-009)
Pharmacokinetics and pharmacodynamics of chloroprocaine with or without epinephrine for epidural blockade Chinese Journal of Anesthesiology. 2006-05.

If these are foreign language articles, translation has to be provided. In addition, identify the bioanalytical methodology employed in these publications and indicate how they relate bioanalytical methods you have employed in terms of sensitivity, specificity, accuracy and precision.

Please provide this information via return email (attachment is fine) by **Monday October 17, 2016**. Please follow up with a duplicate copy to the NDA. Please confirm receipt of this email.

Thank you.

Sincerely,

Selma Kraft PharmD.
Regulatory Health Project Manager
Division of Anesthesia, Analgesia, and Addiction Products (DAAAP)
Food and Drug Administration
Phone: 240.402.9700
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селма s kraft
10/06/2016
Dear Craig,

During our preliminary review of your submitted labeling, we found that you did not provide a review and summary of the available clinical and nonclinical information to support the changes in the Pregnancy, Lactation, and Females and Males of Reproductive Potential sections of labeling.

**Resubmit the following information by 10/31/2016**

- a review and summary of available nonclinical information, including published literature regarding chloroprocaine injection use in pregnant and lactating animals and the effects of chloroprocaine injection on male and female animal fertility (include search parameters),
- a review and summary of all available published literature regarding chloroprocaine injection use in pregnant and lactating women and the effects of chloroprocaine injection on male and female fertility (include search parameters),
- a cumulative review and summary of relevant cases reported in your pharmacovigilance database (from the time of product development to present),
- an interim report of an ongoing pregnancy registry or a final report on a closed pregnancy registry *(if applicable)*,
- a revised labeling incorporating the above information (in Microsoft Word format) that complies with PLLR.


Please provide this information via return email (attachment is fine) initially so that we can expedite the review. Please follow up with a duplicate copy to the NDA. Please confirm receipt of this email.

Thank you.

Sincerely,

Selma Kraft PharmD.
Regulatory Health Project Manager
Division of Anesthesia, Analgesia, and Addiction Products (DAAAP)
Food and Drug Administration
Phone: 240.402.9700
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SELMA S KRAFT
10/06/2016
Dear Craig,

Please see the Information Request below and acknowledge receipt. The review team requests a response by 4 pm Eastern Standard Time on Monday, October 3, 2016. If you are unable to meet this timeline, please contact me right away and let me know.

1) Please indicate where in your NDA submission we can locate your rationale for assuming the applicability of foreign data to U.S. population/practice of medicine. Provide this information if not present in the NDA submission.

2) We have received your debarment certification. The certification is worded correctly and signed by the applicant. However, Sintetica SA is a foreign applicant, and the US Agent must also sign the certification. VPCI must co-sign the debarment certification.

Please provide this information via return email (attachment is fine) initially so that we can expedite the review. Please follow up with a duplicate hard copy to the NDA.

Thank you.

Sincerely,

Selma Kraft PharmD.
Regulatory Health Project Manager
Division of Anesthesia, Analgesia, and Addiction Products (DAAAP)
Food and Drug Administration
Phone: 240.402.9700

Reference ID: 3992328
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SELMA S KRAFT
09/29/2016