CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

208614Orig1s000

PRODUCT QUALITY REVIEW(S)

QUALITY ASSESSMENT

Recommendation: APPROVAL
(including the Facility Review/Overall Manufacturing Inspection Recommendation)

NDA 208614
Review #2
Review Date (see last page)

Drug Name/Dosage Form	doxercalciferol solution
Strength	2 mcg/mL as 4 mcg/2 mL vial or 10 mcg/5 mL vial
Route of Administration	IV injection
Rx/OTC Dispensed	Rx
Applicant	Hospira

SUBMISSION(S) REVIEWED in Review #1	DOCUMENT DATE
0000	11/30/16
0002	1/17/17
0004	6/1/17
0005	7/14/17
SUBMISSION(S) REVIEWED in Review #2	
0006	**1/26/2018**

Quality Review Team

DISCIPLINE	REVIEWER	DIVISION/OFFICE
Regulatory Business Process Manager	Anika Lalmansingh	Regulatory Business Process Management I/OPRO
Application Technical Lead	Suong (Su) Tran	New Drug Products II/ONDP
API	Fred Burnett/Donna Christner	New Drug API/ONDP
Drug Product	Ravi Kasliwal/Danae Christodoulou	New Drug Products II/ONDP
Process	Brian Rogers/Yong Hu	Process Assessment II/OPF
Facility	Sherry Shen/B.J. Ryan Carl Lee/Vidya Pai	Inspectional Assessment/OPF
Biopharmaceutics	Hansong Chen/Haritha Mandula	Biopharmaceutics/ONDP
Microbiology	Ash Bekele/Stephen Langille	Microbiology Assesment/OPF

Executive Summary

I. Recommendation

The recommendation from the Office of Pharmaceutical Quality (OPQ) is for Approval, including the Overall Manufacturing Inspection Recommendation dated 5/17/2018.

II. Summary

This current recommendation for Approval replaces the previous Review #1 recommendation for a Complete Response due to a "Withhold" recommendation for the commercial drug product manufacturer Hospira at 1776 N. Centennial Drive, McPherson KS 67460 (FEI# 1925262).

- As per the attached Facilities review, recent inspections of Hospira at 1776 N. Centennial Drive, McPherson KS 67460 (FEI# 1925262) in October of 2017 and February of 2018 resulted in a Voluntary Action Indicated classification and a No Action Indicated classification, respectively, which led to the current OPQ recommendation for Approval.

This current recommendation for Approval also replaces the previous Review #1 recommendation for a Complete Response due to a "Withhold" recommendation for Hospira (b) (4)

- As per the attached Facilities review, Hospira (b) (4) was recently inspected in (b) (4) with GMP observations issued in a 483; FDA's evaluation of the inspection results is ongoing. Any risk related to the GMP observations is mitigated by the lack of application-specific deficiencies, apparent lack of impact on application data, and lack of any commercial function in this application.

OVERALL ASSESSMENT AND SIGNATURE: EXECUTIVE SUMMARY

Application Technical Lead Signature:

Suong (Su) Tran, Ph.D.
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Su (Suong) Tran

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QUALITY REVIEW

Recommendation: COMPLETE RESPONSE
(including the Facility Review/Overall Manufacturing Inspection Recommendation)

NDA 208614
Review #1
Review Date (see last page)

Drug Name/Dosage Form	doxercalciferol solution
Strength	2 mcg/mL as 4 mcg/2 mL vial or 10 mcg/5 mL vial
Route of Administration	IV injection
Rx/OTC Dispensed	Rx
Applicant	Hospira

SUBMISSION(S) REVIEWED	DOCUMENT DATE
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Quality Review Team

DISCIPLINE	REVIEWER	DIVISION/OFFICE
Regulatory Business Process Manager	Anika Lalmansingh	Regulatory Business Process Management I/OPRO
Application Technical Lead	Suong (Su) Tran	New Drug Products II/ONDP
API	Fred Burnett/Donna Christner	New Drug API/ONDP
Drug Product	Ravi Kasliwal/Danae Christodoulou	New Drug Products II/ONDP
Process	Brian Rogers/Yong Hu	Process Assessment II/OPF
Facility	Sherry Shen/B.J. Ryan	Inspectional Assessment/OPF
Biopharmaceutics	Hansong Chen/Haritha Mandula	Biopharmaceutics/ONDP
Microbiology	Ash Bekele/Stephen Langille	Microbiology Assesment/OPF

Quality Review Data Sheet

1. **RELATED/SUPPORTING DOCUMENTS:**
   - **A. DMFs:** Adequate (see Chapter II)
   - **B. Other Documents:** not applicable
2. **CONSULTS:** not applicable

Executive Summary

I. Recommendation and Conclusion on Approvability

The final OPQ recommendation is for Complete Response, including the overall manufacturing inspection recommendation.

Summary of Complete Response issue:
Hospira at 1776 N. Centennial Drive, McPherson KS 67460 (FEI# 1925262) is the proposed commercial drug product manufacturing site, and Hospira Healthcare India Private Ltd. in Sriperumbudur, India (FEI# 3008386908) is the proposed drug product testing site. This facility received a Warning Letter on 2/14/17 based on an inspection in 2016; the many GMP violations have not been resolved to date (see Chapter VI of this review for details).

Action letter language:
"During recent inspections of the drug product manufacturing facility - Hospira (FEI# 1925262) and testing facility - Hospira (b) (4)), our field investigators observed objectionable conditions at the facilities and conveyed that information to the representatives of the facilities at the close of the inspections. Satisfactory resolution of the observations is required before this application may be approved."

II. Summary of Quality Assessment

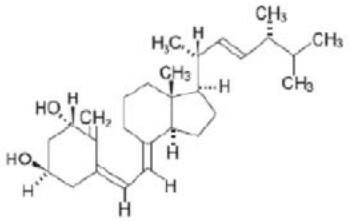
A. Product Overview

The drug substance is doxercalciferol, a small synthetic molecule vitamin D2 analog. The drug product is a sterile solution for intravenous injection, 2 mcg/mL, packaged as 2 strengths: 4 mcg/2 mL vials and 10 mcg/5 mL vials, both being multiple-dose containers.
NDA 208614 is a 505(b)(2) application for doxercalciferol, relying on FDA's findings of safety and effectiveness for the listed HECTOROL. The two NDAs have different applicants with no right of reference. Both products have the same active ingredient and excipients (i.e., same qualitative and quantitative composition). The only difference between the two NDAs is the additional larger fill size of 5 mL of the new NDA.
No clinical study was conducted with the new product subject of NDA 208614. A biowaiver is granted based on 21 CFR 320.22(b)(1) requirements: the new product and HECTOROL have the same qualitative and quantitative composition, and both are solutions for IV use (self-evident bioavailability).

Proposed Indication(s)	[not finalized by GRMP goal; see CDTL's memo]
Duration of Treatment	[not finalized by GRMP goal; see CDTL's memo]
Maximum Daily Dose	[not finalized by GRMP goal; see CDTL's memo]
Alternative Methods of Administration	n/a

B. Quality Assessment Overview

Drug Substance



Molecular Formula: $C_{28}H_{44}O_2$ Molecular Weight: 412.66

(b) (4) is referenced for all CMC information on the drug substance and is currently adequate.

Drug Product

The drug product is a sterile solution for intravenous injection, 2 mcg/mL, packaged as 2 strengths: 4 mcg/2 mL vials and 10 mcg/5 mL vials, both being multiple-dose containers.

- There is no difference in the qualitative and quantitative compositions of this product and the listed drug HECTOROL (the new product uses 96% ethanol and Hectorol uses 100% ethanol, but the final concentration is the same based on the ethanol volume).

Excipients (per mL): ethanol 96% 0.078 mL, polysorbate 20 10 mg, sodium chloride 1.5 mg, butylated hydroxytoluene 0.02 mg, sodium phosphate dibasic, heptahydrate 14.4 mg, sodium phosphate monobasic, monohydrate 1.8 mg, disodium edetate 1.1 mg, and water for injection q.s. (b) (4) Target pH: 7.0-8.0. All excipients are compendial. There is no novel excipient, and there is no human/animal-derived excipient.

The drug product manufacturing process consists of (b) (4)

(b) (4)

The regulatory drug product specification is standard for this type of dosage form (sterile solution, injectable).

The product has an excess fill of (b) (4) mL for the 2 mL vial and (b) (4) mL for the 5 mL vial, both adequate to ensure sufficient withdrawal of the drug solution from the container.

(b) (4)

The proposed parametric release criteria (for sterility assurance) are found adequate by the Microbiology reviewer.

Primary container closure system: The product contact components are amber Type (b) glass vials with (b) (4) . Primary stability batches were stored in this primary container closure system. The NDA includes adequate information to mitigate any risk of extractables/leachables from the product-contact packaging components.

Expiration Date & Storage Conditions: The shelf life of the drug product is 24 months at 5°C.

Primary stability data are from three batches of each container size (2 mL and 5 mL), manufactured at the commercial site and (b) (4) % the commercial size (b) (4) using the commercial drug substance, formulation, packaged in the commercial container closure system. Primary data covered 12 months at 25 °C/60% RH and 6 months at 40 °C/75% RH. In-use stability data covered 28 days at room temperature in support of the labeled 14-day use of an open multi-dose vial.

C. **Special Product Quality Labeling Recommendation**: not applicable

D. **Life Cycle Knowledge Information/ Final Risk Assessment:**

API	none
Drug product	p. 43-44 of Chapter II
Process	none
Facilities	none
Biopharmaceutics	none
Microbiology	none

Application Technical Lead Signature:
I concur with the reviewers' recommendations.

Suong (Su) Tran, Ph.D.
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LABELING

NDA 208614

R Regional Information

1.14 Labeling

- ***Immediate Container Label***

(b) (4)

[redacted]

Reviewer's Assessment: The vials for the container labels are of 2 mL and 5 mL size. Therefore the size of the labels is relatively small. If a small label contains the proprietary and established name of the drug, the identifying lot number and the name of the manufacturer, it is deemed to comply with the regulations (21CFR 201.10(i)), provided the carton or outer container contains all the relevant information. The container labels contain all the necessary identifying information. Further these labels differentiate strengths, i.e., 10 mcg/5 ml and the 4 mcg/2 mL on the basis of different colors. Hospira is proposing the pink background color for the 10 mcg/5 mL carton to differentiate itself from the Brown background color of the innovator's 4 mcg/2 mL presentation. This is preferred and is acceptable.

I recommend following revision to the labels, since photo-stability study indicated that the drug product should be stored in primary packaging in combination with secondary packaging.

Revise statement [redacted] (b) (4) to "Store vial in original container; discard 14 days after opening"

- ***Carton Labeling***

(b) (4)

[redacted]

Reviewer's Assessment:

The labels contain all the necessary information and are accurate from a CMC perspective, except in following respects.

I recommend following revision to the labels, since photo-stability study indicated that the drug product should be stored in primary packaging in combination with secondary packaging.

- Add statement "Store opened vial in original container" immediately in front of the statement "Discard vial 14 days after opening".

The product does contain [redacted] (b) (4) *Hence the statement* [redacted] (b) (4) *may be misleading and should be deleted.*

- *Delete* [redacted] (b) (4) *statement form the carton labels.*

- ***Package Insert:***

2.2 Storage of opened multi-dose vials

After initial vial use, the contents of the multi-dose vial remain stable up to14 days when stored at room temperature. Discard unused portion of multi-dose vial after 14 days *[see How Supplied/Storage and Handling (16)]*.

3 DOSAGE FORMS AND STRENGTHS

Doxercalciferol Injection is available as multi-dose injection:

- 4 mcg/2 mL in a multi-dose glass vial
- 10 mcg/5 mL in a multi-dose glass vial

Reviewer's Assessment:

- The 14 day in-use time is justified on the basis of CMC technical stability study, provided it is acceptable from a microbiology perspective. I recommend adding following statement after the first sentence: "Store unused portion in the original carton".

- The dosage form and strength description is acceptable from a CMC point of view.

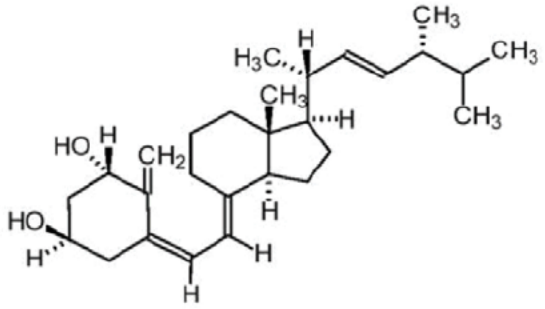
11 DESCRIPTION

Doxercalciferol is a synthetic vitamin D_2 analog that undergoes metabolic activation *in vivo* to form 1α,25-dihydroxy vitamin D_2 (1α,25-$(OH)_2D_2$), a naturally occurring, biologically active form of vitamin D_2. Doxercalciferol Injection is available as a sterile, clear, colorless aqueous solution for intravenous injection.

Doxercalciferol is a colorless crystalline compound with a calculated molecular weight of [redacted] (b) (4) and a molecular formula of $C_{28}H_{44}O_2$. It is soluble in oils and organic solvents, but is relatively insoluble in water.

Chemically, doxercalciferol is (1α,3β,5Z,7E,22E)-9,10-secoergosta-5,7,10(19),22-tetraene-1,3-diol and has the structural formula presented in Figure 1.

Figure 1: Chemical Structure of Doxercalciferol



Other names frequently used for doxercalciferol are 1α-hydroxyvitamin D_2, 1α-OH-D_2, and 1α-hydroxyergocalciferol.

(b) (4)

Each milliliter (mL) of solution contains doxercalciferol, 2 mcg; ethanol, 96%, 0.078 mL; Polysorbate 20, 10 mg; sodium chloride, 1.5 mg; butylated hydroxytoluene, 0.02 mg; sodium phosphate dibasic, heptahydrate, 14.4 mg; sodium phosphate monobasic, monohydrate, 1.8 mg; and disodium edetate, 1.1 mg.

Reviewer's Assessment:

Following changes to the description section are recommended:

- The USAN indicates that the molecular weight of the compound is 412.65. Hence the molecular weight above should be changed from (b) (4) to 412.65.
- A statement to indicate the pH of the solution should be added at the end of composition statement. I recommend adding, "The pH of the solution is between 7.0 and 8.0".

The other aspects of the description section are accurate from a CMC perspective.

16 HOW SUPPLIED/STORAGE AND HANDLING

Doxercalciferal Injection is supplied in multi-dose amber glass vials containing 4 mcg doxercalciferal in 2 mL of solution or 10 mcg doxercalciferol in 5 mL of solution. The closure consists of a fluorocarbon-coated chlorobutyl stopper, with an aluminum seal and (b) (4) plastic flip-off cap.

(b) (4)

STORAGE
Store multi-dose vials at 20° to 25°C (68° to 77°F) [see USP controlled room temperature].

QUALITY ASSESSMENT

Reviewer's Assessment:

The "How Supplied" and "Storage" statements are accurate from a CMC perspective and are acceptable.

List of Deficiencies:

1. In container labels, revise statement [redacted] (b) (4) to "Store vial in original container; discard 14 days after opening".

2. In carton labels:

    a. Add statement "Store opened vial in original container" immediately in front of the statement "Discard vial 14 days after opening".

    b. Delete "Contains preservative" statement form the carton labels, [redacted] (b) (4) [redacted] (b) (4)

3. In section 2.2 (storage of opened multi dose vials) of the package insert, add statement "Store unused portion in the original carton", after the first sentence.

4. In section 11 (Description) of the package insert:

    a. Revise the molecular weight of the drug to be 412.65 from [redacted] (b) (4) as USAN indicates that the molecular weight of the compound is 412.65.

    b. Add statement, "The pH of the solution is between 7.0 and 8.0" at the end of composition statement.

Primary Labeling Reviewer Name and Date:

Ravindra K. Kasliwal, Ph.D. — August 9, 2017
CMC Reviewer
Branch VI, DNDP-II
ONDP / OPQ

Secondary Reviewer Name and Date — **August 10, 2017**

I concur with the reviewer's assessment.

Danae D. Christodoulou, Ph.D.
Branch Chief
Branch VI, DNDP-II
ONDP/ OPQ

Ravindra Kasliwal

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Danae Christodoulou

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CHAPTER III: Environmental Analysis

see chapter II

CHAPTER IV: Labeling

see chapter II

CHAPTER VII: Biopharmaceutics

QUALITY ASSESSMENT

BIOPHARMACEUTICS

Product Background:

NDA/ANDA: NDA 208614

Drug Product Name / Strength: Doxercalciferol Injection, 4 mcg/2 mL and 10 mcg/5 mL Multi Dose Vials

Route of Administration: IV injection

Applicant Name: Hospira, Inc.

Review Summary:

The Listed Drug Hectorol® (Doxercalciferol) Injection, 2 mcg/mL, developed by Genzyme Corp., was approved by the FDA under NDA 021027 on 4/6/2000. It is indicated for the treatment of secondary hyperparathyroidism in patients with chronic kidney disease on dialysis.

Hospira, Inc. developed Doxercalciferol Injection, 4 mcg/2 mL and 10 mcg/5 mL and submitted the application under NDA 208614 to seek approval from the Agency through 505(b)(2) pathway on 11/30/2016.

The Biopharmaceutics review focuses on the side-by-side comparison between the proposed product and the Listed Drug for the active and inactive ingredients including pH and osmolality, as well as the Applicant's waiver request on the in vivo BA/BE for its proposed drug product.

From the Biopharmaceutics perspective, NDA 208614 for Doxercalciferol Injection, 4 mcg/2 mL and 10 mcg/5 mL was reviewed and found adequate, and the wavier for the proposed product is also granted. This NDA is, therefore, recommended for approval.

List Submissions being reviewed (table):

SUBMISSION(S) REVIEWED	DOCUMENT DATE
0000	11/30/16
0002	1/17/17
0004	6/1/17
0005	7/14/17

Highlight Key Outstanding Issues from Last Cycle: None.

Concise Description Outstanding Issues Remaining: N/A

BCS Designation

Reviewer's Assessment: Not reported.

Solubility:

Doxercalciferol is soluble in methanol and ethyl acetate and practically insoluble in water over a (b) (4)

Permeability: not reported.

Dissolution: N/A

Bridging of Formulations

Reviewer's Assessment: N/A

Biowaiver Request

Reviewer's Assessment:

1. Background

The Applicant developed Doxercalciferol Injection, 4 mcg/2 mL and 10 mcg/5 mL and submitted this application under NDA 208614 on 11/30/2016 seeking approval through 505(b)(2) path. The listed drug is Hectorol® (Doxercalciferol) Injection, 2 mcg/mL. The proposed product and the Listed Drug, Hectorol® have the same active ingredient and inactive ingredients in the same concentrations. Here is the side-by-side comparison of the components and composition of these two products.

Table 1. Formulation Comparison between Hospira' Doxercalciferol Injection, 4 mcg/2 mL and 10 mcg/5 mL and Listed Drug, Hectorol® (Doxercalciferol) injection 2 mcg/mL

Product Detail	Reference Listed Drug (RLD)		Hospira Product	
Product Name	Hectorol®		Doxercalciferol Injection	
Company Name	Genzyme Corp.		Hospira, Inc.	
Drug Substance	Doxercalciferol		Doxercalciferol	
Inactive Ingredients	Alcohol USP	0.075 mL*	Alcohol USP	***0.078 mL****
	Polysorbate 20 NF	10.0 mg	Polysorbate 20 NF	10.0 mg
	Butylated Hydroxy Toluene, NF	0.02 mg	Butylated Hydroxy Toluene, NF	0.02 mg
	Sodium Chloride, USP	1.5 mg	Sodium Chloride, USP	1.5 mg
	Sodium Phosphate Dibasic Heptahydrate, USP	14.4 mg	Sodium Phosphate Dibasic Heptahydrate, USP	14.4 mg
	Sodium Phosphate Monobasic Monohydrate, USP	1.8 mg	Sodium Phosphate Monobasic Monohydrate, USP	1.8 mg
	Disodium Edetate, USP	1.1 mg	Disodium Edetate, USP	1.1 mg
	[redacted] (b) (4)			
Strength(s)	4 mcg/2 mL		4 mcg/2 mL, ***10 mcg/5 mL***	
Concentration	2 mcg/mL		2 mcg/mL	
Route of Administration	Injection (Intravenous)		Injection (Intravenous)	
Dosage Form	Injectable		Injectable	

The first difference between these two products is that different concentrations of ethanol were used during manufacturing. The proposed product contains 0.078 mL of 96% ethanol, whereas the LD Hectorol® contains 0.075 mL of 100% ethanol. [redacted] (b) (4)

The second difference between them is that the proposed product , Doxercalciferol Injection 4 mcg/2 mL and 10 mcg/5 mL is supplied as 2 mL and 5 mL multi-dose vials. The Listed Drug has only one dose vial 4 mcg/ 2mL.

The Applicant also provided the side-by-side comparison of physico-chemical parameters of these two products (Table 2).

Table 2. Comparison of Physico-chemical Parameters between Hospira' Doxercalciferol Injection, 4 mcg/2 mL and 10 mcg/5 mL and Listed Drug, Hectorol® (Doxercalciferol) injection 2 mcg/mL

		Reference Listed Drug (RLD)		Hospira Product			
Name of the product		Hectorol®		Doxercalciferol Injection 10 mcg/5 mL			
Batch Number		4RM014 (Exp Date: 08/2016) Loading date:23 July 2015)		PD5-169		PD5-170	
Test parameters	**Specifications**	**Initial**	**40°C/ 75% RH-6M**	**Initial**	**40°C/ 75% RH-6M**	**Initial**	**40°C/ 75% RH-6M**
Description	A clear colorless solution	Clear colorless solution	Clear colorless solution	Clear colorless solution	Clear colorless solution	Clear colorless solution	Clear colorless solution
pH	7.0 to 8.0						(b) (4)
Assay by HPLC							(b) (4)
Related Substances by HPLC (% w/w)							
(b) (4)	NMT (b) (4)	< PQL	ND	< PQL	ND	< PQL	ND
Any unspecified impurity	NMT	(b) (4)	ND	(b) (4)	ND	(b) (4)	ND
Total Impurities	NMT		ND		ND		ND
Osmolality	240-340 (mOsm/Kg)		NA		NA		NA

ND-Not detected; PQL= (b) (4)%; NA-Not Applicable

Table 2 shows that the proposed product and the LD have very similar osmolality and pH.

2. Biowaiver Request

The Applicant requested the waiver of the in vivo BA/BE for their proposed product by citing 21 CFR 320.22(b) (1). The Applicant stated that both drug products have the same active ingredient and inactive ingredients (b) (4) In addition, the proposed product and the LD have similar physico-chemical properties, such as osmolality and pH.

Reviewer's comment:

The criteria for a biowaiver under 21 CFR 320.22(b)(1) is fully met:

1. *The proposed drug product and the listed Drug product are for intravenous use, and their bioavailability is self-evident.*
2. *The proposed drug product contains the same active and inactive ingredients* (b) (4) *as the Listed Drug that has been approved by FDA under NDA 021027 .*
3. *The tiny differences in pH and osmolality between two products do not bring any safety issues.*

Conclusion

As consistent with 21 CFR 320.24(b)(1), the Applicant provided adequate information supporting the relative bioavailability of Hospira' s proposed drug product to the Listed Drug and a scientific bridge has been established to the Agency's finding of safety and effectiveness to the Listed Drug. Thus, additional in vivo bioequivalence (BE) bridging study is not needed. NDA 208614 for Doxercalciferol Injection, 4 mcg/2 mL and 10 mcg/5 mL is adequate and is recommended for approval from the Biopharmaceutics perspective.

R Regional Information

Comparability Protocols: None

Reviewer's Assessment:

Post-Approval Commitments

Reviewer's Assessment: N/A

Lifecycle Management Considerations; N/A

List of Deficiencies: *N/A*

Primary Biopharmaceutics Reviewer Name and Date:

Hansong Chen, Pharm.D., Ph.D.,4/27/201, 8/2/2017

Biopharmaceutics reviewer,

Division of Biopharmaceutics/ONDP/OPQ

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

Haritha Mandula, Ph.D., 8/19/2017

Acting Biopharmaceutics Lead,

Division of Biopharmaceutics/ONDP/OPQ

Hansong Chen

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Haritha Mandula

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MICROBIOLOGY

IQA Review Guide Reference

Product Background: -

NDA: 208614

Drug Product Name / Strength: Doxercalciferol Injection, 4 mcg/2 mL, 2 mL fill in 2 mL multiple dose vials and 10 mcg/5 mL, 5 mL fill in 5 mL multiple dose vials

Route of Administration: Intravenous injection

Applicant Name: Hospira, Inc. 275 N. Field Drive, Dept. 0389/Bldg. H2-2
Lake Forest, IL, 60045, USA
Ph. +1 224-212-4268
Email: kristina.mcintyre@pfizer.com

Manufacturing Site: Hospira, 1776 N. Centennial Drive, McPherson, KS, USA 67460

Method of Sterilization: (b) (4)

(b) (4)

Review Summary: Recommended for approval.

List Submissions being reviewed 11/30/16

Highlight Key Outstanding Issues from Last Cycle: N/A

Concise Description Outstanding Issues Remaining: The submission lacks specific information regarding the container-closure integrity testing, and the acceptance criteria for the (b) (4)

(b) (4) .

S Drug Substance—The drug substance is not reviewed since [redacted]

P.1 Description of the Composition of the Drug Product

- **Description of drug product** — The drug product, Doxercalciferol Injection is a [redacted] sterilized multi-dose preparation containing ethanol [redacted] It is a clear and colorless solution presented in USP Type [redacted] amber glass vials. It is available as 4 mcg/2 mL in a 2 mL multiple dose vial, and 10 mcg/5mL in a 5 mL multiple dose vial.

- [redacted] It is noted that this is a 505 (b) (2) submission.

Table 1. Composition of the drug product

Component	Drug Code Number	Quality Standard	Function
Doxercalciferol	EX000834	[redacted]	
Ethanol	11402815		
Polysorbate 20	11737442		
Sodium Chloride	11826234		
Butylated Hydroxytoluene	11148103		
Sodium phosphate dibasic, heptahydrate	11841253		
Sodium phosphate monobasic, monohydrate	11818830		
Disodium edetate	11350080		

- **Description of container closure system** – (reference is made to 3.2.P.2.4 Container Closure System). The proposed drug product is manufactured in two configurations, 2 mL fill in 2 mL vials and 5 mL fill in 5 mL vials. Both vials are USP Type - [redacted] amber tubular glass vials with a 13mm neck, stoppered with 13 mm chlorobutyl stoppers and sealed with 13 mm orange or grey colored plastic button with aluminum seal. [redacted]

Table 2. Descriptions of the containers and closures

Primary Packaging Component	Description	Hospira Commodity Number	Supplier Name and Address
Container	USP Type- [redacted] Vial, Amber, 2 mL, 13mm	[redacted]	[redacted]
	USP Type- [redacted] Vial, Amber, 5 mL, 13mm		
Closure	[redacted] 13 mm , [redacted] Gray chlorobutyl rubber stopper with [redacted] Coating [redacted]		
Seal	Seal, 13 mm, Orange, Flip Off [redacted]		
	Seal, 13 mm, Gray, Flip Off [redacted]		

Reviewer's Assessment (Adequate).
The applicant provided an adequate description of the drug product, its composition and the container closure system designed to maintain product sterility.

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P.7 Container Closure— See P.1 for additional descriptions

Table 17. Summary table of the container closure system proposed

Primary Packaging Component	Description	Hospira Commodity Number	Supplier Name and Address
Container	USP Type- (b) (4) Vial, Amber, 2 mL, 13mm	(b) (4)	(b) (4)
	USP Type- (b) (4) Vial, Amber, 5 mL, 13mm		
Closure	13 mm Gray chlorobutyl rubber stopper (b) (4) (b) (4)		
Seal	Seal, 13 mm, Orange, Flip Off (b) (4)		
	Seal, 13 mm, Gray, Flip Off (b) (4)		

Reviewer's Assessment(Adequate)

P.8 Stability

P. 8.1 Stability Summary and Conclusion

Reviewer's Assessment: (Adequate)

A six month accelerated (40°C ± 2 °C / 75% ± 5% RH) and 36 month long term (25 °C ± 2 °C / 60% ± 5% RH) stability program with the three exhibit batches for each presentation of the subject drug product (PD5-166, PD5-167, PD5-168, PD5-169, PD5-170, PD5-171) is being carried out. The compendial microbiological tests of sterility USP <71>, endotoxin limits USP <85> and antimicrobial effectiveness test will be performed as per the stability schedule(Table 18). The listed acceptance criteria for product sterility (must be sterile), an endotoxins limit of NMT (b) (4) EU/mcg of the drug product and the AET should meet the USP <51>. Based on the available six months accelerated and 18 months long term stability data, the proposed expiry date of the product is 24 months and the recommended storage condition is 20 to 25°C (68 to 77°F).

Table 18. Stability schedule

	Storage conditions								
		Months							
		0	3	6	9	12	18	24	36
Sterility	Long term (25°C±2°C/60%±5%RH)	X				X		X	X
Bacterial endotoxins		X		X		X		X	X
AET		X						X	
		0	1	2	3	6			
Sterility	Accelerated (40 °C/75% RH)	X			X	X			
Bacterial endotoxins		X			X	X			
AET		X				X			

P. 8.2 Post-Approval Stability Protocol and Stability Commitment

Reviewer's Assessment (Adequate)

The applicant commits to perform stability testing on long term storage conditions (25 ºC ± 2 oC / 60% ± 5% RH) of the drug product from the first three commercial batches. Thereafter, a minimum of one batch will also be tested annually for stability as per the long term stability requirements.

P.8.3 Stability Data

Reviewer's Assessment (Adequate)

The applicant submitted stability data from three exhibit batches of the subject drug product at accelerated (40°C ± 2 oC / 75% ± 5% RH) and long term (25 ºC ± 2 ₒC / 60% ± 5% RH) conditions. Microbiological tests included sterility, AET and bacterial endotoxins tests, and the results met USP specifications.

Appendices

A.2 Adventitious Agents Safety Evaluation

Reviewer's Assessment: (Not applicable)

A.2.1 Materials of Biological Origin

Reviewer's Assessment: (Not applicable)

A.2.2 Testing at Appropriate Stages of Production

Reviewer's Assessment: (Not applicable)

A.2.3. Viral Testing of Unprocessed Bulk

Reviewer's Assessment: (Not applicable)

A. 2.4 Viral Clearance Studies

Reviewer's Assessment: (Not applicable)

R Regional Information

The executed batch records for three batches per product strength are provided.

Reviewer's Assessment:

Comparability Protocols—No comparability protocol is provided

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

2.A. Package Insert

Post-dilution/constitution hold time- N/A

Post-Approval Commitments: - N/A

List of Deficiencies: None

Primary Microbiology Reviewer Name and Date:
Ash Z. Bekele, Ph.D. July 18, 2017

Secondary Reviewer Name and Date (and Secondary Summary, as needed):
Stephen E. Langille, Ph.D. – Acting Branch Chief, July 18, 2017

Ash Bekele

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