

**CENTER FOR DRUG EVALUATION AND
RESEARCH**

APPLICATION NUMBER:

202106Orig1s000

CHEMISTRY REVIEW(S)



My Work Projects Reporting Timesheet



NDA 202106-Orig1-Resubmission/Class 2(14) - Manufacturing Facility Inspection

Overall Manufacturing Inspection Recommendation

Task Summary Task Details Issues Updates **Inspection Management Form**

Request More Access | Task Actions

Assigned To

OPF Reviewer

Steven Hertz

Edit Assignment

This was done on
Apr 29, 2015
(Today)

Status
Complete

This task is waiting on
2 Tasks

Last Update
Apr 29, 2015

Submitted On
Oct 31, 2014

Reference Number
2863201

Inspection Management Form

As of 2:25 PM

Inspection Management Form

NDA 202106-Orig1-Resubmission/Class 2(14)

Facility - (b) (4) | 3002806297 | (b) (4) Approve

⚠ FACTA FARMACEUTICI SPA | 3006028606 | (b) (4)
DRUGS | Approve Facility - 2016-05-23

Facility DUNS Number:
430264268

Action Indicated Status: Official Action Indicated ⚠

District Office Recommendation:
Approve Facility

District Office Recommendation
Reasons:
Adequate Firm Response

District Office Decision Factors:

Office of Process and Facilities
Recommendation:
Approve Facility

Office of Process and Facilities
Recommendation Reasons:
District Recommendation

Office of Process and Facilities
Re-Evaluation Date:
2016-05-23

Overall Manufacturing Inspection Recommendation

Approve
Withhold

Overall Application Re-evaluation Date
10/17/14

Cancel

Facilities

NDA 202106

Meropenem for Injection USP and Sodium Chloride Injection USP in the Duplex Container

B. Braun Medical Inc.

Lin Qi, Ph.D.
Review Chemist

PABVII/DPAIII/OPF

For the Division of Anti-Infective Products

Table of Contents

CMC Review Data Sheet	3
The Executive Summary	7
I. Recommendations	7
A. Recommendation and Conclusion on Approvability	7
B. Recommendation on Phase 4 (Post-Marketing) Commitments, Agreements, and/or Risk Management Steps, if Approvable	7
II. Summary of CMC Assessments	7
A. Description of the Drug Product(s) and Drug Substance(s)	7
B. Description of How the Drug Product is Intended to be Used	8
C. Basis for Approvability or Not-Approval Recommendation	9
III. Administrative	9
Review Note:	10

CMC Review Data Sheet

CMC Review Data Sheet

1. NDA 202106

2. REVIEW #: 2

3. REVIEW DATE: 4/29/15

4. REVIEWERS:

Primary: Lin Qi, Ph.D.
Secondary: Dorota Matecka, Ph.D.
Balajee Shanmugam, Ph.D.

5. PREVIOUS DOCUMENTS:

<u>Previous Documents</u>	<u>Document Date</u>
CMC only pre-NDA meeting	11/4/2010
Original NDA Submission	9/27/2013
Amendment	1/6/2014
Amendment	3/24/2014
Amendment	3/25/2014
Amendment	5/12/2014
Amendment	5/27/2014
Amendment	6/12/2014
Amendment	6/19/2014

6. SUBMISSION(S) BEING REVIEWED:

<u>Submission(s) Reviewed</u>	<u>Document Date</u>
Original NDA/Resubmission	10/30/2014
Amendment/Labeling	4/10/2015

7. NAME & ADDRESS OF APPLICANT:

Name: B. Braun Medical Inc.
Address: 901 Marcon Blvd.
Allentown, PA 18109
USA

Representative: Rebecca Stolarick

CMC Review Data Sheet

Telephone: 610-596-2536
Email: Rebecca.stolarick@bbraun.com

8. DRUG PRODUCT NAME/CODE/TYPE:

- a) Proprietary Name: N/A
b) Non-Proprietary Name: Meropenem for Injection USP and Sodium Chloride Injection USP in the Duplex Container
c) Code Name/# (ONDQA only): N/A
d) Chem. Type/Submission Priority (ONDQA only):
 - Chem. Type: 3
 - Submission Priority: S

9. LEGAL BASIS FOR SUBMISSION: 505(b)(2)

10. PHARMACOL. CATEGORY: Antibiotic

11. DOSAGE FORM: Injection

12. STRENGTH/POTENCY: 0.5 gram and 1 gram

13. ROUTE OF ADMINISTRATION: Intravenous

14. Rx/OTC DISPENSED: Rx OTC15. [SPOTS \(SPECIAL PRODUCTS ON-LINE TRACKING SYSTEM\)](#):

SPOTS product – Form Completed

Not a SPOTS product

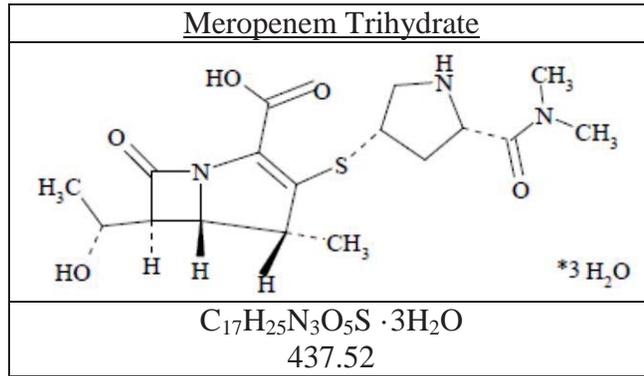
16. CHEMICAL NAME, STRUCTURAL FORMULA, MOLECULAR FORMULA, MOLECULAR WEIGHT:

CHEMICAL NAME:

1-Azabicyclo[3.2.0]hept-2-ene-2-carboxylic acid, 3-[[5-[(dimethylamino)carbonyl]-3-pyrrolidinyl]thio]-6-(1-hydroxyethyl)-4-methyl-7-oxo, trihydrate, [4R-[3(3S*,5S*),4 α ,5 β ,6 β (R*)]]-

CMC Review Data Sheet

STRUCTURAL FORMULA:



(b) (4)

17. RELATED/SUPPORTING DOCUMENTS:

A. DMFs:

DMF #	TYPE	HOLDER	ITEM REFERENCED	CODE ¹	STATUS ²	DATE REVIEW COMPLETED	COMMENTS (LOA Date)
(b) (4)	II	(b) (4)	(b) (4)	1	Adequate	6/20/2014	3/15/2013
(b) (4)	III	(b) (4)	(b) (4)	4	N/A		7/13/2010
(b) (4)	III	(b) (4)	(b) (4)	4	N/A		7/21/2010
(b) (4)	III	(b) (4)	(b) (4)	4	N/A		7/12/2010
(b) (4)	III	(b) (4)	(b) (4)	4	N/A		7/19/2010
(b) (4)	III	(b) (4)	(b) (4)	4	N/A		2/4/2009
(b) (4)	III	(b) (4)	(b) (4)	4	N/A		11/19/2009
(b) (4)	III	(b) (4)	(b) (4)	4	N/A		3/8/2010

¹ Action codes for DMF Table:

1 – DMF Reviewed.

Other codes indicate why the DMF was not reviewed, as follows:

2 –Type 1 DMF

3 – Reviewed previously and no revision since last review

CMC Review Data Sheet

- 4 – Sufficient information in application
- 5 – Authority to reference not granted
- 6 – DMF not available
- 7 – Other (explain under "Comments")

² Adequate, Inadequate, or N/A (There is enough data in the application, therefore the DMF did not need to be reviewed)

B. Other Documents: None

18. STATUS:

ONDQA:

CONSULTS/ CMC RELATED REVIEWS	RECOMMENDATION	DATE	REVIEWER
Biometrics			
EES	Acceptable	4/29/2015	Steven Hertz
Pharm/Tox			
Biopharm	Acceptable	6/2/2014	Elsbeth Chikhale
LNC			
Methods Validation	Acceptable	6/20/2014	Lin Qi
DMEPA*	Acceptable with labeling comments	6/10/2014	Aleksander Winiarski
EA	Categorical exclusion (see review)	6/20/2014	Lin Qi
Microbiology	Acceptable	6/30/2014	Vinayak Pawar

*DMEPA: Division of Medication Error Prevention and Analysis

Executive Summary Section

The CMC Review for NDA 202106

The Executive Summary

I. Recommendations

A. Recommendation and Conclusion on Approvability

The CMC information as amended in the NDA is adequate to assure the identity, strength, purity, and quality of Meropenem for Injection USP and Sodium Chloride Injection USP. The Overall Manufacturing Inspection Recommendation by the Office of Process and Facility is “Acceptable”.

Labeling and labels are considered acceptable by the review team.

Therefore, from the CMC perspective, this NDA is recommended for approval.

B. Recommendation on Phase 4 (Post-Marketing) Commitments, Agreements, and/or Risk Management Steps, if Approvable

No recommendations at this time.

II. Summary of CMC Assessments

A. Description of the Drug Product(s) and Drug Substance(s)

(1) Drug Substance

The drug substance, Meropenem for Injection (Sterile Bulk) is a sterile mixture of Meropenem Trihydrate and Sodium Carbonate USP/NF. The chemistry, manufacturing, and controls information for Meropenem for Injection (Sterile Bulk) is provided in the Type II DMF (b) (4) held by (b) (4) the drug substance manufacturer. A Letter of Authorization dated March 15, 2013 is provided in Module 1.4.1. The most recent DMF Review#4 dated June 20, 2014 found DMF (b) (4) adequate to support the current NDA.

Executive Summary Section

(2) Drug Product

The drug product (Meropenem for Injection USP and Sodium Chloride Injection USP in the Duplex® Container) is sterile, nonpyrogenic and packaged in a single use, dual chamber container. It consists of Meropenem for Injection (Sterile Bulk) in one chamber and 0.9% Sodium Chloride Injection USP (diluent) in the other chamber. The sterile bulk powder and the diluent were filled into separate chambers (b) (4) in FACTA FARMACEUTICI S.p.A., Teramo, Italy. The sterile bulk used in the current product is USP compendial (b) (4)

The drug product (Meropenem for Injection USP) is controlled by testing for Appearance, Identification, Constituted Solution USP, Particulate Matter, Clarity of Solution, Color of Solution, pH, Reconstitution time, Loss on drying, Assay, Uniformity of dosage, Impurities, Content of Sodium, Filling weight, Filling volume, Sterility, and Bacterial Endotoxin. The diluent (Sodium Chloride Injection USP) is controlled by testing Appearance, Identification, Assay, Iron, pH, and Heavy metals. Sterility and Bacterial Endotoxin tests are not performed on the diluent, since they are performed on the reconstituted solution. No residual solvents or metal catalysts are introduced during the manufacturing of the drug product, since the drug product contains only the drug substance.

The Duplex container system is the same container system used in all of B. Braun marketed drug products. The proposed expiry dating under the proposed storage conditions for the drug product is supported by 12 months long-term and 6 months accelerated stability data.

Proposed Storage Conditions:

Prior to reconstitution: Store the unactivated unit at 20–25°C (68–77°F). Excursion permitted to 15–30°C. [See USP Controlled Room Temperature.] Protect from freezing. After reconstitution: Use within 1 hour if stored at room temperature or within 15 hours if stored under refrigeration.

Expiration Dating for Meropenem for Injection USP and Sodium Chloride Injection USP in the DUPLEX (b) (4) Container:

Manufactured Configuration (Intact):	24 months
After Removal of Foil Strip:	7 days
After Activation:	1 hour at room temperature (25°C (b) (4)) or 15 hours under refrigeration (5°C (b) (4))

B. Description of How the Drug Product is Intended to be Used

Meropenem for Injection USP and Sodium Chloride Injection USP is a penem antibacterial indicated as single agent therapy for the treatment of complicated skin and skin structure infections and complicated intra-abdominal infections.

Executive Summary Section

The finished drug product consists of Meropenem for Injection (Sterile Bulk) in one chamber and 0.9% Sodium Chloride Injection USP in the other chamber. The two chambers are separated by a peelable seal which is activated prior to use to constitute the drug powder in the diluent. Prior to administration, the peelable foil is removed and pressure is applied on the diluent chamber to release the diluent into the drug chamber. This allows the drug substance, Meropenem for Injection (Sterile Bulk), to be mixed and dissolved in the diluent in a closed and sterile system. Two strengths, 500 mg and 1 g, were proposed for the drug product. The dosage of the drug product is 500 mg or 1 g every 8 hours by intravenous infusion over 15 to 30 minutes.

C. Basis for Approvability or Not-Approval Recommendation

Basis for Approvability:

- The formulation and manufacturer of the sterile bulk powder is [REDACTED] (b) (4)
- As amended, the tests and acceptance criteria in the updated drug product specification will provide reasonably consistent product controls.
- The available stability data support the proposed expiring dating under the proposed storage conditions.
- Dr. Elsbeth G Chikhale recommended for “Approval” in her Biopharmaceutics Review dated June 2, 2014.
- Dr. Pawar, Vinayak recommended for “Approval” in his Quality Microbiology Review dated June 30, 2014.
- Satisfactory inspection results were obtained for re-inspection of the drug product manufacturer. The Overall Manufacturing Inspection Recommendation by the Office of Process and Facility is “Acceptable”.
- Labeling and labels are considered acceptable by the review team. The [REDACTED] (b) (4) [REDACTED] was replaced with “Duplex Container” in the labeling of the current NDA as recommended.

III. Administrative

A. Reviewer’s Signature: See Page 10 for signatures

Lin Qi, CMC Reviewer, for NDPBIII/DNDPI/ONDP

B. Endorsement Block:

Balajee Shanmugam, Branch Chief, NDPBIII/DNDPI/ONDP

C. CC Block: *(entered electronically in Panorama)*

CMC Assessment Section

Review Note:

A CR letter was sent to the applicant in July 25, 2014, because the Overall Recommendation from the Office of Compliance was “WITHHOLD”. The labeling and labels were not finalized at that time. One labeling comment was sent in the CR letter recommending to replace [redacted] (b) (4) with “Duplex Container”.

A resubmission was provided in 10/30/2014. The [redacted] (b) (4) was replaced with “Duplex Container” in the current labeling as recommended. The updated labeling and labels were considered acceptable by the review team. Satisfactory inspection results were obtained from the re-inspection of the drug product manufacturer. The Overall Manufacturing Inspection Recommendation by the Office of Process and Facilities is “**Approval**”.

The CMC information as amended in the NDA is adequate to assure the identity, strength, purity, and quality of Meropenem for Injection USP and Sodium Chloride Injection USP. Therefore, from the CMC perspective, this NDA is recommended for **APPROVAL**.

Lin Qi
4/29/15

Lin Qi -S

Digitally signed by Lin Qi -S
DN: c=US, o=U.S. Government,
ou=HHS, ou=FDA, ou=People,
cn=Lin Qi -S,
0.9.2342.19200300.100.1.1=1300
213682
Date: 2015.04.29 14:55:34 -04'00'

Balajee Shanmugam
4/29/15

Balajee
Shanmugam -
S

Digitally signed by Balajee
Shanmugam -S
DN: c=US, o=U.S. Government,
ou=HHS, ou=FDA, ou=People,
0.9.2342.19200300.100.1.1=130021
7143, cn=Balajee Shanmugam -S
Date: 2015.04.29 15:09:48 -04'00'

NDA 202106

Meropenem for Injection USP and Sodium Chloride Injection USP in the Duplex Container

B. Braun Medical Inc.

Lin Qi, Ph.D.
Review Chemist

**Office of New Drug Quality Assessment
Division II, Branch V**

For the Division of Anti-Infective Products

Table of Contents

CMC Review Data Sheet.....3

The Executive Summary7

I. Recommendations.....7

 A. Recommendation and Conclusion on Approvability..... 7

 B. Recommendation on Phase 4 (Post-Marketing) Commitments, Agreements, and/or Risk Management Steps, if Approvable..... 7

II. Summary of CMC Assessments7

 A. Description of the Drug Product(s) and Drug Substance(s)..... 7

 B. Description of How the Drug Product is Intended to be Used..... 8

 C. Basis for Approvability or Not-Approval Recommendation..... 9

III. Administrative.....10

 Review Note:..... 11

 Attachment: Establishment Evaluation Report..... 12

CMC Review Data Sheet

CMC Review Data Sheet

1. NDA 202106

2. REVIEW #: 1 - Addendum #1

3. REVIEW DATE: 7/23/2014

4. REVIEWERS:

Primary: Lin Qi, Ph.D.

Secondary: Dorota Matecka, Ph.D.

Rapti Madurawe, Ph.D.

5. PREVIOUS DOCUMENTS:

Previous Documents

CMC only pre-NDA meeting

Document Date

11/4/2010

6. SUBMISSION(S) BEING REVIEWED:

Submission(s) Reviewed

Original NDA Submission

Amendment

Amendment

Amendment

Amendment

Amendment

Amendment

Amendment

Document Date

9/27/2013

1/6/2014

3/24/2014

3/25/2014

5/12/2014

5/27/2014

6/12/2014

6/19/2014

7. NAME & ADDRESS OF APPLICANT:

Name: B. Braun Medical Inc.

Address: 901 Marcon Blvd.
Allentown, PA 18109
USA

Representative: Rebecca Stolarick

Telephone: 610-596-2536

Email: Rebecca.stolarick@bbraun.com

CMC Review Data Sheet

8. DRUG PRODUCT NAME/CODE/TYPE:

- a) Proprietary Name: N/A
b) Non-Proprietary Name: Meropenem for Injection USP and Sodium Chloride Injection USP in the Duplex Container
c) Code Name/# (ONDQA only): N/A
d) Chem. Type/Submission Priority (ONDQA only):
 - Chem. Type: 3
 - Submission Priority: S

9. LEGAL BASIS FOR SUBMISSION: 505(b)(2)

10. PHARMACOL. CATEGORY: Antibiotic

11. DOSAGE FORM: Injection

12. STRENGTH/POTENCY: 0.5 gram and 1 gram

13. ROUTE OF ADMINISTRATION: Intravenous

14. Rx/OTC DISPENSED: Rx OTC15. [SPOTS \(SPECIAL PRODUCTS ON-LINE TRACKING SYSTEM\)](#): SPOTS product – Form Completed Not a SPOTS product

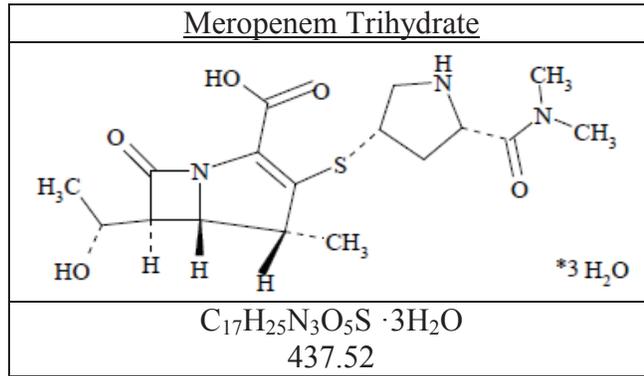
16. CHEMICAL NAME, STRUCTURAL FORMULA, MOLECULAR FORMULA, MOLECULAR WEIGHT:

CHEMICAL NAME:

1-Azabicyclo[3.2.0]hept-2-ene-2-carboxylic acid, 3-[[5-[(dimethylamino)carbonyl]-3-pyrrolidinyl]thio]-6-(1-hydroxyethyl)-4-methyl-7-oxo, trihydrate, [*4R*-[3(*3S**,*5S**),*4α*,*5β*,*6β*(*R**)]]-

CMC Review Data Sheet

STRUCTURAL FORMULA:



(b) (4)

17. RELATED/SUPPORTING DOCUMENTS:

A. DMFs:

DMF #	TYPE	HOLDER	ITEM REFERENCED	CODE ¹	STATUS ²	DATE REVIEW COMPLETED	COMMENTS (LOA Date)
(b) (4)	II	(b) (4)	(b) (4)	1	Adequate	6/20/2014	3/15/2013
(b) (4)	III	(b) (4)	(b) (4)	4	N/A		7/13/2010
(b) (4)	III	(b) (4)	(b) (4)	4	N/A		7/21/2010
(b) (4)	III	(b) (4)	(b) (4)	4	N/A		7/12/2010
(b) (4)	III	(b) (4)	(b) (4)	4	N/A		7/19/2010
(b) (4)	III	(b) (4)	(b) (4)	4	N/A		2/4/2009
(b) (4)	III	(b) (4)	(b) (4)	4	N/A		11/19/2009
(b) (4)	III	(b) (4)	(b) (4)	4	N/A		3/8/2010

¹ Action codes for DMF Table:

1 – DMF Reviewed.

Other codes indicate why the DMF was not reviewed, as follows:

2 –Type 1 DMF

3 – Reviewed previously and no revision since last review

CMC Review Data Sheet

- 4 – Sufficient information in application
- 5 – Authority to reference not granted
- 6 – DMF not available
- 7 – Other (explain under "Comments")

² Adequate, Inadequate, or N/A (There is enough data in the application, therefore the DMF did not need to be reviewed)

B. Other Documents: None

18. STATUS:

ONDQA:

CONSULTS/ CMC RELATED REVIEWS	RECOMMENDATION	DATE	REVIEWER
Biometrics			
EES	Withhold	7/17/2014	E. Dobbin
Pharm/Tox			
Biopharm	Acceptable	6/2/2014	Elsbeth Chikhale
LNC			
Methods Validation	Acceptable	6/20/2014	Lin Qi
DMEPA*	Acceptable with labeling comments	6/10/2014	Aleksander Winiarski
EA	Categorical exclusion (see review)	6/20/2014	Lin Qi
Microbiology	Acceptable	6/30/2014	Vinayak Pawar

*DMEPA: Division of Medication Error Prevention and Analysis

Executive Summary Section

The CMC Review for NDA 202106

The Executive Summary

I. Recommendations

A. Recommendation and Conclusion on Approvability

Concerns regarding the manufacturing process were conveyed to the Investigator for evaluation during site inspection. Solving of these concerns depends on satisfactory inspection results. This site is currently listed as OAI. The Overall Recommendation by the Office of Compliance is WITHHOLD.

Therefore, from the CMC perspective, this NDA is not recommended for approval.

Labeling and labels are not finalized at this time (See the non-deficiency comment in IIC).

B. Recommendation on Phase 4 (Post-Marketing) Commitments, Agreements, and/or Risk Management Steps, if Approvable

No recommendations at this time.

II. Summary of CMC Assessments

A. Description of the Drug Product(s) and Drug Substance(s)

(1) Drug Substance

The drug substance, Meropenem for Injection (Sterile Bulk) is a sterile mixture of Meropenem Trihydrate and Sodium Carbonate USP/NF. The chemistry, manufacturing, and controls information for Meropenem for Injection (Sterile Bulk) is provided in the Type II DMF (b) (4) held by (b) (4) the drug substance manufacturer. A Letter of Authorization dated March 15, 2013 is provided in Module 1.4.1. The most recent DMF Review#4 dated June 20, 2014 found DMF (b) (4) adequate to support the current NDA (pending an "Acceptable" recommendation from the quality microbiology review).

Executive Summary Section

(2) Drug Product

The drug product (Meropenem for Injection USP and Sodium Chloride Injection USP in the Duplex® Container) is sterile, nonpyrogenic and packaged in a single use, dual chamber container. It consists of Meropenem for Injection (Sterile Bulk) in one chamber and 0.9% Sodium Chloride Injection USP (diluent) in the other chamber. The sterile bulk powder and the diluent were filled into separate chambers (b) (4) in FACTA FARMACEUTICI S.p.A., Teramo, Italy. The sterile bulk used in the current product is USP compendial (b) (4)

The drug product (Meropenem for Injection USP) is controlled by testing for Appearance, Identification, Constituted Solution USP, Particulate Matter, Clarity of Solution, Color of Solution, pH, Reconstitution time, Loss on drying, Assay, Uniformity of dosage, Impurities, Content of Sodium, Filling weight, Filling volume, Sterility, and Bacterial Endotoxin. The diluent (Sodium Chloride Injection USP) is controlled by testing Appearance, Identification, Assay, Iron, pH, and Heavy metals. Sterility and Bacterial Endotoxin tests are not performed on the diluent, since they are performed on the reconstituted solution. No residual solvents or metal catalysts are introduced during the manufacturing of the drug product, since the drug product contains only the drug substance.

The Duplex container system is the same container system used in all of B. Braun marketed drug products. The proposed expiry dating under the proposed storage conditions for the drug product is supported by 12 months long-term and 6 months accelerated stability data.

Proposed Storage Conditions:

Prior to reconstitution: Store the unactivated unit at 20–25°C (68–77°F). Excursion permitted to 15–30°C. [See USP Controlled Room Temperature.] Protect from freezing. After reconstitution: Use within 1 hour if stored at room temperature or within 15 hours if stored under refrigeration.

Expiration Dating for Meropenem for Injection USP and Sodium Chloride Injection USP in the DUPLEX (b) (4) Container:

Manufactured Configuration (Intact):	24 months
After Removal of Foil Strip:	7 days
After Activation:	1 hour at room temperature (25°C (b) (4)) or 15 hours under refrigeration (5°C (b) (4))

B. Description of How the Drug Product is Intended to be Used

Meropenem for Injection USP and Sodium Chloride Injection USP is a penem antibacterial indicated as single agent therapy for the treatment of complicated skin and skin structure infections and complicated intra-abdominal infections.

Executive Summary Section

The finished drug product consists of Meropenem for Injection (Sterile Bulk) in one chamber and 0.9% Sodium Chloride Injection USP in the other chamber. The two chambers are separated by a peelable seal which is activated prior to use to constitute the drug powder in the diluent. Prior to administration, the peelable foil is removed and pressure is applied on the diluent chamber to release the diluent into the drug chamber. This allows the drug substance, Meropenem for Injection (Sterile Bulk), to be mixed and dissolved in the diluent in a closed and sterile system. Two strengths, 500 mg and 1 g, were proposed for the drug product. The dosage of the drug product is 500 mg or 1 g every 8 hours by intravenous infusion over 15 to 30 minutes.

C. Basis for Approvability or Not-Approval Recommendation

Basis for Approvability:

- The formulation and manufacturer of the sterile bulk powder is [REDACTED] (b) (4)
- As amended, the tests and acceptance criteria in the updated drug product specification will provide reasonably consistent product controls.
- The available stability data support the proposed expiring dating under the proposed storage conditions.
- Dr. Elsbeth G Chikhale recommended for “Approval” in her Biopharmaceutics Review dated June 2, 2014.
- Dr. Pawar, Vinayak recommended for “Approval” in his Quality Microbiology Review dated June 30, 2014.

Basis for Not-Approval Recommendation:

- Concerns regarding the manufacturing process, such as [REDACTED] (b) (4) were conveyed to the Investigator for evaluation during site inspection. Solving of these concerns depends on satisfactory inspection results. This site is currently listed as OAI in EES. The Overall Recommendation from the Office of Compliance is “WITHHOLD”. Therefore, from the CMC perspective, this NDA is not recommended for approval.

Labeling:

- Labeling and Labels are not finalized at this time and the following non-deficiency comment is to be conveyed to the applicant:
 - *We recommend replacing [REDACTED] (b) (4) with “Duplex Container” in the labeling of the current NDA, because the phrase [REDACTED] (b) (4)*

Executive Summary Section

III. Administrative**A. Reviewer's Signature:**

(See appended electronic signature page)

Lin Qi, CMC Reviewer

B. Endorsement Block:

(See appended electronic signature page)

Dorota Matecka, CMC Lead

Rapti Madurawe, Branch Chief, Branch V/Division II, ONDQA

C. CC Block: *(entered electronically in DARRTS)*

CMC Assessment Section

Review Note:

After the CMC review #1 was filed (June 20, 2014), the product quality microbiology review recommended for “Approval” on June 30, 2014.

Concerns regarding the manufacturing process, such as [REDACTED] (b) (4) [REDACTED] were conveyed to the Investigator for evaluation during site inspection. Solving of these concerns depends on satisfactory inspection results. This site is currently listed as OAI in EES. The Overall Recommendation from the Office of Compliance is “WITHHOLD”. Therefore, from the CMC perspective, this NDA is not recommended for approval.

The labeling and labels are not finalized at this time. One labeling issue remains unsolved, that is to replace [REDACTED] (b) (4) with “Duplex Container” in the labeling. The following comment is to be conveyed to the applicant:

- We recommend replacing [REDACTED] (b) (4) with “Duplex Container” in the labeling of the current NDA, because [REDACTED] (b) (4)

After this NDA is approved, the following can be used as a follow-up labeling comment:

- The applicant needs to submit a bundled supplement provide for a change in the labeling to allow the claim of [REDACTED] (b) (4) [REDACTED] when/if approved.

CMC Assessment Section

Attachment: Establishment Evaluation Report

FDA CDER EES
ESTABLISHMENT EVALUATION REQUEST
DETAIL REPORT

Application: NDA 202106/000 Action Goal:
Stamp Date: 27-SEP-2013 District Goal: 28-MAY-2014
Regulatory: 27-JUL-2014
Applicant: B BRAUN MEDCL INC Brand Name: MEROPENEM FOR INJECTION, USP AND SODIUM
901 MARCON BLVD Estab. Name:
ALLENTOWN, PA 18109 Generic Name: MEROPENEM FOR INJECTION, USP AND SODIUM
Priority: 4 Product Number; Dosage Form; Ingredient; Strengths
Org. Code: 520 001; SOLUTION, INJECTION; MEROPENEM; .5GM
002; SOLUTION, INJECTION; MEROPENEM; 1GM

Application Comment:

FDA Contacts:	L. QI	Prod Qual Reviewer	3017961438
	V. PAWAR	Micro Reviewer (HFD-805)	3017961587
	N. BHANDARI	Product Quality PM	2404023815
	M. DILLON PARKER	Regulatory Project Mgr (HFD-520)	3017960706

Overall Recommendation:	WITHHOLD	on 17-JUL-2014	by E. DOBBIN	()	2404024266
	PENDING	on 07-MAY-2014	by EES_PROD		
	ACCEPTABLE	on 09-NOV-2013	by EES_PROD		
	PENDING	on 16-OCT-2013	by EES_PROD		

CMC Assessment Section

FDA CDER EES
ESTABLISHMENT EVALUATION REQUEST
DETAIL REPORT

Establishment: CFN: (b) (4) FEI: (b) (4)

DMF No: (b) (4) AADA:

Responsibilities: DRUG SUBSTANCE MANUFACTURER
DRUG SUBSTANCE OTHER TESTER
DRUG SUBSTANCE STABILITY TESTER

Establishment Comment: DRUG SUBSTANCE MANUFACTURER. CHEMICAL TESTING AND STABILITY TESTING. CHEMICAL, ENDOTOXIN, STERILITY AND STABILITY TESTING OF THE DRUG SUBSTANCE. (on 16-OCT-2013 by N. BHANDARI () 2404023815)

Profile: (b) (4) OAI Status: NONE

Milestone Name	Milestone Date	Request Type	Planned Completion	Decision	Creator
<u>Comment</u>					
OAI Submit To OC					
Request to Extend Re-eval Date To					
Extension Request Comment					
<u>Reason</u>					
SUBMITTED TO OC	16-OCT-2013				BHANDARIN
SUBMITTED TO DO	17-OCT-2013	10-Day Letter			HEAYNM
DO RECOMMENDATION CSS COVERED IN (b) (4) INSPECTION	23-OCT-2013			ACCEPTABLE	MROSE
OC RECOMMENDATION	29-OCT-2013			ACCEPTABLE	SAFAAIJAZIR



CMC Assessment Section

FDA CDER EES ESTABLISHMENT EVALUATION REQUEST DETAIL REPORT

Establishment: CFN: FEI: 3006028606

FACTA FARMACEUTICI SPA
NUCLEO INDUSTRIALE S. ATTO
TERAMO, TE, ITALY

DMF No: AADA:

Responsibilities: FINISHED DOSAGE LABELER
FINISHED DOSAGE MANUFACTURER
FINISHED DOSAGE PACKAGER
FINISHED DOSAGE STABILITY TESTER

Establishment Comment: DRUG PRODUCT MANUFACTURING, PROCESSING, PACKAGING, LABELING AND STABILITY. THIS FACILITY PERFORMS MANUFACTURING, PROCESSING, TESTING AND PACKAGING OF THE DRUG PRODUCT INTO DUPLEX CONTAINERS. DUPLEX CONTAINERS ARE MANUFACTURED AND SUPPLIED BY THE B. BRAUN FACILITY LOCATED IN IRVINE, CA, WHICH HAS NOT BEEN ENTERED INTO EES FOR THIS NDA PER RECOMMENDATION FROM EES QUESTIONS. (on 16-OCT-2013 by N. BHANDARI () 2404023815)

Profile: (b) (4) OAI Status: OAI ALERT

Table with columns: Milestone Name, Milestone Date, Request Type, Planned Completion, Decision, Creator. Includes rows for OAI Submit To OC, Request to Extend Re-eval Date To, Extension Request Comment, Reason.

Main table with columns: Milestone Name, Milestone Date, Request Type, Planned Completion, Decision, Creator. Rows include: SUBMITTED TO OC (16-OCT-2013, BHANDARIN), SUBMITTED TO DO (23-OCT-2013, 10-Day Letter, CAPACCIDANIC), DO RECOMMENDATION (23-OCT-2013, ACCEPTABLE, MROSE), OC RECOMMENDATION (29-OCT-2013, ACCEPTABLE, SAFAAJAZIR), SUBMITTED TO DO (07-MAY-2014, Product Specific and GMP Inspection, SHARPT), ASSIGNED INSPECTION TO IB (14-MAY-2014, Product Specific and GMP Inspection, MROSE), INSPECTION SCHEDULED (16-MAY-2014, 23-MAY-2014, SBERRYMA), INSPECTION PERFORMED (23-MAY-2014, 23-MAY-2014, Justin.Boyd), SUBMITTED TO DO (17-JUL-2014, 10-Day Letter, DOBBINE).

July 23, 2014 12:04 PM

FDA Confidential - Internal Distribution Only

Page 3 of 4

CMC Assessment Section

**FDA CDER EES
ESTABLISHMENT EVALUATION REQUEST
DETAIL REPORT**

DO RECOMMENDATION	17-JUL-2014	WITHHOLD	MROSE
OC RECOMMENDATION	17-JUL-2014	WITHHOLD	DOBBINE

This is a representation of an electronic record that was signed electronically and this page is the manifestation of the electronic signature.

/s/

LIN QI
07/23/2014

DOROTA M MATECKA
07/24/2014

RAPTI D MADURawe
07/24/2014

NDA 202106

Meropenem for Injection USP and Sodium Chloride Injection USP in the Duplex Container

B. Braun Medical Inc.

Lin Qi, Ph.D.
Review Chemist

**Office of New Drug Quality Assessment
Division II, Branch V**

For the Division of Anti-Infective Products

Table of Contents

CMC Review Data Sheet.....4

The Executive Summary8

I. Recommendations.....8

 A. Recommendation and Conclusion on Approvability.....8

 B. Recommendation on Phase 4 (Post-Marketing) Commitments, Agreements, and/or Risk Management Steps, if Approvable.....8

II. Summary of CMC Assessments8

 A. Description of the Drug Product(s) and Drug Substance(s).....8

 B. Description of How the Drug Product is Intended to be Used.....9

 C. Basis for Approvability or Not-Approval Recommendation.....10

III. Administrative.....11

CMC Assessment.....12

I. Review Of Common Technical Document-Quality (Ctd-Q) Module 3.2: Body Of Data.....12

 S. DRUG SUBSTANCE (Meropenem for Injection (Sterile Bulk))12

 Nomenclature.....12

 Manufacturer13

 Batch Analyses13

 P. DRUG PRODUCT14

 P.1 Description and Composition of the Drug Product.....14

 P.2 Pharmaceutical Development.....14

 P.2.1 Components of the Drug Product.....14

 P.2.1.1 Drug Substance (DS).....14

 P.2.2 Drug Product.....16

 P.2.2.1 Formulation Development & P.2.2.2 Overages.....16

 P.2.2.3 Physicochemical and Biological Properties.....21

 P.2.3 Manufacturing Process Development21

 P.2.4 Container Closure System.....21

 P.2.5 Microbiological Attributes.....22

 P.2.6 Compatibility.....22

 P.3 Manufacture22

 P.3.1 Manufacturers22

 P.3.2 Batch Formula.....23

 P.3.3 Description of Manufacturing Process and Process Controls.....24

 P.3.4 Controls of Critical Steps and Intermediates.....31

 P.3.5 Process Validation and/or Evaluation33

 P.4 Control of Excipients33

 P.4.1 Specifications.....33

 P.4.2 Analytical Procedures34

 P.4.3 Validation of Analytical Procedures34

 P.4.4 Justification of Specifications34

 P.4.5 Excipients of Human or Animal Origin34

P.4.6	Novel Excipients.....	34
P.5	Control of Drug Product	35
P.5.1	Specification	35
P.5.2 & P.5.3	Analytical Procedures and Validation of Analytical Procedures	37
P.5.4	Batch Analyses	40
P.5.5	Characterization of Impurities.....	41
P.5.6	Justification of Specification.....	41
P.6	Reference Standards or Materials	43
P.7	Container Closure System.....	43
P.8	Stability	45
P.8.1	Stability Summary and Conclusion.....	45
P.8.2	Postapproval Stability Protocol and Stability Commitment.....	55
P.8.3	Stability Data	55
A.	APPENDICES	55
A.1	Facilities and Equipment (biotech only)	55
A.2	Adventitious Agents Safety Evaluation	55
A.3	Novel Excipients.....	55
R.	REGIONAL INFORMATION	55
R1	Executed Batch Records	55
R2	Comparability Protocols	55
R3	Methods Validation Package	55
II.	Review Of Common Technical Document-Quality (Ctd-Q) Module 1	55
A.	Labeling & Package Insert.....	55
B.	Environmental Assessment Or Claim Of Categorical Exclusion	57
C.	Establishment Evaluation Report.....	58
III.	List Of Deficiencies Communicated.....	60

CMC Review Data Sheet

CMC Review Data Sheet

1. NDA 202106
2. REVIEW #: 1
3. REVIEW DATE: 6/20/2014
4. REVIEWERS:
 - Primary: Lin Qi, Ph.D.
 - Secondary: Dorota Matecka, Ph.D.
Rapti Madurawe, Ph.D.

5. PREVIOUS DOCUMENTS:

Previous Documents
CMC only pre-NDA meeting

Document Date
11/4/2010

6. SUBMISSION(S) BEING REVIEWED:

Submission(s) Reviewed
Original NDA Submission
Amendment
Amendment
Amendment
Amendment
Amendment
Amendment

Document Date
9/27/2013
1/6/2014
3/24/2014
3/25/2014
5/12/2014
5/27/2014
6/12/2014

7. NAME & ADDRESS OF APPLICANT:

Name: B. Braun Medical Inc.
Address: 901 Marcon Blvd.
Allentown, PA 18109
USA

Representative: Rebecca Stolarick
Telephone: 610-596-2536
Email: Rebecca.stolarick@bbraun.com

CMC Review Data Sheet

8. DRUG PRODUCT NAME/CODE/TYPE:

- a) Proprietary Name: N/A
b) Non-Proprietary Name: Meropenem for Injection USP and Sodium Chloride Injection USP in the Duplex Container
c) Code Name/# (ONDQA only): N/A
d) Chem. Type/Submission Priority (ONDQA only):
 - Chem. Type: 3
 - Submission Priority: S

9. LEGAL BASIS FOR SUBMISSION: 505(b)(2)

10. PHARMACOL. CATEGORY: Antibiotic

11. DOSAGE FORM: Injection

12. STRENGTH/POTENCY: 0.5 gram and 1 gram

13. ROUTE OF ADMINISTRATION: Intravenous

14. Rx/OTC DISPENSED: Rx OTC15. [SPOTS \(SPECIAL PRODUCTS ON-LINE TRACKING SYSTEM\)](#):

SPOTS product – Form Completed

Not a SPOTS product

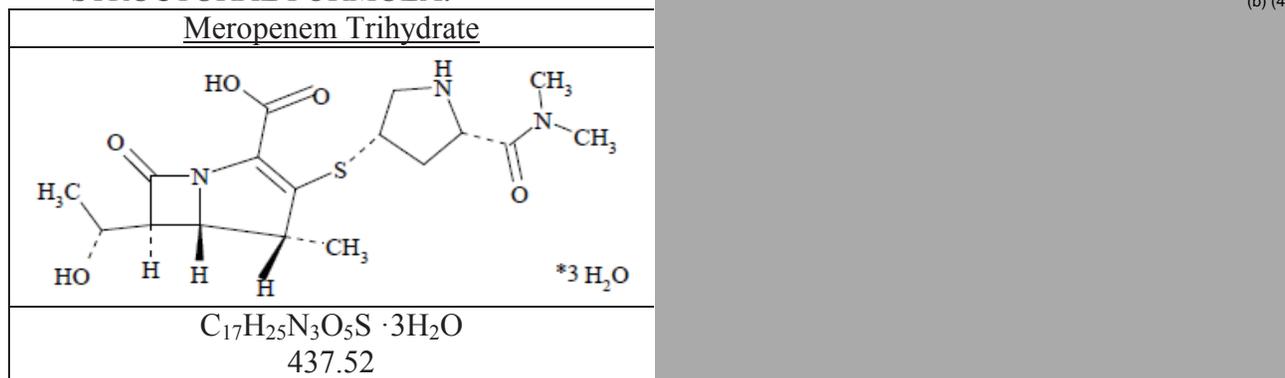
16. CHEMICAL NAME, STRUCTURAL FORMULA, MOLECULAR FORMULA, MOLECULAR WEIGHT:

CHEMICAL NAME:

1-Azabicyclo[3.2.0]hept-2-ene-2-carboxylic acid, 3-[[5-[(dimethylamino)carbonyl]-3-pyrrolidinyl]thio]-6-(1-hydroxyethyl)-4-methyl-7-oxo, trihydrate, [*4R*-[3(*3S**,*5S**),*4α*,*5β*,*6β*(*R**)]]-

CMC Review Data Sheet

STRUCTURAL FORMULA:



17. RELATED/SUPPORTING DOCUMENTS:

A. DMFs:

DMF #	TYPE	HOLDER	ITEM REFERENCED	CODE ¹	STATUS ²	DATE REVIEW COMPLETED	COMMENTS (LOA Date)
(b) (4)	II	(b) (4)	(b) (4)	1	Adequate	6/20/2014	3/15/2013
	III			4	N/A		7/13/2010
	III			4	N/A		7/21/2010
	III			4	N/A		7/12/2010
	III			4	N/A		7/19/2010
	III			4	N/A		2/4/2009
	III			4	N/A		11/19/2009
	III			4	N/A		3/8/2010

¹ Action codes for DMF Table:

1 – DMF Reviewed.

Other codes indicate why the DMF was not reviewed, as follows:

2 –Type 1 DMF

3 – Reviewed previously and no revision since last review

CMC Review Data Sheet

- 4 – Sufficient information in application
- 5 – Authority to reference not granted
- 6 – DMF not available
- 7 – Other (explain under "Comments")

² Adequate, Inadequate, or N/A (There is enough data in the application, therefore the DMF did not need to be reviewed)

B. Other Documents: None

18. STATUS:

ONDQA:

CONSULTS/ CMC RELATED REVIEWS	RECOMMENDATION	DATE	REVIEWER
Biometrics			
EES	Pending		
Pharm/Tox			
Biopharm	Acceptable	6/2/2014	Elsbeth Chikhale
LNC			
Methods Validation	Acceptable	6/20/2014	Lin Qi
DMEPA*	Acceptable with labeling comments	6/10/2014	Aleksander Winiarski
EA	Categorical exclusion (see review)	6/20/2014	Lin Qi
Microbiology	Pending		

*DMEPA: Division of Medication Error Prevention and Analysis

Executive Summary Section

The CMC Review for NDA 202106

The Executive Summary

I. Recommendations

A. Recommendation and Conclusion on Approvability

The product quality microbiology review is pending as of the date of this review. In addition, concerns regarding the drug product manufacturing process were conveyed to the FDA Investigator for evaluation during inspection of the drug product manufacturing facility. This facility is currently listed as OAI in EES and the overall site recommendation from the Office of Compliance is pending as of the date of this review. Therefore, from a CMC perspective, this NDA is not recommended for approval until all pending issues are satisfactorily resolved and an Overall Acceptable recommendation is made by the Office of Compliance.

Labeling discussions are pending a team review.

Therefore, from the CMC perspective, this NDA is not recommended for approval.

B. Recommendation on Phase 4 (Post-Marketing) Commitments, Agreements, and/or Risk Management Steps, if Approvable

No recommendations at this time.

II. Summary of CMC Assessments

A. Description of the Drug Product(s) and Drug Substance(s)

(1) Drug Substance

The drug substance, Meropenem for Injection (Sterile Bulk) is a sterile mixture of Meropenem Trihydrate and Sodium Carbonate USP/NF. The chemistry, manufacturing, and controls information for Meropenem for Injection (Sterile Bulk) is provided in the Type II DMF (b) (4) held by (b) (4) the drug substance manufacturer. A Letter of Authorization dated March 15, 2013 is provided in Module 1.4.1. The most recent DMF Review#4 dated June 20, 2014 found DMF (b) (4) adequate to support the current NDA (pending an "Acceptable" recommendation from the quality microbiology review).

Executive Summary Section

(2) Drug Product

The drug product (Meropenem for Injection USP and Sodium Chloride Injection USP in the Duplex® Container) is sterile, nonpyrogenic and packaged in a single use, dual chamber container. It consists of Meropenem for Injection (Sterile Bulk) in one chamber and 0.9% Sodium Chloride Injection USP (diluent) in the other chamber. The sterile bulk powder and the diluent were filled into separate chambers (b) (4) in FACTA FARMACEUTICI S.p.A., Teramo, Italy. The sterile bulk used in the current product is USP compendial (b) (4)

The drug product (Meropenem for Injection USP) is controlled by testing for Appearance, Identification, Constituted Solution USP, Particulate Matter, Clarity of Solution, Color of Solution, pH, Reconstitution time, Loss on drying, Assay, Uniformity of dosage, Impurities, Content of Sodium, Filling weight, Filling volume, Sterility, and Bacterial Endotoxin. The diluent (Sodium Chloride Injection USP) is controlled by testing Appearance, Identification, Assay, Iron, pH, and Heavy metals. Sterility and Bacterial Endotoxin tests are not performed on the diluent, since they are performed on the reconstituted solution. No residual solvents or metal catalysts are introduced during the manufacturing of the drug product, since the drug product contains only the drug substance.

The Duplex container system is the same container system used in all of B. Braun marketed drug products. The proposed expiry dating under the proposed storage conditions for the drug product is supported by 12 months long-term and 6 months accelerated stability data.

Proposed Storage Conditions:

Prior to reconstitution: Store the unactivated unit at 20–25°C (68–77°F). Excursion permitted to 15–30°C. [See USP Controlled Room Temperature.] Protect from freezing. After reconstitution: Use within 1 hour if stored at room temperature or within 15 hours if stored under refrigeration.

Expiration Dating for Meropenem for Injection USP and Sodium Chloride Injection USP in the DUPLEX (b) (4) Container:

Manufactured Configuration (Intact):	24 months
After Removal of Foil Strip:	7 days
After Activation:	1 hour at room temperature (25°C (b) (4) °C) or 15 hours under refrigeration (5°C (b) (4) °C)

B. Description of How the Drug Product is Intended to be Used

Meropenem for Injection USP and Sodium Chloride Injection USP is a penem antibacterial indicated as single agent therapy for the treatment of complicated skin and skin structure infections and complicated intra-abdominal infections.

Executive Summary Section

The finished drug product consists of Meropenem for Injection (Sterile Bulk) in one chamber and 0.9% Sodium Chloride Injection USP in the other chamber. The two chambers are separated by a peelable seal which is activated prior to use to constitute the drug powder in the diluent. Prior to administration, the peelable foil is removed and pressure is applied on the diluent chamber to release the diluent into the drug chamber. This allows the drug substance, Meropenem for Injection (Sterile Bulk), to be mixed and dissolved in the diluent in a closed and sterile system. Two strengths, 500 mg and 1 g, were proposed for the drug product. The dosage of the drug product is 500 mg or 1 g every 8 hours by intravenous infusion over 15 to 30 minutes.

C. Basis for Approvability or Not-Approval Recommendation

Basis for Approvability:

- The formulation and manufacturer of the sterile bulk powder is [REDACTED] (b) (4)
- As amended, the tests and acceptance criteria in the updated drug product specification will provide reasonably consistent product controls.
- The available stability data support the proposed expiring dating under the proposed storage conditions.
- Dr. Elsbeth G Chikhale recommended for “Approval” in her Biopharmaceutics Review dated June 2, 2014.

Basis for Not-Approval Recommendation:

- Concerns regarding the manufacturing process, such as [REDACTED] (b) (4) [REDACTED] were conveyed to the Investigator for evaluation during site inspection. The site is currently listed as OAI in EES.
- The recommendations from the quality microbiology reviews are pending as of the date of this review.
- Labeling discussions are pending a team review.
- The site recommendation from the Office of Compliance is pending as of the date of this review.

Therefore, from the CMC perspective, this NDA is not recommended for approval.

Executive Summary Section

III. Administrative**A. Reviewer's Signature:**

(See appended electronic signature page)

Lin Qi, CMC Reviewer

B. Endorsement Block:

(See appended electronic signature page)

Dorota Matecka, CMC Lead

Rapti Madurawe, Branch Chief, Branch V/Division II, ONDQA

C. CC Block: *(entered electronically in DARRTS)*

CMC Assessment Section

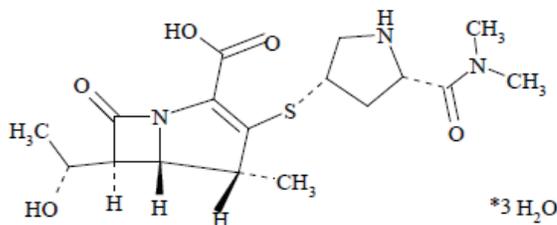
CMC Assessment**I. Review Of Common Technical Document-Quality (Ctd-Q) Module 3.2:
Body Of Data****S. DRUG SUBSTANCE (Meropenem for Injection (Sterile Bulk))**

Reviewer's Evaluation: The drug substance (DS), Meropenem for Injection (Sterile Bulk) is a sterile mixture of Meropenem Trihydrate and Sodium Carbonate USP/NF. The chemistry, manufacturing, and controls information for Meropenem for Injection (Sterile Bulk) is provided in the Type II DMF (b) (4) held by (b) (4) the drug substance manufacturer. A Letter of Authorization 3/15/2013 is provided in Module 1.4.1. The most recent review dated June 20, 2014 found the DMF (b) (4) **adequate** to support the current NDA pending an "Acceptable" recommendation from quality microbiology review of the referenced Type V DMF (b) (4)

For information purposes, the nomenclature of the drug substance, compliance status of the manufacturer, and batch analysis results are listed in this section.

Nomenclature

Structural Formula of the Drug Substance:

Meropenem Trihydrate

Molecular Formula:

C₁₇H₂₅N₃O₅S *3 H₂O

Relative Molecular Mass:

437.52

Chemical Name of Meropenem Trihydrate:

1-Azabicyclo[3.2.0]hept-2-ene-2-carboxylic acid, 3-[[5-[(dimethylamino)carbonyl]-3-pyrrolidinyl]thio]-6-(1-hydroxyethyl)-4-methyl-7-oxo, trihydrate, [4*R*-[3(3*S**,5*S**),4*α*,5*β*,6*β*(*R**)]]-

or:

(4*R*,5*S*,6*S*)-3-[[[(3*S*,5*S*)-5-(Dimethylcarbamoyl)-3-pyrrolidinyl]thio]-6-[(1*R*)-1-hydroxyethyl]-4-methyl-7-oxo-1-azabicyclo[3.2.0]hept-2-ene-2-carboxylic acid, trihydrate.

CAS NUMBER: 119478-56-7

CMC Assessment Section

Manufacturer

Drug substance manufacturing and testing site:



Comment: An “Acceptable” recommendation for this facility was made on [redacted] (b) (4) by the Office of Compliance based on district recommendation. However, the overall recommendation from the Office of Compliance is pending as of the date of this review.

Batch Analyses

The table below lists selected testing results of the three Meropenem for Injection (Sterile Bulk) batches, which were used to manufacture the registration batches of drug products:

Tests	Acceptance Criteria	Lot 33077185032 Scale: (b) (4) kg	Lot 33077185022 Scale: (b) (4) kg	Lot 33077185052 Scale: (b) (4) kg
Potency	(b) (4) % w/w	[redacted]	[redacted]	[redacted]
pH	7.3 to 8.3	[redacted]	[redacted]	[redacted]
Related substances (b) (4)	(b) (4)	[redacted]	[redacted]	[redacted]
- Individually impurity	≤ (b) (4) %	[redacted]	[redacted]	[redacted]
- Other impurities	≤ (b) (4) %	[redacted]	[redacted]	[redacted]
Loss on Drying	9.0 to 12.0%	[redacted]	[redacted]	[redacted]
Dissolution Time	≤ (b) (4) minutes	[redacted]	[redacted]	[redacted]
Bulk Density	(b) (4) g/ml	[redacted]	[redacted]	[redacted]
Tap Density	(b) (4) g/ml	[redacted]	[redacted]	[redacted]
Compressibility	(b) (4) %	[redacted]	[redacted]	[redacted]
Foreign Particles	USP<788>Method I	[redacted]	[redacted]	[redacted]
- Particles ≥ (b) (4)	≤ (b) (4) particles/g	[redacted]	[redacted]	[redacted]
- Particles ≥ (b) (4)	≤ (b) (4) particles/g	[redacted]	[redacted]	[redacted]
Sodium Carbonate (b) (4)	(b) (4) %	[redacted]	[redacted]	[redacted]
(b) (4)	≤ (b) (4) %	[redacted]	[redacted]	[redacted]
Sterility	Complies	[redacted]	[redacted]	[redacted]
Bacterial Endotoxins (LAL Test)	≤ 0.125 EU/mg	[redacted]	[redacted]	[redacted]

CMC Assessment Section

Comment: *The batch analysis results met the specification. Acceptable.*

P. DRUG PRODUCT

P.1 Description and Composition of the Drug Product

The drug product (DP), Meropenem for Injection USP and Sodium Chloride Injection USP in the Duplex® Container, is sterile, nonpyrogenic and packaged in a single use, dual chamber container. The finished drug product consists of Meropenem for Injection (Sterile Bulk) in one chamber and 0.9% Sodium Chloride Injection USP in the other chamber. The two chambers are separated by a peelable seal which is activated prior to use to constitute the drug powder in the diluent. Prior to administration, the peelable foil is removed and pressure is applied on the diluent chamber to release the diluent into the drug chamber. This allows the drug substance, Meropenem for Injection (Sterile Bulk), to be mixed and dissolved in the diluent in a closed and sterile system. Two strengths, 500 mg and 1 g, were proposed for the drug product (See Table P.1).

Table P.1: Composition of Meropenem for Injection USP and Sodium Chloride Injection USP

Components	Strengths		Target Fills
Meropenem for Injection, USP (Sterile Bulk)	500 mg	1 g	(b) (4) % of label claim of meropenem
0.9% Sodium Chloride Injection USP	50 mL	50 mL	(b) (4) mL

Comment: *In the original application, a (b) (4) % filling overage was proposed for meropenem for injection (sterile bulk). Based on the review team’s discussion, a (b) (4) % overage was considered acceptable. See P.2.2.2 for the discussion on the allowable overage. The overfill proposed for sodium chloride solution is acceptable, since it does not affect dosing. Adequate.*

P.2 Pharmaceutical Development

P.2.1 Components of the Drug Product

P.2.1.1 Drug Substance (DS)

Meropenem for Injection (Sterile Bulk): See Section S of this review for information. Meropenem for Injection (Sterile Bulk) is a sterile mixture of Sterile Meropenem Trihydrate and Sodium Carbonate. (b) (4)

Sodium Chloride

Sodium Chloride (brand name: (b) (4)), manufactured by (b) (4) is used for the preparation of the diluent (0.9% sodium chloride injection).

The manufacturing process for sodium chloride includes the following steps (See Section 3.2.P.3.3 of the application for detailed information):

CMC Assessment Section



The proposed specification for sodium chloride is listed in Table P.2.1-1.

Table P.2.1-1: Proposed Specification of Sodium Chloride

Test	Specification	Unit
Assay	≥ (b) (4)	%
Identification (Chloride; Sodium)	Positive	-
Appearance of Solution	Clear, Colorless	-
Acidity or alkalinity	Conforms	-



Comment: According to a discussion with the CMC review team, the manufacturer of sodium chloride does not need to be entered into EES as the sodium chloride is to be controlled as an excipient referencing recently approved NDAs for several antibiotics and 5% Dextrose in Duplex bags (e.g. NDAs 50821, 50823, 50796). ***Adequate.***

CMC Assessment Section

P.2.2 Drug Product***P.2.2.1 Formulation Development & P.2.2.2 Overages***

Meropenem for Injection USP and Sodium Chloride Injection USP in the Duplex container is developed as a ready-to-use drug product. The Duplex container system is the same container system used in all of B. Braun marketed drug products (See Table 1 in the Product Development Report of the submission). The sterile bulk powder is filled into one chamber, while the diluent is filled into a separate chamber [REDACTED] ^{(b) (4)}. The drug product is made ready for use just by activation of the peelable seal that separates the drug powder and the diluent.

For product development, the applicant compared their drug product with the listed drug, Merrem IV of AstraZeneca. The comparison information is reproduced in Table P.2.2-1 below.

CMC Assessment Section

Table P.2.2-1: Comparison of the Current Product with the Listed Product

Item	B. Braun	RLD (AstraZeneca)
1. Name	Meropenem for Injection USP and Sodium Chloride Injection USP	Merrem IV (Meropenem for Injection)
2. Container	Duplex® (This container system is the same container system used in all of B. Braun drug products approved by the FDA as shown in Table1)	Glass Vial
3. Use	After Constitution with the diluent in the Duplex bag	After Constitution with the diluent and transferred to a suitable IV container for further dilution prior to use
4. Storage	Manufactured State: Controlled Room Temperature, 20-25°C Constituted State: 25°C, 5°C	Manufactured State: Room Temperature, 20-25°C Constituted State: 25°C, 5°C
6. API (blend of Meropenem trihydrate USP and Sodium Carbonate USP/NF)	Meropenem: 500 mg and 1 g Sodium Carbonate, Added as buffer agent (b) (4) mg of Sodium Carbonate (which correspond to (b) (4) mg of sodium) per 500 mg of Meropenem (anhydrous equivalent) (b) (4) mg of Sodium Carbonate (which correspond to (b) (4) mg of sodium) per 1 g of Meropenem (anhydrous equivalent) (b) (4)	Meropenem: 500 mg and 1 g Sodium Carbonate, Added as buffer agent - (b) (4) mg of Sodium Carbonate (which correspond to 45.1 mg of sodium) per 500 mg of Meropenem (anhydrous equivalent) - (b) (4) mg of Sodium Carbonate (which correspond to 90.2 mg of sodium) per 1 g of Meropenem (anhydrous equivalent)
7. Diluent	0.9% Sodium Chloride Inj., USP	Sodium Chloride Inj. 0.9% (And other diluents listed in Labeling)
8. Diluent Volume, mL	50mL	10mL for 500mg/vial 20mL for 1g/vial
9. Route of Administration	Intravenous Infusion	Intravenous Infusion Intravenous Bolus
10. Manufacturer	B. Braun Medical, Inc. 500 mg NDC# 0264-3183-11 1 g NDC# 0264-3185-11	AstraZeneca Pharmaceuticals LP 500 mg NDC#0310-0325-20 1 g NDC#0310-0321-30

Because an overage of (b) (4)% is proposed, the target fill weight of the drug powder is (b) (4)% of the label claim. The target fill volume for the diluent in the Duplex container system is (b) (4) mL. The unit target fill weight calculation was performed according to the following formula:

(b) (4)

[Redacted Formula]

The assay values and impurity profiles after reconstitution were compared between the proposed product and the listed drug. The quantitative comparison of the assay values and impurities are reproduced in Table P.2.2-2 and Table P.2.2-3, respectively.

CMC Assessment Section

(b) (4)

P.2.2.3 Physicochemical and Biological Properties

The Meropenem for Injection is a sterile, white to yellow powder. Refer to DMF (b) (4) for detailed information on Meropenem for Injection (Sterile Bulk).

P.2.3 Manufacturing Process Development

See section P.3.3 for a description of the manufacturing process.

P.2.4 Container Closure System

The B. Braun Duplex container is designed physically separating the sterile drug powder (Sterile Meropenem for Injection USP) from the sterile diluent (Sodium Chloride Injection USP) during manufacturing. Prior to use, the container is “activated” by gentle squeezing of the diluent chamber of the bag that allows the diluent to flow into the drug chamber and mix to dissolve the drug powder. The entire constitution process of the Duplex container takes place in a closed, self-contained and sterile system. Therefore, the entire activation and use process is needle free. The constitution process of the B. Braun Meropenem for Injection USP and Sodium Chloride Injection USP in the Duplex container system is reproduced in Figure P.2.4-1.

CMC Assessment Section

(b) (4)

Comments: *The Duplex container system is the same container system used in all of B.Braun marketed drug products in Duplex containers (See P.7). Adequate.*

P.2.5 Microbiological Attributes

Comment: *Refer to the quality microbiology review by Dr. Vinayak Pawar.*

P.2.6 Compatibility

Comment: (b) (4)
The diluent, 0.9% sodium chloride USP is one of the diluents used for Merrem. Refer to P.7 for the compatibility of the drug product and the container closure system. Adequate.

P.3 Manufacture**P.3.1 Manufacturers**

Manufacturing and testing sites:

FACTA FARMACEUTICI S.p.A.
Nucleo Industriale S. Atto - S. Nicolò a Tordino
64020 Teramo - Italy

Legal address: viale Emilio Caldara 24/A
20122 Milano - Italy
FDA Drug Establishment Registration Number: 3006028606

US Agent (both for FACTA FARMACEUTICI S.p.A. and (b) (4))
Attention: Joseph M. Pizza
INTERCHEM CORPORATION

CMC Assessment Section

120 Route 17 North
Suite 115
Paramus, New Jersey 07652
Tel.: (201) 261-7333
Fax: (201) 261-7339

Duplex Container Manufacturing Site:
B. Braun Medical Inc.
2525 McGaw Avenue
Irvine, CA 92614
Establishment Number: 2021236

Comment: *The following concerns identified during the process review were conveyed to the Compliance Officer and Investigators via emails and a t-con (5/12/2014):*



(b) (4)

The recommendation from the Office of Compliance is pending for this facility. The above concerns have not been resolved as of the date of this review.

P.3.2 Batch Formula

The proposed commercial batch size is (b) (4) units. The registration batch sizes are shown below:

<u>FACTA Lot #</u>	<u>Actual Registration Batch Size</u>
F1000984 0001D2 (500 mg)	(b) (4) units
F1000984 0002D2 (500 mg)	(b) (4) units
F1000984 0003D2 (500 mg)	(b) (4) units
F1000985 0001D2 (1 g)	(b) (4) units
F1000985 0002D2 (1 g)	(b) (4) units
F1000985 0003D2 (1 g)	(b) (4) units

The theoretical amount of Meropenem for Injection (Sterile Bulk), in Kg, for the proposed commercial batch is listed in Table P.3.2-1 below.

CMC Assessment Section

Table P.3.2-1: Theoretical Amount of Meropenem for Injection (Sterile Bulk) in the Proposed Commercial Batch (with (b)(4)% Overage)

Strength	Maximum Batch Size (Number of Unit)	Theoretical Amount of Meropenem for Injection (Sterile Bulk) per Commercial Batch Size (Kg)
500 mg		(b)(4)
1 g		

Note: The theoretical amount of Meropenem for Injection (Sterile Bulk), in Kg, for a proposed commercial batch is calculated, as shown in the formula below, considering a minimum “as is” assay value of Meropenem for Injection of (b)(4)% w/w and a (b)(4)% target fill.

Comment: The batch formula were updated in the amendment dated May 27, 2014 to reflect the revision from a (b)(4)% overage to a (b)(4)% overage. See P.2.2.1 for overage discussions. **Adequate.**

P.3.3 Description of Manufacturing Process and Process Controls

(b)(4)



CMC Assessment Section



(b) (4)

P.6 Reference Standards or Materials

Comment: *Facta Farmaceutici uses a working standard, batch WS 0001 2 (supplied by (b) (4)), which was qualified against Meropenem USP RS, Lot# I0J244. The Certificate of Analysis for Meropenem Trihydrate Working Standard Batch WS 0001 2 is provided in the submission. Adequate.*

P.7 Container Closure System

Duplex® Container

Packaging Size: 50mL

Catalog Number: 3183-11 (0.5g) and 3185-11 (1g)



(b) (4)

Table P.7-1: Duplex Finished Drug Products Approved by the FDA

Product	Application#	Status
Cefazolin for Inj. USP and Dextrose Inj. USP	NDA 50-779	Approved by FDA
Cefuroxime for Inj. USP and Dextrose Inj. USP	NDA 50-780	Approved by FDA
Cefotaxime for Inj. and Dextrose Inj.	NDA 50-792	Approved by FDA
Cefoxitin for Inj. and Dextrose Inj.	NDA 65-214	Approved by FDA
Ceftriaxone for Inj. and Dextrose Inj.	NDA 50-796	Approved by FDA
Cefotetan for Inj. USP and Dextrose Inj. USP	NDA 65-430	Approved by FDA
Cefepime for Injection USP and Dextrose Inj. USP	NDA 50-821	Approved by FDA
Ceftazidime for Injection USP and Dextrose Inj. USP	NDA 50-823	Approved by FDA

The B. Braun Duplex® III container is a dual chamber, latex-free, (b) (4) single use IV container/closure system. A peelable seal separates the diluent and drug chambers. The contents of each chamber remain separated until manual activation by applying pressure on the diluent chamber. Applying pressure to the diluent chamber separates the peelable seal releasing diluent into the drug chamber. A second application of pressure allows the second peelable seal to open and allows reconstituted drug product to flow to the setport for administration. The registration batches for Meropenem for Injection USP and Sodium Chloride Injection USP in the Duplex® Container were manufactured (b) (4)

(b) (4) B. Braun proposes to use th (b) (4) for future commercial production batches of Meropenem for Injection USP and Sodium Chloride Injection USP in the Duplex® Container.

CMC Assessment Section

The duplex contains the following components:



Comment: *Specifications of the Duplex Bags and components were provided in the submission. A visible particulate matter inspection for Duplex empty containers is included in the container specification. The leachable study results for the Duplex bag with 0.9% sodium chloride solution over the proposed shelf life was requested in an IR letter.*

Evaluation of Response: *The leachable studies for 0.9% NaCl in Duplex container system has been conducted up to 24 months and the complete results are provided in "RPT-PH-1005201, version 4.0" in the amendment.*

A rectangular area of the document is redacted with a solid grey fill. The text "(b) (4)" is visible in the top right corner of the redacted area.

The leachables profiles of both solutions are also comparable. Adequate.

CMC Assessment Section

P.8 Stability**P.8.1 Stability Summary and Conclusion**

Comments: It is noted that the testing points at 18 and 24 months are (b) (4) in the stability protocols. The following comments were sent to applicant:

- The long term stability study should be conducted through the proposed shelf life. Therefore, testing results at 18 months and 24 months are required to support the proposed shelf life of 24 months. Please provide the revised stability protocol without the word (b) (4) at 18 and 24 months testing points.

Evaluation of Response: The applicant provided the revised stability protocols (for Meropenem for Injection USP in Duplex and the RLD) and a revision to the Introduction section of Stability Module 3.2.P.8.1 from the original submission without the word (b) (4) at 18 and 24 months testing points in Module 3.2.P.8.1 of this response to the information request. Stability testing will be conducted at the 18 and 24 month intervals.

Because only 6 months stability data were available in the original application, stability data at the 12 month time point were submitted in the amendment dated May 12, 2014 as requested. In the following section, the stability protocol is listed as (a) and the available stability data are summarized as (b) under each storage condition:

CMC Assessment Section

(b) (4)

Proposed Shelf-Life:

The applicant currently proposes the following expiration dating for Meropenem for Injection USP and Sodium Chloride Injection USP in the DUPLEX (b) (4) Container based on the data obtained from the stability study and statistical analysis of those data.

Manufactured Configuration (Intact): 24 months

After Removal of Foil Strip: 7 days

After Activation: (b) (4) hour at room temperature (25°C (b) (4)) or
(b) (4) hours under refrigeration (5°C (b) (4))

Comment: The shelf life after activation should be “1 hour at room temperature (25°C (b) (4)) or 15 hours under refrigeration (5°C (b) (4)) according to the proposed labeling”.

The following comment was sent to the applicant on June 5, 2014:

- According to the draft labeling, the proposed drug product shelf life after activation is “1 hour at room temperature (25°C (b) (4)) or 15 hours under refrigeration (5°C (b) (4))”. However, in the stability section of application, the proposed product shelf life after activation is (b) (4) hours at room temperature (25°C (b) (4)) or (b) (4) hours under refrigeration (5°C (b) (4))”, which is not supported by the stability data. Please revise the proposed shelf life after activation to “1 hour at room temperature (25°C (b) (4)) or 15 hours under refrigeration (5°C ± (b) (4))” in the application (P.8).

Evaluation of Response: In the amendment dated June 12, 2014, the applicant provided the following revised expiration dating for Meropenem for Injection USP and Sodium Chloride Injection USP in the DUPLEX (b) (4) Container.

Manufactured Configuration (Intact): 24 months

After Removal of Foil Strip: 7 days

After Activation: 1 hour at room temperature (25°C (b) (4)) or
15 hours under refrigeration (5°C (b) (4))

The proposed storage conditions are:

Prior to reconstitution: Store the unactivated unit at 20–25°C (68–77°F). Excursion permitted to 15–30°C. [See USP Controlled Room Temperature.] Protect from freezing.

Use only if prepared solution is clear and free from particulate matter.

After reconstitution: Use only if prepared solution is clear and free from particulate matter. Use within 1 hour if stored at room temperature or within 15 hours if stored under refrigeration.

The proposed expiry dating under the proposed storage conditions are supported by the available stability data. **Acceptable.**

CMC Assessment Section

P.8.2 Postapproval Stability Protocol and Stability Commitment

Comment: *The applicant commits to follow the stability protocols listed in P.8.1. Following approval of the product, Facta Farmaceutici S.p.A. will place the first three production lots (including at least one lot of each concentration) of the proposed finished product into the commercial stability program in accordance with the proposed post-approval stability tests summarized in in Module 3.2.P.8.1 for Meropenem for Injection USP and Sodium Chloride Injection USP in the Duplex® (b) (4) container. Adequate.*

P.8.3 Stability Data

Comment: *See Stability Data Summary in P.8.1.*

A. APPENDICES

- A.1 Facilities and Equipment (biotech only)**
N/A
- A.2 Adventitious Agents Safety Evaluation**
N/A
- A.3 Novel Excipients**
N/A

R. REGIONAL INFORMATION

- R1 Executed Batch Records**
Provided in 3.2.R. See discussions in P.3 of this review.
- R2 Comparability Protocols**
N/A
- R3 Methods Validation Package**
Methods validation results were **Acceptable** (evaluated in P.5.3).

II. Review Of Common Technical Document-Quality (Ctd-Q) Module 1**A. Labeling & Package Insert****1. Package Insert**

Comment: *CMC editing was performed on sections #11 and #16 and these sections with CMC edits were conveyed to the review team. The labeling will be further discussed pending team review.*

CMC Assessment Section

Meropenem for Injection USP and Sodium chloride Injection USP is supplied sterile and nonpyrogenic in the DUPLEX® (b) (4) (b) (4) containers packaged 24 units per case.

<u>NDC</u>	<u>REF</u>	<u>Dose</u>	<u>Volume</u>
0264-3183-11	3183-11	500 mg	50 mL
0264-3185-11	3185-11	1 g	50 mL

*Anhydrous basis.

Store the unactivated unit at 20–25°C (68–77°F). Excursion permitted to 15-30°C. [See USP Controlled Room Temperature.]

Protect from freezing.

Use only if prepared solution is clear and free from particulate matter.

Manufactured for:

B. Braun Medical Inc.

Bethlehem, PA 18018-3524 USA

1-800-227-2862

www.bbraun.com

(b) (4)

FACTA FARMACEUTICI S.p.A (b) (4)

2. Container Labels

Comment: Container labels texts were provided for both 500 mg and 1 g strength products. The recommended editing for the container labels is to specify the manufacturer and the applicant as:

Manufactured for:

B. Braun Medical Inc.

(b) (4)

Labels will be further discussed pending team review.

B. Environmental Assessment Or Claim Of Categorical Exclusion

Pursuant to 21 CFR §25.31(a), B. Braun claims a categorical exclusion from the requirement of an Environmental Impact Analysis statement. Under 21 CFR §25.31(a), a

CMC Assessment Section

categorical exclusion exists for action on an NDA, abbreviated application, application for marketing approval of a biologic product, or a supplement to such applications, or action on an OTC monograph, if the action does not increase the use of the active moiety.

Comment: Acceptable.

C. Establishment Evaluation Report

FDA CDER EES
ESTABLISHMENT EVALUATION REQUEST
SUMMARY REPORT

Application:	NDA 202106/000	Sponsor:	B BRAUN MEDCL INC
Org. Code:	520		901 MARCON BLVD
Priority:	4		ALLENTOWN, PA 18109
Stamp Date:	27-SEP-2013	Brand Name:	MEROPENEM FOR INJECTION, USP AND SODIUM
PDUFA Date:	27-JUL-2014	Estab. Name:	
Action Goal:		Generic Name:	MEROPENEM FOR INJECTION, USP AND SODIUM
District Goal:	28-MAY-2014	Product Number; Dosage Form; Ingredient; Strengths	002; SOLUTION, INJECTION; MEROPENEM; 1GM 001; SOLUTION, INJECTION; MEROPENEM; .5GM

FDA Contacts:	L. QI	Prod Qual Reviewer	3017961438
	S. FONG	Micro Reviewer	(HFD-003) 3017961501
	N. BHANDARI	Product Quality PM	2404023815
	M. DILLON PARKER	Regulatory Project Mgr	(HFD-520) 3017960706

Overall Recommendation:	PENDING	on 07-MAY-2014	by EES_PROD	
	ACCEPTABLE	on 09-NOV-2013	by J. WILLIAMS	() 3017964196
	PENDING	on 16-OCT-2013	by EES_PROD	

Establishment:	CFN: (b) (4)	FEI: (b) (4)	
DMF No:	[REDACTED]		AADA:
Responsibilities:	DRUG SUBSTANCE MANUFACTURER DRUG SUBSTANCE OTHER TESTER DRUG SUBSTANCE STABILITY TESTER		
Profile:	[REDACTED] (b) (4)	OAI Status:	NONE
Last Milestone:	OC RECOMMENDATION		
Milestone Date:	29-OCT-2013		
Decision:	ACCEPTABLE		
Reason:	DISTRICT RECOMMENDATION		



CMC Assessment Section

**FDA CDER EES
ESTABLISHMENT EVALUATION REQUEST
SUMMARY REPORT**

Establishment: **CFN:** **FEI:** 3006028606
FACTA FARMACEUTICI SPA
NUCLEO INDUSTRIALE S. ATTO
TERAMO, TE, ITALY

DMF No: **AADA:**

Responsibilities: FINISHED DOSAGE LABELER
FINISHED DOSAGE MANUFACTURER
FINISHED DOSAGE PACKAGER
FINISHED DOSAGE STABILITY TESTER

Profile: (b) (4) **OAI Status:** NONE

Last Milestone: INSPECTION PERFORMED

Milestone Date: 23-MAY-2014

CMC Assessment Section

III. List Of Deficiencies Communicated**IR Sent in 2/28/2014:**

1. It is noted that the assay values of meropenem were (b) (4)%, (b) (4)%, and (b) (4)% of label claim for the 500 mg registration batches and (b) (4)%, (b) (4)%, and (b) (4)% for the 1 g registration batches, as a (b) (4)% overage was applied. However, the assay values of meropenem were (b) (4)% and (b) (4)% of label claim for the 500 mg and 1 g listed drug (Merrem), respectively. To ensure the bioequivalence between the proposed drug product and the listed drug, please remove the overage and revise the relevant sections in the application.
2. The following comments relate to the observations on executed batch records:
 - a. For drug product batch 0001 D1 and 0001 D2, it is observed that although the amount of bulk drug used was sufficient to fill (b) (4) and (b) (4) bags, respectively, only ~ (b) (4) and (b) (4) bags were found to be compliant (i.e., manufacturing yields were (b) (4)% and (b) (4)%, respectively). Explain why a large number of bags were non-compliant and the reasons for any process upsets or failures that may have occurred. (b) (4)
What is the expected “compliant bag yield” range during full-scale commercial manufacture?
 - b. (b) (4)
3. (b) (4)
4. Per ICH Q6A, either one specific or two non-specific identification tests should be included in the drug product specification. Please add another identification test for meropenem in the drug product specification, since the HPLC test is non-specific and by itself is not adequate.
5. To ensure product quality, it is recommended that tests on “Clarity of solution” and “Color” with appropriate acceptance criteria be included in the drug product specification for release and stability.
6. Instead of (b) (4) or (b) (4), include clear descriptors or numeric values as acceptance criteria of the following tests in the drug product specification:
 - a. Identification tests for meropenem and sodium
 - b. Constituted solution

CMC Assessment Section

- c. Clarity of solution
 - d. Color
 - e. Labeling
7. The long term stability study should be conducted through the proposed shelf life. Therefore, testing results at 18 months and 24 months are required to support the proposed shelf life of 24 months. Provide revised stability protocols without the word (b) (4) at 18 and 24 months testing points.
 8. Because the leachable data found in this application is only on dextrose solution in the Duplex bag, provide leachable testing results for the proposed diluent (0.9% sodium chloride solution) in Duplex bag through the proposed shelf life. If no data is available through expiry, provide leachable testing results on available stability samples (including after 6 months storage at 40°C) and update Section P.8.2 (Postapproval Stability Protocol and Stability Commitment) to include a test for leachables through the end of shelf-life for the first 3 commercial batches (as a one-time study).

IR Sent in 5/2/2014:

1. (b) (4)
2. According to “21 CFR § 211.101 (a)-Charge-in of Components” which states “the batch shall be formulated with the intent to provide not less than 100 percent of the labeled or established amount of active ingredient”, the formulations are targeted at 100% of the labeled claim or established amount of active ingredient. The stability data should not be used to justify bioequivalence. Based on the assay values provided in your response, an overage of (b) (4)%, instead of (b) (4)%, is recommended. Please revise the filling weight specification for Meropenem for Injection in Duplex accordingly and provide the updated drug product specification.
3. The stability data at the 12 month time point should be available for the registration batches. Please provide the updated stability data to support the proposed shelf life.

IR Sent in 5/22/2014:

1. We acknowledge that the acceptance criteria of assay for Meropenem for Injection have been revised to (b) (4)% and the target fill weight has been revised to (b) (4)% of the label claim of meropenem. However, the acceptance criterion for filling weight ((b) (4) % of label claim of meropenem) has not been updated. Please provide drug product specification with updated fill weight acceptance criteria ((b) (4) % of label claim of meropenem).
2. Revise relevant sections of the application (batch formula, manufacture, etc.) with filling overage updated from (b) (4)% to (b) (4)%.

CMC Assessment Section

IR Sent in 6/5/2014:

1. According to the draft labeling, the proposed drug product shelf life after activation is “1 hour at room temperature (25°C ^{(b) (4)}) or 15 hours under refrigeration (5°C ^{(b) (4)})”. However, in the stability section of application, the proposed product shelf life after activation is ^{(b) (4)} hours at room temperature (25°C ^{(b) (4)}) or ^{(b) (4)} hours under refrigeration (5°C ^{(b) (4)})”, which is not supported by the stability data. Please revise the proposed shelf life after activation to “1 hour at room temperature (25°C ^{(b) (4)}) or 15 hours under refrigeration (5°C ^{(b) (4)})” in the application (P.8).

This is a representation of an electronic record that was signed electronically and this page is the manifestation of the electronic signature.

/s/

LIN QI
06/20/2014

DOROTA M MATECKA
06/20/2014

RAPTI D MADURawe
06/20/2014