CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

204957Orig1s000

OTHER REVIEW(S)

FOOD AND DRUG ADMINISTRATION
Center for Drug Evaluation and Research
Office of Prescription Drug Promotion

****Pre-decisional Agency Information****

Memorandum

Date: January 29, 2021

To: Ning Hu, M.D., Clinical Reviewer
Division of Anesthesiology, Addiction Medicine, and Pain Medicine (DAAP)

Jaimin Patel, Regulatory Project Manager, DAAP

Lisa Basham, Associate Director for Labeling, DAAP

From: L. Sheneé Toombs, Regulatory Review Officer
Office of Prescription Drug Promotion (OPDP)

CC: Sam Skariah, Team Leader, OPDP

Subject: OPDP Labeling Comments for ACETAMINOPHEN injection, for intravenous use

NDA: NDA 204957

In response to DAAP's consult request dated October 21, 2020, OPDP has reviewed the proposed product labeling (PI), and carton and container labeling for the original NDA/BLA submission for ACETAMINOPHEN injection, for intravenous use.

Labeling: OPDP's comments on the proposed labeling are based on the draft labeling received by electronic mail from DAAP on January 21, 2021, and are provided below.

Carton and Container Labeling: OPDP has reviewed the attached proposed carton and container labeling received by electronic mail from DAAP on January 21, 2021, and we do not have any comments.

Thank you for your consult. If you have any questions, please contact Sheneé Toombs at (301) 796-4174 or latoya.toombs@fda.hhs.gov.

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MEMORANDUM

REVIEW OF REVISED LABEL AND LABELING
Division of Medication Error Prevention and Analysis (DMEPA)
Office of Medication Error Prevention and Risk Management (OMEPRM)
Office of Surveillance and Epidemiology (OSE)
Center for Drug Evaluation and Research (CDER)

Date of This Memorandum:	November 10, 2020
Requesting Office or Division:	Division of Anesthesiology, Addiction Medicine, and Pain Medicine (DAAP)
Application Type and Number:	NDA 204957
Product Name and Strength:	Acetaminophen injection, 1,000 mg/100 mL (10 mg/mL); 500 mg/50 mL (10 mg/mL)
Applicant/Sponsor Name:	B Braun Medical, Inc.
OSE RCM #:	2018-2112-2
DMEPA Safety Evaluator:	Cameron Johnson, PharmD
DMEPA Team Leader:	Otto L. Townsend, PharmD

1 PURPOSE OF MEMORANDUM

The Applicant submitted revised container label and carton labeling received on November 4, 2020 for Acetaminophen. The Division of Anesthesiology, Addiction Medicine, and Pain Medicine (DAAP) requested that we review the revised container label and carton labeling for Acetaminophen (Appendix A) to determine if they are acceptable from a medication error perspective. The revisions are in response to recommendations that we made during a previous label and labeling review.[a]

2 DISCUSSION

In our previous label and labeling review we noted that the expiration date format was not defined and requested that B Braun include one of the FDA-recommended expiration date formats (i.e. YYYY-MM-DD, YYYY-MM, or YYYY-MMM) on the container labels and carton labeling. In response[b] to our recommendation, B Braun stated that the proposed expiration

[a] Johnson, C. Label and Labeling Review Memo for Acetaminophen (NDA 204957). Silver Spring (MD): FDA, CDER, OSE, DMEPA (US); 2020 OCT 29. RCM No.: 2018-211201.
[b] Quality Information Amendment_Labeling for Acetaminophen (NDA 204957). Allentown (PA): B Braun Medical, Inc.; 2020 NOV 04. Available from: \\CDSESUB1\evsprod\nda204957\0034\m1\us\111-info-amend\inforamend.pdf

date is "EXP MM/YY" using all numerals. B Braun noted that due to their printing system limitations, this is the only format that they are able to apply to the PAB container. They also noted that the day is not included in the expiration date so it is presumed to be the last day of the month. Furthermore, B Braun stated that this format is used on all of the currently marketed products available in a PAB. We find B Braun's justification for including their expiration date as "EXP MM/YY" acceptable from a medication error perspective.

We also noted in our previous review that the carton labeling did not include product identifiers. We recommended that B Braun determine if product identifier requirements applied to their product. In their response[b], B Braun stated that the shipper case, containing 24 units is the smallest individual saleable unit. Therefore the product identifiers are applied to the shipper case and not the carton. B Braun confirmed that the shipper case is in compliance with the product identifier requirements. We find their justification for the product identifiers acceptable from a medication error perspective.

Lastly, in our previous review we requested that B Braun revise the product code portion of the National Drug Code (NDC) so that they were not the same for the 500 mg/50 mL and 1,000 mg/100 mL container label and carton labeling. In their response, B Braun updated the product code portion of the NDC for the 1,000 mg/100 mL container label and carton labeling and submitted the updated labeling for our review.

3 CONCLUSION

B Braun's responses to our previous recommendations as well as their revisions to the 1,000 mg/100 mL container label and carton labeling are acceptable from a medication error perspective. We have no additional recommendations at this time.

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MEMORANDUM

REVIEW OF REVISED LABEL AND LABELING
Division of Medication Error Prevention and Analysis (DMEPA)
Office of Medication Error Prevention and Risk Management (OMEPRM)
Office of Surveillance and Epidemiology (OSE)
Center for Drug Evaluation and Research (CDER)

Date of This Memorandum:	October 29, 2020
Requesting Office or Division:	Division of Anesthesiology, Addiction Medicine, and Pain Medicine (DAAP)
Application Type and Number:	NDA 204957
Product Name and Strength:	Acetaminophen injection, 1,000 mg/100 mL (10 mg/mL); 500 mg/50 mL (10 mg/mL)
Applicant/Sponsor Name:	B Braun Medical, Inc.
OSE RCM #:	2018-2112-1
DMEPA Safety Evaluator:	Cameron Johnson, PharmD
DMEPA Team Leader:	Otto L. Townsend, PharmD

1 PURPOSE OF MEMORANDUM

As part of their Class 2 Resubmission, B Braun submitted revised container label and carton labeling received on October 24, 2019 for Acetaminophen. The revisions are in response to recommendations that we made during a previous label and labeling review.[a] Also, on October 15, 2020, B Braun submitted, and we received, the proposed Prescribing Information that was updated to reflect the labeling for the listed drug product, Ofirmev. The Division of Anesthesiology, Addiction Medicine, and Pain Medicine (DAAP) requested that we review the revised labels and labeling for Acetaminophen (Appendix A) to determine if they are acceptable from a medication error perspective.

2 REGULATORY HISTORY

B Braun submitted their original NDA on December 13, 2016. We reviewed the proposed container labels, carton labeling and Prescribing Information (PI) and identified areas of vulnerability that may lead to medication errors. However, on September 28, 2017, a Complete Response (CR) Letter was issued for NDA 204957 due to facilities inspection deficiencies and our recommendations for the container label and carton labeling were conveyed to B Braun in

[a] Shah, M. Label and Labeling Review for Acetaminophen (NDA 204957). Silver Spring (MD): FDA, CDER, OSE, DMEPA (US); 2019 JAN 30. RCM No.: 2018-2112.

the CR letter. Thus, on September 27, 2018 B Braun submitted their complete response to the deficiencies included in the CR letter as a Class 2 resubmission. In their resubmission, they also included revised container labels and carton labeling that incorporated our recommendations that were included in the CR letter. Upon reviewing the revised container labels and carton labeling we identified additional medication error issues with the carton labeling. However, on March 27, 2019, a second CR Letter was issued due to facilities inspection deficiencies and our additional recommendations for the carton labeling were conveyed to B Braun in the CR letter. Thus, on October 24, 2019 B Braun submitted their complete response to the deficiency included in the CR letter as a Class 2 resubmission and included the container labels and revised carton labeling that incorporated our recommendations that were included in the CR letter. A third CR letter was issued due to facilities inspection deficiencies. Thus, B. Braun submitted their complete response to the CR letter on August 27, 2020 as a Class 2 Resubmission. In their resubmission, they noted that there had been no changes to the labeling since the third cycle resubmission received on October 24, 2019. However, DAAP noted that there were additional updates that needed to made to the PI based on the Listed Drug Product's labeling and requested that B Braun submit the revised PI once those updates were incorporated. Thus, B Braun submitted a revised PI on October 15, 2020. The container labels and carton labeling submitted on October 24, 2019 and the PI submitted on October 15, 2020 are the subject of this review.

3 FINDINGS AND RECOMMENDATIONS

Tables 1 and 2 below include the identified medication error issues with the submitted PI, container label and carton labeling, our rationale for concern, and the proposed recommendation to minimize the risk for medication error.

Table 1. Identified Issues and Recommendations for Division of Anesthesiology, Addiction Medicine, and Pain Medicine (DAAP)

	IDENTIFIED ISSUE	RATIONALE FOR CONCERN	RECOMMENDATION
Prescribing Information – General Issues			
1.	Numbers greater than or equal to 1,000 are presented without the use of a comma throughout the Prescribing Information.	Misinterpretation of thousands "1000" as hundreds "100" or ten-thousands "10000" may occur.	Present numbers greater than or equal to 1,000 with a comma.
Full Prescribing Information – Section 2 Dosage and Administration			

Table 1. Identified Issues and Recommendations for Division of Anesthesiology, Addiction Medicine, and Pain Medicine (DAAP)			
	IDENTIFIED ISSUE	RATIONALE FOR CONCERN	RECOMMENDATION
1.	The container labels include a preparation instruction for how to prepare a dose if the entire contents of the bag will not be needed for a prescribed dose. For example on the 1,000 mg/100 mL bag the statement is included as "Doses less than 1,000 mg require aseptic transfer to a separate container prior to dispensing. Discard unused portion." This important instruction has not been included in the Prescribing Information.	There is a risk of overdose medication errors if the prescribed dose (not equal to 1,000 mg or 500 mg) is not withdrawn from the 1,000 mg/100 mL bag or the 500 mg/50 mL bag because the user may inadvertently infuse the full contents of the bag.	To reduce the risk of overdose medication errors add the statements "Doses less than 1,000 mg require aseptic transfer to a separate container prior to dispensing. Discard unused portion." and "Doses less than 500 mg require aseptic transfer to a separate container prior to dispensing. Discard unused portion." to the Dosage and Administration section. Furthermore add more detailed information about the appropriate transfer such as: "Using aseptic technique, withdraw the appropriate dose (650 mg or weight-based) from an intact sealed PAB container and place the measured dose in a separate empty, sterile container (e.g., glass bottle, plastic intravenous container, or syringe) for intravenous infusion to avoid the inadvertent delivery and administration of the total volume of the commercially available container. The entire 100 mL container is not intended for use in patients weighing less than 50 kg. Acetaminophen injection is supplied in a single-dose container and the unused portion must be discarded. Place small volume pediatric doses up to 60 mL in volume in a syringe and administer over 15 minutes using a syringe pump."
Full Prescribing Information – Section 16 How Supplied/Storage and Handling			
1.	The table in the How Supplied section	Including the heading "(b) (4) to describe the	Remove the "(b) (4) and "(b) (4) (b) (4) headings and add a heading

Table 1. Identified Issues and Recommendations for Division of Anesthesiology, Addiction Medicine, and Pain Medicine (DAAP)			
	IDENTIFIED ISSUE	**RATIONALE FOR CONCERN**	**RECOMMENDATION**
	includes the headings, "(b) (4) and (b) (4) Also, the concentration has been omitted.	total quantity of drug product in the bag may lead to confusion because (b) (4) (b) (4)	titled "Strength" and include the strengths as "500 mg/50 mL" and "1,000 mg/100 mL". Also, include the concentration, 10 mg/mL, in this section. For example, "Acetaminophen injection (10 mg/mL) is supplied…"
2.	As currently presented, the product code (middle digits) in the National Drug Code (NDC) number for 500 mg/50 mL strength (-4500-) is the same as the product code in the NDC number for 1,000 mg/100 mL strength (-4500-).	The product code identifies a specific strength, dosage form, and formulation.[b] Using the same product code for different strengths can lead to wrong strength errors because barcode scanners may only read the first 10 digits of the NDC codes (i.e., "00264-4500-") and pharmacists may rely on the product code (middle digits) as a manual check.	We have provided a recommendation in Table 2 for the Applicant to revise the product code in the NDC to ensure that the middle 4 digits for the 500 mg/50 mL container label and carton labeling is different from the product code portion of the NDC for the 1,000 mg/100 mL container label and carton labeling.
3.	The How Supplied section does not include the color of the solution.	This information should be included in the How Supplied section per 21 CFR 201.57(c)(17).	Include that the solution is clear and colorless.

Table 2. Identified Issues and Recommendations for B Braun Medical, Inc (entire table to be conveyed to Applicant)

[b] National Drug Code Directory. Available from: https://www.fda.gov/drugs/drug-approvals-and-databases/national-drug-code-directory

	IDENTIFIED ISSUE	RATIONALE FOR CONCERN	RECOMMENDATION
Container Label(s) and Carton Labeling			
1.	The format for expiration date is not defined.	Clearly defining the expiration date will minimize confusion and risk for deteriorated drug medication errors.	Identify the expiration date format you intend to use. FDA recommends that the human-readable expiration date on the drug package label include a year, month, and non-zero day. FDA recommends that the expiration date appear in YYYY-MM-DD format if only numerical characters are used or in YYYY-MMM-DD if alphabetical characters are used to represent the month. If there are space limitations on the drug package, the human-readable text may include only a year and month, to be expressed as: YYYY-MM if only numerical characters are used or YYYY-MMM if alphabetical characters are used to represent the month. FDA recommends that a hyphen or a space be used to separate the portions of the expiration date.
2.	As currently presented, the product code (middle digits) in the National Drug Code (NDC) for 500 mg/50 mL strength (-(b) (4) is the same as the product code in the NDC for 1,000 mg/100 mL strength (-(b) (4)	The product code identifies a specific strength, dosage form, and formulation. Having the same product code portion of the NDC for different strengths can lead to wrong strength errors because barcode scanners may only read the first 10 digits of the NDC codes (i.e., (b) (4)) and pharmacists may rely on the product code (middle digits) as a manual check.	Revise the product code in the NDC to ensure that the middle 4 digits for the 500 mg/50 mL container label and carton labeling is different from the product code portion of the NDC for the 1,000 mg/100 mL container label and carton labeling.

Carton Labeling			
1.	The carton labeling does not include product identifiers.	In September 2018, FDA released draft guidance on product identifiers required under the Drug Supply Chain Security Act.[c] The Act requires manufacturers and repackagers, respectively, to affix or imprint a product identifier to each package and homogenous case of a product intended to be introduced in a transaction in(to) commerce beginning November 27, 2017, and November 27, 2018, respectively.	We recommend that you review the draft guidance to determine if the product identifier requirements apply to your product's labeling.

4 CONCLUSION

Our evaluation of the proposed Acetaminophen PI, container labels and carton labeling identified areas of vulnerability that may lead to medication errors. Above, we have provided recommendations in Table 1 for the Division and 2 for the Applicant. We ask that the Division convey 2 in its entirety to B Braun Medical, Inc so that recommendations are implemented prior to approval of this NDA.

APPENDIX A. LABEL AND LABELING RECEIVED ON OCTOBER 24, 2019AND OCTOBER 15, 2020

Container labels

[c] The draft guidance is available from: https://www.fda.gov/ucm/groups/fdagov-public/@fdagov-drugs-gen/documents/document/ucm621044.pdf

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LABEL AND LABELING REVIEW
Division of Medication Error Prevention and Analysis (DMEPA)
Office of Medication Error Prevention and Risk Management (OMEPRM)
Office of Surveillance and Epidemiology (OSE)
Center for Drug Evaluation and Research (CDER)

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Date of This Review:	January 30, 2019
Requesting Office or Division:	Division of Anesthesia, Analgesia, and Addiction Products (DAAAP)
Application Type and Number:	NDA 204957
Product Name and Strength:	Acetaminophen injection 1,000 mg/100 mL, 500 mg/50 mL (10 mg/mL)
Product Type:	Single ingredient
Rx or OTC:	Rx
Applicant/Sponsor Name:	B Braun Medical, Inc.
FDA Received Date:	September 27, 2018
OSE RCM #:	2018-2112
DMEPA Safety Evaluator:	Millie Shah, PharmD, BCPS
DMEPA Team Leader:	Otto L. Townsend, PharmD

1 PURPOSE OF REVIEW

This review evaluates the proposed labels and labeling for Acetaminophen injection (NDA 204957) to identify areas of vulnerability that may lead to medication errors. DAAAP requested this review as part of their evaluation of the 505(b)(2) submission for Acetaminophen injection. The listed drug product (Ofirmev, NDA 022450) was approved in November 2010.

2 BACKGROUND/REGULATORY HISTORY

NDA 204957 received a Complete Response Letter on September 28, 2017 due to facilities inspection. Thus, B. Braun Medical submitted their response to the Complete Response Letter on September 27, 2018.

3 MATERIALS REVIEWED

Table 1. Materials Considered for this Label and Labeling Review

Material Reviewed	Appendix Section (for Methods and Results)
Product Information/Prescribing Information	A
Previous DMEPA Reviews	B
ISMP Newsletters	C-N/A
FDA Adverse Event Reporting System (FAERS)*	D-N/A
Other	E-N/A
Labels and Labeling	F

N/A=not applicable for this review
*We do not typically search FAERS for our label and labeling reviews unless we are aware of medication errors through our routine postmarket safety surveillance

4 FINDINGS AND RECOMMENDATIONS

We reviewed the proposed labeling for Acetaminophen injection during the previous review cycle (see Appendix B) and we confirmed that our previous recommendations were implemented or considered. In our review of the label and labeling included with this submission, we identified additional medication error issues. Tables 2 and 3 below include the identified medication error issues, DMEPA's rationale for concern, and the proposed recommendation to minimize the risk for medication error.

Table 2: Identified Issues and Recommendations for Division of Anesthesia, Analgesia, and Addiction Products (DAAAP)

	IDENTIFIED ISSUE	RATIONALE FOR CONCERN	RECOMMENDATION
General Issues			
1.	The package type term (b) (4) is used throughout the labeling (including container labels and carton labeling).	(b) (4) is not a recommended package type term.	We defer to the Office of Pharmaceutical Quality (OPQ) to determine the correct package type term for this product and convey this to the Applicant.
Prescribing Information			
1.	Numbers greater than or equal to 1,000 are presented without the use of a comma throughout the Prescribing Information.	Misinterpretation of thousands "1000" as hundreds "100" or ten-thousands "10000" may occur.[a]	Present numbers greater than or equal to 1,000 with a comma.

Table 3: Identified Issues and Recommendations for B Braun Medical, Inc. (entire table to be conveyed to Applicant)

	IDENTIFIED ISSUE	RATIONALE FOR CONCERN	RECOMMENDATION
Carton Labeling			
1.	The carton containing 4 units uses the same NDC number as the container label.	The container label of one unit and the carton labeling of 4 units should have different NDC package codes (last 2 digits of the NDC) to minimize the risk for confusion.	Revise the NDC numbers so that the carton labeling and vial labels use a different NDC package code (last 2 digits of the NDC).
2.	The top flap contains a space for (b) (4) (b) (4)	It is unclear why there is space for (b) (4) (b) (4) included on the	Remove (b) (4) (b) (4) or provide your rationale for including.

[a] ISMP's List of Error-Prone Abbreviations, Symbols, and Dose Designations [Internet]. Horsham (PA): Institute for Safe Medication Practices. 2015 [cited 2018 NOV 29]. Available from: http://www.ismp.org/tools/errorproneabbreviations.pdf.

		carton because (b) (4) [redacted] (b) (4)	

5 CONCLUSION

Our evaluation of the proposed label and labeling identified areas of vulnerability that may lead to medication errors. Above, we have provided recommendations in Table 2 for the Division and Table 3 for the Applicant. We ask that the Division convey Table 3 in its entirety to the Applicant so that recommendations are implemented prior to approval of this NDA.

APPENDICES: METHODS & RESULTS FOR EACH MATERIALS REVIEWED

APPENDIX A. PRODUCT INFORMATION/PRESCRIBING INFORMATION

Table 4 presents relevant product information for Acetaminophen injection that B. Braun Medical submitted on September 27, 2018, and the listed drug (LD).

Table 4. Relevant Product Information for Listed Drug and Acetaminophen injection		
Product Name	Acetaminophen injection	Ofirmev
Initial Approval Date	Not Applicable	11/20/2010
Active Ingredient	acetaminophen	acetaminophen
Indication	• 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 • Reduction of fever in adult and pediatric patients (b) (4)	• 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 Reduction of fever in adult and pediatric patients
Route of Administration	intravenous	intravenous
Dosage Form	injection	injection
Strength	1,000 mg/100 mL and 500 mg/50 mL (10 mg/mL)	1,000 mg/100 mL (10 mg/mL)
Dose and Frequency	Adults and Adolescents Weighing 50 kg and Over: • 1,000 mg every 6 hours or 650 mg every 4 hours to a maximum of 4,000 mg per day. Minimum dosing interval of 4 hours. Adults and Adolescents Weighing Under 50 kg: • 15 mg/kg every 6 hours or 12.5 mg/kg every 4 hours to a maximum of 75 mg/kg per day. Minimum dosing interval of 4 hours. Children:	Adults and Adolescents Weighing 50 kg and Over: •1000 mg every 6 hours or 650 mg every 4 hours to a maximum of 4000 mg per day. Minimum dosing interval of 4 hours. Adults and Adolescents Weighing Under 50 kg: •15 mg/kg every 6 hours or 12.5 mg/kg every 4 hours to a maximum of 75 mg/kg per day. Minimum dosing interval of 4 hours. Children:

	• Children 2 to 12 years of age: 15 mg/kg every 6 hours or 12.5 mg/kg every 4 hours to a maximum of 75 mg/kg per day. Minimum dosing interval of 4 hours	•Children 2 to 12 years of age: 15 mg/kg every 6 hours or 12.5 mg/kg every 4 hours to a maximum of 75 mg/kg per day. Minimum dosing interval of 4 hours. Neonates and Infants: •Neonates including premature neonates born at ≥ 32 weeks gestational age to 28 days chronological age, 12.5 mg/kg every 6 hours to a maximum of 50 mg/kg per day. Minimum dosing interval of 6 hours. Infants (29 days to 2 years of age): 15 mg/kg every 6 hours to a maximum of 60 mg/kg per day. Minimum dosing interval of 6 hours.
How Supplied/ Container Closure	50 mL and 100 mL fill PAB containers packaged 24 per case	100 mL glass vial in cartons of 24 vials 100 mL bag in cartons of 24 bags
Storage	20 °C to 25 °C (68 °F to 77 °F) [see USP Controlled Room Temperature]	20°C to 25°C (68°F to 77°F) [see USP Controlled Room Temperature]

APPENDIX B. PREVIOUS DMEPA REVIEWS

B.1 Methods

On November 20, 2018, we searched the L:drive and AIMS using the terms, "acetaminophen injection" to identify reviews previously performed by DMEPA.

B.2 Results

Our search identified one previous review[b] relevant to the current review and we confirmed our recommendations were implemented or considered.

[b] Shah, M. Label and Labeling Review for Acetaminophen injection (NDA 204957). Silver Spring (MD): FDA, CDER, OSE, DMEPA (US); 2017 MAY 12. RCM No.: 2016-2967.

APPENDIX C. N/A

APPENDIX D. N/A

APPENDIX E. N/A

APPENDIX F. LABELS AND LABELING

F.1 List of Labels and Labeling Reviewed

Using the principles of human factors and Failure Mode and Effects Analysis,[c] along with postmarket medication error data, we reviewed the following Acetaminophen injection labels and labeling submitted by B. Braun Medical on September 27, 2018.

- Container label received on September 27, 2018
- Carton labeling received on September 27, 2018
- Prescribing Information (Image not shown) received on September 27, 2018: \\cdsesub1\evsprod\nda204957\0021\m1\us\114-labeling\114a-draft-label\spl\3a864045-6b3f-4723-8e8c-c0cb02547b68.xml

F.2 Label and Labeling Images

Container Label-100 mL

[c] Institute for Healthcare Improvement (IHI). Failure Modes and Effects Analysis. Boston. IHI:2004.

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LABEL AND LABELING REVIEW

Division of Medication Error Prevention and Analysis (DMEPA)

Office of Medication Error Prevention and Risk Management (OMEPRM)

Office of Surveillance and Epidemiology (OSE)

Center for Drug Evaluation and Research (CDER)

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Date of This Review:	May 12, 2017
Requesting Office or Division:	Division of Anesthesia, Analgesia, and Addiction Products (DAAAP)
Application Type and Number:	NDA 204957
Product Name and Strength:	Acetaminophen injection 1,000 mg/100 mL, 500 mg/50 mL (10 mg/mL)
Product Type:	Single ingredient
Rx or OTC:	Rx
Applicant/Sponsor Name:	B Braun Medical, Inc.
Submission Date:	December 13, 2016 and March 15, 2017
OSE RCM #:	2016-2967
DMEPA Primary Reviewer:	Millie Shah, PharmD, BCPS
DMEPA Team Leader:	Otto L. Townsend, PharmD

1 REASON FOR REVIEW

This review provides our evaluation of the proposed labels and labeling for Acetaminophen injection from a medication error perspective. The Division of Anesthesia, Analgesia, and Addiction Products (DAAAP) requested this review as part of their evaluation of the 505(b)(2) NDA submission for Acetaminophen injection.

2 MATERIALS REVIEWED

We considered the materials listed in Table 1 for this review. The Appendices provide the methods and results for each material reviewed.

Table 1. Materials Considered for this Label and Labeling Review

Material Reviewed	Appendix Section (for Methods and Results)
Product Information/Prescribing Information	A
Previous DMEPA Reviews	B
Human Factors Study	C-N/A
ISMP Newsletters	D-N/A
FDA Adverse Event Reporting System (FAERS)*	E-N/A
Other	F-N/A
Labels and Labeling	G

N/A=not applicable for this review
*We do not typically search FAERS for our label and labeling reviews unless we are aware of medication errors through our routine postmarket safety surveillance

3 OVERALL ASSESSMENT OF THE MATERIALS REVIEWED

We performed a risk assessment of the proposed container label, carton labeling, and prescribing information to identify deficiencies that may lead to medication errors and other areas that can be improved.

Container Labels and Carton Labeling

The container labels and carton labeling present the strength without a comma (for example, 1000 mg). Thus, we recommend 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,"[a] which could result in an underdose or overdose.

We identified that the statement, "CAUTION: DO NOT ADD SUPPLEMENTARY MEDICATION" is located in the middle of the principal display panel. Thus, we recommend relocating this

[a] Guidance for Industry: Safety Considerations for Container Labels and Carton Labeling Design to Minimize Medication Errors. Food and Drug Administration. 2013. Available from http://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/UCM349009.pdf

caution statement to a more prominent location on the principal display panel to minimize the risk of healthcare professionals overlooking this important information.

We note that healthcare professionals may withdraw less than 1,000 mg or 500 mg if a patient requires a smaller dose and save the remaining dose for a later time. However, the statement, "Doses less than 500 mg require aseptic transfer to a separate container prior to dispensing. Discard unused portion." addresses this risk and we do not have recommendations at this time.

We note that the NDC number on the carton labeling is not located in a prominent location on the principal display panel. Because the NDC number is often used as an additional verification prior to drug dispensing in the pharmacy, it is an important safety feature that should be prominently displayed in the top third of principal display panel of the labeling in accordance with 21 CFR 207.35(b)(3)(i). Thus, we recommend the Applicant relocate the NDC number to the top third of the principal display panel.

We identified that the lot number and expiration date are missing from the carton labeling. Thus, we recommend the Applicant add the lot number and expiration date to the carton labeling.

We identified that the package type term "Single (b) (4) container" is present throughout the labels and labeling. We notified the Office of Pharmaceutical Quality (OPQ) reviewer and we defer to OPQ to determine the correct package type term for this product and convey this to the Applicant. We recommend that the Applicant relocate the package type statement to below the statement "CAUTION: DO NOT ADD SUPPLEMENTARY MEDICATION" on the container label to increase its prominence.

Prescribing Information

Our review of the prescribing information identified the presentation of numbers greater than 1,000 without the use of a comma. Thus, we recommend 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."[b]

4 CONCLUSION & RECOMMENDATIONS

We identified areas in the proposed labels and labeling that can be improved to increase clarity and prominence of important information to promote the safe use of this product.

If you have further questions or need clarifications, please contact Davis Mathew, OSE Project Manager, at 240-402-4559.

4.1 RECOMMENDATIONS FOR THE DIVISION

We revised the *Dosage and Administration* and *How Supplied* sections of the Highlights of Prescribing Information and Full Prescribing Information and provided a detailed summary below for review and consideration by DAAAP.

[b] Guidance for Industry: Safety Considerations for Container Labels and Carton Labeling Design to Minimize Medication Errors. Food and Drug Administration. 2013. Available from http://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/UCM349009.pdf

A. General Comment

1. We identified the package type term (b) (4) throughout the labels and labeling. We defer to the Office of Pharmaceutical Quality (OPQ) to make the final determination of the correct package type term for this product. Ensure that the OPQ-determined package type is consistent throughout labels and labeling and is conveyed to the Applicant.

B. Highlights of Prescribing Information and Full Prescribing Information

1. We recommend 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."[c]

4.2 RECOMMENDATIONS FOR B BRAUN MEDICAL, INC.

We recommend the Applicant implement the following prior to approval of this NDA:

A. Container Labels

1. We recommend 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.

B. Carton Labeling

1. See A.1
2. 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.
3. Relocate the NDC number to the top third of the principal display panel in accordance with 21 CFR 207.35(b)(3)(i).
4. 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.[d]

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[c] Guidance for Industry: Safety Considerations for Container Labels and Carton Labeling Design to Minimize Medication Errors. Food and Drug Administration. 2013. Available from http://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/UCM349009.pdf

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

5. 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.

APPENDICES: METHODS & RESULTS FOR EACH MATERIALS REVIEWED

APPENDIX A. PRODUCT INFORMATION/PRESCRIBING INFORMATION

Table 2 presents relevant product information for Acetaminophen injection that B Braun Medical, Inc. submitted on December 13, 2016, and the listed drug (LD).

Table 2. Relevant Product Information for Acetaminophen injection and the Listed Drug

Product Name	**Acetaminophen injection**	**Ofirmev**
Initial Approval Date	Not Applicable	11/20/2010
Active Ingredient	acetaminophen	acetaminophen
Indication	• the management of mild to moderate pain • the management of moderate to severe pain with adjunctive opioid analgesics • the reduction of fever.	• 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 • Reduction of fever in adult and pediatric patients
Route of Administration	intravenous	intravenous
Dosage Form	injection	injection
Strength	1,000 mg/100 mL and 500 mg/50 mL (10 mg/mL)	1,000 mg/100 mL (10 mg/mL)
Dose and Frequency	Adults and Adolescents Weighing 50 kg and Over: • 1000 mg every 6 hours to a maximum of 4000 mg per day. Adults and Adolescents Weighing Under 50 kg: • 15 mg/kg every 6 hours to a maximum of 75 mg/kg per day. Children: • Children 2 to 12 years of age: 15 mg/kg every 6 hours to a maximum of 75 mg/kg per day	Adults and Adolescents Weighing 50 kg and Over: •1000 mg every 6 hours or 650 mg every 4 hours to a maximum of 4000 mg per day. Minimum dosing interval of 4 hours. Adults and Adolescents Weighing Under 50 kg: •15 mg/kg every 6 hours or 12.5 mg/kg every 4 hours to a maximum of 75 mg/kg per day. Minimum dosing interval of 4 hours. Children: •Children 2 to 12 years of

		age: 15 mg/kg every 6 hours or 12.5 mg/kg every 4 hours to a maximum of 75 mg/kg per day. Minimum dosing interval of 4 hours. Neonates and Infants: •Neonates including premature neonates born at ≥ 32 weeks gestational age to 28 days chronological age, 12.5 mg/kg every 6 hours to a maximum of 50 mg/kg per day. Minimum dosing interval of 6 hours. Infants (29 days to 2 years of age): 15 mg/kg every 6 hours to a maximum of 60 mg/kg per day. Minimum dosing interval of 6 hours.
How Supplied/ Container Closure	50 mL and 100 mL fill PAB containers packaged 24 per case	100 mL glass vial in cartons of 24 vials 100 mL bag in cartons of 24 bags
Storage	20 °C to 25 °C (68 °F to 77 °F) [see USP Controlled Room Temperature]	20°C to 25°C (68°F to 77°F) [see USP Controlled Room Temperature]

APPENDIX B. PREVIOUS DMEPA REVIEWS

B.1 Methods

On April 6, 2017, we searched the L:drive and AIMS using the terms, “acetaminophen injection,” to identify reviews previously performed by DMEPA.

B.2 Results

Our search did not identify any previous reviews relevant to the current review.

APPENDIX C. N/A

APPENDIX D. N/A

APPENDIX E. N/A

APPENDIX F. N/A

APPENDIX G. LABELS AND LABELING

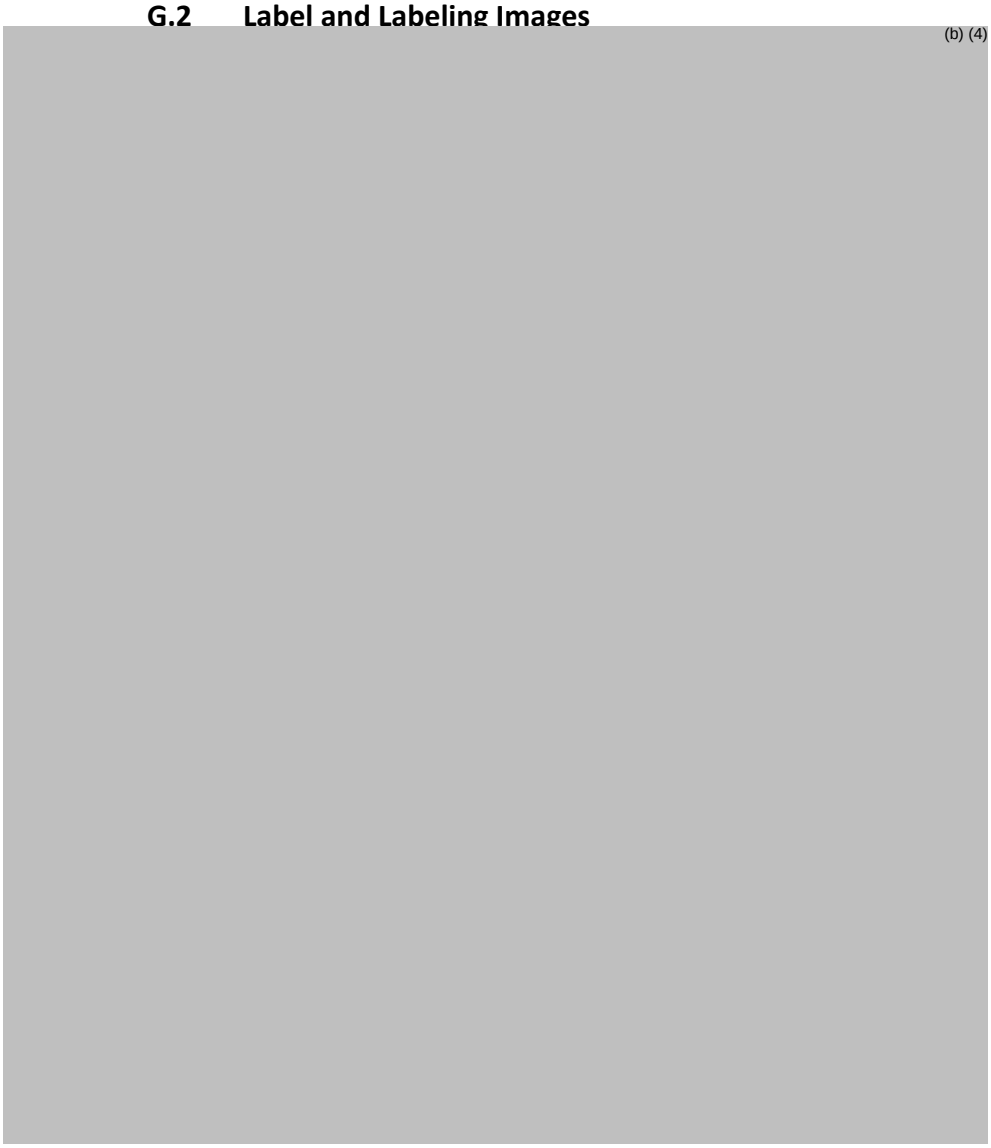
G.1 List of Labels and Labeling Reviewed

Using the principles of human factors and Failure Mode and Effects Analysis,[e] along with postmarket medication error data, we reviewed the following Acetaminophen injection labels and labeling submitted by B Braun Medical on December 13, 2016.

- Container label
- Carton labeling

G.2 Label and Labeling Images

(b) (4)



[e] Institute for Healthcare Improvement (IHI). Failure Modes and Effects Analysis. Boston. IHI:2004.

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/s/

MILLIE C BRAHMBHATT
05/15/2017

OTTO L TOWNSEND
05/15/2017

M E M O R A N D U M

DEPARTMENT OF HEALTH AND HUMAN SERVICES
PUBLIC HEALTH SERVICE
FOOD AND DRUG ADMINISTRATION
CENTER FOR DRUG EVALUATION AND RESEARCH

DATE: 4/17/2017

TO: Division of Anesthesia Analgesia and Addiction Products
Office of Drug Evaluation II

FROM: Division of New Drug Bioequivalence Evaluation (DNDBE)
Office of Study Integrity and Surveillance (OSIS)

SUBJECT: **Recommendation to accept data without an on-site inspection**

RE: NDA 204957

The Division of New Drug Bioequivalence Evaluation (DNDBE) within the Office of Study Integrity and Surveillance (OSIS) recommends accepting data without an on-site inspection. The rationale for this decision is noted below.

Rationale

OSIS recently inspected the sites listed below. The inspectional outcome from the inspections was classified as No Action Indicated (NAI).

Inspection Sites

Facility Type	Facility Name	Facility Address
Clinical	PPD Phase I Clinic	7551 Metro Center Drive, Suite 200, Austin, TX
Analytical	(b) (4)	

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/s/

SHILA S NKAH
04/17/2017