CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

209566Orig1s000

PRODUCT QUALITY REVIEW(S)

Recommendation: Approve

NDA 209566
Review 1

Drug Name/Dosage Form	Midazolam Injection
Strength	50 mg/10 mL (5 mg/mL)
Route of Administration	Intramuscular
Rx/OTC Dispensed	Rx
Applicant	Meridian Medical Technologies (division of Pfizer Inc.)
US agent, if applicable	N/A

Quality Review Team

Discipline	Primary Reviewer	Secondary Reviewer
Drug Substance, Product and Labeling	Stephanie Emory	Wendy Wilson-Lee
Process	Yueshing Ye	Nallaperumal Chidambaram
Microbiology	Lisa Ashmore	Bryan Riley
Facility	Yuesheng Ye	Derek Smith
Biopharmaceutics	Gerlie Gieser	Ta-Chen Wu
Regulatory Business Process Manager	Dahlia Walters	--
Application Technical Lead	Martha Heimann	--
Laboratory (OTR)	N/A	
ORA Lead	N/A	
Environmental	N/A	

Submission(s) Reviewed	Document Date	Discipline(s) Affected
SD-01, Original submission	11/16/2017	All
SD-02, Response to IR	01/23/2018	Biopharmaceutics
SD-07, Container labeling	03/28/2018	Labeling
SD-09, Container labeling	08/03/2018	Labeling

Quality Review Data Sheet

1. RELATED/SUPPORTING DOCUMENTS

A. DMFs:

DMF #	Type	Holder	Item Referenced	Status	Date Review Completed	Comments
(b) (4)	II	(b) (4)	Midazolam	N/A [1]	--	
	II		Midazolam	N/A [1]	--	
	V		(b) (4)	N/A [1]	--	
	III			N/A [1]	--	

[1] The DMFs were previously found adequate to support the cross-referenced ANDA 75923 and do not require re-review now.

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

Document	Application Number	Description
NDA	18654	Hoffman LaRoche NDA for Versed (midazolam hydrochloride) injection is referenced under 505(b)(2) to support safety of midazolam.
ANDA	75923	Approved Hospira ANDA for Midazolam Hydrochloride Injection, USP is cross-referenced for CMC information to support 50 mg/10 mL vial.
IND	68432	US Army, Midazolam Autoinjector 10 mg/2 mL,
NDA	(b) (4)	
IND	102254	Dr. Silbergleit, clinical trial of midazolam for treatment of status epilepticus using Midazolam Autoinjector, 10 mg/2 mL.

2. CONSULTS

None

Executive Summary

I. Recommendations and Conclusion on Approvability

The OPQ review team recommends APPROVAL of NDA 209566 for Seizalam (midazolam injection), for intramuscular administration.

II. Summary of Quality Assessments

A. Product Overview

Proposed Indication(s) Including Intended Patient Population	Treatment of status epilepticus in adults
Duration of Treatment	Acute
Maximum Daily Dose	10 mg
Alternative Methods of Administration	None

Midazolam is a short-acting sedative/hypnotic of the benzodiazepine class originally approved as Versed® (midazolam hydrochloride) injection in 1985. Approved indications include sedation/anxiolysis/amnesia prior to, or during, diagnostic or therapeutic procedures and induction of general anesthesia, and sedation of intubated and mechanically ventilated patients.

(b) (4)

Meridian seeks approval of an existing generic product manufactured by another Pfizer subsidiary, Hospira, for the status epilepticus indication. The Hospira product is a multiple-dose vial containing 50 mg/10 mL (5 mg/mL) midazolam as the HCl salt, sodium chloride, disodium edetate, benzyl alcohol (preservative), hydrochloric acid, and if necessary sodium hydroxide for pH adjustment.

B. Quality Assessment Overview

As the applicant cross-references an approved application for the CMC information to support the to-be marketed product, the OPQ review team focused on evaluation of information to support the new indication, verification that there are no outstanding

regulatory activities under the Hospira ANDA that would preclude approval of the current NDA, evaluation of manufacturing and testing facilities, and CMC-related labeling.

Drug Substance and Product

All supporting information for midazolam drug substance and Seizalam (midazolam) injection are incorporated by cross reference to ANDA 75293. No changes will be made to the drug substance and product other than labeling. One CMC supplement to ANDA 75293 was addressed during the review (see Microbiology below).

Linkage to Clinical Trial Product and Listed Drug/Biopharmaceutics

There are slight differences between the midazolam autoinjector formulation used in the clinical study for the status epilepticus indication and the commercial vial formulation, including benzyl alcohol content (10 mg/mL versus 10.45 mg/mL) and target solution pH (3.0 versus 3.3). The applicant requested a waiver of bioequivalence studies between the autoinjector and the commercial product; however, the biowaiver request is not needed to support the proposed new indication for the already marketed drug product because PK data were provided to allow for a cross-study comparison of the manually injected (test) and the auto-injected (reference) midazolam solution drug products. The adequacy of the relative PK data was confirmed with the clinical pharmacology reviewer. The proposed product is qualitatively and quantitatively (Q1/Q2) the same as the listed drug, Versed®.

Microbiology

(b) (4)

reviewed and found acceptable from a Microbiology perspective. The product contains benzyl alcohol as an antimicrobial preservative; however, antimicrobial effectiveness test (AET) results could not be found in the cross-referenced ANDA. Upon request to the applicant, the information was submitted to ANDA 75293 (submit date 06/16/2018) and found adequate on review.

Manufacturing Process

The manufacturing process for Seizalam includes the following manufacturing steps:

(b) (4)

The manufacturing process information in ANDA 75293 (original and subsequent supplements) is deemed adequate from a Process perspective.

Facilities

The manufacturing facilities for NDA 209566 are found to be acceptable. No inspections were conducted as the facilities were cross referenced from approved ANDA 075293. The applicant clarified that the Hospira (b) (4) facility would only test an excipient and therefore it is not considered in the final recommendation.

Environmental Assessment

The applicant submitted a claim for categorical exclusion under 21 CFR § 25.31 (b). The claim for categorical exclusion is granted.

C. Special Product Quality Labeling Recommendations

The applicant requests approval for use in adult patients. Per FDA recommendation, the labeling will state that the product is not indicated for use in neonates and infants due to the presence of benzyl alcohol in the formulation.

D. Final Risk Assessment

Not applicable. An initial risk assessment was not performed since the application cross-references an approved ANDA to support the product.

E. List of Deficiencies

Not applicable.

Martha Heimann

Digitally signed by Martha Heimann
Date: 8/20/2018 11:45:25AM
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DRUG SUBSTANCE

Review Recommendation: Adequate

Review Summary: *Midazolam HCl, a water-soluble benzodiazepine, is formed in situ* (b) (4)

All CMC information in this application is incorporated by reference to approved ANDA-075293 (Hospira) for Midazolam Injection, USP (Novaplus®). No changes will be made to the product other than labeling, and there are no outstanding CMC supplements for the referenced ANDA, therefore the application is found to be adequate for drug substance.

List Submissions being reviewed:

Supporting Document #	Serial #	Description	Received Date
1	1	Original NDA submission	16Nov2017

Highlight Key Outstanding Issues from Last Cycle: N/A

Concise Description Outstanding Issues Remaining: N/A

Stephanie Emory

Digitally signed by Stephanie Emory
Date: 8/09/2018 10:45:14AM
GUID: 56eb17470045bc2d4c3c9462af6ca8e3

Wendy Wilson- Lee

Digitally signed by Wendy Wilson- Lee
Date: 8/09/2018 10:46:51AM
GUID: 50816dbc000085595ca3284bbca465a8

DRUG PRODUCT

Product Background: Referenced to ANDA-075293 (paper application, paper review). No changes to product except labeling. The drug product is an aqueous solution of midazolam, benzyl alcohol, edetate sodium, sodium chloride, hydrochloric acid, sodium hydroxide, (b) (4) available as 10-mL stoppered glass vials containing 50 mg Midazolam.

NDA/ANDA (review cycle number): 209566 (1)

Drug Product Name / Strength: SEIZALAM™ (midazolam injection), 50 mg in 10mL per vial

Route of Administration: for intramuscular use

Applicant Name: Meridian Medical Technologies, Inc.

Review Recommendation: Adequate

Review Summary: *The drug product is an aqueous solution of midazolam, benzyl alcohol, edetate sodium, sodium chloride, hydrochloric acid, sodium hydroxide,* (b) (4) *available as 10-mL stoppered glass vials containing 50 mg Midazolam. All CMC information in this application is incorporated by reference to approved ANDA-075293 (Hospira) for Midazolam Injection, USP (Novaplus®). The environmental claim for categorical exclusion was found acceptable. No changes will be made to the product other than labeling, and there are no outstanding CMC supplements for the referenced ANDA, therefore the application is found to be adequate for drug product.*

List Submissions being reviewed (table):

Supporting Document #	Serial #	Description	Received Date
1	1	Original NDA submission	16Nov2017

Highlight Key Outstanding Issues from Last Cycle: N/A

Concise Description Outstanding Issues Remaining: N/A

R Regional Information

Environmental

The applicant has requested a claim of categorical exclusion pursuant to 21 CFR 25.31(b) and states that no extraordinary circumstances exist as described in 21 CFR 25.21. The Expected Introduction Concentration ($EIC_{aquatic}$) is calculated to be (b) (4) µg/ L.

Reviewer's Assessment: ***Adequate***

The EIC is well below 1 part per billion based on reasonable calculations.

Wendy Wilson- Lee

Digitally signed by Wendy Wilson- Lee
Date: 8/02/2018 01:02:30PM
GUID: 50816dbc000085595ca3284bbca465a8

Stephanie Emory

Digitally signed by Stephanie Emory
Date: 8/02/2018 02:33:10PM
GUID: 56eb17470045bc2d4c3c9462af6ca8e3

PROCESS

IQA Review Guide Reference

Product Background: The proposed drug product, Seizalam (midazolam injection), is a 505(b)(2) new drug application. Seizalam is indicated as a treatment of status epilepticus in adults. The manufacturing process includes the following manufacturing steps: (b) (4)

NDA/ANDA: NDA 209566

Drug Product Name / Strength: Midazolam Injection / (b) (4)

Route of Administration: Intramuscular injection

Applicant Name: Meridian Medical Technologies, Inc.

Review Recommendation: **Adequate**

Theme (ANDA only): **N/A**

Justification (ANDA only): N/A

Review Summary:
The manufacturing process information for NDA 209566 was cross-referenced to ANDA 075293 which was approved in 2000.

Adequate from the process standpoint for this NDA submission.

List Submissions being reviewed (table):

Document Reviewed	Description
11/16/2017	Original submission
01/23/2018	Quality information
03/28/2018	Quality information

Highlight Key Outstanding Issues from Last Cycle: N/A

Concise Description Outstanding Issues Remaining: N/A

List Number of Comparability Protocols (ANDA only): N/A

P.3 Manufacture

Batch Formula

(b) (4)

[redacted]

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(b) (4)

Applicant's Submission:
Please see the Microbiology review for detailed comments.

Reviewer's Assessment:

Please see the Microbiology review for detailed comments.

Comparability Protocols

Applicant's Submission:
N/A.

Reviewer's Assessment: N/A

Post-Approval Commitments (For NDA only)

Applicant's Submission:
N/A

Reviewer's Assessment: N/A

Lifecycle Management Considerations

Applicant's Submission:
N/A

Reviewer's Assessment:
N/A

List of Deficiencies:

None

Primary Process Reviewer Name and Date:

Yuesheng Ye, 8/01/2018.

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

I concur

N. Chidambaram, Ph.D., 08/02/2018

Yuesheng Ye

Digitally signed by Yuesheng Ye
Date: 8/02/2018 01:21:52PM
GUID: 5203e2c70001f9a26cd12224ab5f697d

Nallaperumal Chidambaram

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Date: 8/02/2018 03:07:53PM
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FACILITIES

IQA Review Guide Reference

Product Background: The proposed drug product, Seizalam (midazolam injection), is a 505(b)(2) new drug application. Seizalam is indicated as a treatment of status epilepticus in adults. The manufacturing process includes the following manufacturing steps: (b) (4)

NDA/ANDA: NDA 209566

Drug Product Name / Strength: Midazolam Injection / (b) (4)

Route of Administration: Intramuscular injection

Applicant Name: Meridian Medical Technologies, Inc

Review Recommendation: **Adequate**

Review Summary:
Following a review of the application and inspectional documents, there are no significant, outstanding manufacturing or facility risks that prevent approval of this application. The manufacturing facilities for NDA 209566 are found to be acceptable. No inspections were conducted as the facilities were cross referenced from approved ANDA 075293. The applicant clarified that the Hospira (b) (4) facility would only test an excipient and therefore is not considered in the final recommendation. However, it is noted that the pOAI findings do not implicate concerns about chemical testing capability or data reliability.

List Submissions being reviewed (table):

Document Reviewed	Description
11/16/2017	Original submission
08/17/2018	Facility Amendment

Highlight Key Outstanding Issues from Last Cycle: N/A

Concise Description Outstanding Issues Remaining: N/A

3.2.S.2 Manufacture

Summary of Facility Information:

(b) (4)

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(b) (4)

[redacted]

Comparability Protocols

Reviewer's Assessment:

N/A

Post-Approval Commitments (For NDA only)

Reviewer's Assessment:

N/A

Lifecycle Management Considerations

N/A

List of Deficiencies: None

Primary Facilities Reviewer Name and Date: Yuesheng Ye, 04/25/2018, 05/08/2018, 8/2/2018, 8/16/2018.

Secondary Reviewer Name and Date: Derek S. Smith, 05/08/2018, 8/20/2018

Yuesheng Ye

Digitally signed by Yuesheng Ye
Date: 8/20/2018 09:14:05AM
GUID: 5203e2c70001f9a26cd12224ab5f697d

Derek Smith

Digitally signed by Derek Smith
Date: 8/20/2018 10:07:14AM
GUID: 508da7480002bfe5d5fe14a12da3599d

BIOPHARMACEUTICS

Product Background:

NDA: 209566; 505(b)(2)

Drug Product Name / Strength: Seizalam® (midazolam hydrochloride) Injection, [Vial] 50 mg/10 mL (5 mg/mL)

Route of Administration: For Intramuscular Injection
Proposed New Indication: Treatment of Status Epilepticus in Patients ≥18 years old
Proposed Dosage: (b) (4) via intramuscular injection

Applicant Name: Meridian Medical Technologies (a Pfizer company)

Review Recommendation:
From the Biopharmaceutics perspective, NDA 209566 for Midazolam Injection, 50 mg/10 mL is recommended for **APPROVAL**.

Review Summary:
The proposed drug product (Hospira's Midazolam Injection, 50 mg/10 mL) was previously approved under ANDA 75293, based on the PK, efficacy and safety data of the Reference Listed Drug (RLD), Versed® (midazolam) Injection (NDA 18654, held by Hoffman La Roche). In the current 505(b)(2) NDA, the Applicant is seeking a new indication (i.e., treatment of status epilepticus) for the proposed drug product by relying on the PK, efficacy and safety data generated by the Applicant for Midazolam Auto-Injector (investigated under INDs 068432, 102540, and 102254; (b) (4) and PK data available for manually injected midazolam from approved labeling and literature based PK studies. Per 21 CFR 320.22(b)(1), the Applicant requested FDA to waive the requirement to conduct a formal *in vivo* BE study to directly compare Midazolam for Manual Injection and Midazolam Auto-Injector.

This Biopharmaceutics Review focused on the evaluation of the Applicant's biowaiver request, and formulation bridging.

This Biopharmaceutics Reviewer concludes that the Applicant's biowaiver request is not needed to support the proposed new indication for the already marketed drug product because PK data were provided to allow for a cross-study comparison of the manually injected (test) and the auto-injected (reference) midazolam solution drug products. From a formulation bridging perspective, it is acceptable/appropriate to consider the existing PK data provided for the manually injected midazolam solution in this NDA to support the bridge especially the literature PK data generated using Versed® that is qualitatively and quantitatively (Q1/Q2) the same as the proposed drug product. Additionally, the compositions of the midazolam solutions in (as well as the physico-chemical and microbiological properties of) the proposed drug product (Midazolam for Manual Intramuscular Injection) and Midazolam IM Auto-Injector (which was used in the clinical PK, efficacy, safety trials conducted to support

approval of the status epilepticus indication) are the same, except for a slightly lower benzyl alcohol content (10 versus 10.45 mg/mL), and target solution pH (3.0 vs. 3.3) for the proposed drug product. Such slight difference in benzyl alcohol content and solution pH between these two formulations is not expected to contribute significantly to PK and safety differences following intramuscular injection of the same midazolam doses, i.e., if assuming that the difference in the manner of administrations (manual vs. auto-injection) does not affect midazolam PK. The PK (and consequently, clinical efficacy and safety) bridge between the proposed drug product and the Investigational drug product is considered established because (1) the Clinical Pharmacology Reviewer confirmed the Applicant's claim of comparable midazolam PK between the manually injected solution product (e.g., Versed® [NDA 18654]) and the investigational auto-injected midazolam solution drug product that was tested in status epilepticus patients, and (2) Versed® and the proposed drug product [ANDA 75293] are Q1/Q2 the same. Of note, in relation to the benzyl alcohol excipient (as preservative (b) (4)), per FDA recommendation, the labeling will state that Midazolam for Manual Injection is not indicated for use in neonates and infants.

List of Submissions reviewed:
SDN-1, 11/16/2017 (Original NDA)
SDN-2, 1/23/2018 (Response to Quality Information Request)

Concise Description Outstanding Issues Remaining:
None

Bridging of Formulations

Reviewer's Assessment: *ADEQUATE*

Between the Proposed Drug Product and the Midazolam for Manual Intramuscular (IM) Injection Products used in Literature-Based PK Studies

Note that 1 of the 4 published PK studies (i.e.,Wermeling 2006) explicitly identified Versed® as the drug product evaluated; the remaining literature-based PK studies used US or globally sourced Hoffmann-La Roche midazolam products. Formulation bridging *per se* is not needed between the proposed drug product (Midazolam for Manual Injection) and the formulation evaluated in the Wermeling (2006) PK study because the proposed drug product (approved under ANDA 75293, and the designated Reference Standard [RS]) is Q1/Q2 the same as Versed® (the Reference Listed Drug [RLD]).

Between the Proposed Drug Product (Midazolam for Manual Intramuscular [IM] Injection] and the Product Investigated in Status Epilepticus Trials (Midazolam IM Auto-Injector]

The formulations of the midazolam solution in the marketed generic product (Midazolam for Manual IM Injection) and the Investigational Drug Product (Midazolam IM Auto-Injector) are essentially the same, i.e., with only minor differences in benzyl alcohol content [(10.45 mg/mL (1% w/v) vs 10 mg/mL (1% w/v)]

and target solution pH (3.3 vs. 3.0). [For a detailed comparison of the formulation and other quality attributes of the test and reference midazolam injectable solution drug products, refer to Table 1 of Section 1.12.15 Biowaiver Request.] These small differences in benzyl alcohol content and solution pH are typically not anticipated to impact the relative (midazolam) PK, efficacy and safety of the parenteral solution. However, because there is a difference in the mode/manner of intramuscular injection between these two drug products (i.e., manual vs. auto- injection), in addition to the supportive *in vitro*-based formulation bridging, evidence of *in vivo* PK comparability to the Midazolam Auto-Injectors (investigated in clinical efficacy and safety trials involving status epilepticus patients) is needed to support the approval of the proposed new indication of the current NDA (marketed generic) Midazolam for Manual Injection.

Note that based on the data provided in Table 1A of 1.12.15 Biowaiver Request, the functional performance characteristics (i.e., activation force, volume dispensed, dispensing time, extended needle length, and leakage rate) of the various Investigational Midazolam Auto-Injectors used during clinical development are either the same or comparable.

Biowaiver Request

Reviewer's Assessment:
BIOEQUIVALENCE (BE) BIOWAIVER REQUEST NOT NEEDED

The Applicant requested FDA to waive the requirement to conduct a head-to-head relative bioavailability study between Midazolam for Manual IM injection and Midazolam IM Auto-Injector, i.e., the proposed drug product and the drug product that was investigated in the relevant clinical efficacy/safety/PK trials, respectively. The Applicant specifically cited 21 CFR 320.22(b)(1) as the basis of this biowaiver request because the formulation composition of the midazolam solution in the ANDA/NDA drug product (presented as a vial, for manual injection) is [essentially] the same as that used in the IND (auto-injector) product, and both solution drug products are intended solely for parenteral administration. As indicated above, the critical PK bridge between the Applicant's Midazolam IM Auto-Injectors (IND products) and the marketed generic Midazolam for Manual IM Injection (the current 505b2 NDA product) is based on cross-study comparison of the PK data generated in studies conducted by the Applicant using the Investigational Products (INDs 068432 and 102540), and the PK data reported in four published literature studies and the approved labeling for the Manual Injection product.

This Reviewer determines that the Applicant's biowaiver request is NOT needed because *in vivo* PK data or information are available for the proposed and the two reference drug products.

- The proposed drug product is qualitatively and quantitatively (Q1/Q2) the same as Versed® (RLD), and is now the designated Reference Standard (RS) because the RLD is no longer marketed (not for reasons related to safety and efficacy). Thus, it

is appropriate to extrapolate to the proposed drug product the PK data of Versed® (as is reflected in the approved US package inserts of the RS and the RLD), and consequently, to extend to the proposed drug product any PK bridge established between the Applicant's Midazolam Auto-Injector and Versed®.

- Following single dose intramuscular administration [into the vastus lateralis] of 5 mg midazolam as the Auto-Injector in PK Study 11903, the mean C_{max}, mean $AUC_{0\text{-}inf}$ and median T_{max} (61.7 ng/mL, 214.5 ng*h/mL, 0.60 h) appear to be similar to those following single dose IM administration [into an unspecified site] of 5 mg midazolam as Versed® (59 ng/mL, 175 ng*h/mL, 0.50 h; Wermeling 2006). Note that the Applicant considers PK Study 11903 and the study conducted by Wermeling (2006) to be of similar study design. Note also that the Clinical Pharmacology Reviewer (Dr. Dawei Li) confirmed that following administrations of Midazolam IM-Injector and Midazolam IM Manual Injection, the midazolam PK parameters are comparable in studies with similar design and demographic.
- For the comparison of the PK parameters following administration of the Midazolam IM Auto-Injector in the Applicant's PK Studies and following administration of Midazolam Manual IM Injection in the 3 other literature-based PK studies, and the study design information, refer to Table 3 of Section 1.12.15 Biowaiver Request. This Reviewer notes that the exact formulation compositions of the midazolam injection drug products used in the PK studies conducted by Bell 1991 (Hypnoval® 10 mg/mL, Roche Products Ltd./United Kingdom), Holazo 1988 (midazolam, Hoffmann La-Roche/New Jersey), and Crevoisier 1981 (Dormicum®, Hoffman La-Roche/Basel) were not provided in these publications. According to online sources, the composition of Dormicum® and Hypnoval® might not be exactly the same as the proposed drug product; however, refer to the accompanying PK information. Consult the Clinical Pharmacology Review for the evaluation of the provided midazolam PK data in the literature studies.

For the evaluation of the acceptability of the Applicant's proposed new indication and dosage (i.e., single 10 mg IM dose for the treatment of status epilepticus in patients ≥18 years of age) for the already approved generic drug product, this Reviewer defers to the Medical and Clinical Pharmacology Reviewers.

List of Deficiencies:
None

Primary Biopharmaceutics Reviewer Name and Date:
Gerlie Gieser, Ph.D. (8/1/2018)

Secondary Reviewer Name and Date:
Ta-Chen Wu, Ph.D. (8/1/2018)

Gerlie Gieser

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Date: 8/01/2018 12:52:02PM
GUID: 507592ba00003d190b2ea34fe8fb8ccb

Ta-Chen Wu

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MICROBIOLOGY

Product Background

NDA: 209566

Drug Product Name / Strength: Seizalam (midazolam injection) Multiple-Dose Vials (packaged as 50 mg in 10 mL, 10 mL fill in a 10 mL vial)

Route of Administration: IM injection

Applicant Name: Meridian Medical Technologies, Inc.

Manufacturing Site:
Hospira, Inc.
(b) (4)

Method of Sterilization: (b) (4)

Review Recommendation: **Adequate**

Theme (ANDA only): **N/A**

Justification (ANDA only): N/A

Review Summary: ANDA 075293 is cited for the entirety of the CMC. The drug product is (b) (4) released by parametric release rather than by sterility testing.

List Submissions Being Reviewed:

Submit	Received	Assigned to Reviewer
11/16/17	11/16/17 (SD#1)	11/21/17
02/13/18	02/13/18 (SD#4) [a]	N/A

[a] Response to Filing Communication, includes updated labeling

Highlight Key Outstanding Issues from Last Cycle: N/A. This is a first cycle review.

Remarks: The subject of review is submitted electronically (eCTD). Some tables in this review are excerpted from the electronic submission. All references to Module, Section, and pdf documents in this review are from the ANDA submission dated 11/16/17 except where noted otherwise.

Concise Description Outstanding Issues Remaining: None

Supporting Documents:

- ANDA 075293 (approved 06/20/2000) and associated microbiology reviews 75-293.doc, 06/29/99, by A. High and A075293S019MR01.doc, 05/31/18, L. Ashmore – for original ANDA and AET
- ANDA 062420 (b) (4) including ANDA 75293/ (b) (4), cited in the NDA) and associated microbiology review A62420S026R01.doc, 05/08/18, L. Ashmore – for (b) (4) clarification of parametric release parameters, and tightening of specifications.

List Number of Comparability Protocols (ANDA only): N/A

Filename: N209566MR01.docx

S Drug Substance – N/A

P Drug Product

Note to reviewer: Sections 3.2.P.1, 3.2.P.2, 3.2.P.3, 3.2.P.5, and 3.2.P.7 refer to ANDA 075293 (Hospira). An LOA is provided in Section 1.4.2. A table in Section 1.4.4, Cross-Reference to Previously Submitted Information (cross-ref.pdf, pp. 1-6 of 6) indicates the location in the ANDA 075293 (i.e., submission type, SN number, and submit date) that corresponds to each NDA Module 3 eCTD section heading. The pertinent information is excerpted below.

Previously Submitted Module 3 Sections	CTD Format (Yes/No)	Location of Information in Current ANDA			Additional Information
		Submission Type	Submission (Serial) Number	Submission Date	
3.2.P.1 – Description and Composition of the Drug Product					
3.2.P.1	Yes	Prior Approval Supplement	S-14	03 JUN 2011	(b) (4)
3.2.P.2 – Pharmaceutical Development					
3.2.P.2	No	Original ANDA	Original Submission	06 JUL 2004	
3.2.P.3 – Manufacture					
3.2.P.3.1	Yes	Annual Report	R-17	08 AUG 2017	
3.2.P.3.3	Yes	Annual Report	R-17	08 AUG 2017	
3.2.P.3.4	Yes	Annual Report	R-17	08 AUG 2017	
3.2.P.3.5	Yes	Annual Report	R-17	08 AUG 2017	
3.2.P.3.7	Yes	CBE-30	Submisison sequence number 0004	01 NOV 2016	
3.2.P.3.8	Yes	CBE-30	Submisison sequence number 0004	01 NOV 2016	

(b) (4)

3.2.P.3.3.9	Yes	CBE-30	Submisison sequence number 0004	01 NOV 2016
3.2.P.3.3.10	Yes	CBE-30	Submisison sequence number 0004	01 NOV 2016
3.2.P.3.3.11	Yes	CBE-30	Submisison sequence number 0004	01 NOV 2016
3.2.P.3.4	Yes	Annual Report	R-17	08 AUG 2017
3.2.P.3.5 and 3.2.P.3.5.1	Yes	CBE-30	Submisison sequence number 0004	01 NOV 2016
3.2.P.5 – Control of Drug Product				
3.2.P.5.1	Yes	CBE-30	Submisison sequence number 0004	01 NOV 2016
3.2.P.7 – Container Closure System				
3.2.P.7	Yes	Annual Report	R-17	07 AUG 2015
3.2.P.8 – Stability				
3.2.P.8	Yes	Annual Report	R-17	08 AUG 2017
3.2.A – Appendices				
3.2.A	No	N/A	N/A	N/A
3.2.R – Regional Information				
3.2.R (32R1)	Yes	Prior Approval Supplement	S-14	03 JUN 2011

(excerpt from SN0001, 11/16/17, Section 1.4.4, cross-ref.pdf, pp. 3-6 of 6)

This reviewer has confirmed that the referenced information is acceptable on the basis of sterility assurance as indicated below.

P.1 Description of the Composition of the Drug Product

Refers to ANDA 075293 (Hospira) for details regarding the description and composition of the drug product.

Notes to reviewer:

- The description and composition of the drug product has been reviewed and found adequate in ANDA 75-293/S-014 (approved 05/20/12) (quality review 75293S14_75856S08_75857S11.pdf, 05/16/12, by M. Rahman).
- ANDA 075293 includes two strengths and three vial sizes (see table below). The NDA 209566 356h and package insert indicate that only one strength / vial size (i.e., the 5 mg/mL (50 mg/10 mL) strength, 10 mL fill in 10 mL vial) is included in the subject NDA.

Current ANDA 075293

List No.	Strength	Fill volume	Container size
2587	1 mg/mL (10 mg/10 mL) *	10 mL	10 mL *
2596	5 mg/mL (25 mg/5 mL)	5 mL fill	5 mL
2596	5 mg/mL (50 mg/10 mL)	10 mL fill	10 mL

*In the original ANDA, the 1 mg/mL strength was supplied as a 1 mL fill in a 2 mL vial. In the current ANDA, the 1 mg/mL strength is supplied as a 10 mL fill in a 10 mL vial.

Note: Only the 5 mg/mL (50 mg/10 mL) strength, 10 mL fill in a 10 mL vial is included in this NDA.

Reviewer's Assessment: ***Adequate***

P.2 Pharmaceutical Development

Refers to ANDA 075293 (Hospira) for details regarding pharmaceutical development of the drug product. Section 3.2.P.2 remains unchanged since the original ANDA.

Note to reviewer: The original ANDA 075293 (approved 06/20/2000) has been reviewed and found adequate (microbiology review 75-293.doc, 06/29/99, by A. High). However, the original ANDA did not include any antimicrobial effectiveness testing. The applicant was requested to provide such testing for this multiple dose drug product. See comment below. The requested information was provided in ANDA 075293 (b) (4) (submit date 05/16/18), reviewed and found adequate (microbiology review A075293S019MR01.doc, 05/31/18, L. Ashmore).

Comment: *(conveyed to the applicant via Information Request (IR) dated 04/30/18) It is noted that the subject drug product is intended for multiple doses and contains benzyl alcohol as a preservative. Information to demonstrate the antimicrobial effectiveness of this preservative could not be located in the referenced ANDA 075293. Please provide the location within the ANDA (e.g., submission date, section, page) or else please provide a data summary for the Antimicrobial Effectiveness Test (AET), as per USP <51> or equivalent. Testing should be performed on product formulated with the preservative, at or below the lowest preservative concentration listed on the finished product release specification or stability specification, whichever is lower.*

Reviewer's Assessment: ***Adequate***

P.3 Manufacture

Refers to ANDA 075293 (Hospira) for details regarding the manufacture of the drug product including manufacturers, batch formula, description of manufacturing process and process controls, controls of critical steps, and process validation and/or evaluation.

Note to reviewer: The original ANDA 075293 (approved 06/20/2000) has been reviewed and found adequate (microbiology review 75-293.doc, 06/29/99, by A. High). Additional ANDA supplements since then have been reviewed and found acceptable.

Reviewer's Assessment: ***Adequate***

P.5 Control of Drug Product

Refers to ANDA 075293 (Hospira) for details regarding the control of the drug product including specifications, analytical procedures, and validation of analytical procedures.

Note to reviewer: The original ANDA 075293 (approved 06/20/2000) was previously reviewed and found adequate (microbiology review 75-293.doc, 06/29/99, by A. High). Additional ANDA supplements since then have been reviewed and found acceptable.

Reviewer's Assessment: ***Adequate***

P.7 Container Closure

Refers to ANDA 075293 (Hospira) for details regarding the container closure system.

Notes to reviewer: The original ANDA 075293 (approved 06/20/2000) was previously reviewed and found adequate (microbiology review 75-293.doc, 06/29/99, by A. High). Additional ANDA supplements since then have been reviewed and found acceptable.

Reviewer's Assessment: ***Adequate***

P.8 Stability

Refers to ANDA 075293 (Hospira) for details regarding stability including the stability summary and conclusion, postapproval stability protocol and stability commitment, and stability data.

Note to reviewer: The original ANDA 075293 (approved 06/20/2000) was previously reviewed and found adequate (microbiology review 75-293.doc, 06/29/99, by A. High). This reviewer confirms that the most recent stability data (Annual Report 17, 08/08/17) complies with the specifications for the microbiological tests.

Reviewer's Assessment: ***Adequate***

A Appendices

A.2 Adventitious Agents Safety Evaluation

Refers to ANDA 075293 (Hospira) for details regarding adventitious agents safety evaluation.

Note to reviewer: The original ANDA 075293 (approved 06/20/2000) was previously reviewed and found adequate (microbiology review 75-293.doc, 06/29/99, by A. High).

Reviewer's Assessment: ***Adequate***

A.2.1 Materials of Biological Origin – N/A

A.2.2 Testing at Appropriate Stages of Production – N/A

A.2.3. Viral Testing of Unprocessed Bulk – N/A

A.2.4 Viral Clearance Studies – N/A

R Regional Information

Refers to ANDA 075293 (Hospira) for any details regarding executed batch records and comparability protocols.

Note to reviewer: The original ANDA 075293 (approved 06/20/2000) was previously reviewed and found adequate (microbiology review 75-293.doc, 06/29/99, by A. High). There are no comparability protocols.

Reviewer's Assessment: ***Adequate***

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

2.A. Package Insert

Storage temperature: 20-25°C
Route of administration: IM injection
Container: Multiple dose vial

Reviewer's Assessment: ***Adequate***

Post-Approval Commitments: **N/A**

List of Deficiencies: None

Primary Microbiology Reviewer Name and Date: Lisa S.G. Ashmore, Ph.D., 05/31/18
Secondary Reviewer Name and Date (and Secondary Summary, as needed): Bryan S. Riley, Ph.D., 05/31/18

Lisa Ashmore (Shelton)

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/s/

HAROLD S SANO
09/18/2018