CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

210906Orig1s000

OTHER REVIEW(S)

MEMORANDUM

REVIEW OF REVISED LABEL AND LABELING

Division of Medication Error Prevention and Analysis (DMEPA)

Office of Medication Error Prevention and Risk Management (OMEPRM)

Office of Surveillance and Epidemiology (OSE)

Center for Drug Evaluation and Research (CDER)

*** This document contains proprietary information that cannot be released to the public***

Date of This Review:	October 29, 2018
Requesting Office or Division:	Division of Metabolism and Endocrinology Products (DMEP)
Application Type and Number:	NDA 210906
Product Name and Strength:	Calcium Gluconate in Sodium Chloride injection, 20 mg per mL
Total Product Strength:	1,000 mg per 50 mL and 2,000 mg per 100 mL
Applicant/Sponsor Name:	HQ Specialty Pharma Corporation
FDA Received Date:	October 29, 2018
OSE RCM #:	2017-2005-1
DMEPA Safety Evaluator:	Susan Rimmel, PharmD
DMEPA Team Leader (Acting):	Teresa McMillan, PharmD

1 PURPOSE OF REVIEW

The Division of Metabolism and Endocrinology Products (DMEP) requested that we review the revised container labels (infusion bag and aluminum overwrap) and carton labeling for Calcium Gluconate in Sodium Chloride injection 20 mg/mL (Appendix A) to determine if it is acceptable from a medication error perspective. The revisions are in response to recommendations that we made during a previous label and labeling review.[a]

We note the following additional revisions to the container labels and carton labeling:

- The product title was revised from (b) (4) to "Calcium Gluconate in Sodium Chloride injection."
- The strength expression was revised from:
  - "1,000 mg/50 mL (20 mg/mL)" to "1,000 mg per 50 mL (20 mg per mL)."
  - "2,000 mg/100 mL (20 mg/mL)" to "2,000 mg per 100 mL (20 mg per mL)."
- The total elemental calcium per infusion bag was added as follows:
  - 93 mg (4.65 mEq) for the 1,000 mg per 50 mL (20 mg per mL) strength
  - 186 mg (9.3 mEq) for the 2,000 mg per 100 mL (20 mg per mL) strength

2 CONCLUSIONS

The revised container labels and carton labeling for Calcium Gluconate in Sodium Chloride injection is acceptable from a medication error perspective. We have no further recommendations at this time.

2 Page(s) of Draft Labeling have been Withheld in Full as b4 (CCI/TS) immediately following this page

[a] Rimmel S. Label and Labeling Review for Calcium Gluconate in Sodium Chloride (NDA 210906). Silver Spring (MD): FDA, CDER, OSE, DMEPA (US); 2018 OCT 24. RCM No.: 2017-2005.

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/s/

SUSAN RIMMEL
10/29/2018

TERESA S MCMILLAN
10/29/2018

FOOD AND DRUG ADMINISTRATION
Center for Drug Evaluation and Research
Office of Prescription Drug Promotion

****Pre-decisional Agency Information****

Memorandum

Date: October 25, 2018

To: Marina Zemskova, M.D., Medical Officer
Division of Metabolism and Endocrinology Products (DMEP)

Meghna Jairath, Project Manager, (DMEP)

Monika Houstoun, Associate Director for Labeling, (DMEP)

From: Charuni Shah, Regulatory Review Officer
Office of Prescription Drug Promotion (OPDP)

CC: Melinda McLawhorn, Team Leader, OPDP

Subject: OPDP Labeling Comments for CALCIUM GLUCONATE IN SODIUM CHLORIDE injection, for intravenous use

NDA: 210906

In response to DMEP's consult request dated October 25, 2017, OPDP has reviewed the proposed product labeling (PI) for a 505(b)(2) application for CALCIUM GLUCONATE IN SODIUM CHLORIDE injection, for intravenous use (calcium gluconate).

PI: OPDP's review of the proposed labeling is based on the draft PI and submitted electronically by the Division of Metabolism and Endocrinology on October 11, 2018, and is provided below.

Thank you for your consult. If you have any questions, please contact Charuni Shah at (240) 402-4997 or charuni.shah@fda.hhs.gov.

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/s/

CHARUNI P SHAH
10/25/2018

LABEL AND LABELING REVIEW
Division of Medication Error Prevention and Analysis (DMEPA)
Office of Medication Error Prevention and Risk Management (OMEPRM)
Office of Surveillance and Epidemiology (OSE)
Center for Drug Evaluation and Research (CDER)

*** This document contains proprietary information that cannot be released to the public***

Date of This Review:	October 24, 2018
Requesting Office or Division:	Division of Metabolism and Endocrinology Products (DMEP)
Application Type and Number:	NDA 210906
Product Name and Strength:	Calcium Gluconate injection, 20 mg/mL
Total Product Strength:	1,000 mg/50 mL and 2,000 mg/100 mL
Product Type:	Single Ingredient
Rx or OTC:	Rx
Applicant/Sponsor Name:	HQ Specialty Pharma Corporation
FDA Received Date:	September 29, 2017
OSE RCM #:	2017-2005
DMEPA Safety Evaluator:	Susan Rimmel, PharmD
DMEPA Team Leader (Acting):	Teresa McMillan, PharmD

1 PURPOSE OF REVIEW

The Division of Metabolism and Endocrinology Products (DMEP) consulted us to evaluate the Prescribing Information (PI), container labels (infusion bag and aluminum overwrap), and carton labeling for Calcium Gluconate injection 20 mg/mL, available as 1,000 mg/50 mL and 2,000 mg/100 mL, submitted under NDA 210906 on September 29, 2017. This 505(b)(2) is based upon the reference listed drug (RLD) Calcium Gluconate (NDA 208418), which is available in vials.

2 MATERIALS REVIEWED

We considered the materials listed in Table 1 for this review. The Appendices provide the methods and results for each material reviewed.

Table 1. Materials Considered for this Label and Labeling Review

Material Reviewed	Appendix Section (for Methods and Results)
Product Information/Prescribing Information	A
Previous DMEPA Reviews	B
Human Factors Study	C – N/A
ISMP Newsletters	D – N/A
FDA Adverse Event Reporting System (FAERS)*	E – N/A
Other	F – N/A
Labels and Labeling	G

N/A=not applicable for this review
*We do not typically search FAERS for our label and labeling reviews unless we are aware of medication errors through our routine postmarket safety surveillance

3 FINDINGS AND RECOMMENDATIONS

Tables 2 and 3 below include the identified medication error issues with the submitted PI, container labels, and carton labeling, DMEPAs rationale for concern, and the proposed recommendation to minimize the risk for medication error.

3.1 TABLE 2: IDENTIFIED ISSUES AND RECOMMENDATIONS FOR THE DIVISION OF METABOLISM AND ENDOCRINOLOGY PRODUCTS (DMEP)

Highlights of Prescribing Information (PI)			
Dosage and Administration			
	IDENTIFIED ISSUE	RATIONALE FOR CONCERN	RECOMMENDATION
1.	The proposed product, contained in an infusion bag, should not be diluted. We note that currently marketed calcium gluconate injection products, contained in vials, must be diluted.	Healthcare professionals may be unaware or confused by this change in preparation and administration of the proposed products (do not dilute) compared to currently marketed products (must dilute).	Add a precautionary statement that calcium gluconate in the infusion bag should not be diluted.
Dosage Forms and Strengths			
	IDENTIFIED ISSUE	RATIONALE FOR CONCERN	RECOMMENDATION
2.	The strength is presented as a large dose and does not include a comma.	Users may misinterpret the strength expression of large doses if a comma is not present, such as ten-thousands interpreted as thousands (e.g., 10000 mg vs. 1000 mg).	Add a comma to the total product strength expression, such as: • Revise "Calcium gluconate (1000 mg/50 mL)" to "Calcium gluconate 1,000 mg/50 mL" • Revise "Calcium gluconate (2000 mg/100 mL)" to "Calcium gluconate 2,000 mg/100 mL"
3.	The concentration per milliliter (mL) is missing.	Important information relevant for dosing considerations should be readily available to the healthcare professional.	Add the concentration per mL after the total product strength expression, such as: • Revise "Calcium gluconate (1000 mg/50 mL)" to "Calcium gluconate 1,000 mg/50 mL (20 mg/mL)" • Revise "Calcium gluconate (2000 mg/100 mL)" to "Calcium gluconate 2,000 mg/100 mL (20 mg/mL)"

Full PI			
Section 2 Dosage and Administration, 2.2 Recommended Dosage			
	IDENTIFIED ISSUE	RATIONALE FOR CONCERN	RECOMMENDATION
1.	The unit of measure is not included after each numerical expression.	Healthcare professionals may misinterpret the recommended dosage if the unit of measure is not clearly defined in areas where dosing is described.	Add the unit of measure after each numerical expression, such as revise "100…" to "100 mg/kg…"
2.	The recommended dosage range is expressed with a hyphen (-).	Error-prone symbols where dosing is described can lead to confusion and misinterpretation of the recommended dosage.	Replace hyphens with the intended meaning (e.g., revise "100 – 200 mg/kg" to "100 mg/kg to 200 mg/kg").
3.	The indicated patient population is expressed using symbols (e.g., ≤, >, and <).	Error-prone symbols where dosing is described can lead to confusion and misinterpretation of the recommended dosage.	Replace symbols with the intended meaning (e.g., revise "Pediatric (> 1 month to < 17 years)" to "Pediatric (greater than 1 month to less than 17 years)"
4.	The recommended dosage is presented as a large dose and does not include a comma.	Users may misinterpret the recommended dosage of large doses if a comma is not present, such as ten-thousands interpreted as thousands (e.g., 10000 mg vs. 1000 mg).	Add a comma to the recommended dosage of numbers greater than or equal to 1,000 (e.g., revise "1000…" to "1,000…").
Section 3 Dosage Forms and Strengths			
5.	See Highlights of PI, Dosage Forms and Strengths Recommendation 2.		
6.	See Highlights of PI, Dosage Forms and Strengths Recommendation 3.		
Section 16 How Supplied/Storage and Handling			
7.	See Highlights of PI, Dosage Forms and Strengths Recommendation 2.		
8.	See Highlights of PI, Dosage Forms and Strengths Recommendation 3.		

3.2 TABLE 3: IDENTIFIED ISSUES AND RECOMMENDATIONS FOR HQ SPECIALTY PHARMA CORPORATION (ENTIRE TABLE TO BE CONVEYED TO APPLICANT)

Container Labels (Infusion Bag and Aluminum Overwrap)			
	IDENTIFIED ISSUE	RATIONALE FOR CONCERN	RECOMMENDATION
1.	The middle digits of the National Drug Code (NDC) number is denoted with a placeholder (e.g., 44567-xxx-24).	Similarity of NDC numbers between strengths has led to selecting and dispensing of the wrong drug.	Please assign the middle digits of the NDC numbers and submit for our review, including updating the Prescribing Information. In addition, please consider that sequential numbering for the middle digits is not an effective differentiating feature. If for some reason the proposed middle digits cannot be revised, increase the prominence of the middle digits by increasing their size in comparison to the remaining digits in the NDC number or put them in bold type (e.g., 44567-XXX-24).
2.	The container labels (b) (4) as the carton labeling (b) (4)	The container label of one unit and the carton labeling of 24 units (b) (4)	Revise the package code numbers (b) (4)
3.	The strength is presented as a large dose and does not include a comma.	Users may misinterpret the strength expression of large doses if a comma is not present, such as ten-thousands interpreted as thousands (e.g., 10000 mg vs. 1000 mg).	Add a comma to the total product strength expression, such as: • Revise "1000 mg/50 mL" to "1,000 mg/50 mL • Revise "2000 mg/100 mL" to "2,000 mg/100 mL"
4.	The proposed product, contained in an infusion bag, should not be diluted. We note that	Healthcare professionals may be unaware or confused by this change in preparation and	We recommend adding the important precautionary statement, "Do Not Dilute"

	currently marketed calcium gluconate injection products, contained in vials, must be diluted.	administration of the proposed products (do not dilute) compared to currently marketed products (must dilute).	on the principal display panel (PDP).
5.	The format for the expiration date is not defined.	We are unable to determine if the format of your intended expiration date is such that it minimizes confusion and reduces the risk for deteriorated drug medication errors.	Identify the expiration date format you intend to use. We recommend that the human-readable expiration date on the drug package label include a year, month, and non-zero day. We recommend that the expiration date appear in YYYY-MM-DD format if only numerical characters are used or in YYYY-MMM-DD if alphabetical characters are used to represent the month. If there are space limitations on the drug package, the human-readable text may include only a year and month, to be expressed as: YYYY-MM if only numerical characters are used or YYYY-MMM if alphabetical characters are used to represent the month. We recommend that a hyphen or a space be used to separate the portions of the expiration date.[a]
6.	The statement, "Rev. 07/2017" on the PDP is in close proximity to the expiration date.	Numbers in close proximity to the expiration date may be mistaken as the intended expiration date.	If the intent is to maintain "Rev. 07/2017" on the intend-to-market product, we recommend relocating this information away from

[a] Draft Guidance: Product Identifiers Under the Drug Supply Chain Security Act-Questions and Answers, September 2018 (lines 277-283). Found at: https://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/UCM621044.pdf.

			the expiration date to ensure it is not mistaken as the expiration date.
Carton Labeling			
1.	See Container Labels Recommendation 1.		
2.	See Container Labels Recommendation 2.		
3.	See Container Labels Recommendation 3.		
4.	See Container Labels Recommendation 4.		

4 CONCLUSION

Our evaluation of the proposed PI, container labels, and carton labeling identified areas of vulnerability that may lead to medication errors. Above, we have provided recommendations in Table 2 for the Division and Table 3 for the Applicant. We ask that the Division convey Table 3 in its entirety to HQ Specialty Pharma Corporation so that recommendations are implemented prior to approval of this NDA.

APPENDICES: METHODS & RESULTS FOR EACH MATERIALS REVIEWED

APPENDIX A. PRODUCT INFORMATION/PRESCRIBING INFORMATION

Table 2 presents relevant product information for Calcium Gluconate received on September 29, 2017, from HQ Specialty Pharma Corporation, and the Listed Drug (LD).

Table 2. Relevant Product Information for Calcium Gluconate and the LD		
Product Name	Calcium Gluconate (NDA 210906)	Calcium Gluconate (NDA 208418)
Initial Approval Date	N/A (proposed)	June 15, 2017 (marketed without NDA approval since 1941)
Active Ingredient	Calcium Gluconate	
Indication	Treatment of acute symptomatic hypocalcemia in pediatrics and adults	
Route of Administration	Intravenous (bolus or continuous infusion)	
Dosage Form	Injection	
Strength	1,000 mg/50 mL (20 mg/mL) 2,000 mg/100 mL (20 mg/mL)	1,000 mg per 10 mL (100 mg per mL) 5,000 mg per 50 mL (100 mg per mL) 10,000 mg per 100 mL (100 mg per mL)
Dose and Frequency	Administer intravenously (bolus or continuous infusion) via a secure intravenous line.	
	Do not dilute prior to use. Any unused portion should be discarded immediately.	Dilute prior to use in 5% dextrose or normal saline and assess for potential drug or IV fluid incompatibilities. Use the diluted solution immediately after preparation. • For bolus intravenous administration: Dilute the dose in 5% dextrose or normal saline to a concentration of 10-50 mg/mL prior to administration. • For continuous intravenous infusion: Dilute in 5% dextrose or normal saline to a concentration of 5.8 mg/mL to 10 mg/mL prior to administration.

<table>
<tr><th colspan="3">Table 2. Relevant Product Information for Calcium Gluconate and the LD</th></tr>
<tr><td>Product Name</td><td>Calcium Gluconate (NDA 210906)</td><td>Calcium Gluconate (NDA 208418)</td></tr>
<tr><td></td><td colspan="2">For bolus intravenous administration: Administer the dose slowly and DO NOT exceed an infusion rate of 200 mg/minute in adults or 100 mg/minute in pediatric patients, including neonates. Monitor patients, vitals, and electrocardiograph (ECG) during administration.
For continuous intravenous infusion: Administer at the rate recommended (see table below) and monitor patients, vitals, calcium, and ECG during the infusion.
Individualize the dose within the recommended range in adults and pediatric patients depending on the severity of symptoms of hypocalcemia, the serum calcium level, and the acuity of onset of hypocalcemia.
<table>
<tr><th rowspan="2">Patient Population</th><th rowspan="2">Initial Dose</th><th colspan="2">Subsequent Doses (if needed)</th></tr>
<tr><th>Bolus</th><th>Continuous Infusion</th></tr>
<tr><td>Neonate (≤ 1 month)</td><td>100 – 200 mg/kg</td><td>100 - 200 mg/kg every 6 hours</td><td>Initiate at 17-33 mg/kg/hour</td></tr>
<tr><td>Pediatric (> 1 month to < 17 years)</td><td>29 - 60 mg/kg</td><td>29 - 60 mg/kg every 6 hours</td><td>Initiate at 8-13 mg/kg/hour</td></tr>
<tr><td>Adult</td><td>1000 - 2000 mg</td><td>1000 - 2000 mg every 6 hours</td><td>Initiate at 5.4 - 21.5 mg/kg/hour</td></tr>
<tr><td colspan="4">For bolus administration, DO NOT exceed an infusion rate of:
• 200 mg/minute in adult patients
• 100 mg/minute in pediatric patients
For continuous infusions, adjust rate as needed based on serum calcium levels</td></tr>
</table>
For patients with renal impairment, initiate at the lowest dose of the recommended dose ranges for all age groups and monitor serum calcium levels every 4 hours.
Measure serum calcium during intermittent infusions every 4 to 6 hours and during continuous infusion every 1 to 4 hours.</td></tr>
<tr><td>How Supplied</td><td>1,000 mg/50 mL (20 mg/mL) solution for injection single-dose infusion bag contained in a carton of 24 infusion bags (NDC 44567-[XXX]-24)
2,000 mg/100 mL (20 mg/mL) solution for injection single-dose infusion bag contained in a carton of 24 infusion bags (NDC 44567-[XXX]-24)</td><td>
<table>
<tr><th>NDC</th><th>Strength/Vial Size (mL)</th></tr>
<tr><td>63323-360-19</td><td>1,000 mg calcium gluconate per 10 mL (100 mg per mL), in a 10 mL plastic, single-dose vial, packaged in a tray of 25.</td></tr>
<tr><td>63323-360-59</td><td>5,000 mg calcium gluconate per 50 mL (100 mg per mL), in a 50 mL plastic, single-dose vial, packaged in a tray of 25.</td></tr>
<tr><td>63323-360-61</td><td>10,000 mg calcium gluconate per 100 mL (100 mg per mL), in a 100 mL plastic, Pharmacy Bulk Package vial, packaged in a tray of 20.</td></tr>
</table>
</td></tr>
</table>

Table 2. Relevant Product Information for Calcium Gluconate and the LD		
Product Name	Calcium Gluconate (NDA 210906)	Calcium Gluconate (NDA 208418)
Storage	Store at 20° to 25°C (68° to 77°F) [see USP Controlled Room Temperature]. Do not freeze. Preservative Free. Discard any unused portion in the single-dose vial or single-dose infusion bag immediately.	
		Discard any unused portion in the Pharmacy Bulk Package vial within 4 hours after initial closure puncture. Each dose dispensed from the Pharmacy Bulk Package vial must be used immediately. The diluted solution must be used immediately.
Container Closure	100 mL infusion bag with an aluminum overwrap	plastic 100 mL vials contained in a tray

APPENDIX B. PREVIOUS DMEPA REVIEWS

On May 15, 2018, we searched DMEPAs previous reviews using the term, Calcium Gluconate. Our search identified three (3) previous reviews,[bcd] and we confirmed that our previous recommendations were implemented or considered.

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[b] Vee, S. Label and Labeling Review for Calcium Gluconate NDA 208418. Silver Spring (MD): FDA, CDER, OSE, DMEPA (US); 2016 NOV 21. RCM No.: 2016-1264.

[c] Vee, S. Label and Labeling Review for Calcium Gluconate NDA 208418. Silver Spring (MD): FDA, CDER, OSE, DMEPA (US); 2017 JAN 09. RCM No.: 2016-1264-1.

[d] Rimmel, S. Label and Labeling Review for Calcium Gluconate NDA 208418/S-001. Silver Spring (MD): FDA, CDER, OSE, DMEPA (US); 2017 OCT 18. RCM No.: 2017-1490.

APPENDIX G. LABELS AND LABELING

G.1 List of Labels and Labeling Reviewed

Using the principles of human factors and Failure Mode and Effects Analysis,[e] along with postmarket medication error data, we reviewed the following Calcium Gluconate labels and labeling submitted by HQ Specialty Pharma Corporation.

- Container Labels received on September 29, 2017
- Carton Labeling received on September 29, 2017
- Prescribing Information (image not shown) received on September 29, 2017

G.2 Label and Labeling Images

Container Labels

Infusion Bags

[e] Institute for Healthcare Improvement (IHI). Failure Modes and Effects Analysis. Boston. IHI:2004.

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/s/

SUSAN RIMMEL
10/24/2018

TERESA S MCMILLAN
10/24/2018

DEPARTMENT OF HEALTH & HUMAN SERVICES Public Health Service

Food and Drug Administration
Center for Drug Evaluation and Research
Office of New Drugs
Office of Drug Evaluation IV
Division of Pediatric and Maternal Health
Silver Spring, MD 20993
Telephone 301-796-2200
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M E M O R A N D U M

From: Erica Radden, M.D., Medical Officer
Division of Pediatric and Maternal Health (DPMH)
Office of Drug Evaluation IV (ODE IV)
Office of New Drugs (OND)

Through: Mona Khurana, M.D., Pediatric Team Leader
DPMH, ODE IV, OND

To: Division of Metabolic and Endocrine Products (DMEP)

Drug: Calcium Gluconate Injection

Application Number: NDA 210906

Sponsor: HQ Specialty Pharma Corp.

Proposed Indication: For the treatment of acute symptomatic hypocalcemia in adults and pediatric patients

Dosage Form: 1gm/50mL and 2gm/100mL single use bags

Route of Administration: Intravenous (IV) administration

Proposed Dosing Regimen:

Patient Population	**Initial Dose**	**Subsequent Doses (if needed)**	
		Bolus	**Continuous Infusion**
Neonate (≤ 1 month)	100 – 200 mg/kg	100 – 200 mg/kg every 6 hours	Initiate at 17-33 mg/kg/hour
Pediatric (> 1 month to < 17 years)	29 - 60 mg/kg	29 – 60 mg/kg every 6 hours	Initiate at 8-13 mg/kg/hour

Adult	1000 - 2000 mg	1000 – 2000 mg (b) (4) every 6 hours	Initiate at 5.4 - 21.5 mg/kg/hour
For bolus administration, DO NOT exceed an infusion rate of: •200 mg/minute in adult patients •100 mg/minute in pediatric patients For continuous infusions, adjust rate as needed based on serum calcium levels			

Consult Request: DMEP consulted DPMH on September 24, 2018 to evaluate the proposed pediatric dosing and provide assistance with labeling recommendations for pediatric use.

Materials Reviewed:

- DPMH consult request (September 24, 2018)
- Prior DPMH consult review for Calcium Gluconate Injection under Fresenius Kabi USA, NDA 208418 (May 14, 2017 in DARRTS)
- Current Calcium Gluconate Injection labeling for NDA 208418 (June,15, 2017 in Drugs@FDA)
- Applicant's Proposed Labeling for NDA 210906 (submitted on September 29, 2017)
- Relevant documents under NDA 210906 in DARRTS

I. Regulatory History of this Application

On September 29, 2017, HQ Specialty Pharma Corp. submitted a New Drug Application (NDA) for Calcium Gluconate Injection, 1gm/50mL and 2gm/100mL for the treatment of acute symptomatic hypocalcemia in adults and pediatric patients under Section 505 (b)(2) of the Federal Food, Drug, and Cosmetic Act. The applicant proposes to rely on a similar calcium gluconate injection product marketed under Fresenius Kabi USA (NDA 208418) as the listed drug. The Fresenius Kabi product, which was approved on June 15, 2017, is a concentrate of 100 mg/mL in single dose vials (1,000 mg/10mL and 2,000 mg/ 50 mL) and a pharmacy bulk package (10,000 mg/ 100 mL) that must be further diluted prior to use. The proposed HQ Specialty product is a ready to use solution with a concentration of 20 mg/mL in single use bags (1,000 mg/50 mL and 2,000 mg/100 mL).

Under PREA, 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. HQ Specialty is seeking approval for the same indication and dosing recommendations as the

approved Fresenius Kabi product; therefore, none of these triggers apply to this application. DMEP consulted DPMH to review the pediatric dosing recommendations, specifically with regards to the volume required in neonates for this fixed dose formulation and to provide labeling recommendations for pediatric use.

Of note, On June 28, 2018, the Agency issued a review extension for this NDA after applicant submitted a major amendment on June 22, 2018 including additional data to support the impurity analysis.

II. DPMH Review of Pediatric Use Labeling

DPMH provided a labeling review for the Fresenius Kabi product and therefore, will not provide a detailed review, but rather discuss differences in the assessment and labeling recommendations between the approved Fresenius Kabi and the proposed HQ Specialty calcium gluconate products. (See the prior DPMH review for Fresenius Kabi's Calcium Gluconate Injection, NDA 208418, filed May 14, 2017 in DARRTS.)

The approved Fresenius Kabi Calcium Gluconate Injection labeling and the applicant's proposed labeling for the HQ Specialty Calcium Gluconate product are nearly identical except for the following relevant sections:

- Dosing and Administration: The instructions for the preparation of Fresenius Kabi product recommend that it be diluted to 10-50 mg/mL for bolus IV administration and to 5.8-10 mg/mL for continuous IV infusion. In contrast, proposed instructions for the HQ product, which is 20 mg/mL, do not recommend any dilution.
- The HQ Specialty product contains relatively less aluminum than the FK product (i.e., up to 25 mcg/L for the HQ specialty product versus up to 400 mcg/L for the Fresenius Kabi product).

The proposed dosing is the same. When compared to the fully reconstituted Fresenius Kabi product, the undiluted HQ Specialty product would be administered at a similar concentration for bolus administration but at a higher concentration for continuous infusion. Consequently, the volume that will ultimately be administered by the HQ Specialty product would be similar (for bolus administration) or less (for continuous infusion). However, for continuous infusion, the proposed concentration for the HQ Specialty product will be twice that of the approved Fresenius Kabi product (i.e., a maximum of 10 mg/mL for the FK product vs 20 mg/mL for the HQ product). Although labeling for both products discusses the risk of tissue necrosis and calcinosis due to transient increase in local calcium concentration, we recommend the division request the applicant provide safety data to support administration of this higher concentration via

continuous infusion in pediatric patients down to neonates. Otherwise, DPMH agrees with the applicant's proposed labeling.

III. DPMH Actions and Labeling Recommendations

DPMH reviewed the applicant's draft labeling. DPMH provided recommended labeling for the pediatric population in accordance with 21 CFR 201.57(c)(9)(iv). DPMH's input will be reflected in the final labeling and the approval letter. Final labeling will be negotiated with the applicant and may not fully reflect recommendations proposed above.

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/s/

ERICA D RADDEN
10/17/2018

MONA K KHURANA
10/18/2018