CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

204957Orig1s000

PRODUCT QUALITY REVIEW(S)

Recommendation: Complete Response

NDA 204957
Review #1

Drug Name/Dosage Form	Acetaminophen Injection in the PAB® Container Solution
Strength	500mg/100mL and 1000mg/100mL
Route of Administration	Intravenous (Infusion)
Rx/OTC Dispensed	Rx
Applicant	B. Braun Medical, Inc.
US agent, if applicable	

Quality Review Team

DISCIPLINE	REVIEWER	BRANCH/DIVISION
Drug Substance	Erika Englund	OPQ/ONDP/DNDPAPI/BII
Drug Product	Chris Hough	OPQ/ONDP/DNDPII/BIV
Process	Hillary Holback	OPQ/OPF/DPAII/BVI
Microbiology	Nutan Mytle	OPQ/OPF/DMA/BII
Facility	Rebecca Dombrowski	OPQ/OPF/DIA/BII
Biopharmaceutics	Kelly Kitchens/Haritha Mandula	OPQ/ONDP/DB/BII
Regulatory Business Process Manager	Steven Kinsley	OPQ/OPRO/RBPMI/BI
Application Technical Lead	Ciby Abraham	OPQ/ONDP/DNDPII/BIV
Laboratory (OTR)		
ORA Lead	Caryn McNab/Michael Tollon	
Environmental Analysis (EA)		

Executive Summary

Recommendations and Conclusion on Approvability

Based on the recommendation of withhold from facilities, CMC will recommend a Complete Response for Acetaminophen Injection in the PAB® Container Solution 500mg/100mL and 1000mg/100mL. Drug substance, biopharmaceutics, process, microbiology, and drug product, recommends approval.

I. Summary of Quality Assessments

A. Product Overview

The drug substance, Acetaminophen (APAP), USP, is supplied by two different manufacturers. Acetaminophen is manufactured by (b) (4) (b) (4) and is referenced in DMF# (b) (4) (adequate, last reviewed 9/24/2016) and manufactured by (b) (4). and is referenced in DMF (b) (4) (adequate, last reviewed 10/19/2016). APAP is a white crystalline powder with an approximate solubility of 1 g/70 mL in water. Acetaminophen is packaged in (b) (4) (b) (4) The drug substance from (b) (4) has a re-test period of (b) (4) years (b) (4) The drug substance from (b) (4) has a retest period of (b) (4) years.

Acetaminophen Injection 500 mg/50 mL and 1000 mg/100 mL (10 mg/mL) is a sterile, clear, colorless (b) (4) non-pyrogenic, isotonic solution that is chemically stable if stored at 20 °C to 25 °C (68 °F to 77 °F). The finished drug product is a non-salicylate antipyretic and non-opioid analgesic agent and is intended for sterile injection. The container closure is a PAB® Container (b) (4)

(b) (4)

Facilities recommends a Withhold of this application due to the compliance status of B. Braun Medical Inc., FEI 2021236 and significant concerns over this site's ability to (b) (b) (4)

(b) (4) According to Rebecca Dombrowski, the facilities reviewer, "these deficiencies were conveyed to the firm during the 4/18-5/11/2016 inspection of this site and a resultant Warning Letter issued to the firm. As a result, a recommendation to Withhold this site under this application is entered for B. Braun Medical Inc. under FEI 2021236. Resolution of the product specific and GMP compliance concerns at this site as presented during the 4/2016 inspection and the 5/2017 Warning Letter should be documented and re-reviewed under any re-submission." Based on these concerns CMC recommends a Complete Response.

B. Special Product Quality Labeling Recommendations (NDA only) -N/A

C. Final Risk Assessment

From Initial Quality Assessment			Review Assessment		
Product attribute/ CQA	**Factors that can impact the CQA**	**Risk Ranking***	**Risk Mitigation Approach**	**Risk Evaluation**	**Lifecycle Considerations / Comments****
Assay, stability	• Formulation • Raw materials • Process parameters • Scale/equipment • Site	L	-	N/A	-
Physical stability (API)	• Formulation • Raw materials • Process parameters • Scale/equipment • Site	L	-	N/A	-
Content uniformity	• Formulation • Raw materials • Process parameters • Scale/equipment • Site	L	-	N/A	-
Microbial-Limits	• Formulation • Raw materials • Process parameters • Scale/equipment	L	-	-	-
In Vitro Dissolution	• Formulation • Raw materials • Process parameters • Scale/equipment • Site • Exclude major reformulations • Alcohol dose dumping	L	-	-	-

*Risk ranking applies to product attribute/CQA
**For example, post marketing commitment, knowledge management post approval, etc.

Administrative

A. Reviewer's Signature

_____

Ciby J. Abraham, Ph.D.
Quality Assessment Lead (Acting)
Application Technical Lead
ONDP/DIVII/Branch IV

NDA 204957
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1.14.1.1 DRAFT LABELING TEXT
CARTON LABEL ACETAMINOPHEN INJECTION 500 mg/50 mL

Acetaminophen Injection

500 mg/50mL (10 mg/mL)

Four 50 mL fill PAB® Containers

REF DA4500

NDC 0264-4500-80

For Intravenous Use Only

Each 50 mL contains 500 mg Acetaminophen, USP, 1900 mg Mannitol, USP, 15 mg Sodium Citrate Dihydrate, USP, Water for Injection, USP qs

pH is adjusted with glacial acetic acid.

Single Use Container. Doses less than 500 mg require aseptic transfer to a separate container prior to dispensing. Discard unused portion.

Protect from light until use.

CAUTION: DO NOT ADD SUPPLEMENTARY MEDICATION

Store at controlled room temperature, 20°C to 25°C (68°F to 77°F). Do not freeze. Do not expose the product under light. Keep the products in the box until use.

See Package Insert for recommended dosage and Full Prescribing Information.

Not made with natural rubber latex, PVC or DEHP.

PAB is a registered trademark of B. Braun Medical Inc.

Rx only

B. Braun Medical Inc.

Bethlehem, PA 18018-3524 USA

1-800-227-2862

Prepared in USA with API from either China or USA

X12-002-481 LD-553-1

>

Reviewer's Assessment:

The carton label contains what is required in the required order

List of Deficiencies: None

Primary Labeling Reviewer Name and Date: Christopher Hough, Ph.D. Aug. 8, 2017

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

APPEARS THIS WAY ON ORIGINAL

Christopher Hough

Digitally signed by Christopher Hough
Date: 9/13/2017 05:25:58PM
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Julia Pinto

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BIOPHARMACEUTICS

Product Background: The Applicant is seeking approval of Acetaminophen Injection, 500 mg/50 mL and 1000 mg/100 mL, in the PAB® Container under the 505(b)(2) path. The approval is based on the previous findings of safety and efficacy for the reference listed drug (RLD), Ofirmev® (acetaminophen) injection, under NDA 22450.The drug product is indicated for:

- Management of mild to moderate pain in adult and pediatric patients 2 years and older;
- Management of moderate to severe pain with adjunctive opioid analgesics in adult and pediatric patients 2 years and older; and,
- Reduction of fever in adult and pediatric patients.

NDA: 204957

Drug Product Name / Strength: Acetaminophen Injection in the PAB® Container, 500 mg/50 mL and 1000 mg/100 mL (10mg/mL)

Route of Administration: Intravenous (Infusion)

Applicant Name: B. Braun Medical, Inc.

Review Summary:

The Applicant requested a biowaiver for the 500 mg/50 mL strength of Acetaminophen Injection per 21 CFR 320.22 (d)(2). The following 21 CFR 320.22 (d)(2) criteria were met:

1. The bioavailability of this other drug product has been measured;
2. Both drug products meet an appropriate in vitro test approved by FDA; and
3. The applicant submits evidence showing that both drug products are proportionally similar in their active and inactive ingredients.

Therefore, the biowaiver is granted for the 500 mg/50 mL strength.

From the Biopharmaceutics perspective, NDA 204957 for Acetaminophen Injection, 500 mg/50 mL and 1000 mg/100 mL, is recommended for **approval.**

List Submissions being reviewed:

Submission Date	Purpose of Submission
December 13, 2016	Original

Highlight Key Outstanding Issues from Last Cycle: N/A

Concise Description Outstanding Issues Remaining: N/A

BCS Designation

Reviewer's Assessment: N/A for intravenous product

Solubility:

Permeability:

Dissolution:

Biowaiver Request

Reviewer's Assessment: ADEQUATE

- The proposed Acetaminophen Injection product contains the same active ingredient in the same concentration as the approved reference product, Ofirmev® (acetaminophen) Injection. However, the excipients of the proposed and reference products are not qualitatively and quantitatively (Q1/Q2) the same. Therefore, the Applicant conducted study no. HC-G-H-1506 to demonstrate the bioequivalence of the proposed product (1000 mg/100 mL) to the reference product.
- The Applicant requests a waiver of the requirement for in vivo bioavailability testing of the proposed drug product, 500 mg/50 mL strength, per 21 CFR 320.22 (d)(2):
    - The bioavailability of the 1000 mg/100 mL strength has been measured in bioequivalence study HC-G-H-1506 (Module 5.3.1.2);
    - Both drug products meet an appropriate in vitro test approved by FDA (Module 3.2.P.5.4); and,
    - The applicant submits evidence showing that both drug products are proportionally similar in their active and inactive ingredient (Module 3.2.P.1).

Table 2: Formulation Comparison of IVA (BBM) vs Ofirmev®

Name of Ingredient	Name	Acetaminophen Injection	Ofirmev®
	Description	Acetaminophen (10 mg/mL) Solution in PAB® Container	Acetaminophen (10 mg/mL) Solution in Glass Vials
	NDC No:	0264-4500-80 & 0264-(b) (4)90	43825-102-01
	Container Type	Plastic (PAB®)	Glass vials
	Container Size	100 mL & 150 mL	100 mL
	Fill Volume	50 mL & 100 mL	100 mL
	Function	100 mL contains: (w/v, %)	100 mL contains: (w/v, %)
Acetaminophen USP, g	Active	1.00	1.00
Sodium Citrate $2H_2O$ USP, g	(b) (4)	0.03	N/A
Mannitol USP, g		3.80	3.85
Glacial Acetic Acid USP, g*	pH Adjuster	(b) (4)	N/A
Water for Injection, g**	(b) (4)	QS	QS
HCl, g*		N/A	pH Adjuster
NaOH, g*		N/A	pH Adjuster
Cysteine HCl, H_2O, USP, mg		N/A	25.0
Na_2HPO_4, USP, mg		N/A	10.4
pH		(b) (4)	~5.5
(b) (4)			
Osmolality, mOs/kg^3		~290	~290

* AR: As required, used for pH adjustments.
** QS: Quantity sufficient to bring to volume.

Reviewer's comments:

- The adequacy of bioequivalence study HC-G-H-1506 was evaluated by the Office of Clinical Pharmacology (OCP). The OCP determined that bioequivalence study HC-G-H-1506 is adequate. Refer to the Clinical Pharmacology review by Dr. Srikanth Nallani.
- There are no in vitro tests approved by the Agency for injectable solutions. The applicant reported the following critical quality attributes (CQAs), which will be reviewed by the drug product reviewer, Dr. Christopher Hough:
  - Appearance
  - Identification
  - pH
  - Color
  - Acetaminophen assay
  - Citrate
  - Mannitol
  - Related substances/known impurities

  - Subvisible particles
  - Bacterial endotoxin
  - Sterility
- The 500 mg/50 mL and 1000 mg/100 mL strengths are proportionally similar since the strengths have the same final concentration.
- Based on the information provided, a biowaiver is granted for the 500 mg/50 mL strength per 21 CFR 320.22 (d)(2).

List of Deficiencies: N/A

Primary Biopharmaceutics Reviewer Name and Date:

Kelly M. Kitchens, Ph.D., May 11, 2017

Secondary Reviewer Name and Date:

Haritha Mandula, Ph.D., June 15, 2017

Product Quality Microbiology Review

15 May 2017

NDA: 204957

Drug Product Name
Proprietary: N/A
Non-proprietary: Acetaminophen Injection in the PAB container

Review Number: #1

Dates of Submission(s) Covered by this Review

Submit	Received	Review Request	Assigned to Reviewer
12/13/2016	12/13/2016	N/A	12/29/2016
5/3/2017*	5/3/2017	N/A	5/5/2017

*IR Response

Submission History (for 2nd Reviews or higher)

Submit Date(s)	Microbiology Review #	Review Date(s)
N/A	-	-

Applicant/Sponsor
Name: B. Braun Medical, Inc.
Address: 901 Marcon Boulevard
Allentown, PA 18109-9341
Representative: Cindy Katsempris, Director- Regulatory Affairs,
Telephone: 610-596-2710
Fax: 610-266-4962

Name of Reviewer: Nutan Mytle, Ph.D.

Conclusion: The submission **is recommended** for approval on the basis of sterility assurance.

Product Quality Microbiology Data Sheet

A. 1. TYPE OF SUBMISSION: Original NDA

2. SUBMISSION PROVIDES FOR: Initial marketing of sterile drug product.

3. MANUFACTURING SITE: B. Braun Medical Inc., 2525 McGaw Avenue, Irvine CA-92614

4. DOSAGE FORM, ROUTE OF ADMINISTRATION AND STRENGTH/POTENCY: Sterile solution, IV infusion, 500mg/50mL and 1000mg/100mL, filled in 100 mL and 150 mL PAB containers, single (b) (4) container.

5. METHOD(S) OF STERILIZATION: (b) (4)

6. PHARMACOLOGICAL CATEGORY: Used for -the management of mild to moderate pain, - the management of moderate to severe pain with adjunctive opioid analgesics, - the reduction of fever.

B. SUPPORTING/RELATED DOCUMENTS:
None

C. REMARKS: Electronic submission. An IR letter dated 4/10/2017 was conveyed to the applicant following the microbiology review. The applicant's responses dated 5/3/2017 are included in relevant sections of this review.

Filename: N204957MR01.doc

Executive Summary

I. Recommendations

A. Recommendation on Approvability -

The submission is **recommended** for approval on the basis of sterility assurance.

B. Recommendations on Phase 4 Commitments and/or Agreements, if Approvable – N/A

II. Summary of Microbiology Assessments

A. Brief Description of the Manufacturing Processes that relate to Product Quality Microbiology –

The bulk drug is (b) (4) filled into 150 mL and 100 mL PAB containers. The filled product is (b) (4) (b) (4)

B. Brief Description of Microbiology Deficiencies – None identified

C. Contains Potential Precedent Decision(s) - ☐ Yes ☒ No

III. Product Quality Microbiology Risk Assessment

A. Initial Product Quality Microbiology Risk Assessment

(b) (4)

B. Final Risk Assessment - No microbiology deficiencies were identified. The applicant demonstrates an adequate level of sterility assurance for the manufacturing process.

IV. Administrative

A. Reviewer's Signature _____

B. Endorsement Block

Microbiologist/Nutan Mytle, Ph.D.
Microbiology Secondary Reviewer//Neal J. Sweeney, Ph.D.

.

C. CC Block

cc: Field Copy

Product Quality Microbiology Assessment

1. REVIEW OF COMMON TECHNICAL DOCUMENT-QUALITY (CTD-Q) MODULE 3.2: BODY OF DATA

P DRUG PRODUCT

P.1 Description of the Composition of the Drug Product

- **Description of drug product –** Clear, colorless (b) (4) solution .
- **Drug product composition –**
  The composition of the drug product shown below in table is reproduced from the submission. (Section 3.2 P.1 description and composition).

Component	Grade	Function	500 mg/50 mL Concentration (g/50 mL)	1000 mg/100 mL Concentration (g/100 mL)
Acetaminophen	USP	Active Ingredient	0.50	1.00
Mannitol	USP	(b) (4)	1.90	3.80
Sodium citrate dihydrate	USP		0.015	0.03
Glacial acetic acid	USP	pH Adjuster	AR[1] (b) (4)	AR[1] (b) (4)
Water for Injection (WFI)	USP	(b) (4)	QS[2]	QS[2]

(b) (4)

- **Description of container closure system –** (b) (4)

(b) (4)

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(b) (4)

[redacted]

Acceptable

P.7 Container Closure System –
See P.1.

P.8 Stability
P.8.1 Stability Summary and Conclusion
(3.2 P 8, stability-data-4.pdf)
Both BET and sterility stability studies are being conducted at following accelerated, intermediate and long term conditions:
Long term study: 25ºC± 2ºC /≤ 40% RH for 0, 12, 18 and 24 months
Intermediate study: 30ºC± 2ºC / ≤ 40% RH for 0, 6, 9 and 12 months
Accelerated study: 40ºC± 2ºC / ≤ 20% RH for 0, 3 and 6 months

Proposed Expiry: 18 months

Acceptable

P.8.2 Post-Approval Stability Protocol and Stability Commitment
(3.2 P 8.2, post-approval stability commitment)

The product stability specification includes the following microbiological tests:

Test	Test Method	Acceptance Criteria
Bacterial Endotoxins	USP<85>	NMT (b) (4) EU/mL
Sterility	USP<71>	Sterile

The testing schedule in the post-approval protocol is as follows:

Long Term Storage: 25°C ± 2°C/≤ 40% RH

	Time (Months)			
Stability Test	0	12	18	24
Endotoxins	√	√	√	√
Sterility	√	√	√	√

Post Approval Stability Commitment
The applicant commits to placing the first three commercial lots of the subject drug product into their stability program. Thereafter, on an annual basis, one production lot will be added to the stability program.

Acceptable

P.8.3 Stability Data
Results of initial, 3 months and 6 months of accelerated data and initial data of long term study has been provided and the results comply with the specifications.

Test	Accelerated 40±2°C/75±5% RH	Long Term: 25±2°C/≤ 40% RH
Bacterial endotoxins	0M: (b) (4) EU/mL 3M (b) (4) EU/mL 6M: (b) (4) EU/mL	0M: (b) (4) EU/mL 12M: (b) (4) EU/mL
Sterility	0M: Sterile 3M: Sterile 6M: Sterile	0M: Sterile 12M: Sterile

Acceptable

A APPENDICES- N/A

A.2 Adventitious Agents Safety Evaluation –

A.2.1 Materials of Biological Origin –
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

R.1 Executed Batch Record

Executed batch records for lot #(s): 500 mg/50mL: STB J5H721, STB J5H722, STB J5H723, STB J5H724, S6C652, S6C653; 1000mg/100mL: STB J5H725, STB J5H726, STB J5H728; STB J5J677, S6C651, S6C683: The batch records confirm that validated (b) (4) process was used for the manufacture of the exhibit batches. Product filled in PAB containers are (b) (4)

Acceptable

R.2 Comparability Protocol – No CP was included in the application.

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

A. PACKAGE INSERT

(1.14.1.3 Draft-text-package-insert-ld-551-1-y36-002-929.doc)
Storage temperature: 20°C to 25°C (68° to 77°F); Route of administration: IV; Single-(b) (4) The product should be used immediately after opening. Do not freeze. Discard unused portion. Do not expose the product under light. Keep the products in the box until use.

Acceptable

Neal Sweeney

Digitally signed by Neal Sweeney
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Nutan Mytle

Digitally signed by Nutan Mytle
Date: 6/28/2017 01:07:52PM
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ATTACHMENT II: List of Deficiencies for Complete Response

A. Drug Substance Deficiencies (N/A)

B. Drug Product Deficiencies (N/A)

C. Environmental Analysis Deficiencies (N/A)

D. Labeling Deficiencies (N/A)

E. Process Deficiencies (N/A)

F. Facilities Deficiencies

During a recent inspection of the B. Braun Medical Inc. (FEI 2021236) manufacturing facility, our field investigator observed objectionable conditions at the facility and conveyed that information to the representative of the facility at the close of the inspection. Satisfactory resolution of the observations is required before this NDA may be approved.

G. Biopharmaceutics Deficiencies (N/A)

H. Microbiology Deficiencies (N/A)

OVERALL ASSESSMENT AND SIGNATURES:

Application Technical Lead Name and Date:

This is a representation of an electronic record that was signed electronically. Following this are manifestations of any and all electronic signatures for this electronic record.

/s/

JAIMIN S PATEL
02/25/2021 10:37:22 AM

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U.S. FOOD & DRUG ADMINISTRATION

RECOMMENDATION

☒ Approval
☐ Approval with Post-Marketing Commitment
☐ Complete Response

NDA 204957
Assessment 4

Drug Product Name	Acetaminophen Injection in the PAB Container
Dosage Form	Solution for injection
Strength	10 mg/mL (500 mg/50 mL and 1000 mg/100 mL)
Route of Administration	Intravenous injection
Rx/OTC Dispensed	Rx
Applicant	B. Braun Medical, Inc.
US agent, if applicable	N/A

Submission(s) Assessed	Document Date	Discipline(s) Affected
Supporting document 32; eCTD 0032	27 Aug 20	Facilities
Supporting document 36; eCTD 0036	4 Dec 20	Drug product

QUALITY ASSESSMENT TEAM

Discipline	Primary Assessment	Secondary Assessment
Drug Substance	N/A	N/A
Drug Product	N/A	N/A
Manufacturing	Yoon Oh	Jonathan Swoboda
Microbiology	N/A	N/A
Biopharmaceutics	N/A	N/A
Regulatory Business Process Manager	Anika Lalmansingh	
Application Technical Lead	Valerie Amspacher	
Laboratory (OTR)	N/A	N/A
Environmental	N/A	N/A

EXECUTIVE SUMMARY

I. RECOMMENDATIONS AND CONCLUSION ON APPROVABILITY

CMC recommends approval of this application based on the facilities review. Also see previous CMC IQA's dated 15 Sep 2017, 6 Mar 20, 17 Apr 20.

The proposed expiry of 18 months is acceptable when stored at 20 °C to 25 °C (68 °F to 77 °F) [see USP Controlled Room Temperature].

II. SUMMARY OF QUALITY ASSESSMENTS

A. Product Overview

Acetaminophen Injection 500 mg/50 mL and 1000 mg/100 mL (10 mg/mL) is a sterile, clear, colorless (b) (4) non-pyrogenic, isotonic solution. Acetaminophen Injection is packaged in the B. Braun PAB container with a blocked port to prevent admixture. The finished drug product is a non-salicylate antipyretic and non-opioid analgesic agent and is intended for sterile injection.

This is review #4 of this NDA. This resubmission dated 27 Aug 20 in response to Complete Response letter dated 24 Apr 20.

Resubmission dated 24 Oct 2019 in response to Complete Response letter dated 27 Mar 2019 due to facility issues. This resubmission was not approved. Complete Response letter dated 24 Apr 20 sent due to facility issues.

Resubmission dated 27 Sep 2018 in response to Complete Response letter sent 28 Sep 2017. This resubmission was not approved. Complete Response letter dated 27 Mar 2019 sent due to facility issues. There were additional comments in the Complete Response letter that were not deficiencies but which the letter stated the sponsor must address prior when the NDA is resubmitted.

NDA originally submitted 13 Dec 2016, complete response letter sent 28 Sep 2017 due to facility issues. There were additional comments in the Complete Response letter that were not deficiencies but which the letter stated the sponsor must address prior to resubmitting their NDA.

The proposed expiry of 18 months is acceptable when stored at 20 °C to 25 °C (68 °F to 77 °F) [see USP Controlled Room Temperature].

Proposed Indication(s)	Management of moderate to severe pain with adjunctive opioid analgesics in adult and pediatric patients 2 years and older

including Intended Patient Population	Reduction of fever in adult and pediatric patients
Duration of Treatment	acute
Maximum Daily Dose	4 grams
Alternative Methods of Administration	N/A

B. Quality Assessment Overview

Drug Substance: Adequate

See CMC IQA's dated 15 Sep 2017, 6 Mar 20, 17 Apr 20

Drug Product: Adequate

See CMC IQA's dated 15 Sep 2017, 6 Mar 20, 17 Apr 20

An IR was sent to clarify the shelf-life the sponsor was requesting for the drug product. Although 24 months of stability data is provided, the applicant confirmed that an 18 month shelf-life is appropriate for the drug product at this time. This reviewer agrees.

Labeling: Adequate

See CMC IQA's dated 15 Sep 2017, 6 Mar 20, 17 Apr 20

Manufacturing: Adequate

Following review of the inspection documentation and application documents, the main finished dosage form manufacturing facility for NDA 204957 Resubmission 32 has been found acceptable.

Resubmission 32 due to the OAI classification of previous inspection inspection at the main, finished dosage form production site. This inspection occurred 06/22/2020 to 7/23/2020 and as documented under CMS WA 344468, this inspection has been classified as VAI. Facilities are acceptable to perform proposed responsibility for this application.

Biopharmaceutics: Adequate

See CMC IQA's dated 15 Sep 2017, 6 Mar 20, 17 Apr 20

Microbiology (if applicable): Adequate

See CMC IQA's dated 15 Sep 2017, 6 Mar 20, 17 Apr 20

QUALITY ASSESSMENT DATA SHEET

1. RELATED/SUPPORTING DOCUMENTS

A. DMFs:

DMF #	Type	Holder	Item Referenced	Status	Date Assessment Completed	Comments
(b) (4)	II	(b) (4)	(b) (4)	1	19 Apr 2019	
	II			1	12 Jun 2018	
	III			4		
	III			4		
	III			4		
	III			4		
	III			4		
	III			4		
	III			4		
	III			4		
	III			4		

Action codes for DMF Table:
1 – DMF Reviewed.
2 –Type 1 DMF
3 – Reviewed previously and no revision since last review
4 – Sufficient information in application
5 – Authority to reference not granted
6 – DMF not available
7 – Other (explain under "Comments")

B. OTHER DOCUMENTS: *IND, RLD, RS, Approved NDA*

Document	Application Number	Description
IND	111161	
NDA	022450	Ofirmev

2. CONSULTS

Discipline	Status	Recommendation	Date	Assessor
Biostatistics				
Pharmacology/Toxicology				
CDRH-ODE				
CDRH-OC				
Clinical				
Other				

Inspection View Screenshot showing approval (taken 2 Dec 20)

(b) (4)

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Valerie Amspacher

Digitally signed by Valerie Amspacher
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This is a representation of an electronic record that was signed electronically. Following this are manifestations of any and all electronic signatures for this electronic record.

/s/

VALERIE R AMSPACHER
12/08/2020 03:56:56 PM

QUALITY ASSESSMENT

Recommendation:
NDA:Complete Response

NDA 204957
Review
Review Date

Drug Name/Dosage Form	Acetominophen for Injection
Strength	500mg/10ml and 1000mg/100ml
Route of Administration	Intravenous
Rx/OTC Dispensed	Rx
Applicant	B. Braun Medical Inc.
US agent, if applicable	

SUBMISSION(S) REVIEWED	DOCUMENT DATE
Resubmission eTCD # 28	October 1, 2019

Quality Review Team

DISCIPLINE	REVIEWER	BRANCH/DIVISION
Drug Substance	N/A	
Drug Product	Jizhou Wang	ONDP/Division II/Branch IV
Process	N/A	
Microbiology	N/A	
Facility	Jonathan Swoboda	OPMA
Biopharmaceutics	N/A	
Project/Business Process Manager	Anika Lalmansingh	OPRO
Application Technical Lead	Julia PInto	ONDP/Division II/Branch IV
Laboratory (OTR)	N/A	
ORA Lead	N/A	
Environmental Assessment (EA)	N/A	

Executive Summary

I. Recommendations: Complete Response

A. Recommendation and Conclusion on Approvability

In the last review cycle in March 2019, this NDA was recommended for CR because of a facility inspection status of OAI (official action indicated) for the B. Braun drug product facility. In addition, the following two recommendations were included in the CR letter of March 29, 2019. These were not considered safety concerns .

1. Your reporting of leachables compounds at and above (b) (4) mcg/mL (i.e., (b) (4) mcg/day taking into consideration the maximum daily dose of acetaminophen) is not acceptable as this exceeds the recommended qualification threshold of 5 mcg/day. Identify all leachable compounds above 5 mcg/day and submit a toxicological risk assessment for any newly identified compound that exceeds the 5 mcg/day threshold of concern.

2. You have not provided adequate safety justification for the unknown compound at RRT. Identify this unknown compound and submit an accompanying toxicological risk.

In October 2019, the Sponsor filed a response to the CR, to address the two recommendations as well as the OAI for the B.Braun Facility.
The Drug Product reviewer has evaluated the additional data submitted by the Sponsor in response to the Agency's requests in the March 29, 2019 CR letter, (review below by J. Wang, Ph.D.) and as found the data submitted adequate.

However, the Office of Manufacturing Assessment (OPMA) continues to recommend an OAI for the B. Braun Facility. The issues found during inspection have not yet been resolved. Below is from Panorama and received by email from Jonathan Swoboda, April 15 2020.

During a recent inspection of B. Braun Medical Inc. (FEI 2021236) DP manufacturer for this application, our field investigator conveyed deficiencies to the representative of the facility. Satisfactory resolution of these deficiencies is required before this application may be approved.

Overall Recommendataion : Complete Response

Julia C. Pinto, Ph.D.
Application Technical Lead

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/s/

JULIA C PINTO
04/17/2020 12:54:13 PM

Overall Recommendation: Complete Response

NDA 204957 Resubmission 2

Acetaminophen Injection 500 mg/50 mL and 1000 mg/100 mL (10 mg/mL) in the PAB® container

Executive Summary

The Applicant is seeking approval for, Acetaminophen Injection 500 mg/50 mL and 1000 mg/100 mL (10 mg/mL). The container closure is a PAB® Container (b) (4) (b) (4) (b) (4) n the original submission, sufficient data were provided to support the quality of the drug product, and to support the requested expiry of 18 months. The complete response recommendation from OPQ was due to Compliance issues identified at the B. Braun manufacturing facility. In the current resubmission package, the Applicant has provided updated stability report for their 4 additional stability batches with up to 24 months of stability data in addition to leachable data at the 24 month timepoint with the associated toxicology data to support the identified leachables.

In the last review cycle, Office of Facilities had recommended a withhold of this application due to the compliance status of B. Braun Medical Inc., (FEI 20212360). There were significant concerns over the site's ability to (b) (4) (b) (4) These same Compliance issues identified at B. Braun are still not resolved and the OPQ Office of Facilities, continues to recommend Withhold for the B. Braun Site.

From CMC drug product perspective, the application remains adequate. However because of the continued compliance issues with the B. Braun manufacturing facility and the withhold recommendation by the OPQ's Office of Facilities, the overall OPQ recommendation for this Resubmission, is a **Complete Response**.

CHAPTER II: DRUG PRODUCT

Product Information	
NDA Number	204957
Assessment Cycle Number	2
Drug Product (DP) Name / Strength	Acetaminophen Injection 500 mg/50 mL and 1000 mg/100 mL (10 mg/mL) in the PAB® container
Route of Administration	Intravenous (infusion)
Drug Product Manufacturer	B Braun Medical, Inc.

RLD Information (Brand Name of Product, Applicant)	Ofirmev, Mallinckrodt Hosp
RLD/RS Number	022450
Proposed Indication	• the management of mild to moderate pain • the management of moderate to severe pain with adjunctive opioid analgesics • the reduction of fever

Assessment Recommendation: **Adequate**

Assessment Summary: *A Complete Response (CR) letter was sent to the Applicant on September 28, 2017 due to product specific and GMP compliance issues observed during the inspection of B. Braun Medical, Inc. manufacturing facility. The Applicant has submitted their response to the CR letter on September 27, 2018. No CMC drug product deficiency was found in the original submission.The Applicant has submitted the following CMC drug product information in response to the CR comments by Pharmacology/Toxicology (P/T) Reviewer:*

- ***a)*** *Updated specifications with revised 4-aminophenol and 4-nitrophenol acceptance criteria from (b) (4) % to (b) (4) %*
- ***b)*** *Updated stability report with long-term stability data up to 24 months (RPT-PH-1008521 (v. 4), RPT-PH-1007742 (v. 4))*
- ***c)*** *Updated leachability study report for Acetaminophen Injection in PAB® Container System (b) (4), 24 months (RPT-PH-1007289, version 3.0). The Applicant has also included leachable assessment for 8 stability batches at the 24-month time-point.*
- ***d)*** 24 months leachables Study Report for Metronidazole Injection USP 500 mg (5 mg/mL) in PAB® Container Closure System (b) (4) (b) (4)

*This review is for assessment of the drug product information submitted by the Applicant in their resubmission package dated Sep 27, 2018 and CMC IR responses dated 04 January, 2019 and 19 February, 2019. See "**Background and Summary**" section below for the detailed summary of the past and current submissions and assessments. From CMC drug product perspective only, the submitted information is **adequate**.*

List Submissions being assessment (table):

Document(s) Assessed	Date Received
0021 (21) ORIG-1/Resubmission/Class 2	September 27, 2018
0023 (23) ORIG-1/Quality/Response to Information Request	January 04, 2019
0025 (CMC/PT IR response)	February 19, 2019

Highlight Key Issues from Last Cycle and Their Resolution: No CMC drug product related approvability issues or deficiencies were identified in the last review cycle. Accordingly, the CMC drug product reviewer, Dr. Chris Hough, had concluded that the original submission was adequate. The new CMC information has been submitted in resubmission package to address deficiencies from Pharmacology/Toxicology (P/T) reviewer that were identified in the CR letter; these P/T deficiencies were not identified as approvability issues.

Concise Description of Outstanding Issues (List Bullet Points with Key Information and Update as Needed): None from CMC Drug Product perspective.

Following editorial revisions will sent to the Applicant through an IR regarding their proposed carton and container label and labeling

"Replace the terminology (b) (4) *with "single dose" on your proposed carton and container labels and in Section 16 of the proposed PI labeling text."*

Background and Summary: The Applicant is seeking approval for its proposed drug product, Acetaminophen Injection 500 mg/50 mL and 1000 mg/100 mL (10 mg/mL). The container closure is a PAB® Container (b) (4) (b) (4) (b) (4) In the original submission, sufficient data were provided to support the quality of the drug product, and to support the requested expiry of 18 months. However, facilities had recommended a withhold of this application due to the compliance status of B. Braun Medical Inc Inc., FEI 2021236 and significant concerns over the site's ability (b) (4) (b) (4) (b) (4) Additionally, P/T reviewer had deficiencies regarding the specification for (b) (4) (b) (4) in drug product and levels of certain unknown and known leachables observed during the leachability study. In the original submission the applicant had provided 12 months of long-term (25ºC/60%RH) and 6 months of accelerated stability data (40ºC/75%RH) for 8 primary stability batches (4 batches of each configuration). The applicant had also provided up to six months of stability data for 4 additional stability batches, (b) (4) as a risk mitigation plan in the original submission (2 batches per configuration). Later in the amendment submitted on 09/12/2017, the applicant had provided updated stability report containing up to 24 months and 12 months long-term stability data for the 8 primary and

4 additional stability batches, respectively; these additional stability data were not reviewed during the first review cycle. In the current resubmission package, the Applicant has provided updated stability report for their 4 additional stability batches with up to 24 months of stability data. The new stability data submitted since the first review cycle do not indicate any new stability trend that was not observed before during the first review cycle. The new stability data continue to support the originally proposed 18-month shelf-life, which was deemed acceptable during the first review cycle. The stability data and the proposed analytical method also support the revised acceptance criteria for both *4-aminophenol and 4-nitrophenol from* (b) (4) *% w/w to* (b) (4) *% w/w.*

In the original submission, the applicant had provided primary leachability study results for the samples stored up to 6 months at accelerated and 12 months at long-term storage conditions. In the current submission the Applicant has provided their final leachability study report with up to 24 months of leachability data from the long-term storage condition. Additionally, the Applicant has also provided leachability data for the 24-month stability time-point samples of their eight primary stability batches. Additionally, the Applicant has provided comparison of unknown leachables observed in the proposed drug product and US approved metronidazole injection (5mg/mL) in PAB® container. The new leachability data do not indicate any new trend with respect to known and unknown leachables. The Applicant has provided adequate data and justification to demonstrate that unknown leachables observed in their proposed drug products are the same, and at lower levels, as those observed in the US approved metronidazole injection in PAB container.

From CMC drug product perspective, the application remains **adequate**.

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Renishkumar Delvadia

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Rebecca Dombrowski

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Julia Pinto

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