CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

204957Orig1s000

CLINICAL REVIEW(S)

Division Director Summary Review for Regulatory Action

Date	(electronic stamp)
From	Naomi Lowy, MD
Subject	Division Director Summary Review
NDA/BLA # and Supplement #	NDA 204957
Applicant	B. Braun Medical, Inc.
Date of Submission	10/24/2019
PDUFA Goal Date	04/24/2020
Proprietary Name	Acetaminophen Injection in the PAB® Container
Established or Proper Name	acetaminophen
Dosage Form(s)	injection
Applicant Proposed Indication(s)/Population(s)	Management of mild to moderate pain, management of moderate to severe pain with adjunctive opioid analgesics, and reduction of fever
Action or Recommended Action:	*Complete Response*

Material Reviewed/Consulted OND Action Package, including:	Names of discipline reviewers
Pharmacology Toxicology Review	Carlic K. Huynh, PhD, Newton H. Woo, PhD, R. Daniel Mellon, PhD
OPQ Review	Jizhou Wang, PhD, Jonathan Swoboda, PhD, Julia Pinto, PhD

OPQ=Office of Pharmaceutical Quality

Executive Summary

Following completion of the second cycle review of NDA 204957, the following three deficiencies prevented approval of the NDA:

1. objectionable conditions at the inspected facility and a withhold recommendation,
2. updated letters from Mallinckrodt that clearly indicate a specific date upon which the application can be approved were not submitted, and
3. documentation of notices of patent certifications were not submitted.

The Office of Manufacturing Assessment (OPMA) continues to recommend an OAI (official action indicated) 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.

Based on this, the Office of Facilities continues to recommend withholding approval. I concur with the recommendation from the Office of Facilities and the chemistry manufacturing and controls review team that based on the withhold recommendation, this NDA resubmission is a Complete Response.

Regarding the second deficiency listed above, considering this application was headed toward a CR because of a facilities issue, legal review is not complete. Therefore, this may or may not continue to be a deficiency. The 505(b)(2) committee has suggested the following language to communicate this issue:

> We refer to the following deficiency communicated to you in our March 27, 2019, complete response (CR) letter and in further detail in our March 25, 2019, information request letter that preceded the CR letter: "Provide updated letters from Mallinckrodt that clearly indicate a specific date upon which your application can be approved."
>
> Your October 17, 2019, response to the CR letter (i.e., resubmission received October 24, 2019) stated "Updated letters from Mallinckrodt (titled "update waiver (b) (4), "update waiver (b) (4) "update consent approval"), clearly indicating a specific date (October 12, 2018) upon which our application can be approved are provided in Module 1.3.5.2." We note that legal review of these updated letters is still pending at this time and therefore we have not made a determination as to whether this is still deficient.

Regarding the third deficiency listed above, documentation of notices of patent certifications was obtained and therefore this is no longer a deficiency.

Background
The Applicant submitted this NDA for Acetaminophen Injection in the Partial Additive Bag (PAB) as a 505(b)(2) submission relying in part on prior findings of safety and efficacy for Ofirmev (Mallinckrodt NDA 22450). To support approval, they provided bioequivalence information between their product and Ofirmev. No clinical studies were required or conducted. The proposed indications and dosing regimen are the same as Ofirmev. The Applicant has proposed two configurations for their product, 1000mg/ 100mL and 500 mg/100 mL.

Pharmacology Toxicology
There were two nonclinical comments communicated in the March 27, 2019 complete response letter that were not approvability issues. The Applicant addressed both of these issues in this resubmission. The following excerpt from the pharmacology/toxicology review summarizes these issues and the conclusions of the pharmacology/toxicology review team:

In the third resubmission, the two non-approval nonclinical issues were addressed. One was the Applicant's reporting of leachable compounds at and above (b) (4) mcg/mL (or (b) (4) mcg/day) threshold based on the maximum daily of the proposed product, which was deemed unacceptable. The Applicant reanalyzed the leachables data using a Limit of Quantitation (LOQ) of (b) (4) mcg/mL, which is below the Reviewer's calculated Analytical

Evaluation Threshold (AET) of (b) (4) mcg/mL based on the maximum daily dose of the proposed product and no new leachable compounds were observed and as such, the response to the first issue is considered acceptable. Another issue was the lack of adequate safety justification for the unknown compound at RRT of (b) (4) min. The Applicant submitted data demonstrating that the unknown compound is an (b) (4) impurity in the drug product that is not a leachable compound from the container closure system. The highest amount of the (b) (4) impurity in stability studies is NMT (b) (4)%, which is below ICH Q3B(R2) identification and qualification thresholds and ICH M7 acceptable intake levels and as such, is adequately qualified. Thus, all nonclinical issues from the second cycle review have been adequately addressed.

From a Pharmacology Toxicology perspective, the proposed drug product is recommended for approval.

Deficiency and Comments to be Conveyed

The CR letter will include the following deficiency in addition to the comment described above regarding the updated letters from Mallinckrodt:

During a recent inspection of B. Braun Medical Inc. (FEI 2021236), drug product 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.

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/

NAOMI N LOWY
04/24/2020 11:33:04 AM

Summary Review for Regulatory Action

Date	(electronic stamp)
From	Ellen Fields, MD, MPH
Subject	Division Deputy Director Summary Review
NDA#	204957
Applicant Name	B. Braun Medical, Inc.
Date of Submission	December 13, 2016
PDUFA Goal Date	October 13, 2017
Proprietary Name / Established (USAN) Name	Acetaminophen Injection in the PAB Container Solution
Dosage Forms / Strength	500 mg/100 mL and 1000 mg/100 mL
Proposed Indication(s)	1. The management of mild to moderate pain 2. The management of moderate to severe pain with adjunctive opioid analgesics 3. The reduction of fever
Action	Complete Response

Material Reviewed/Consulted OND Action Package, including:	**Names of discipline reviewers**
Pharmacology Toxicology Review	Carlic Huynh, PhD, Newton Woo, PhD, R. Daniel Mellon, PhD.
CMC Review/OBP Review	Erika Englund, PhD, Chris Hough, PhD, Hillary Holback PhD, Nutan Myrtle, PhD, Kellly Kitchens PhD, Haritha Mandula PhD, Ciby Abraham, PhD
Clinical Pharmacology Review	David Lee, PhD, Yun Xu, PhD
OSE/DMEPA	Millie Shah, Pharm D, Otto Townsend, PharmD

OND=Office of New Drugs
DDMAC=Division of Drug Marketing, Advertising and Communication
OSE= Office of Surveillance and Epidemiology
DMEPA=Division of Medication Error Prevention and Analysis
DSI=Division of Scientific Investigations
DDRE= Division of Drug Risk Evaluation
DRISK=Division of Risk Management
CDTL=Cross-Discipline Team Leader

Signatory Authority Review Template

1. Introduction

The Applicant submitted this NDA for Acetaminophen Injection in the Partial Additive Bag (PAB) as a 505(b)(2) submission relying in part on prior findings of safety and efficacy for Ofirmev (Mallinckrodt NDA 22450). To support approval, they provided bioequivalence information between their product and Ofirmev. No clinical studies were required or conducted. The proposed indications and dosing regimen are the same as Ofirmev. The Applicant has proposed two configurations for their product, 1000mg/ 100mL and 500 mg/100 mL.

On September 7, 2017, the Applicant notified the Agency of a Notice of Litigation from Mallinckrodt IP and Mallinckrodt Hospital Products against B. Braun for patent infringements on Ofirmev. The complaints were filed in two states.

2. CMC/Device

The drug product and drug substance reviews were found acceptable by the CMC review team.

Facilities recommends a Withhold of this application due to the compliance status of B. Braun Medical Inc., and significant concerns over this site's ability to (b) (4) (b) (4) (b) (4) Based on these concerns, CMC recommends a CR for this application.

I concur with the CR recommendation based on the facilities inspection.

3. Nonclinical Pharmacology/Toxicology

The following is a summary of the nonclinical review taken verbatim from that review.

To support the safety of the APAP intravenous product, the Applicant submitted a 28-day rat IV comparative toxicology study with their proposed formulation (ivAPAP) and an in vitro a blood compatibility assessment of their proposed product. In addition, a negative Ames assay with the drug substance impurity (b) (4) which contains a structural alert for mutagenicity, was submitted to support a specification that exceeds ICH M7. The proposed drug substance and drug product specifications are acceptable.

The proposed PAB container closure system has been used in other FDA-approved drug products. To support safety of the container closure system for this new drug product formulation, the Applicant submitted a series of study reports from other approved products that also utilize the PAB container closure system. The extractable/leachable assessment resulted in 3 known compounds (b) (4) (b) (4) as well as several unknown compounds. In the toxicological risk assessment, (b) (4) and (b) (4) are adequately qualified but (b) (4) is not adequately qualified. Moreover, a total of 3 unknowns and 5 unknowns were detected in leachable studies with the PAB® container above the recommended qualification threshold under normal and accelerated conditions, respectively. Therefore, there is a lack of adequate data to support the safety of the container closure system based on current approaches employed by the Division. However, as this container closure system has been used in several FDA-approved drug products with similar physicochemical properties and for similar doses and durations of treatment, the lack of a modern assessment will not be considered an approval issue if this NDA can be approved in this cycle. If approved this cycle, we would recommend further assessments as a post-marketing requirement.

To confirm that the reformulated drug product should not result in any differential safety profile compared to the referenced drug product, a 28-day IV toxicology study in the rat and in vitro blood compatibility studies were completed. In the 28-day comparative IV toxicology study, similar toxicological findings were present both in the ivAPAP groups and the comparator Ofirmev® group, indicating the proposed formulation did not present a greater risk than Ofirmev®. The local NOAEL was the high dose of 400 mg/kg/day administered at a concentration of 10 mg/mL. At the systemic NOAEL of 200 mg/kg/day, the average C_{max} is 34.65 mcg/mL and the average AUC_{0-t} is 42.6 mcg*h/mL on Day 1. The systemic and local exposure margins are approximately 1.

In the blood compatibility assessment of the proposed formulation ivAPAP, ivAPAP inhibited platelet aggregation, which is an expected pharmacology effect, but did not induce hemolysis of red blood cells or flocculation of proteins. There was no difference between the effects of the proposed ivAPAP product and the referenced product Ofirmev®.

In summary, the data support the conclusion that the change in formulation compared to the referenced drug product should not result in any differential safety profile.

From the nonclinical pharmacology toxicology perspective, NDA 204957 may be approved. Several nonclinical issues were identified but were not deemed approvability issues. These issues can be addressed as postmarketing requirements should this NDA be approved in this cycle. If the NDA is not approved this cycle, we recommend that these issues be addressed, if possible, prior to resubmission.

I concur with the conclusions reached by the pharmacology/toxicology reviewer that there are no outstanding pharm/tox issues that preclude approval.

4. Clinical Pharmacology/Biopharmaceutics

In Study HC-G-H-1506, following a single IV infusion of Acetaminophen Injection 1000 mg and Ofirmev 1000 mg, mean plasma concentrations versus time profiles of acetaminophen, acetaminophen sulfate, and acetaminophen glucuronide looked similar between the two treatments. The results indicated that Acetaminophen Injection is bioequivalent to Ofirmev based on the 90% CIs (within the predefined bioequivalence acceptance limits of 80% to 125%) for the geometric least squares means ratios for AUC0-t, AUC0-inf, and Cmax for acetaminophen, acetaminophen sulfate, and acetaminophen glucuronide

The following table is from Dr. Lee's review:

Table 1 Mean (SD) Plasma Pharmacokinetic Parameters of Acetaminophen (Pharmacokinetic Population)

Parameter (unit)	Acetaminophen Injection 1000 mg (N = 28)	Ofirmev® 1000 mg (N = 28)
AUC_{0-t} (µg•h/mL)	57.23 (17.33)	58.77 (17.0)
AUC_{0-inf} (µg•h/mL)	59.91 (18.60)	61.68 (18.34)
C_{max} (µg/mL)	24.92 (8.40)	24.98 (7.57)
T_{max} (h)[a]	0.25 (0.08, 0.50)	0.250 (0.25, 0.50)
$t_{1/2}$ (h)	2.67 (0.36)	2.72 (0.39)
CL (L/h)	17.72 (5.37)	17.38 (4.40)
V_z (L)	67.69 (20.59)	67.49 (17.04)

Abbreviations: SD: standard deviation; h: hours; N: number of subjects in the population; PK: pharmacokinetic.
a For Tmax, the median (minimum, maximum) values are presented.
Subjects (b) (6) and (b) (6) did not complete both treatments and were excluded from the PK population.
Source: End-of-Text Table 14.2.2.1.

Since the current submission is solely based on Study HC-G-H-1506, a request was submitted to Office of Study Integrity and Surveillance (OSIS) inspect the clinical study site(s). OSIS recommended that the Division accept the Applicant's data without an on-site inspection (DARRTS date 04/17/2017; Shila S Nkah). The rationale for this decision is based on the fact that "OSIS recently inspected the sites" listed in the Consult form and that the "inspection outcome from the inspections was classified as No Action Indicted (NAI)":

I concur with the conclusions reached by the clinical pharmacology/biopharmaceutics reviewer that there are no outstanding clinical pharmacology issues that preclude approval."

5. Other Relevant Regulatory Issues

The Division of Medication Error Prevention and Analysis (DMEPA) reviewed the label and carton and container for this NDA and provided recommendations to the Applicant . Comments will be included in the CR letter to be addressed during the next review cycle.

6. Decision/Action/Risk Benefit Assessment

- Action

Complete Response

- Risk Benefit Assessment

Based on the Withhold recommendation from the facilities inspection this application will review a Complete Response. The Applicant can resubmit this NDA once the facilities issues are resolved.

Upon resubmission, final approval of this application cannot be granted until:

1. a. expiration of the 30-month period provided for in Section 505(c)(3)(C) beginning on the date of receipt of the 45-day notice required under Section 505(b)(3), unless the court has extended or reduced the period because of the failure of either party to reasonably cooperate in expediting the action, or
   b. the date the court decides that the patent(s) is/are invalid or not infringed as described in section 505(c)(3)(C)(i), (ii), (iii,) or (iv) of the Act, or,
   c. the listed patent(s) has/have expired, and
2. we are assured there is no new information that would affect whether final approval should be granted.

- Recommendation for Postmarketing Risk Evaluation and Mitigation Strategies

N/A

- Recommendation for other Postmarketing Requirements and Commitments

N/A

Facilities comment for the CR Letter

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.

Additional comments for Applicant to address upon resubmission of application (not related to approvability)

CARTON AND CONTAINER LABELING

Submit draft carton and container labeling revised as follows:

Container Labels

1. Revise the stating numbers greater than or equal to 1,000 with a comma to prevent the reader from misinterpreting thousands "1000" as hundreds "100" or ten-thousands "10000."

2. Relocate the statement, "CAUTION: DO NOT ADD SUPPLEMENTARY MEDICATION" to under the statement "For Intravenous Use Only" to increase its prominence and minimize the risk of healthcare professionals overlooking this important information.

3. Relocate the package type statement to below the statement "CAUTION: DO NOT ADD SUPPLEMENTARY MEDICATION" to increase its prominence.

Carton Labeling

4. See Item 1, above.

5. Relocate the statement, "CAUTION: DO NOT ADD SUPPLEMENTARY MEDICATION" from the side panel to a prominent location on the principal display panel to minimize the risk of healthcare professionals overlooking this important information.

6. Relocate the NDC number to the top third of the principal display panel in accordance with 21 CFR 207.35(b)(3)(i).

7. Add the lot number in accordance with 21 CFR 201.10(i)(1). Ensure that there are no other numbers located in close proximity to the lot number where they can be mistaken as the lot number. 1

8. Add the expiration date in accordance with 21 CFR 201.17. Ensure that there are no other numbers located in close proximity to the expiration date where they can be mistaken as the expiration date.

[1] Institute for Safe Medication Practices. Safety briefs: The lot number is where? ISMP Med Saf Alert Acute Care. 2009; 14(15):1-3.

NONCLINICAL COMMENTS

Although the following nonclinical concerns are not approvability issues, the following comments should be addressed prior to a subsequent NDA submission:

1. Tighten the drug product specification for 4-aminophenol and 4-nitrophenol based on long-term stability data to as low as technically feasible.

2. In your leachables study, 3 unknown compounds (RT (b) (4) and (b) (4) under normal conditions as well as 5 unknown compounds (RT (b) (4) (b) (4) under accelerated conditions were present in your leachable samples. As we cannot conduct a toxicological risk assessment on unknowns, either provide identification for these unknown compounds along with an adequate toxicological risk assessment or confirm that these compounds are present in other FDA-approved products that use the same container closure system at comparable total daily intake levels.

3. The safety of (b) (4) has not been adequately addressed by the submitted 28-day and 14-day toxicology studies. Either provide data that demonstrates (b) (4) and related compounds are present at comparable total daily intake levels in other FDA-approved products that use the same container closure system or conduct an adequately designed 14-day toxicology study that identifies a NOAEL that establishes adequate safety margins.

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

/s/

ELLEN W FIELDS
09/28/2017