APPLICATION NUMBER:

208418Orig1s000

ADMINISTRATIVE and CORRESPONDENCE DOCUMENTS
# ACTION PACKAGE CHECKLIST

## APPLICATION INFORMATION

<table>
<thead>
<tr>
<th>NDA #</th>
<th>208418</th>
<th>NDA Supplement #</th>
<th>BLA #</th>
<th>BLA Supplement #</th>
<th>If NDA, Efficacy Supplement Type: (an action package is not required for SE8 or SE9 supplements)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Proprietary Name:</td>
<td></td>
<td>Established/Proper Name: Calcium Gluconate Injection, USP 10%</td>
<td>Dosage Form: injection</td>
<td></td>
<td>Applicant: Fresenius Kabi USA, LLC Agent for Applicant (if applicable):</td>
</tr>
<tr>
<td>RPM:</td>
<td>Meghna M. Jairath, Pharm.D.</td>
<td>Division: Division of Metabolism and Endocrinology Products</td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

### NDA Application Type:
- □ 505(b)(1)
- □ 505(b)(2)
- □ 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)

---

### Actions

- **Proposed action**
  - User Fee Goal Date is June 15, 2016

- **Previous actions (specify type and date for each action taken)**
  - □ AP  □ TA  □ CR  □ None

- **If accelerated approval or approval based on efficacy studies in animals, were promotional materials received?**
  - □ Received

- **Application Characteristics**
  - □ 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.

---

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

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

3. Answer all questions in all sections in relation to the pending application, i.e., if the pending application is an NDA or BLA supplement, then the questions should be answered in relation to that supplement, not in relation to the original NDA or BLA.
Review priority:  ☒ Standard  ☐ Priority
Chemical classification (new NDAs only):  Type 7- Drug Already Marketed without Approved NDA
(confirm chemical classification at time of approval)

☐ Fast Track
☐ Rolling Review
☐ Orphan drug designation
☐ Breakthrough Therapy designation

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

NDAs: Subpart H
☐ Accelerated approval (21 CFR 314.510)
☐ Restricted distribution (21 CFR 314.520)
Subpart I
☐ Approval based on animal studies

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

BLAs: Subpart E
☐ Accelerated approval (21 CFR 601.41)
☐ Restricted distribution (21 CFR 601.42)
Subpart H
☐ Approval based on animal studies

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

Comments:

- BLAs only: Is the product subject to official FDA lot release per 21 CFR 610.2 (approvals only)
  ☐ Yes  ☐ No

- Public communications (approvals only)

  - Office of Executive Programs (OEP) liaison has been notified of action
    ☐ Yes  ☐ No

  - Indicate what types (if any) of information were issued
    None
    ☐ FDA Press Release
    ☐ FDA Talk Paper
    ☐ CDER Q&As
    ☐ Other

- Exclusivity

  - Is approval of this application blocked by any type of exclusivity (orphan, 5-year NCE, 3-year, pediatric exclusivity)?
    ☒ No  ☐ Yes

  - If so, specify the type

- Patent Information (NDAs only)

  - Patent Information:
    Verify that form FDA-3542a was submitted for patents that claim the drug for which approval is sought.
    ☐ Verified
    ☐ Not applicable because drug is an old antibiotic.

 CONTENTS OF ACTION PACKAGE

 Officer/Employee List

- List of officers/employees who participated in the decision to approve this application and consented to be identified on this list (approvals only)
  ☐ Included

Documentation of consent/non-consent by officers/employees
  ☐ Included

Reference ID: 4116229
### Action Letters

- Copies of all action letters *(including approval letter with final labeling)*
  - Action(s) and date(s)
  - Approval-6/16/17

### Labeling

<table>
<thead>
<tr>
<th>Description</th>
<th>Included/Not Included</th>
</tr>
</thead>
<tbody>
<tr>
<td>Package Insert <em>(write submission/communication date at upper right of first page of PI)</em></td>
<td>Included/Not Included</td>
</tr>
<tr>
<td>Most recent draft labeling <em>(if it is division-proposed labeling, it should be in track-changes format)</em></td>
<td>Included/Not Included</td>
</tr>
<tr>
<td>Original applicant-proposed labeling</td>
<td>Included/Not Included</td>
</tr>
<tr>
<td>Medication Guide/Patient Package Insert/Instructions for Use/Device Labeling <em>(write submission/communication date at upper right of first page of each piece)</em></td>
<td>Medication Guide/Not Included</td>
</tr>
<tr>
<td>Most recent draft labeling <em>(if it is division-proposed labeling, it should be in track-changes format)</em></td>
<td>Included/Not Included</td>
</tr>
<tr>
<td>Original applicant-proposed labeling</td>
<td>Included/Not Included</td>
</tr>
<tr>
<td>Labels <em>(full color carton and immediate-container labels)</em> <em>(write submission/communication date on upper right of first page of each submission)</em></td>
<td>Included/Not Included</td>
</tr>
<tr>
<td>Proprietary Name</td>
<td>None was submitted by the sponsor</td>
</tr>
<tr>
<td>Acceptability/non-acceptability letter(s) <em>(indicate date(s))</em></td>
<td>RPM: 7/28/16</td>
</tr>
<tr>
<td>Review(s) <em>(indicate date(s))</em></td>
<td>DMFPA: 1/10/17; 11/22/16</td>
</tr>
<tr>
<td>Labeling reviews <em>(indicate dates of reviews)</em></td>
<td>DMPP/PLT (DRISK): None</td>
</tr>
<tr>
<td></td>
<td>OPDP: 6/1/17</td>
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<tr>
<td></td>
<td>SEALD: None</td>
</tr>
<tr>
<td></td>
<td>CSS: None</td>
</tr>
<tr>
<td></td>
<td>Product Quality None</td>
</tr>
<tr>
<td></td>
<td>Other: DPMH- 5/11/17</td>
</tr>
<tr>
<td></td>
<td>(maternal); 5/14/17 (peds)</td>
</tr>
</tbody>
</table>

### Administrative / Regulatory Documents

- RPM Filing Review*/Memo of Filing Meeting* *(indicate date of each review)*
  - 7/29/16
- All NDA 505(b)(2) Actions: Date each action cleared by 505(b)(2) Clearance Committee
- Cleared by the Clearance Committee via email on 6/8/17
- 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
  - 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) □ Yes □ No

- Pediatrics (approvals only)
  - Date reviewed by PeRC 4/26/2017 (PERC meeting)
  - 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) (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)
  - n/a

- Minutes of Meetings □ N/A
  - If not the first review cycle, any end-of-review meeting (indicate date of mtg)
  - Pre-NDA/BLA meeting (indicate date of mtg) □ No mtg
  - EOP2 meeting (indicate date of mtg) □ No mtg
  - Mid-cycle Communication (indicate date of mtg) □ N/A
  - Late-cycle Meeting (indicate date of mtg) □ N/A
  - Other milestone meetings (e.g., EOP2a, CMC focused milestone meetings) (indicate dates of mtgs) n/a

- Advisory Committee Meeting(s) □ No AC meeting
  - Date(s) of Meeting(s)

---

**Decisional and Summary Memos**

- Office Director Decisional Memo (indicate date for each review) □ None

- Division Director Summary Review (indicate date for each review) 6/15/17

- Cross-Discipline Team Leader Review (indicate date for each review) 6/9/17

- PMR/PMC Development Templates (indicate total number) □ None

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**Clinical**
<table>
<thead>
<tr>
<th><strong>Clinical Reviews</strong></th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td>• Clinical Team Leader Review(s) <em>(indicate date for each review)</em></td>
<td>☒ No separate review</td>
</tr>
<tr>
<td>• Clinical review(s) <em>(indicate date for each review)</em></td>
<td>5/26/17; 7/19/16</td>
</tr>
<tr>
<td>• Social scientist review(s) (if OTC drug) <em>(indicate date for each review)</em></td>
<td>☒ None</td>
</tr>
<tr>
<td><strong>Financial Disclosure reviews(s) or location/date if addressed in another review</strong> OR</td>
<td>No clinical studies were referenced. See clinical review dated 5/26/17 pg 10.</td>
</tr>
<tr>
<td>If no financial disclosure information was required, check here ☒ and include a review/memo explaining why not <em>(indicate date of review/memo)</em></td>
<td></td>
</tr>
<tr>
<td><strong>Clinical reviews from immunology and other clinical areas/divisions/Centers <em>(indicate date of each review)</em></strong></td>
<td>☒ None</td>
</tr>
<tr>
<td><strong>Controlled Substance Staff review(s) and Scheduling Recommendation <em>(indicate date of each review)</em></strong></td>
<td>☒ N/A</td>
</tr>
<tr>
<td><strong>Risk Management</strong></td>
<td></td>
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<tr>
<td>• REMS Documents and REMS Supporting Document <em>(indicate date(s) of submission(s))</em></td>
<td>☒ None</td>
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<tr>
<td>• REMS Memo(s) and letter(s) <em>(indicate date(s))</em></td>
<td></td>
</tr>
<tr>
<td>• Risk management review(s) and recommendations (including those by OSE and CSS) <em>(indicate date of each review and indicate location/date if incorporated into another review)</em></td>
<td></td>
</tr>
<tr>
<td><strong>OSI Clinical Inspection Review Summary(ies) <em>(include copies of OSI letters to investigators)</em></strong></td>
<td>☒ None requested</td>
</tr>
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</table>

<table>
<thead>
<tr>
<th><strong>Clinical Microbiology</strong></th>
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<tr>
<td>• Clinical Microbiology Team Leader Review(s) <em>(indicate date for each review)</em></td>
<td>☒ No separate review</td>
</tr>
<tr>
<td>• Clinical Microbiology Review(s) <em>(indicate date for each review)</em></td>
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<table>
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<tr>
<th><strong>Biostatistics</strong></th>
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<tr>
<td>• Statistical Division Director Review(s) <em>(indicate date for each review)</em></td>
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<tr>
<td>• Statistical Team Leader Review(s) <em>(indicate date for each review)</em></td>
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<tr>
<td>• Statistical Review(s) <em>(indicate date for each review)</em></td>
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<table>
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<tr>
<th><strong>Clinical Pharmacology</strong></th>
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<tbody>
<tr>
<td>• Clinical Pharmacology Division Director Review(s) <em>(indicate date for each review)</em></td>
<td>☒ No separate review</td>
</tr>
<tr>
<td>• Clinical Pharmacology Team Leader Review(s) <em>(indicate date for each review)</em></td>
<td>☒ No separate review</td>
</tr>
<tr>
<td>• Clinical Pharmacology review(s) <em>(indicate date for each review)</em></td>
<td>☒ None 2/11/17; 7/8/16</td>
</tr>
<tr>
<td>• OSI Clinical Pharmacology Inspection Review Summary <em>(include copies of OSI letters)</em></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).
<table>
<thead>
<tr>
<th>Nonclinical</th>
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<tbody>
<tr>
<td><strong>Pharmacology/Toxicology Discipline Reviews</strong></td>
<td></td>
</tr>
<tr>
<td>• ADP/T Review(s) <em>(indicate date for each review)</em></td>
<td>☒ No separate review</td>
</tr>
<tr>
<td>• Supervisory Review(s) <em>(indicate date for each review)</em></td>
<td>☒ No separate review</td>
</tr>
<tr>
<td>• Pharm/tox review(s), including referenced IND reviews <em>(indicate date for each review)</em></td>
<td>☐ None 5/11/17, 6/29/16</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 carc</td>
</tr>
<tr>
<td>• ECAC/CAC report/memo of meeting</td>
<td>☒ None 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>

<table>
<thead>
<tr>
<th>Product Quality</th>
<th>None</th>
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</thead>
<tbody>
<tr>
<td><strong>Product Quality Discipline Reviews</strong></td>
<td></td>
</tr>
<tr>
<td>• Tertiary review <em>(indicate date for each review)</em></td>
<td>☒ None</td>
</tr>
<tr>
<td>• Secondary review <em>(e.g., Branch Chief)</em> <em>(indicate date for each review)</em></td>
<td>☒ None</td>
</tr>
<tr>
<td>• Integrated Quality Assessment (contains the Executive Summary and the primary reviews from each product quality review discipline) <em>(indicate date for each review)</em></td>
<td>☐ None 5/17/17</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></td>
</tr>
<tr>
<td>☒ Categorical Exclusion <em>(indicate review date)</em> <em>(all original applications and all efficacy supplements that could increase the patient population)</em></td>
<td>5/15/17</td>
</tr>
<tr>
<td>☐ Review &amp; FONSI <em>(indicate date of review)</em></td>
<td></td>
</tr>
<tr>
<td>☐ Review &amp; Environmental Impact Statement <em>(indicate date of each review)</em></td>
<td></td>
</tr>
<tr>
<td><strong>Facilities Review/Inspection</strong></td>
<td></td>
</tr>
<tr>
<td>☒ Facilities inspections <em>(indicate date of recommendation)</em> <em>(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>
<tr>
<td>☐ Withhold recommendation</td>
<td></td>
</tr>
<tr>
<td>☐ Not applicable</td>
<td></td>
</tr>
</tbody>
</table>

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

Reference ID: 4116229
## Day of Approval Activities

<table>
<thead>
<tr>
<th>Task</th>
<th>Status</th>
</tr>
</thead>
<tbody>
<tr>
<td>For all 505(b)(2) applications:</td>
<td></td>
</tr>
<tr>
<td>• Check Orange Book for newly listed patents and/or exclusivity</td>
<td>☒ No changes</td>
</tr>
<tr>
<td>(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>n/a</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>n/a</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>n/a</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>n/a</td>
</tr>
<tr>
<td>Send approval email within one business day to CDER-APPROVALS</td>
<td>X Done</td>
</tr>
<tr>
<td>Take Action Package (if in paper) down to Document Room for scanning within two business days</td>
<td>Done</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/

MEGHNA M JAIRATH
06/24/2017
Hello,
This the final version of the label. Please do not make any further changes besides formatting. No language should be changed in the C/C and USPI besides what we have agreed upon. Please submit the labeling to the NDA ASAP.

Thanks,
Meghna

Good Morning Meghna!

Any news on the PI? I am almost ready to send the FPL submission, just waiting on the 'green light' for the PI.

Best Regards,
Raul R. Salmeron
Regulatory Specialist
Innovation & Development, Generics

Fresenius Kabi USA, LLC
Three Corporate Drive
Lake Zurich, Illinois 60047
T: +1 847-550-2939
F: +1 847-550-7121
C: 
raul.salmeron@fresenius-kabi.com
www.fresenius-kabi.us

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From: Raul.Salmeron@fresenius-kabi.com
Sent: Wednesday, June 14, 2017 5:23 PM
To: Jairath, Meghna
Subject: RE: USPI VS 4 clean and track changes NDA 208418

Getting ready! :-)

Best Regards,
Raul R. Salmeron
Regulatory Specialist
Innovation & Development, Generics
Fresenius Kabi USA, LLC
Three Corporate Drive
Lake Zurich, Illinois 60047
T: +1 847-550-2939
F: +1 847-550-7121
C: raul.salmeron@fresenius-kabi.com
www.fresenius-kabi.us

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---

From: "EXTERN Jairath, Meghna" <Meghna.Jairath@fda.hhs.gov>
To: "Raul.Salmeron@fresenius-kabi.com" <Raul.Salmeron@fresenius-kabi.com>
Date: 06/14/2017 04:19 PM
Subject: RE: USPI VS 4 clean and track changes NDA 208418

Just get it ready…hopefully I get my final clearance by tonight or tomorrow AM.

From: Raul.Salmeron@fresenius-kabi.com
Sent: Wednesday, June 14, 2017 5:17 PM
To: Jairath, Meghna
Subject: RE: USPI VS 4 clean and track changes NDA 208418

Fantastic Meghna! I am getting the FPL submission ready for Thursday. I'll email you as soon as we push it through the ESG.
Thank you for the update!
Hello,
I am still waiting for one more clearance. I think we agree with all of your changes. Please be ready to submit the USPI and C/C to NDA once I send you an email.

Thanks,
Meghna

Best Regards,
Raul R. Salmeron
Regulatory Specialist
Innovation & Development, Generics
Hi Meghna,

Attached are round 4 revisions.

Best Regards,
Raul R. Salmeron
Regulatory Specialist
Innovation & Development, Generics
Hello,
I am attaching a clean version and the track changes version of the USPI.

If you have no additional changes then please let me know via email.

Please respond to us by tomorrow morning, June 14, 2017.

Thanks,
Meghna

Reference ID: 4112363
This is a representation of an electronic record that was signed electronically and this page is the manifestation of the electronic signature.

/s/

MEGHNA M JAIRATH
06/15/2017

Reference ID: 4112363
Hello,
I am attaching a clean version and the track changes version of the USPI.

If you have no additional changes then please let me know via email.

Please respond to us by tomorrow morning, June 14, 2017.

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

/s/

MEGHNA M JAIRATH
06/13/2017
Hello,

Please view the attached label. Please accept the changes you agree with when responding. Please add comments in the bubble if you do not agree with the rationale.

Please revise the carton & container labels as well.
1. Revise the 10 mL and 50 mL container and carton labels to state “Single Dose Vial” and “Single Dose Vials”.
2. In the 10 mL container label, add “Discard unused portion” in front of “Do not freeze.”
3. In the 100 mL container and carton labels, add “Dispensed aliquots must be used immediately and cannot be stored. See insert for further details.”

Please do not submit a final label USPI and carton and container to NDA until we have a final agreement.

Please submit a response by **June 7, 2017**.

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

/s/

MEGHNA M JAIRATH
06/06/2017
Hello,
Please view the attached label. Please accept the changes you agree with when responding. Please add comments in the bubble if you do not agree with the rationale.

Please do not submit a final label to NDA until we have agree upon that.

Please submit a response by **May 31, 2017**.

Thanks,
Meghna
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/s/

MEGHNA M JAIRATH
05/26/2017
Hello,
Please view the attached label. Please accept the changes you agree with when sending this back. Please add comments in the bubble if you do not agree with your rationale.

Please do not submit a final label to NDA until we have agree upon that.

Please submit a response by **May 17, 2017**.

Thanks,
Meghna
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/s/

MEGHNA M JAIRATH
05/12/2017
Hello,

For the neonatal dosing recommendations, you reference the monographs listed below, but you did not submit them. Please submit pdf copies to the NDA. You do not need to submit the entire book, just the relevant pages and references, if applicable.

References not provided:

You can send me a courtesy email of the response.

Thanks,
Meghna
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/s/

MEGHNA M JAIRATH
04/21/2017
Hello,

Your proposed release specification limit for aluminum content in your drug product is NMT [redacted] and your observed levels of Al content in the exhibit batches are [redacted]. You have mentioned that the proposed specification limit for Aluminum is based on historical data generated from batches of currently marketed Calcium Gluconate Injection but you did not provide a safety justification.

a) Include a safety justification for your proposed Al content for review.

b) Provide the source and reason for the high levels of Al content in your drug product.

c) Explain all the necessary measures taken to reduce the Al content.

Thanks,
Meghna
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/s/

MEGHNA M JAIRATH
04/06/2017
Hello,
Please see the attached study you submitted to the NDA. There are some sort of artifact (black rectangles) obscuring Figures 1 and 3. Please submit another copy without the black rectangles.

Thanks,
Meghna
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/s/

MEGHNA M JAIRATH
03/20/2017
NDA 208418

Fresenius Kabi USA, LLC
Attention: Raul Salmeron
Regulatory Affairs Specialist
Three Corporate Drive
Lake Zurich, IL 60047

Dear Mr. Salmeron:

Please refer to your New Drug Application (NDA) dated and received, May 16, 2016, submitted under section 505(b) (2) of the Federal Food, Drug, and Cosmetic Act (FDCA) for calcium gluconate injection, USP 10%.

On February 10, 2017, we received your letter, a major amendment to this application. Therefore, we are extending the goal date by three months to provide time for a full review of the submission. The extended user fee goal date is June 16, 2017.

In addition, we are establishing a new timeline for communicating labeling changes and/or postmarketing requirements/commitments in accordance with “PDUFA REAUTHORIZATION PERFORMANCE GOALS AND PROCEDURES – FISCAL YEARS 2013 THROUGH 2017.” If major deficiencies are not identified during our review, we plan to communicate proposed labeling and, if necessary, any postmarketing requirement/commitment requests by May 23, 2017.

If you have any questions, call me at (301) 796-4267.

Sincerely,

Meghna M. Jairath, Pharm.D.
Regulatory Project Manager
Division of Metabolism and Endocrinology Products
Office of Drug Evaluation II
Center for Drug Evaluation and Research

Reference ID: 4060180
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/s/

MEGHNA M JAIRATH
02/23/2017
Information Request
NDA 208418

Hello,

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 (if applicable) information to support the changes in the Pregnancy, Lactation, and Females and Males of Reproductive Potential sections of labeling.

Please provide the following information by 12/16/16:
• a review and summary of available nonclinical information, including published literature regarding use of Calcium Gluconate injection in pregnant and lactating animals and their potential effects on mating and male and female fertility in animal studies (include search parameters),
• a review and summary of all available published literature regarding Calcium Gluconate injection use in pregnant and lactating women and the effects of Calcium Gluconate 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).


Please acknowledge the receipt of the this email. You can email me a courtesy copy of the response but an official copy should be submitted to the NDA.

Thanks,
Meghna
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/s/

MEGHNA M JAIRATH
12/12/2016
Information Request
NDA 208418

Hello,
We have the following comment below which needs a written response by December 5, 2016.

Delete [redacted] from the carton and
container labeling.

(b)(4)

Please acknowledge the receipt of this email. You can email me a courtesy copy of the response but an official copy should be submitted to the NDA.

Thanks,
Meghna
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/s/

MEGHNA M JAIRATH
12/01/2016
NDA 208418

FILING COMMUNICATION -
FILING REVIEW ISSUES IDENTIFIED

Fresenius Kabi USA, LLC
Attention: Raul Salmeron
Regulatory Affairs Specialist
Three Corporate Drive
Lake Zurich, IL 60047

Dear Mr. Salmeron:

Please refer to your New Drug Application (NDA) dated and received May 16, 2016, submitted pursuant to section 505(b)(2) of the Federal Food, Drug, and Cosmetic Act (FDCA), for calcium gluconate injection, USP 10%.

We have completed our filing review and have determined that your application is sufficiently complete to permit a substantive review. Therefore, in accordance with 21 CFR314.101(a), this application is considered filed 60 days after the date we received your application. The review classification for this application is Standard. Therefore, the user fee goal date is March 16, 2017.

We are reviewing your application according to the processes described in the Guidance for Review Staff and Industry: Good Review Management Principles and Practices for PDUFA Products. Therefore, we have established internal review timelines as described in the guidance, which includes the timeframes for FDA internal milestone meetings (e.g., filing, planning, mid-cycle, team and wrap-up meetings). Please be aware that the timelines described in the guidance are flexible and subject to change based on workload and other potential review issues (e.g., submission of amendments). We will inform you of any necessary information requests or status updates following the milestone meetings or at other times, as needed, during the process. If major deficiencies are not identified during the review, we plan to communicate proposed labeling and, if necessary, any postmarketing commitment requests by February 16, 2017.

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

Chemistry, Manufacturing, and Controls

1. In the Pharmaceutical Development, you state that the drug substance

   (b) (4)

   » Provide stability data to show the historical trend of this issue and safety information on the use of this product

   (b) (4)

Reference ID: 3965169
Information) and/or not diluted. Provide data to show the disposition of the drug

2. Your Quality Target Product Profile indicates that 100 mg/mL calcium gluconate is the target dosage strength. Explain how the quantitative composition of 94 mg of calcium gluconate and 4.5 mg of calcium saccharate tetrahydrate per mL was developed to reach the target dosage strength.

3. Provide historical batch data to support the product pH range of 6.0-8.2. Citing the USP monograph as justification for this wide range is not sufficient because the regulatory drug product specification should be product-specific.

4. The proposed labeling includes statements but these attributes are not included in the drug product specification. Explain the discrepancy. Provide historical batch data to support these two targets/limits.

5. Provide information to show that the primary (product-contact) container closure system meets requirements for leachables and extractables in the current USP <1> (official as of May 1, 2016). This information should include leachables data to support the step in the drug product manufacture as well as the 60-80 °C heating step in the Prescribing Information.

6. In the Pharmaceutical Development, you state that the drug product is a “super saturated solution” and the Prescribing Information includes instructions to heat the drug product to 60-80 °C. Provide data to support these instructions, including stability data and compatibility data when diluted with 5% dextrose, normal saline, and any other diluent included in the Prescribing Information.

7. Explain why the drug product was developed to be a “super saturated solution” that requires heating to a high temperature by the care provider.

8. Provide the location in the NDA of the elemental impurities risk assessment for the drug product as per ICH Q3D “Elemental Impurities”.

**Clinical**

9. Provide additional data to support safety in the pediatric population (age 1 month to 17 years). In general, the submitted safety database appears to be acceptable for the adult and neonatal (less than one month of age) populations. During review of the initial Pediatric Study Plan, we recommended that you submit all available data from published literature and hospital and other proprietary
databases available for research purposes to support the safe and effective use of calcium gluconate across the entire pediatric age range. The published literature and FAERS search you submitted do not appear to be sufficient. We recommend that you perform additional searches in automated databases (i.e. computerized databases containing medical care data available associated with hospitals, health maintenance organizations, commercial insurers or the U.S. Government), claims databases, and medical record databases to support safety in the pediatric population (age 1 month to 17 years) and submit your findings to the application.

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

**PRESCRIBING INFORMATION**

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

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

During our preliminary review of your submitted labeling, we have identified the following labeling issues and have the following labeling comments or questions:

**Under Table of Contents (TOC)**

1. In the TOC, all subsection headings must be indented and not bolded. The headings should be in title case [first letter of all words are capitalized except first letter of prepositions (for, of, to) and articles (a, an, the), or conjunctions (or, and)]. **Please change the first letter of the following words "in" and "with" to upper case.**

2. The section and subsection headings in the TOC must match the section and subsection headings in the FPI. **Please add the number "10" preceding "OVERDOSAGE".**
We request that you resubmit labeling (in Microsoft Word format) that addresses these issues by **August 19, 2016**.

The resubmitted labeling will be used for further labeling discussions. Use the SRPI checklist to correct any formatting errors to ensure conformance with the format items in regulations and guidances.

At the end of labeling discussions, use the SRPI checklist to ensure that the PI conforms with format items in regulations and guidances.

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

In the meantime, we encourage you to submit revised labeling that meets the half page requirement.

We acknowledge your request for a waiver of the requirement that the **Highlights** of Prescribing Information be limited to no more than one-half page. We will consider your request during labeling discussions. In the meantime, we encourage you to submit revised labeling that meets the half page requirement.

**PROMOTIONAL MATERIAL**

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

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

Alternatively, you may submit a request for advisory comments electronically in eCTD format. For more information about submitting promotional materials in eCTD format, see the draft Guidance for Industry (available at: [http://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/UCM443702.pdf](http://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/UCM443702.pdf)).
Do not submit launch materials until you have received our proposed revisions to the package insert (PI), and you believe the labeling is close to the final version.

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

REQUIRED PEDIATRIC ASSESSMENTS

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

This application triggers a requirement for a pediatric assessment under PREA since the proposed drug product contains a new active ingredient not previously approved for the proposed indication. We acknowledge an agreed initial pediatric study plan was included in your application at the time of submission.

ADDITIONAL COMMENTS FROM DIVISION OF PRESCRIPTION DRUGS, OFFICE OF COMPLIANCE

Thank you for seeking to comply with the Federal Food, Drug & Cosmetic Act by submitting an application for FDA approval of your product. When a company obtains FDA approval of a drug that had previously been marketed as an unapproved drug, the FDA typically evaluates whether other companies continue to market unapproved versions of the same product. If so, the Agency will generally seek to remove the unapproved products from the market following a transition period. The pace of this transition depends in part on a sponsor’s ability to meet market demand. More information on FDA’s current enforcement policy on unapproved drugs is explained in the policy document entitled: “Marketed Unapproved Drugs – Compliance Policy Guide, Sec. 440.100 – Marketed New Drugs Without Approved NDAs or ANDAs,” dated September 19, 2011. See: http://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/UCM070290.pdf

If you have any questions, call Meghna M. Jairath, Pharm.D., Regulatory Project Manager, at (301) 796-4267.
Sincerely,

{See appended electronic signature page}

Jean-Marc Guettier, M.D.
Director
Division of Metabolism and Endocrinology Products
Office of Drug Evaluation II
Center for Drug Evaluation and Research
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/s/

JEAN-MARC P GUETTIER
07/29/2016
NDA 208418

DEPARTMENT OF HEALTH AND HUMAN SERVICES

Food and Drug Administration
Silver Spring MD 20993

NDA ACKNOWLEDGMENT

Fresenius Kabi USA, LLC
Attention: Raul Salmeron
Regulatory Affairs Specialist
Three Corporate Dr.
Lake Zurich, IL 60047

Dear Mr. Salmeron:

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

Name of Drug Product: **Calcium Gluconate Injection, USP 10%**

Date of Application: **May 16, 2016**
Date of Receipt: **May 16, 2016**

Our Reference Number: **NDA 208418**

Unless we notify you within 60 days of the receipt date that the application is not sufficiently complete to permit a substantive review, we will file the application on **July 15, 2016**, in accordance with 21 CFR 314.101(a).

If you have not already done so, promptly submit the content of labeling [21 CFR: 14.50(l)(1)(i) in structured product labeling (SPL) format as described at [http://www.fda.gov/ForIndustry/DataStandards/StructuredProductLabeling/default.htm](http://www.fda.gov/ForIndustry/DataStandards/StructuredProductLabeling/default.htm). Failure to submit the content of labeling in SPL format may result in a refusal-to-file action under 21 CFR 314.101(d)(3). The content of labeling must conform to the content and format requirements of revised 21 CFR 201.56-57.

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

The NDA number provided above should be cited at the top of the first page of all submissions to this application. Send all submissions, electronic or paper, including those sent by overnight mail or courier, to the following address:
Secure email between CDER and applicants is useful for informal communications when confidential information may be included in the message (for example, trade secrets or patient information). If you have not already established secure email with the FDA and would like to set it up, send an email request to SecureEmail@fda.hhs.gov. Please note that secure email may not be used for formal regulatory submissions to applications.

If you have any questions, call me, at (301) 796-4267.

Sincerely,

{See appended electronic signature page}
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/s/

MEGHNA M JAIRATH
06/23/2016
Dear Commander Hamilton-Stokes,

I acknowledge receipt of your email. FK USA does not intend to use a proprietary name in the marketing of Calcium Gluconate Injection, USP, 10%. Therefore, FK USA will not be submitting a Request for Proprietary Name as an amendment to our pending application. If you have any further questions please feel free to contact me. Thank you.

Best Regards,
Raul R. Salmeron
Regulatory Specialist
Innovation & Development, Generics
Fresenius Kabi USA, LLC
Three Corporate Drive
Lake Zurich, Illinois 60047
T: +1 847-550-2939
F: +1 847-550-7120
C: raul.salmeron@fresenius-kabi.com
www.fresenius-kabi.us

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Dear Mr. Salmeron,

Please refer to your New Drug Application (NDA) dated and received May 16, 2016, submitted under section 505(b)(2) of the Federal Food, Drug, and Cosmetic Act for Calcium Gluconate Injection, USP, 10%. This email is to notify you that if you intend to market this product with a proprietary name, you must submit a...
Request for Proprietary Name Review as an amendment to your pending application.

A complete request for proprietary name review must be submitted per the Guidance (see attached).

If you have any additional questions regarding the Proprietary Name process, please do not hesitate to contact me.

Please acknowledge receipt of this email.

Kind regards,
Deveonne

Deveonne Hamilton-Stokes, RN, BSN, MA
Commander, United States Public Health Service
Safety Regulatory Project Manager
Office of Surveillance and Epidemiology
Food and Drug Administration
10903 New Hampshire Ave
White Oak Building 22 Room 4441
Silver Spring, MD 20993
Email: deveonne.hamilton-stokes@fda.hhs.gov
Phone: 301-796-2253

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/s/

DEVEONNE G HAMILTON-STOKES
06/03/2016