APPLICATION NUMBER:

208418Orig1s000

PRODUCT QUALITY REVIEW(S)
Recommendation:
APPROVAL
(This Recommendation includes the Overall Manufacturing Inspection Recommendation)

NDA 208418
Review #1
Review Date (see last page)

<table>
<thead>
<tr>
<th>Drug Name/Dosage Form</th>
<th>calcium gluconate injection</th>
</tr>
</thead>
<tbody>
<tr>
<td>Strength</td>
<td>100 mg/mL (presentations: 1g/10 mL, 5g/50 mL, and 10g/100 mL)</td>
</tr>
<tr>
<td>Route of Administration</td>
<td>IV injection</td>
</tr>
<tr>
<td>Rx/OTC Dispensed</td>
<td>Rx</td>
</tr>
<tr>
<td>Applicant</td>
<td>Fresenius Kabi USA, LLC</td>
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</table>

<table>
<thead>
<tr>
<th>SUBMISSION(S) REVIEWED</th>
<th>DOCUMENT DATE</th>
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<td>5/16/17</td>
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<td>0005</td>
<td>2/10/17</td>
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<td>0007</td>
<td>4/26/17</td>
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Quality Review Team

<table>
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<tr>
<th>DISCIPLINE</th>
<th>REVIEWER</th>
<th>DIVISION/OFFICE</th>
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<tbody>
<tr>
<td>Regulatory Business</td>
<td>Anika Lahnansingh</td>
<td>Regulatory Business Process</td>
</tr>
<tr>
<td>Process Manager</td>
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<td>Management I/OPRO</td>
</tr>
<tr>
<td>Application Technical Lead</td>
<td>Snong (Stu) Tran</td>
<td>New Drug Products II/ONDP</td>
</tr>
<tr>
<td>API</td>
<td>Benjamin Stevens/</td>
<td>New Drug API/ONDP</td>
</tr>
<tr>
<td></td>
<td>Donna Christner</td>
<td></td>
</tr>
<tr>
<td>Drug Product</td>
<td>Dhanakshmi Kasi/</td>
<td>New Drug Products II/ONDP</td>
</tr>
<tr>
<td></td>
<td>Danae Christodoulou</td>
<td></td>
</tr>
<tr>
<td>Process</td>
<td>Li Shan Hsieh/</td>
<td>Process Assessment II/OPF</td>
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<td></td>
<td>N. Chidambaram</td>
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<tr>
<td>Facility</td>
<td>Carl Lee/Juandria Williams</td>
<td>Inspectional Assessment/OPF</td>
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<tr>
<td>Biopharmaceutics</td>
<td>An-Chi Lu/Haritha Mandula</td>
<td>Biopharmaceutics/ONDP</td>
</tr>
<tr>
<td>Microbiology</td>
<td>Yuansha Chen/Neal Sweeney</td>
<td>Process Assessment II/OPF</td>
</tr>
</tbody>
</table>

Quality Review Data Sheet

1. RELATED/SUPPORTING DOCUMENTS:
   A. DMFs: Adequate (see p. 28 of Chapter II Drug Product)
   B. Other Documents: not applicable
2. CONSULTS: not applicable
Executive Summary

I. Recommendation and Conclusion on Approvability
The final OPQ recommendation is for Approval - including the Overall Manufacturing Inspection Recommendation.

II. Summary of Quality Assessment

A. Product Overview

This is a 505(b)(2) application for Calcium Gluconate Injection relying on published literature for information on safety and effectiveness (see CDTL’s review).

Each 1 mL provides 100 mg calcium gluconate (as 94 mg of calcium gluconate and 4.5 mg of calcium saccharate tetrahydrate) to yield a total of 9.3 mg elemental calcium. Calcium saccharate tetrahydrate is an excipient used as [see CDTL’s memo], which is acceptable per current USP monograph for Calcium Gluconate Injection.

The applicant’s request for waiver of in vivo bioavailability/bioequivalence studies to bridge this product to products used in the referenced literature is granted. An adequate scientific bridge was established by evidence showing that these calcium gluconate products are for IV injection and are 100% bioavailable. This product does not contain any ingredient that would affect the expected bioavailability.

Adequate evidence is provided to confirm the product sterility during the shelf life storage of an unopened container. The product does not contain an antimicrobial preservative; therefore, the product is labeled “single dose” and the in-use period of the to-be-administered diluted product is limited to four (4) hours.

The drug product quality controls include a limit of [see CDTL’s memo] ppb on aluminum, which would result in aluminum levels below the safety threshold of less than 5 mcg/kg/day for the pediatric populations. The risk of contamination is mitigated by analytical data showing levels below [see CDTL’s memo] ppb in the drug product, lower than the permitted daily exposure in ICH Q3D for pediatric use.

<table>
<thead>
<tr>
<th>Proposed Indication(s)</th>
<th>[see CDTL’s memo]</th>
</tr>
</thead>
<tbody>
<tr>
<td>Duration of Treatment</td>
<td>Short duration (a few days) [see CDTL’s memo]</td>
</tr>
<tr>
<td>Maximum Daily Dose</td>
<td>Dosing by body weight [see CDTL’s memo]</td>
</tr>
<tr>
<td>Alternative Methods of Administration</td>
<td>Calcium Gluconate Injection is diluted with 5% dextrose or normal saline prior to administration.</td>
</tr>
</tbody>
</table>

B. Quality Assessment Overview
**Drug Substance**
Calcium gluconate monohydrate is a white crystalline powder, sparingly (and slowly) soluble in water, freely soluble in boiling water, insoluble in almost all organic solvents.

\[
\text{Ca}^{2+} \quad \text{HO} \quad \text{OH} \quad \text{OH} \quad \text{OH} \quad \text{CO}_{2} \text{H}
\]

Molecular Formula: C\(_{12}\)H\(_{22}\)CaO\(_{14}\) H\(_{2}\)O  
Molecular Mass: 448.39

DMF is referenced for all CMC information on the drug substance. The specification is based on the USP monograph with the addition of Residual Solvents, Bioburden, and Bacterial Endotoxins. The DMF is currently adequate (review dated 2/14/17).

**Drug Product**
The drug product is Calcium Gluconate Injection, a sterile, preservative-free solution to be diluted with 5% Dextrose Injection, 0.9% Sodium Chloride Injection, (adequate compatibility data are provided) for intravenous injection. The product is packaged in three fill sizes: 10 mL, 50 mL, and 100 mL vials.

Each 1 mL provides 100 mg calcium gluconate (as 94 mg of calcium gluconate and 4.5 mg of calcium saccharate tetrahydrate) to yield a total of 9.3 mg elemental calcium per mL. Calcium saccharate tetrahydrate is an excipient used as (b)(4), which is acceptable per current USP monograph for Calcium Gluconate Injection.

Excipients: 4.5 mg of calcium saccharate tetrahydrate, hydrochloric acid and/or sodium hydroxide for pH adjustment (6.0 to 8.2), and sterile water for injection.

The manufacturing process consists of (b)(4) Critical quality attributes are established based on manufacturing experience.

The regulatory drug product specification is based on the USP monograph for the product, with the addition of description, aluminum, container/Closure Integrity, and degradation. The pH range of 6.0 to 8.2 is compendial and (b)(4) due to manufacturing contraints. The original labeling stated mOsmol/L”, which is incorrect and has been deleted from the PI; if necessary, it should state (b)(4) mOsmol/L” to reflect analytical data. The specification includes a limit of (b)(4) ppb on aluminum, which would result in aluminum levels below the safety threshold of less than 5 mcg/kg/day for the pediatric populations. The risk
of contamination is mitigated by analytical data showing levels below ppb in the drug product, lower than the permitted daily exposure in ICH Q3D for pediatric use.

Primary container closure system: The primary container closure system is a vial with a stopper. The USP monograph for this product does not require the use of type I glass. The vials have two different manufacturers, and both were included in the stability studies. Extractable/leachable information is provided for the packaging components. Adequate information is provided on extractables/leachables from the product-contact packaging components (see the Pharmacology Toxicology review for additional information on the safety risk). Compatibility is based on stability data.

Expiration Date & Storage Conditions: The long term shelf life is 24 months at room temperature. The product lacks an antimicrobial preservative; therefore, the in-use period of the to-be-administered diluted product is limited to four hours.

C. Special Product Quality Labeling Recommendation:
- Calcium Gluconate Injection lacks an antimicrobial preservative; therefore, the in-use period of the to-be-administered diluted product is limited to four hours.

D. Life Cycle Knowledge Information/ Final Risk Assessment:
- API: none
- Drug product: none
- Process: none
- Facilities: none
- Biopharmaceutics: none
- Microbiology: none

Application Technical Lead
Signature:
Suong Tr Tran-S

Suong (Su) Tran, Ph.D.
electronic signature also on the last page
CHAPTERS: Primary Quality Assessment

Chapter I: Drug Substance
Chapter II: Drug Product
Chapter III: Environmental Assessment
Chapter IV: Labeling
Chapter V: Process
Chapter VI: Facilities
Chapter VII: Biopharmaceutics
Chapter VIII: Microbiology
Attachment I: Final Risk Assessment (see last page of Executive Summary)
Product Background:

NDA/ANDA: NDA 208418

Drug Product Name / Strength: Calcium Gluconate Injection / 10% (100 mg/mL)

Route of Administration: Injection

Applicant Name: Fresenius Kabi USA, LLC

Review Summary:
The Applicant submits an NDA for Calcium Gluconate Injection, USP 10% (100 mg/mL). The Applicant seeks approval of this NDA via the 505(b)(2) regulatory pathway for the indication of for sterile, non-pyrogenic, supersaturated solution of calcium gluconate for intravenous (IV) use only. The Applicant markets Calcium Gluconate Injection, USP 10% which is currently an unapproved drug. The Applicant intends to rely on the clinical and nonclinical data contained in the peer reviewed scientific literature to support the approval of its proposed product.

The quantitative composition of the formulation for the proposed drug product is provided below:

<table>
<thead>
<tr>
<th>Ingredients</th>
<th>FK USA</th>
</tr>
</thead>
<tbody>
<tr>
<td>Calcium Gluconate, USP</td>
<td>100 mg/mL</td>
</tr>
<tr>
<td>Calcium Saccharate, USP</td>
<td>98 mg/mL</td>
</tr>
<tr>
<td>Water for Injection, USP</td>
<td>4.5 mg/mL</td>
</tr>
<tr>
<td>Hydrochloric Acid, NF</td>
<td>q.s.</td>
</tr>
<tr>
<td>Sodium Hydroxide, NF</td>
<td>As required to adjust pH</td>
</tr>
</tbody>
</table>

The Applicant requests to waive pharmacokinetic/bioavailability studies for the proposed adult and pediatric populations by submitting literature references.

List Submissions being reviewed (table):

Application 208418 - Sequence 0000 - 0000 (1) 05/16/2016 ORIG-1 /Multiple Categories/Subcategories
Application 208418 - Sequence 0002 - 0002 (3) 10/31/2016 ORIG-1 /Multiple Categories/Subcategories

Application 208418 - Sequence 0003 - 0003 (4) 11/07/2016 ORIG-1 /Quality/Quality Information

Highlight Key Outstanding Issues from Last Cycle: None

Concise Description Outstanding Issues Remaining: None

**BCS Designation**

Reviewer’s Assessment: This drug product is an intravenous drug product, therefore BCS classification is not applicable.

Solubility: n/a

Permeability: n/a

Dissolution: n/a

**Dissolution Method and Acceptance Criteria**

Reviewer’s Assessment: There is no dissolution for this injection drug product.

{Assess method development, method robustness, and criteria; modeling approach}

*Clinical relevance of dissolution method & acceptance criteria (e.g., IVIVR, IVIVC, In Silico Modeling, small scale in vivo)*

Reviewer’s Assessment: n/a

**Application of dissolution/IVIVC in QbD**

Reviewer’s Assessment: n/a

**MODIFIED RELEASE ORAL DRUG PRODUCTS –In-Vitro Alcohol Dose Dumping**
<table>
<thead>
<tr>
<th>Section</th>
<th>Reviewer’s Assessment</th>
</tr>
</thead>
<tbody>
<tr>
<td>Reviewer’s Assessment: n/a</td>
<td></td>
</tr>
<tr>
<td><strong>In-Vitro Soft-food Interaction Study</strong></td>
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<tr>
<td>Reviewer’s Assessment: n/a</td>
<td></td>
</tr>
<tr>
<td><strong>In-Vitro Release Testing (IVRT) for Semi-Solid Products</strong></td>
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<tr>
<td>Reviewer’s Assessment: n/a</td>
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<tr>
<td><strong>In-Vitro Permeation Testing (IVPT) for Transdermal/Topical Products</strong></td>
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<td>Reviewer’s Assessment: n/a</td>
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<tr>
<td><strong>In-Vitro Dissolution Testing for Abuse-deterrent Products</strong></td>
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<tr>
<td>Reviewer’s Assessment: n/a</td>
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<tr>
<td><strong>In-Vitro BE Evaluation for Pulmonary Products</strong></td>
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<td>Reviewer’s Assessment: n/a</td>
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<tr>
<td><strong>EXTENDED RELEASE DOSAGE FORMS –Extended Release Claim</strong></td>
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<tr>
<td>Reviewer’s Assessment: n/a</td>
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<tr>
<td><strong>Bridging of Formulations</strong></td>
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</tr>
<tr>
<td>Reviewer’s Assessment: n/a</td>
<td></td>
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</tbody>
</table>
Biowaiver Request

Reviewer’s Assessment:

The Applicant requested that the clinical efficacy and safety data documented in the medical textbooks and medical literature is sufficient to support the submission of Calcium Gluconate Injection for the [(b)(4)] in the adult population without conducting additional clinical studies in the PIND meeting held on 11/21/2011. In addition, the Applicant requested that no additional pharmacokinetic/bioavailability studies would be required and information from medical textbooks and medical literature would be sufficient to support the NDA submission of Calcium Gluconate Injection, USP 10% via 505(b)(2). Therefore, the Applicant requests to waive pharmacokinetic/bioavailability studies for the proposed adult and pediatric populations.

The original NDA submission did not include the information of osmolality and pH of the proposed drug product. Therefore, an Information Request (IR) was sent on 10/7/2016 to request the Applicant to submit the abovementioned information, as well as the following:

“Provide a table with side-by-side comparison of the active and inactive ingredients between your proposed formulation and the formulations (any that is available to you) cited in the published literature in support of the pivotal clinical data. Provide justification for any differences between the two formulations and to demonstrate that the difference for each active and/or inactive ingredient would not affect the pharmacokinetic performance towards any difference in clinical safety and/or efficacy outcome. Indicate specific published literature articles with pivotal studies conducted with your proposed formulation. You may include literature data and/or your study reports to support your biowaiver request.” The Applicant responded on 11/7/2016 with the following information.

With the product density of [(b)(4)] g/mL, the measured osmolality of the six exhibit lots range between [(b)(4)] mOsm/kg. The measured pH of the six exhibit lots range between [(b)(4)] , which is within the proposed pH limit of 6.0 – 8.2 for Calcium Gluconate Injection, USP 10% drug product.

In this NDA, the Applicant cited six published randomized studies to support the efficacy and safety of the proposed product. Among the six studies, none used the proposed Calcium Gluconate Injection USP, 10% product. However, because the active pharmaceutical ingredient is calcium, an electrolyte which is identical among formulations and is not metabolized, the Applicant states that the differences among formulations are minimal and will not affect the activity of calcium when administered intravenously.
The side-by-side comparison between the Applicant’s proposed formulation and the formulations cited in the published literature in support of the pivotal clinical data is presented below in Table 1:

Table 1: Summary of Formulations from the Applicant’s Calcium Gluconate Injection USP, 10% and the Calcium Gluconate Injection Formulations Used in the Pivotal Studies

<table>
<thead>
<tr>
<th>Formulation of Fresenius Kabi’s Calcium Gluconate Injection USP, 10% (Amount/mL)</th>
<th>Composition of Calcium Gluconate Injectable Solutions Used in the Pivotal Studies (Amount/mL)</th>
<th>Comment</th>
</tr>
</thead>
</table>
| • Each mL of the Fresenius Kabi USA drug product provides 9.3 mg elemental calcium (0.465 mEq/mL), equivalent to 100 mg calcium gluconate.  
• Each mL of the Fresenius Kabi USA drug product contains:  
  o 94 mg of calcium gluconate  
  o 4.5 mg of calcium saccharate tetrahydrate  
  o Hydrochloric acid and/or sodium hydroxide for pH adjustment (6.0 – 8.2)  
  o Water for Injection USP, q.s. | (PORCELLI, Jr., 1995)  
Calcium gluconate 100 mg/mL | Similar concentration of calcium gluconate: 100 mg/mL |
| • Each mL of the Fresenius Kabi USA drug product provides 9.3 mg elemental calcium (0.465 mEq/mL), equivalent to 100 mg calcium gluconate.  
• Each mL of the Fresenius Kabi USA drug product contains:  
  o 94 mg of calcium gluconate  
  o 4.5 mg of calcium saccharate tetrahydrate  
  o Hydrochloric acid and/or sodium hydroxide for pH adjustment (6.0 – 8.2)  
  o Water for Injection USP, q.s. | (SCOTT, 1984)  
No information for calcium gluconate formulation was provided. | NA |
| • Each mL of the Fresenius Kabi USA drug product provides 9.3 mg elemental calcium (0.465 mEq/mL), equivalent to 100 mg calcium gluconate.  
• Each mL of the Fresenius Kabi USA drug product contains:  
  o 94 mg of calcium gluconate  
  o 4.5 mg of calcium saccharate tetrahydrate  
  o Hydrochloric acid and/or sodium hydroxide for pH adjustment (6.0 – 8.2)  
  o Water for Injection USP, q.s. | (BROWN, 1981)  
Calcium gluconate solution containing 9% elemental calcium (equivalent to 9 mg elemental calcium/100 mg calcium gluconate) | Similar amount of elemental calcium per mL |
<table>
<thead>
<tr>
<th>Formulation of Fresenius Kabi’s Calcium Gluconate Injection USP, (Amount/mL)</th>
<th>Composition of Calcium Gluconate Injectable Solutions Used in the Pivotal Studies (Amount/mL)</th>
<th>Comment</th>
</tr>
</thead>
</table>
| USA drug product contains:  
- 94 mg of calcium gluconate  
- 4.5 mg of calcium saccharate tetrahydrate  
- Hydrochloric acid and/or sodium hydroxide for pH adjustment (6.0 – 8.2)  
- Water for Injection USP, q.s. | (8.94 mg elemental calcium/mL) | Similar amount of elemental calcium per mL |
| USA drug product provides 9.3 mg elemental calcium (0.465 mEq/mL), equivalent to 100 mg calcium gluconate. | (MARTIN, 1990)  
Calcium gluconate solution yielded approximately 0.453 mEq/mL calcium after dissociation | |

As presented in the published studies  
Calcium saccharate = calcium glutarate; NA = not applicable; q.s = quantity required; USP = United States Pharmacopoeia.

With the differences in formulation used in the referenced studies and the proposed drug product, the Applicant proposed the following justification:

1. Since calcium gluconate is an IV product, similar 100% bioavailability is expected between the proposed drug product and those products used in the published studies.
2. Calcium gluconate IV injection formulations dissociate completely to provide ionized calcium in plasma. The release of ionized calcium from IV administration of calcium gluconate formulations is direct and is not affected by the first pass through the liver or by formulations (Bull, 1980; Heining, 1984; Martin, 1990).

3. Calcium, the active pharmaceutical ingredient of calcium gluconate products, is an electrolyte and does not undergo direct metabolism.

4. Both ionized calcium and gluconate are normal constituents of the body fluids. Saccharate (glutarate) from calcium saccharate, is also a normal constituent of the body. Gluconate and saccharate have no impact on the efficacy or safety of calcium gluconate IV solutions. Calcium saccharate was not used in the referenced literature, however, calcium from calcium saccharate in the proposed drug product may not be significant since the amount of calcium saccharate is minimal (4.5%). For details of calcium saccharate, please refer to the CMC review.

Reviewer’s comments:

The Applicant has established a scientific bridge between the proposed formulation and the formulations used in the literature studies. The proposed formulation will be administered as an intravenous solution and does not contain any ingredients that are expected to affect the bioavailability of the proposed product. In addition, the Clinical Pharmacology reviewer, Dr. Renu Singh, recommended approval from clinical pharmacology perspective (review in DARRTS, dated 2/11/2017). Therefore, published literature is adequate to demonstrate bioavailability of the proposed product.

From the Biopharmaceutics perspective, the Applicant has provided adequate information to waive the requirement for the submission of evidence of in vivo bioavailability or bioequivalence for the proposed drug product. A bridge between the proposed drug product and the LD has been established in accordance with 21 CFR 320.24(b)(6) regulation.

NDA 208418 for Calcium Gluconate Injection, USP 10% (100 mg/mL), is recommended for approval.

Regional Information

Comparability Protocols

Reviewer’s Assessment:
Post-Approval Commitments

Reviewer’s Assessment:

Lifecycle Management Considerations

List of Deficiencies: None

Primary Biopharmaceutics Reviewer Name and Date:

An-Chi Lu, M.S., Pharm.D., 4/7/2017.

Secondary Reviewer Name and Date (and Secondary Summary, as needed):
Haritha Mandula, Ph.D., 4/7/2017.
CHAPTER VIII: Microbiology
MICROBIOLOGY

Product Background:

NDA: 208418

Drug Product Name / Strength: Calcium Gluconate Injection, 100 mg/mL, packaged as 10 mL in 10 mL vial; 50 mL in 50 mL vial; and 100 mL in 100 mL vial, pharmacy bulk.

Route of Administration: IV

Applicant Name: Fresenius Kabi USA, LLC

Manufacturing Site:
Fresenius Kabi USA, LLC (FK USA)
3159 Staley Road
Grand Island, New York 14072 USA

Method of Sterilization: [redacted]

Review Summary: The submission is recommended for approval on the basis of sterility assurance.

List Submissions being reviewed (table):

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<th>Submitted</th>
<th>Received</th>
<th>Assigned to Reviewer</th>
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<tr>
<td>12/9/2016</td>
<td>12/9/2016</td>
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Highlight Key Outstanding Issues from Last Cycle: N/A

Concise Description Outstanding Issues Remaining: N/A. The submission is recommended for approval on the basis of sterility assurance.

1. REVIEW OF COMMON TECHNICAL DOCUMENT-QUALITY (CTD-Q) MODULE 3.2: BODY OF DATA

   P DRUG PRODUCT
   P.1 Description of the Composition of the Drug Product

   • Drug product composition –
### Quality Assessment

<table>
<thead>
<tr>
<th>Ingredient</th>
<th>Content per mL</th>
<th>Function</th>
</tr>
</thead>
<tbody>
<tr>
<td>Calcium Gluconate, monohydrate</td>
<td>98.0 mg/mL</td>
<td>API</td>
</tr>
<tr>
<td>Calcium Saccharate, tetrahydrate</td>
<td>4.5 mg/mL</td>
<td></td>
</tr>
<tr>
<td>Hydrochloric Acid / Sodium Hydroxide</td>
<td></td>
<td>pH Adjuster</td>
</tr>
<tr>
<td>WFI</td>
<td>Q.S.</td>
<td></td>
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</tbody>
</table>

#### Description of Container Closure System

<table>
<thead>
<tr>
<th>Configuration</th>
<th>Component</th>
<th>Description</th>
<th>Manufacturer</th>
</tr>
</thead>
<tbody>
<tr>
<td>10 mL</td>
<td>Vial</td>
<td>10 cc, plastic</td>
<td>(b)(4)</td>
</tr>
<tr>
<td></td>
<td>Stopper</td>
<td></td>
<td>(b)(4)</td>
</tr>
<tr>
<td></td>
<td>Seal</td>
<td></td>
<td>(b)(4)</td>
</tr>
<tr>
<td>50 mL</td>
<td>Vial</td>
<td>50 cc, plastic</td>
<td>(b)(4)</td>
</tr>
<tr>
<td></td>
<td>Stopper</td>
<td></td>
<td>(b)(4)</td>
</tr>
<tr>
<td></td>
<td>Seal</td>
<td></td>
<td>(b)(4)</td>
</tr>
<tr>
<td>100 mL</td>
<td>Vial</td>
<td>100 cc, plastic,</td>
<td>(b)(4)</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>(b)(4)</td>
</tr>
</tbody>
</table>

**Reviewer’s Assessment:** ADEQUATE
Reviewer’s Assessment: ADEQUATE

P.8.3 Stability Data
24 month stability data were provided for lot # (s) R343-037 (10 mL), R343-038 (10 mL), R343-039 (50 mL), R343-040 (50 mL), R343-020 (100 mL), R343-021 (100 mL). Endotoxins were [REDACTED]. CCIT met criteria for all lots.

Reviewer’s Assessment: ADEQUATE

R REGIONAL INFORMATION
R.1 Executed Batch Record
Executed lot # (s): R343-037 (10 mL/vial), R343-038 (10 mL/vial), R343-039 (50 mL/vial), R343-040 (50 mL/vial), R343-020 (100 mL/vial), R343-021 (100 mL/vial).

Note to reviewer: [REDACTED]

Reviewer’s Assessment: ADEQUATE

R.2 Comparability Protocol – No CP was included in the application.

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

A. PACKAGE INSERT
(1.14.1)

Store at 20° to 25°C; Route of administration: IV; Container: 10 ml fill and 50 mL fill [REDACTED]. 100 mL fill is Pharmacy Bulk. Calcium Gluconate Injection
should be diluted with 5% dextrose or saline prior to administration. There is no post dilution storage time indicated.

Pharmacy Bulk
- Product is to be dispensed and administered within 4 hours.

Reviewer’s Assessment: ADEQUATE

List of Deficiencies: None

Primary Microbiology Reviewer Name and Date:

Yuansha Chen, Ph.D.
CDER/OPQ/OPF/DMA
12/13/2016

Secondary Reviewer Name and Date (and Secondary Summary, as needed):

Neal J. Sweeney, Ph.D.
CDER/OPQ/OPF/DMA
1/13/2017
CHAPTER IX: Additional Quality Discipline

n/a
ATTACHMENT I: Final Risk Assessments

See Executive Summary