

**CENTER FOR DRUG EVALUATION AND
RESEARCH**

APPLICATION NUMBER:

209377Orig1s000

PRODUCT QUALITY REVIEW(S)



QUALITY ASSESSMENT



Recommendation: This NDA is recommended for Approval from the OPQ perspective.

NDA 209377

OPQ Review #1

| | |
|-------------------------|--|
| Drug Name/Dosage Form | Zinc Sulfate Injection, USP for intravenous use |
| Strength | 30 mg/10 mL (3 mg/mL) of zinc, 25 mg/ 5 mL (5 mg/mL) of zinc |
| Route of Administration | Injection |
| Rx/OTC Dispensed | Rx |
| Applicant | American Regent, Inc., Shirley, NY |
| US agent, if applicable | N/A |

| SUBMISSION(S) REVIEWED | DOCUMENT DATE | DISCIPLINE(S) AFFECTED |
|------------------------|---------------|------------------------|
| Original | 10/12/2018 | OPQ |
| Amendment | 10/22/2018 | Drug product |
| Amendment | 10/24/2018 | Drug Product |
| Amendment | 10/28/2018 | Drug Product |
| Amendment | 10/29/2018 | Drug Product |
| Amendment | 1/9/2019 | Drug Product |
| Amendment | 1/18/2019 | Process |
| Amendment | 3/22/2019 | Process |
| Amendment | 10/31/2018 | Microbiology |

Quality Review Team

| DISCIPLINE | REVIEWER | Secondary Assessment |
|-------------------------------------|-------------------|----------------------|
| Drug Substance | Jeffrey B. Medwid | Donna Christner |
| Drug Product and Labeling | Zhengfang Ge | Moo-Jhong Rhee |
| Process | Allison Aldridge | Edwin Jao |
| Microbiology | Samata Tiwari | Neal Sweeney |
| Facilities | Allison Aldridge | Vidya Pai |
| Regulatory Business Process Manager | Oumou Barry | N/A |
| Application Technical Lead | Hitesh Shroff | N/A |
| Environmental Analysis (EA) | Zhengfang Ge | Moo-Jhong Rhee |

Quality Review Data Sheet

1. RELATED/SUPPORTING DOCUMENTS

A. DMFs:

| DMF # | Type | Holder | Item Referenced | Status | Date Review Completed | Comments |
|---------|----------|--------|-----------------|---|--|-----------------------|
| (b) (4) | Type II | | (b) (4) | Active | Reviewed by Dr. Jeffrey B. Medwid on March 5, 2019 | LOA: June 25, 2018 |
| | Type III | | Active | Not reviewed, Information provided in NDA | LOA October 9, 2017 | |
| | Type III | | Active | Not reviewed, Information provided in NDA | LOA September 18, 2017 | |
| | Type III | | Active | Not reviewed, Information provided in NDA | LOA October 12, 2018 | |
| | Type III | | Active | Not reviewed, Information provided in NDA | LOA December 11, 2015 | |

B. Other Documents: *IND, RLD, or sister applications*

| DOCUMENT | APPLICATION NUMBER | DESCRIPTION |
|----------|--------------------|--|
| | (b) (4) | American Regent Referenced nonclinical and clinical modules for this NDA |

2. **CONSULTS: None**

| DISCIPLINE | STATUS | RECOMMENDATION | DATE | REVIEWER |
|-------------------------|--------|----------------|------|----------|
| Biostatistics | N/A | | | |
| Pharmacology/Toxicology | N/A | | | |
| CDRH | N/A | | | |
| Clinical | N/A | | | |

Executive Summary

I. Recommendations and Conclusion on Approvability

The applicant has provided sufficient CMC information to assure the identity, strength, purity, and quality of the proposed Zinc Sulfate Injection, in 30mg/10mL (3mg/mL) and 25mg/5mL (5mg/mL) of zinc).

The claim for the Categorical Exclusion for the Environmental Assessment is granted.

The Office of Process and Facilities (OPF) has made a final overall “Approval” recommendation for the facilities involved in this application.

The label/labeling issues have been satisfactorily resolved from the CMC perspective.

Therefore, from the OPQ perspective, this NDA is recommended for **approval** with an expiration dating period of 24-month.

II. Summary of Quality Assessments

A. Product Overview

Zinc sulfate Injection, USP, 3 mg/mL zinc and 5 mg/mL zinc, is a sterile, non-pyrogenic, clear, colorless and odorless solution intended for use as an additive to intravenous solutions for parenteral nutrition.

Zinc Sulfate Injection, USP, products in 3 mg/mL zinc and 5 mg/mL zinc strengths, have been marketed for many years as unapproved drugs for use as supplement to intravenous solutions for parenteral nutrition.

| | |
|---|---|
| Proposed Indication(s) including Intended Patient Population | Zinc Sulfate Injection is a trace element indicated in adult and pediatric patients as a source of zinc for parental nutrition (PN) when oral or enteral nutrition is not possible, insufficient, or contraindicated |
| Duration of Treatment | As needed |
| Maximum Daily Dose | <ul style="list-style-type: none"> ○ <i>Adults:</i> 3 mg/day for metabolically stable patients; (b) (4) ○ <i>Pediatric Patients:</i> <ul style="list-style-type: none"> ▪ 10 kg and above: 50 mcg/kg/day (up to 3 mg/day) ▪ Term neonate: 5 kg to less than 10 kg: 100 mcg/kg/day ▪ Term neonate 3 kg to less than 5 kg: 250 mcg/kg/day ▪ Preterm neonate: Less than 3 kg: 400 mcg/kg/day |
| Alternative Methods of Administration | N/A |

B. Quality Assessment Overview

Drug Substance:

The active ingredient, zinc sulfate, USP is manufactured (b) (4). It is very soluble in water and insoluble in alcohol. Its melting point is 100°C, at 280°C all water is lost, and it is decomposed above 500°C. Its empirical formula is ZnSO₄·7H₂O and its molecular weight is 287.56.

Manufacturing: Zinc sulfate, USP is manufactured by (b) (4). The complete CMC information regarding raw materials, manufacturing, characterization, stability, storage and container closure is provided in DMF (b) (4). A Letter of Authorization was also submitted by the manufacturer.

The overall quality of Zinc sulfate, USP is controlled by its specification, which includes description, identification tests per USP <191> (b) (4), assay, bacterial endotoxins and bioburden. The specification is in agreement with the USP monograph of Zinc sulfate, USP. The particle size and polymorphs of zinc sulfate, USP are not important because the drug product is an injection.

The applicant has provided batch analyses of four batches of zinc sulfate, USP. A re-test period of (b) (4) months is proposed and acceptable, however, the applicant has opted to set the re-test period at (b) (4) which is acceptable. DMF (b) (4) was reviewed by Dr. Jeffrey B. Medwid and was deemed adequate from the CMC perspective. (See **the Drug Substance** review)

The API manufactured by (b) (4) is controlled to conform to the requirements (specification) to produce Zinc sulfate injection, USP.

Drug Product:

Zinc sulfate injection, USP, products with 3 mg/mL of zinc and 5 mg/mL of zinc are sterile, non-pyrogenic, clear, colorless and odorless (b) (4) solution for use as a source for trace element and an additive to parenteral nutrition. It is supplied as 3 mg/mL of zinc (30 mg/10 mL) and 5 mg/mL of zinc (25 mg/5 mL) in bulk package vials. In case of 30 mg/10 mL vial, each mL of solution contains 3 mg of zinc as 7.41 mg of zinc sulfate. In case of 25 mg/5 mL vial, each mL of solution contains 5 mg of zinc as 12.32 mg of zinc sulfate. The pH of the (b) (4) solution is adjusted between 2 to 4 with sulfuric acid. There are no preservatives or antioxidants in the drug product formulation.

Zinc Sulfate Injection, USP 3 mg/mL of zinc will be packaged in 10 mL, (b) (4) tubular, 20-mm (b) (4) vials, with 20-mm (b) (4) stoppers, and sealed with 20-mm (b) (4) seals with no printed text. There are 25 vials per carton.

Zinc Sulfate Injection, USP, 5 mg/mL of zinc will be packaged in 5 mL, (b) (4) tubular, 13-mm (b) (4) vials, with 13-mm (b) (4)

(b) (4) stoppers, and sealed with 13-mm (b) (4) seals with no printed text. There are 25 vials per carton.

The overall control strategy for assuring the drug product's identity, strength, purity and quality is deemed adequate based on raw material controls, drug product specification including tests for description, identity, assay, pH, elemental impurities, volume in container, bacterial endotoxins, particulate matter and sterility. The non-compendial analytical methods were validated per ICH Q2.

Based on satisfactory 24-month long-term stability in upright and inverted positions at 25°C and 6-month accelerated stability data at 40°C from three primary registration batches of each strength, the proposed **24-month of expiration dating period** is granted when stored at room temperature in the proposed container closure system per drug product reviewer, Dr. Zhengfang Ge (see the **Drug Product** review).

Manufacturing:

The drug product is manufactured by American Regent, Inc., NJ (formerly Luitpold Pharmaceuticals, Inc.). The manufacturing process includes: (b) (4)

(b) (4) The approximate drug product batch size is (b) (4) for 5 mg/mL zinc and to (b) (4) for 3 mg/mL zinc injections. The drug product manufacturing process, in-process controls, drug product release tests and executed batch records were reviewed and deemed satisfactory. (See **Manufacturing Integrated Assessment**)

The environmental monitoring a (b) (4) as well as the microbiology related attributes of the drug product specification including bacterial endotoxins, sterility and container closure integrity etc. were reviewed by Dr. Samata Tiwari and recommended this NDA for approval based on drug product sterility assurance. (See the **Microbiology** review)

At low pH, there may be compatibility issues with the glass vial and rubber stopper. The applicant demonstrated that the potential leachables, e.g., (b) (4) levels are below PDEs. Aluminum content is controlled to NMT 2500 µg/L. The immediate container was tested for compatibility per USP <660> and met compendial requirements. Based on the admixture in-use stability study, the drug product appeared to be compatible with Kabiven and Clinimix E solutions.

Facilities:

The Office of Process and Facilities (OPF) has made an "Adequate" recommendation for

all drug substance and drug product manufacturing and testing facilities. (See the **Manufacturing Integrated Assessment** review)

Environmental Assessment: The applicant requested categorical exclusion for environmental analysis on the basis that this product will not significantly affect the quality of the human environment in accordance with 21 CFR 25.15 (c). Therefore, claim of a categorical exclusion from the requirements of an environmental assessment (EA) in accordance with 21 CFR Part 25.31(a) was deemed acceptable. (See the **Drug Product** review)

Labeling: The labels and labeling are reviewed by Dr. Zhengfang Ge and all issues were satisfactorily resolved from the CMC perspective. (see **Labeling Review**)

C. Lifecycle Management Considerations: None

D. Special Product Quality Labeling Recommendations: None

E. Final Risk Assessment (see Attachment)

F. List of Deficiencies: None

Application Technical Lead Name and Date:

Hitesh Shroff, Ph.D.
Application Technical Lead, Branch V
Division of New Drug Products II
June 20, 2019

LABEL FOR NDA 209377

I. PI

1. Highlights of Prescribing Information



(b) (4)

| Item | Information Provided in NDA | Reviewer's Assessment |
|--|------------------------------------|--|
| Product Title (Labeling Review Tool and 21 CFR 201.57(a)(2)) | | |
| Proprietary name and established name | ZINC SULFATE INJECTION, USP | Adequate USP should not appear on the title in Highlight as per labeling guidance |
| Dosage form, route of administration | Injection, for intravenous (b) (4) | Adequate |
| Controlled drug substance symbol (if applicable) | N/A | |
| Dosage Forms and Strengths (Labeling Review Tool and 21 CFR 201.57(a)(8)) | | |

| | | |
|---|---|-----------------|
| Summary of the dosage form and strength | Each mL of Zinc Sulfate Injection provides 3 mg of Zinc | Adequate |
|---|---|-----------------|

This section is not adequate.

- USP should be deleted from the title in the highlight

2. Section 2 Dosage and Administration



(b) (4)



| Item | Information Provided in NDA | Reviewer's Assessment |
|--|---|-----------------------|
| (Refer to Labeling Review Tool and 21 CFR 201.57(c)(12)) | | |
| Special instructions for product preparation (e.g., reconstitution, mixing with food, diluting with compatible diluents) | Zinc Sulfate Injection must be diluted in a parenteral nutrition solution before administration Admix stability is provided and should be used within 24 hours. Inspect visually for particulate matter (b) (4) [Redacted] Preparation of the injection in parenteral nutrition is provided | Adequate |

This section is adequate.

3. Section 3 Dosage Forms and Strengths

(b) (4)



| Item | Information Provided in NDA | Reviewer's Assessment |
|--|---|---|
| (Refer to Labeling Review Tool and 21 CFR 201.57(c)(4)) | | |
| Available dosage forms | Injection | Adequate |
| Strengths: in metric system | 30 mg/10 mL, 25 mg/5 mL | Adequate |
| Active moiety expression of strength with equivalence statement (if applicable) | Not provided | Adequate The equivalence statement is provided in section 11. However, zinc is presented as zinc sulfate should be noted in this section |
| A description of the identifying characteristics of the dosage forms, including shape, color, coating, scoring, and imprinting, when applicable. | Supplied as 10 mL (5 mL) Pharmacy Bulk Package. Packaged in cartons of 25 vials per carton. (b) (4) | Adequate More information provided in section 11 |

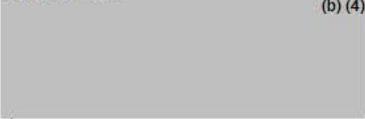
This section is not adequate.

The description should be modified as follows:

- 30 mg/10 mL (3 mg/mL) of zinc present as zinc sulfate (clear, colorless solution) in a 10 mL Pharmacy Bulk Package vial.
- 25 mg/5 mL (5 mg/mL) of zinc present as zinc sulfate (clear, colorless solution) in a 5 mL Pharmacy Bulk Package vial.

4. Section 11 Description



| Item | Information Provided in NDA | Reviewer's Assessment |
|--|--|--|
| (Refer to Labeling Review Tool and 21 CFR 201.57(c)(12), 21 CFR 201.100(b)(5)(iii), 21 CFR 314.94(a)(9)(iii), and 21 CFR 314.94(a)(9)(iv)) | | |
| Proprietary name and established name | Zinc Sulfate Injection | Adequate |
| Dosage form and route of administration | injection | Adequate |
| Active moiety expression of strength with equivalence statement (if applicable) | Each mL of 3 mg/mL or 5 mg/mL...  (b) (4) | Not Adequate Strength should be expressed in terms of zinc with equivalence statement to zinc sulfate content per PQLC recommendation |
| For parenteral, otic, and ophthalmic dosage forms, include the quantities of all inactive ingredients [see 21 CFR 201.100(b)(5)(iii), 21 CFR 314.94(a)(9)(iii), and 21 CFR 314.94(a)(9)(iv)], listed by USP/NF names (if any) in alphabetical order (USP <1091>) | ...inactive ingredients: Water for injection, q.s. | Adequate |
| Statement of being sterile (if applicable) | Provided | Adequate |
| Pharmacological/ therapeutic class | parenteral nutrition | Adequate |
| Chemical name, structural formula, molecular weight | Not provided | Not Adequate |
| If radioactive, statement of important nuclear characteristics. | N/A | |
| Other important chemical or physical properties (such as pKa or pH) | Both presentations are preservative free. The pH range is 2 to 4; pH may be adjusted with sulfuric acid. | Adequate |

This section is not adequate. The following revision should be made:

- The dose strength should be based on the content of zinc with an equivalence statement to express the content of zinc sulfate as follows:
 - 30 mg/10 mL Pharmacy Bulk Package vial:
Each mL contains 3 mg of zinc present as 7.41 mg of zinc sulfate and Water for Injection q.s.
 - 25 mg/5 mL Pharmacy Bulk Package vial:
Each mL contains 5 mg of zinc present as 12.32 mg of zinc sulfate and Water for Injection q.s.
- Add a statement “Zinc Sulfate Injection contains no more than 2500 mcg/L of aluminum”.
- Provide molecular and structural formula, molecular weight of zinc sulfate

5. Section 16 How Supplied/Storage and Handling



| Item | Information Provided in NDA | Reviewer's Assessment |
|--|---|--|
| (Refer to Labeling Review Tool and 21 CFR 201.57(c)(17)) | | |
| Strength of dosage form | 30 mg/10 mL, 25 mg/5 mL | Not Adequate dose strength should be expressed as strength of zinc with equivalence statement to content of zinc sulfate |
| Available units (e.g., bottles of 100 tablets) | Cartons of 25 vials | Adequate |
| Identification of dosage forms, e.g., shape, color, coating, scoring, imprinting, NDC number | Injection | Not Adequate Add appearance of the drug product |
| Special handling (e.g., Dispense in tight and light resistant container as defined in USP) | N/A | Adequate |
| Storage conditions | Store at 20° to 25°C (68° to 77°F) [see USP Controlled Room Temperature] | Not Adequate Add “excursions permitted to 15° to 30°C (59° to 86°F)” |
| Manufacturer/distributor name (21 CFR 201.1(h)(5)) | Provided at after section 17 AMERICAN REGENT, INC. SHIRLEY, NY 11967 | Adequate |

This section is not adequate. The following revision should be made:

- Dose strength should be expressed as strength of zinc with equivalence statement to the content of zinc sulfate
- Add the appearance of the product as “clear, colorless solution”
- Add “excursions permitted to 15° to 30°C (59° to 86°F) to the storage condition

II. Labels:

1. Immediate Container Label

Immediate bottle labels for 3 mg/mL and 5 mg/mL are provided.

| Item | Information Provided in NDA | Reviewer's Assessment |
|--|--|--|
| Proprietary name, established name (font size and prominence (21 CFR 201.10(g)(2))) | (b) (4) Zinc Sulfate Injection, USP | Adequate Proprietary name will not be used |
| Dosage strength Active moiety expression of strength with equivalence statement (if applicable), if space is available | 30 mg/10mL (3 mg/mL) | Not Adequate <ul style="list-style-type: none"> • Dosage strength should be expressed as the content of zinc with “*” on the dose strength. • Side panel should provide an equivalence statement to the content of zinc sulfate |
| Net contents | 10 mL, 5 mL | Adequate |
| “Rx only” displayed prominently on the main panel | Provided | Adequate |
| NDC number (21 CFR 207.35(b)(3)(i)) | Provided | Adequate |
| Lot number and expiration date (21 CFR 201.17) | Provided | Adequate |
| Storage conditions Special handling, e.g., “Dispense in tight and light resistant container as defined in USP”. | Store at 20° to 25°C (68° to 77°F) [see USP] For intravenous use (b) (4) (b) (4) contains no more than 2,500 mcg/L of aluminum Discard unused portion | Not Adequate Add “excursions permitted to 15° to 30°C (59° to 86°F)” |
| Bar code (21CFR 201.25) | Provided | Adequate |
| Name of manufacturer/distributor | Provided | Adequate |

| | | |
|-----------------------------------|--|---|
| And others, if space is available | For intravenous use (b) (4) _____ _____ _____ _____ _____ contains no more than 2,500 mcg/L of aluminum discard unused portion | Not Adequate Strength should be expressed as zinc sulfate with equivalence statement to zinc content |
|-----------------------------------|--|---|

This section is not adequate. The following revision should be made:

- The format of the drug product title should be presented in container and carton labels as follows:
 - Zinc Sulfate Injection, USP
30 mg*/10mL
(3 mg*/mL) of Zinc
 - side panel: “Each mL provide 3 mg of zinc (present as 7.41 mg of zinc sulfate”
- Add “excursions permitted to 15° to 30°C (59° to 86°F) to the storage condition
- Indicate in the container and carton labels that the drug product is sterile

2. Carton Label



| Item | Information Provided in NDA | Reviewer's Assessment |
|---|---|--|
| Proprietary name, established name (font size, prominence) | (b) (4) Zinc Sulfate Injection, USP | Adequate |
| Dosage strength Active moiety expression of strength with equivalence statement (if applicable) in the side panel. | 30 mg/10mL (3 mg/mL) 25 mg/5 mL (5 mg/mL) | Not Adequate <ul style="list-style-type: none"> • Dosage strength should be expressed as the content of zinc with “*” on the dose strength. • Side panel should provide an equivalence statement to the content of zinc sulfate |
| Net quantity of dosage form | 25X10 mL 25X 5 mL | Adequate |
| “Rx only” displayed prominently on the main panel | Provided | Adequate |
| Lot number and expiration date | Provided | Adequate |
| Storage conditions Special handling, e.g., “Dispense in tight and light resistant container as defined in USP”. | Store at 20° to 25°C (68° to 77°F) [see USP] For intravenous use (b) (4) pH adjusted with sulfuric acid (b) (4) Discard unused portion | Not Adequate Add “excursions permitted to 15° to 30°C (59° to 86°F)” |
| Bar code (21CFR 201.25) | Provided | Adequate |
| NDC number (21 CFR 207.35(b)(3)(i)) | Provided | Adequate |
| Manufacturer/distributor's name | Provided | Adequate |
| Quantitative ingredient information (injectables) | Each mL contains: zinc 3 mg, water for injection q.s. pH adjusted with sulfuric acid. (b) (4) | Not Adequate Strength should be expressed as zinc with equivalence statement to zinc sulfate content |
| Statement of being sterile (if applicable) | Not provided | Not Adequate Indicate in the carton label that the drug product is sterile |
| “See package insert for dosage information” | Usual Dosage: see package insert | Adequate |

| | | |
|--|--------------|--|
| “Keep out of reach of children” (Required for OTC in CFR. Optional for Rx drugs) | Not Provided | Adequate Optional |
|--|--------------|--|

This section is not adequate. The following revision should be made:

- The format of the drug product title should be presented in container and carton labels as follows:
 - Zinc Sulfate Injection, USP
30 mg*/10mL
(b) (4) mg*/mL) of Zinc
 - side panel: “Each mL provide 3 mg of zinc (present as 7.41 mg of zinc sulfate”
- Add “excursions permitted to 15° to 30°C (59° to 86°F) to the storage condition
- Indicate in the container and carton labels that the drug product is sterile

List of Deficiencies:

A. Regarding PI

I. Highlights of Prescribing Information

- USP should be deleted from the title in the highlight

II. Full Prescribing Information

For Section 3, “DOSAGE FORMS AND STRENGTHS”

- The description should be modified as follows:
 - 30 mg/10 mL (3 mg/mL) of zinc present as zinc sulfate (clear, colorless solution) in a 10 mL Pharmacy Bulk Package vial.
 - 25 mg/5 mL (5 mg/mL) of zinc present as zinc sulfate (clear, colorless solution) in a 5 mL Pharmacy Bulk Package vial.

For Section 11, “DESCRIPTION”

- The dose strength should be based on the content of zinc with an equivalence statement to express the content of zinc sulfate as follows:
 - 30 mg/10 mL Pharmacy Bulk Package vial:
Each mL contains 3 mg of zinc present as 7.41 mg of zinc sulfate and Water for Injection q.s.
 - 25 mg/5 mL Pharmacy Bulk Package vial:
Each mL contains 5 mg of zinc present as 12.32 mg of zinc sulfate and Water for Injection q.s.
- Add a statement “Zinc Sulfate Injection contains no more than 2500 mcg/L of aluminum”.
- Provide molecular and structural formula, molecular weight of zinc sulfate

For Section 16, “HOW SUPPLIED/STORAGE AND HANDLING”

- Dose strength should be expressed as strength of zinc with equivalence statement to the content of zinc sulfate
- Add the appearance of the product as “clear, colorless solution”
- Add “excursions permitted to 15° to 30°C (59° to 86°F) to the storage condition

B. Regarding Container/Carton Labels:

- The format of the drug product title should be presented in container and carton labels as follows:
 - Zinc Sulfate Injection, USP
30 g*/10mL
(3 mg*/mL) of Zinc
 - side panel: “Each mL provides 3 mg of zinc (present as 7.41 mg of zinc sulfate), ...”
- Add “excursion permitted to 15° to 30°C (59° to 86°F) to the storage condition
- Indicate in the container and carton labels that the drug product is sterile
- Provide mock up for container/carton labels of the 5 mg/mL product

Overall Assessment and Recommendation:

The labeling and labels are **not** deemed ready for approval in its present form per 21 CFR 314.125 (b)(6) from the CMC labeling perspective until the deficiencies are satisfactorily resolved.

Primary Labeling Reviewer Name and Date:

Zhengfang Ge, Ph. D.

Reviewer, BRANCH V/DIVISION II
OFFICE OF NEW DRUG PRODUCT

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

I agree with Dr. Ge's assessment and concur with her statement that this application is not ready for approval in its present form per 21 CFR 314.125(b)(6).

Moo-Jhong Rhee, Ph. D.

Branch Chief, BRANCH V/DIVISION II
OFFICE OF NEW DRUG PRODUCT



Zhengfang
Ge

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Moo Jhong
Rhee

Digitally signed by Moo Jhong Rhee
Date: 4/08/2019 12:29:25PM
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Memorandum

DEPARTMENT OF HEALTH AND HUMAN SERVICES
PUBLIC HEALTH SERVICE
FOOD AND DRUG ADMINISTRATION
CENTER FOR DRUG EVALUATION AND RESEARCH

Date: April 23, 2019

From: Zhengfang Ge, Ph.D.
ONDP/Division II/Branch V

Through: Moo-Jhong Rhee, Ph.D.
Chief, ONDP/Division II/Branch V

To: Labeling Review #1 of NDA 209377

Subject: Final labeling/labels

The Labeling review #1 has noted the following pending issues:

A. Regarding PI

I. Highlights of Prescribing Information

- USP should be deleted from the title in the highlight

II. Full Prescribing Information

For Section 3, “DOSAGE FORMS AND STRENGTHS”

- The description should be modified as follows:
 - 30 mg/10 mL (3 mg/mL) of zinc present as zinc sulfate (clear, colorless solution) in a 10 mL Pharmacy Bulk Package vial.
 - 25 mg/5 mL (5 mg/mL) of zinc present as zinc sulfate (clear, colorless solution) in a 5 mL Pharmacy Bulk Package vial.

For Section 11, “DESCRIPTION”

- The dose strength should be based on the content of zinc with an equivalence statement to express the content of zinc sulfate as follows:
 - 30 mg/10 mL Pharmacy Bulk Package vial:
Each mL contains 3 mg of zinc present as 7.41 mg of zinc sulfate and Water for Injection q.s.
 - 25 mg/5 mL Pharmacy Bulk Package vial:

Each mL contains 5 mg of zinc present as 12.32 mg of zinc sulfate and Water for Injection q.s.

- Add a statement “Zinc Sulfate Injection contains no more than 2500 mcg/L of aluminum”.
- Provide molecular and structural formula, molecular weight of zinc sulfate

For Section 16, “HOW SUPPLIED/STORAGE AND HANDLING”

- Dose strength should be expressed as strength of zinc with equivalence statement to the content of zinc sulfate
- Add the appearance of the product as “clear, colorless solution”
- Add “excursions permitted to 15° to 30°C (59° to 86°F) to the storage condition

B. Regarding Container/Carton Labels:

- The format of the drug product title should be presented in container and carton labels as follows:
 - Zinc Sulfate Injection, USP
30 g*/10mL
(3 mg*/mL) of Zinc
 - side panel: “Each mL provides 3 mg of zinc (present as 7.41 mg of zinc sulfate), ...”
- Add “excursion permitted to 15° to 30°C (59° to 86°F) to the storage condition
- Indicate in the container and carton labels that the drug product is sterile
- Provide mock up for container/carton labels of the 5 mg/mL product

And because of these deficiencies, in the Labeling Review #1, this NDA was not recommended for approval from the labeling perspective.

In the amendment submitted on 10-April-2019, the applicant accepted all the requests with the following exceptions:

1. Due to a limited amount of space for the 5 mL container labels
 - a. storage condition for the “excursions permitted to 15° to 30°C (59° to 86°F)” will not be included
 - b. additional change: (b) (4)
) have been deleted to fit the reworded “Each mL provides 5 mg of zinc (present as 12.32 mg of zinc sulfate)” and “Recommended Dose: see prescribing information” Statements.
2. Due to a limited amount of space for the 10 mL container labels, storage condition for the “excursions permitted to 15° to 30°C (59° to 86°F)” will not be included

3. To allow enough room for the requested changes, the statement “[REDACTED] (b) (4)
[REDACTED]” has been deleted from the 5ml and 10 mL carton labels. Per 21 CFR 201.323, the aluminum statement only needs to appear on the container labels.

The applicant’s justification for the additional changes on the container/carton labels is adequate. The revised container/carton labels are satisfactory and provided in the **Attachment**.

Recommendation:

This NDA is **now** recommended for approval from the labeling perspective.



Zhengfang
Ge

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Moo Jhong
Rhee

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MICROBIOLOGY

NDA: 209377

Drug Product Name / Strength: Zinc Sulfate Injection, USP, 3 mg/mL and 5 mg/mL, Pharmacy Bulk Package

Route of Administration: Sterile solution for injection, intravenous, single dose

Applicant Name: Luitpold Pharmaceuticals, Inc

Manufacturing Site: Luitpold Pharmaceuticals, Inc., One Luitpold Drive, P.O. Box 9001 Shirley, NY 11967

Method of Sterilization: [REDACTED] (b) (4)

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

List Submissions being reviewed: October 12, 2018, October 31, 2018 and January 18, 2019

Highlight Key Outstanding Issues from Last Cycle: N/A

Concise Description Outstanding Issues Remaining: N/A

Supporting/Related Documents:

DMF (b) (4) and associated Microbiology Reviews (b) (4) doc dated 2/3/2017 (adequate) and (b) (4) doc dated 4/25/2017 (adequate)

Remarks Section: Microbiology Information Requests were issued to the applicant on December 19, 2018, and the applicant forwarded responses on January 18, 2019.

S Drug Substance

The drug substance is not the focus of this review [REDACTED] (b) (4)

P.1 Description of the Composition of the Drug Product

(Section 3.2.P.1 Description and Composition.pdf)

Description of drug product

Zinc Sulfate Injection, USP 3 mg/mL (30 mg/10 mL) and 5 mg/mL (25 mg/5 mL) is a single dose, clear, colorless and odorless solution.

Drug product composition –

Quantitative Composition of Zinc Sulfate Injection, USP is provided in the table below:

| Raw material | Function | Content per mL (Bulk Solution) | Content per 10 mL (Fill size (b) (4) mL) |
|----------------------------------|----------------------------------|--------------------------------|--|
| Zinc Sulfate, USP (Heptahydrate) | Active Pharmaceutical Ingredient | 13.20 mg | 132 mg |
| Water for Injection, USP (b) (4) | (b) (4) | Q.S. to 1 mL | Q.S. to 10 mL |
| Sulfuric Acid, NF | pH adjuster | Not Applicable | Not Applicable |

Description of container closure system –

The drug product is packaged as 5 mL and 10 mL in 5 mL and 10 mL vials respectively.

| Component | 10 mL presentation | 5 mL presentation | Manufacturer (b) (4) |
|-----------|--|---------------------------------------|----------------------|
| Vial | 10 mL, 20 mm, (b) (4) Tubular, (b) (4) and | 5 mL, 20 mm, (b) (4) Tubular, (b) (4) | |
| Stopper | 20 mm, (b) (4) | 13 mm, (b) (4) | |
| Cap | 20 mm, (b) (4) | 13 mm, (b) (4) | |

Reviewer’s Assessment:

The applicant provided an adequate description of the drug product composition and the container closure system designed to maintain product sterility.

Acceptable

P.2.5 Microbiological Attributes

Container/Closure and Package Integrity

(Section 3.2.P.2 ccit-microbial-ingress-13mm.pdf and ccit-microbial-ingress-20 mm. pdf)

Glass vial and rubber stopper

5 mL Presentation:

The container/closure system used for validation were (b) (4) 13 mm stoppers (b) (4) (different item # than production) and 5 mL tubular glass vials (b) (4) (same as proposed for production).

10 mL Presentation:

The container/closure system used for validation were (b) (4) 20 mm stoppers type (b) (4) (identical item # as production) and 10 mL tubular glass vials (b) (4) (different from production).

Note to Reviewer: The glass vials used in the CCIT study for 10 mL presentation were different components than proposed 10 mL vials for commercial production and the 13 mm stoppers used for CCIT were not identical (in terms of item #) than proposed for production. Information will be requested.

Test method: Microbial ingress method

Container/closure integrity validation using the microbial challenge method was performed as per SOP-601.01(not provided).

Brief description: Twenty (20) test articles were immersed in two suspensions of *B. diminuta*. Twenty vials served as a negative control. Vacuum is applied to the vessel to reduce the pressure to fifteen inches of mercury for thirty minutes and vials remained immersed for an additional 30 minutes after removal of a vacuum. The test articles were incubated at 30-35°C for 7 days. The applicant states that breached positive vials were used, however, no information was provided regarding the preparation of positive controls and the number of positive units.

Acceptance criteria:

- No evidence of microbial growth is to be observed in any of the test units.
- Breached positive control units shall be positive for growth.
- Negative control units shall be negative for growth.
- Growth promotion testing performed prior to the vacuum test must show growth of the challenge organism.

Results of test performed on 08/31/2018 (5 mL vials) and 01/11/2016 (20 mL vials) are provided and tabulated below:

| Sample | # Positive/ # Tested |
|------------------|----------------------|
| Test Units | 0/20 |
| Positive Control | positive |
| Growth promotion | satisfactory |
| Negative Control | 0/20 |

Note to Reviewer: The applicant has not provided the concentration of the challenge microorganism for immersion and growth promotion. Additionally, the applicant has not mentioned if the vials were subjected to the proposed (b) (4) prior to CCIT, the type of media filled in the test vials, the number of breached positive vials and method to prepare breached positive vials. Information will be requested.

IR#1:

Regarding the validation of the container-closure integrity using microbial immersion method:

- a) Please indicate whether the units were subjected to the proposed (b) (4) cycle prior to container/closure integrity validation testing.
- b) The 10 mL glass vials described in the Container Closure Integrity test (CCIT) reports dated 01/11/2016 in section 3.2.P.2 ccit-microbial-ingress-20 mm. pdf differ from the 10 mL vials proposed for commercial production of the 10 mL vial drug product presentation. Additionally, the 13 mm stoppers (b) (4) used for CCIT in section 3.2.P.2 ccit-microbial-ingress-13mm.pdf differ from the 13 mm (b) (4) stoppers proposed for commercial production of the 5 mL vial drug product presentation. Please indicate whether the test vials and stoppers listed in both the reports are identical or equivalent to the container and closure proposed for production of the drug product. If the vials and stoppers are identical or equivalent to those proposed for production, please provide an explanation (e.g., identical neck dimensions). In the absence of equivalency, please provide new CCIT studies for the proposed containers and closures.
- c) Please indicate the type of media filled inside the vials.
- d) Please indicate the concentration of the challenge organisms used in the microbial immersion test.
- e) Please indicate the concentration of microbial inoculum for growth promotion testing.
- f) Please describe how the positive control units were prepared for the test and the number of positive control units used in the test.

Applicant's Response:

- a) The applicant clarified that the vials used for CCIT were exposed to the proposed (b) (4) process prior to the container/closure validation testing. Vials were filled with Tryptic Soy Broth and then autoclaved at 121.1°C (250°F) for 20 minutes (data provided).

Note to Reviewer: The Reviewer notes that the proposed (b) (4) parameters are (b) (4). However, the applicant has subjected the vials to (b) (4). No information will be requested as (b) (4) was performed.

- b) The applicant states that the neck sizes for the 10-mL vial used for CCIT testing and the 10-mL vial proposed for Zinc Sulfate Injection, USP are identical. The applicant provides a comparison of the neck dimension specifications for the 10-mL (used in CCIT) and proposed 10-mL vials. The inner neck diameter of both the vials is 12.45-12.95 mm. Additionally, the 13 mm stoppers (b) (4) used for CCIT are identical to the 13 mm (b) (4) stoppers proposed for commercial production of the 5 mL vial drug product presentation. The applicant confirmed that both (b) (4) and (b) (4) are 13 mm, (b) (4) stoppers.
- c) The applicant states that the vials were filled with Tryptic Soy Broth (TSB).
- d) The applicant states that the concentration of the challenge organism used in the microbial immersion test was 9.35×10^8 CFU/mL. The applicant has provided an updated report in section 3.2.P.2 to reflect the changes.

- e) The applicant states that the concentration of microbial inoculum for growth promotion testing was 10-100 CFU. Viable plate counts of 49 CFU/plate and 52 CFU/plate were obtained from the two test vials of 10 mL presentation (20-mm neck size and 20-mm Stopper) inoculated with the above concentration of challenge organisms. The viable plate counts of 68 CFU/plate and 78 CFU/plate were obtained from the two test vials of 5 mL presentation with a 13-mm neck size and 13-mm stopper inoculated with 10-100 CFU.
- f) Positive controls were prepared by inserting a piece of capillary tubing into a 16-gauge needle. The needle was then inserted through the rubber stopper of the media filled vial and then subjected to microbial immersion.

Reviewer's Assessment:

The integrity of the proposed container-closure system is validated, and this section was concluded adequate following review of the response to the IR above communicated to the applicant in letter dated December 19, 2018.

Acceptable

Antimicrobial Effectiveness Testing

Not applicable.

Reviewer's Assessment:

The subject drug product is packaged in a single-dose vial; antimicrobial effectiveness testing is not required.

Acceptable

P.3 Manufacture**P.3.1 Manufacturers****Drug product manufacturing:**

Luitpold Pharmaceuticals, Inc.
One Luitpold Drive, P.O. Box 9001, Shirley, NY 11967

Microbiological testing of finished product is also performed at the facility listed below:

(b) (4)

P. 3.3 Description of the Manufacturing Process and Process Controls**Buildings and Facilities**

(3.2.P.3.3.Manf-process-desc-ts-ny.pdf)

A brief description of the manufacturing building and facilities is provided.



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Sweeney

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Samata
Tiwari

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ATTACHMENT I: Final Risk Assessments

A. Final Risk Assessment – NDA 209377

a) Drug Product: Zinc Sulfate Injection, USP, 3 mg/mL zinc and 5 mg/mL zinc

| From Initial Risk Identification | | | Review Assessment | | |
|----------------------------------|---|----------------------------|--------------------------|---|--|
| Attribute/ CQA | Factors that can impact the CQA | Initial Risk Ranking | Risk Mitigation Approach | Final Risk Evaluation | Lifecycle Considerations/ Comments |
| Particulate Matter | (b) (4) | H to M | (b) (4) | Particulate matter remained within acceptable range during the stability testing. Low | None |
| Bioburden | Manufacturing environment and processes | M | | Bioburden is controlled in the drug product at release and stability. Low | None |
| Sterility | Sterilization | M | | Sterility is controlled in drug product at release and stability. Low | None |



Hitesh
Shroff

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