CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

204767Orig1s000

OTHER REVIEW(S)

505(b)(2) ASSESSMENT

Application Information		
NDA # 204767	NDA Supplement #: S-	Efficacy Supplement Type SE-
Proprietary Name: N/A Established/Proper Name: Acetaminophen for Injection Dosage Form: Sterile (b) (4) Solution for Infusion Strengths: 10 mg/mL		
Applicant: Fresenius Kabi USA, LLC		
Date of Receipt: April 30, 2015		
PDUFA Goal Date: October 30, 2015	Action Goal Date (if different): October 28, 2015	
Proposed Indication(s): management of mild to moderate pain, management of moderate to severe pain with adjunctive opioid analgesics, reduction of fever		

GENERAL INFORMATION

1) Is this application for a recombinant or biologically-derived product and/or protein or peptide product *OR* is the applicant relying on a recombinant or biologically-derived product and/or protein or peptide product to support approval of the proposed product?

YES ☐ NO ☒

*If "**YES** "contact the (b)(2) review staff in the Immediate Office, Office of New Drugs.*

INFORMATION PROVIDED VIA RELIANCE (LISTED DRUG OR LITERATURE)

2) List the information essential to the approval of the proposed drug that is provided by reliance on our previous finding of safety and efficacy for a listed drug or by reliance on published literature. *(If not clearly identified by the applicant, this information can usually be derived from annotated labeling.)*

Source of information* (e.g., published literature, name of referenced product)	Information provided (e.g., pharmacokinetic data, or specific sections of labeling)
NDA 022450, Ofirmev (Cadence Pharmaceuticals)	All sections are the same as the Listed drug except referring to the container closure system (including within dosage and administration) and editorial type changes.

*each source of information should be listed on separate rows

3) Reliance on information regarding another product (whether a previously approved product or from published literature) must be scientifically appropriate. An applicant needs to provide a scientific "bridge" to demonstrate the relationship of the referenced and proposed products. Describe how the applicant bridged the proposed product to the referenced product(s). (Example: BA/BE studies)

The Applicant requested a waiver for in-vivo bioavailability/ bioequivalence studies. The biowaiver was granted, in accordance with 21 CFR § 320.22(a), because:

1. ***The proposed product contains the same active ingredient in the same concentration as the reference drug product.***
2. ***The proposed formulation has slight differences in formulation composition*** (b) (4)
3. ***The application contains supportive information comparing quality attributes of the proposed formulation with the reference product, for e.g., pH, impurities etc., (subject of CMC review) and is deemed to be equivalent with respect to these quality attributes.***
4. ***Comparative osmolality data was requested to support that the*** (b) (4) ***change in mannitol concentration does not impact the osmolality. The data provided supported that osmolality is not affected.***
5. ***Acetaminophen Injection for intravenous infusion is a dosage form intended solely for IV administration and is a true solution.***
6. ***The route of administration, dosage form and indications of the proposed product are the same as the reference drug product.***
7. ***No other in vitro pharmacodynamic activity comparison was provided or required by the Office of Clinical Pharmacology for this product.***

RELIANCE ON PUBLISHED LITERATURE

4) (a) Regardless of whether the applicant has explicitly stated a reliance on published literature to support their application, is reliance on published literature necessary to support the approval of the proposed drug product (i.e., the application *cannot* be approved without the published literature)?

YES ☐ NO ☒
*If "**NO**," proceed to question #5.*

(b) Does any of the published literature necessary to support approval identify a specific (e.g., brand name) *listed* drug product?

YES ☐ NO ☐
*If "**NO**", proceed to question #5.*
*If "**YES**", list the listed drug(s) identified by name and answer question #4(c).*

(c) Are the drug product(s) listed in (b) identified by the applicant as the listed drug(s)?

YES ☐ NO ☐

RELIANCE ON LISTED DRUG(S)

Reliance on published literature which identifies a specific approved (listed) drug constitutes reliance on that listed drug. Please answer questions #5-9 accordingly.

5) Regardless of whether the applicant has explicitly referenced the listed drug(s), does the application **rely** on the finding of safety and effectiveness for one or more listed drugs (approved drugs) to support the approval of the proposed drug product (i.e., the application cannot be approved without this reliance)?

YES ☒ NO ☐

*If "**NO**," proceed to question #10.*

6) Name of listed drug(s) relied upon, and the NDA/ANDA #(s). Please indicate if the applicant explicitly identified the product as being relied upon (see note below):

Name of Drug	NDA/ANDA #	Did applicant specify reliance on the product? (Y/N)
Ofirmev (Acetaminophen for Injection) Sponsor: Cadence Pharmaceuticals	NDA 022450	Yes

Applicants should specify reliance on the 356h, in the cover letter, and/or with their patent certification/statement. If you believe there is reliance on a listed product that has not been explicitly identified as such by the applicant, please contact the (b)(2) review staff in the Immediate Office, Office of New Drugs.

7) If this is a (b)(2) supplement to an original (b)(2) application, does the supplement rely upon the same listed drug(s) as the original (b)(2) application?

N/A ☒ YES ☐ NO ☐

*If this application is a (b)(2) supplement to an original (b)(1) application or not a supplemental application, answer **"N/A"**.*

*If "**NO**", please contact the (b)(2) review staff in the Immediate Office, Office of New Drugs.*

8) Were any of the listed drug(s) relied upon for this application:

a) Approved in a 505(b)(2) application?

YES ☒ NO ☐

*If "**YES**", please list which drug(s).*

Name of drug(s) approved in a 505(b)(2) application:
Ofirmev, NDA 22450

b) Approved by the DESI process?

YES ☐ NO ☒

*If "**YES**", please list which drug(s).*

Name of drug(s) approved via the DESI process:

c) Described in a monograph?

YES ☐ NO ☒

*If "**YES**", please list which drug(s).*

Name of drug(s) described in a monograph:

d) Discontinued from marketing?

YES ☐ NO ☒

*If "**YES**", please list which drug(s) and answer question d) i. below.*
*If "**NO**", proceed to question #9.*

Name of drug(s) discontinued from marketing:

i) Were the products discontinued for reasons related to safety or effectiveness?

YES ☐ NO ☐

(Information regarding whether a drug has been discontinued from marketing for reasons of safety or effectiveness may be available in the Orange Book. Refer to section 1.11 for an explanation, and section 6.1 for the list of discontinued drugs. If a determination of the reason for discontinuation has not been published in the Federal Register (and noted in the Orange Book), you will need to research the archive file and/or consult with the review team. Do not rely solely on any statements made by the sponsor.)

9) Describe the change from the listed drug(s) relied upon to support this (b)(2) application (for example, "This application provides for a new indication, otitis media" or "This application provides for a change in dosage form, from capsule to solution").

This application utilizes a different container closure system than the listed drug. Additionally, the proposed drug product omits the sodium phosphate buffer ingredient, and differs in the concentration of the antioxidant cysteine compared to the listed drug.

The purpose of the following two questions is to determine if there is an approved drug product that is equivalent or very similar to the product proposed for approval that should be referenced as a listed drug in the pending application.

*The assessment of pharmaceutical equivalence for a recombinant or biologically-derived product and/or protein or peptide product is complex. If you answered **YES to question #1**, proceed to question #12; if you answered **NO to question #1**, proceed to question #10 below.*

10) (a) Is there a pharmaceutical equivalent(s) to the product proposed in the 505(b)(2) application that is already approved (via an NDA or ANDA)?

*(**Pharmaceutical equivalents** are drug products in identical dosage forms that: **(1)** contain identical amounts of the identical active drug ingredient, i.e., the same salt or ester of the same therapeutic moiety, or, in the case of modified release dosage forms that require a reservoir or overage or such forms as prefilled syringes where residual volume may vary, that deliver identical amounts of the active drug ingredient over the identical dosing period; **(2)** do not necessarily contain the same inactive ingredients; **and** **(3)** meet the identical compendial or other applicable standard of identity, strength, quality, and purity, including potency and, where applicable, content uniformity, disintegration times, and/or dissolution rates. (21 CFR 320.1(c)).*

***Note** that for proposed combinations of one or more previously approved drugs, a pharmaceutical equivalent must also be a combination of the same drugs.*

YES ☒ NO ☐

*If "**NO**" to (a) proceed to question #11.*
*If "**YES**" to (a), answer (b) and (c) then proceed to question #12.*

(b) Is the pharmaceutical equivalent approved for the same indication for which the 505(b)(2) application is seeking approval?

YES ☒ NO ☐

(c) Is the listed drug(s) referenced by the application a pharmaceutical equivalent?

YES ☒ NO ☐

*If "**YES**" to (c) and there are no additional pharmaceutical equivalents listed, proceed to question #12.*
*If "**NO**" or if there are additional pharmaceutical equivalents that are not referenced by the application, list the NDA pharmaceutical equivalent(s); you do not have to individually list all of the products approved as ANDAs, but please note below if approved approved generics are listed in the Orange Book. Please also contact the (b)(2) review staff in the Immediate Office, Office of New Drugs.*

Pharmaceutical equivalent(s):

11) (a) Is there a pharmaceutical alternative(s) already approved (via an NDA or ANDA)?

*(**Pharmaceutical alternatives** are drug products that contain the identical therapeutic moiety, or its precursor, but not necessarily in the same amount or dosage form or as the same salt or ester. Each such drug product individually meets either the identical or its own respective compendial or other applicable standard of identity, strength, quality, and purity, including potency and, where applicable, content uniformity, disintegration times and/or dissolution rates. (21 CFR 320.1(d)) Different dosage forms and strengths within a product line by a single manufacturer are thus pharmaceutical alternatives, as are extended-release products when compared with immediate- or standard-release formulations of the same active ingredient.)*

***Note** that for proposed combinations of one or more previously approved drugs, a pharmaceutical alternative must also be a combination of the same drugs.*

YES ☐ NO ☐

*If "**NO**", proceed to question #12.*

(b) Is the pharmaceutical alternative approved for the same indication for which the 505(b)(2) application is seeking approval?

YES ☐ NO ☐

(c) Is the approved pharmaceutical alternative(s) referenced as the listed drug(s)?

YES ☐ NO ☐

*If "**YES**" and there are no additional pharmaceutical alternatives listed, proceed to question #12.*
*If "**NO**" or if there are additional pharmaceutical alternatives that are not referenced by the application, list the NDA pharmaceutical alternative(s); you do not have to individually list all of the products approved as ANDAs, but please note below if approved generics are listed in*

the Orange Book. Please also contact the (b)(2) review staff in the Immediate Office, Office of New Drugs.

Pharmaceutical alternative(s):

PATENT CERTIFICATION/STATEMENTS

12) List the patent numbers of all unexpired patents listed in the Orange Book for the listed drug for which our finding of safety and effectiveness is relied upon to support approval of the (b)(2) product.

Listed drug/Patent numbers:
N022450/6028222 Aug 5, 2017
N022450/6992218 Jun 6, 2021

No patents listed ☐ *proceed to question #14*

13) Did the applicant address (with an appropriate certification or statement) all of the unexpired patents listed in the Orange Book for the listed drug(s) relied upon to support approval of the (b)(2) product?

YES ☒ NO ☐

*If "**NO**", list which patents (and which listed drugs) were not addressed by the applicant.*

Listed drug/Patent number(s):

14) Which of the following patent certifications does the application contain? *(Check all that apply and identify the patents to which each type of certification was made, as appropriate.)*

☐ No patent certifications are required (e.g., because application is based solely on published literature that does not cite a specific innovator product)

☐ 21 CFR 314.50(i)(1)(i)(A)(1): The patent information has not been submitted to FDA. (Paragraph I certification)

☐ 21 CFR 314.50(i)(1)(i)(A)(2): The patent has expired. (Paragraph II certification)

Patent number(s):

☐ 21 CFR 314.50(i)(1)(i)(A)(3): The date on which the patent will expire. (Paragraph III certification)

Patent number(s): Expiry date(s):

☒ 21 CFR 314.50(i)(1)(i)(A)(4): The patent is invalid, unenforceable, or will not be infringed by the manufacture, use, or sale of the drug product for which the application is submitted. (Paragraph IV certification). *If Paragraph IV certification was submitted, proceed to question #15.*

☐ 21 CFR 314.50(i)(3): Statement that applicant has a licensing agreement with the NDA holder/patent owner (must also submit certification under 21 CFR 314.50(i)(1)(i)(A)(4) above). *If the applicant has a licensing agreement with the NDA holder/patent owner, proceed to question #15.*

☐ 21 CFR 314.50(i)(1)(ii): No relevant patents.

☐ 21 CFR 314.50(i)(1)(iii): The patent on the listed drug is a method of use patent and the labeling for the drug product for which the applicant is seeking approval does not include any indications that are covered by the use patent as described in the corresponding use code in the Orange Book. Applicant must provide a statement that the method of use patent does not claim any of the proposed indications. (Section viii statement)

Patent number(s):
Method(s) of Use/Code(s):

15) Complete the following checklist ***ONLY*** for applications containing Paragraph IV certification and/or applications in which the applicant and patent holder have a licensing agreement:

Patent numbers: N022450/6028222 Aug 5, 2017
N022450/6992218 Jun 6, 2021

(a) Did the applicant submit a signed certification stating that the NDA holder and patent owners were notified that this b(2) application was filed [21 CFR 314.52(b)]?

YES ☒ NO ☐

*If "**NO**", please contact the applicant and request the signed certification.*

(b) Did the applicant submit documentation showing that the NDA holder and patent owner(s) received the notification [21 CFR 314.52(e)]? This is generally provided in the form of a registered mail receipt.

YES ☒ NO ☐

*If "**NO**", please contact the applicant and request the documentation.*

(c) What are the dates on the registered mail receipts (i.e., the dates the NDA holder and patent owners received notification):

Dates: **December 6, 2012 and December 7, 2012**

(d) Has the applicant been sued for patent infringement within 45-days of receipt of the notification listed above? **Sued on January 17, 2013, and January 18, 2013. The Sponsor has submitted a notice of dismissal as well (dated August 8, 2014).**

***Note** that you may need to call the applicant (after 45 days of receipt of the notification) to verify this information **UNLESS** the applicant provided a written statement from the notified patent owner(s) that it consents to an immediate effective date of approval.*

YES ☒ NO ☐ Patent owner(s) consent(s) to an immediate effective date of approval ☐

APPEARS THIS WAY ON ORIGINAL

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

/s/

DIANA L WALKER
10/28/2015

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

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

Memorandum

Date: October 2, 2015

To: Diana Walker
Regulatory Health Project Manager
Division of Anesthesia, Analgesia, and Addiction Products (DAAAP)

Sharon Hertz, MD, Director - DAAAP

From: Koung Lee, Regulatory Review Officer
Office of Prescription Drug Promotion (OPDP)

Through: Jessica Fox, Regulatory Review Officer - OPDP

CC: Olga Salis, Senior Regulatory Project Manager - OPDP

Subject: NDA 204767
Acetaminophen Injection
Professional Labeling Review

As requested in DAAAP's consult dated May 21, 2015, OPDP has reviewed the substantially complete prescribing information for Acetaminophen Injection. The substantially complete prescribing information was provided to OPDP on September 10, 2015, via email by Diana Walker with the filename "\\fdsfs01\ODE2\DAAAP\NDA and sNDA\NDA 204767 (APAP Injection Fresenius)\Cycle 2\Labeling\Working draft-pi-track changes 10sep15 to OPDP.doc."

OPDP has completed the review of the substantially complete prescribing information and the container (b) (4) labeling and has no comments at this time.

Thank you for your consult. OPDP appreciates the opportunity to provide comments. If you have any questions, please contact me at (240) 402-8686 or by email, Koung.Lee@fda.hhs.gov.

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

/s/

KOUNG U LEE
10/02/2015

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:	July 9, 2015
Requesting Office or Division:	Division of Analgesia, Anesthesia, and Addiction Products (DAAAP)
Application Type and Number:	NDA 204767
Product Name and Strength:	Acetaminophen Injection 1,000 mg/100 mL (10 mg/mL)
Submission Date:	July 8, 2015
Applicant/Sponsor Name:	Fresenius Kabi
OSE RCM #:	2015-1115-1
DMEPA Primary Reviewer:	James Schlick, RPh, MBA

1 PURPOSE OF MEMO

Division of Analgesia, Anesthesia, and Addiction Products (DAAAP) requested that we review the revised container label (b) (4) (Appendix A) to determine if it is acceptable from a medication error perspective. The revisions are in response to a recommendation that we made during a previous label and labeling review.[1]

2 CONCLUSIONS

The revised container label (b) (4) are acceptable from a medication error perspective. We have no additional comments at this time.

APPENDIX A. LABEL AND LABELING SUBMITTED ON JULY 8, 2015

[1] Schlick J. Label and Labeling Review for Acetaminophen Injection (NDA 204767). Silver Spring (MD): Food and Drug Administration, Center for Drug Evaluation and Research, Office of Surveillance and Epidemiology, Division of Medication Error Prevention and Analysis (US); 2015 JUN 11. 7 p. OSE RCM No.: 2015-1115.

2 Page(s) of Draft Labeling have been Withheld in Full as b4 (CCI/TS) immediately following this page

---

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

/s/

JAMES H SCHLICK
07/09/2015

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)

***** This document contains proprietary information that cannot be released to the public*****

Date of This Review:	June 11, 2015
Requesting Office or Division:	Division of Analgesia, Anesthesia, and Addiction Products (DAAAP)
Application Type and Number:	NDA 204767
Product Name and Strength:	Acetaminophen Injection 1,000 mg/100 mL (10 mg/mL)
Product Type:	Single Ingredient
Rx or OTC:	Rx
Applicant/Sponsor Name:	Fresenius Kabi
Submission Date:	April 30, 2015
OSE RCM #:	2015-1115
DMEPA Primary Reviewer:	James Schlick, RPh, MBA
DMEPA Team Leader:	Vicky Borders-Hemphill, PharmD

1 REASON FOR REVIEW

The Division of Analgesia, Anesthesia, and Addiction Products requested that we review the revised Prescribing Information, container labels and carton labeling (Appendix A) to determine if they are acceptable from a medication error perspective. Fresenius Kabi submitted revised labels and labeling as part of a Class 2 resubmission on April 30, 2015.

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	N/A C
ISMP Newsletters	N/A D
FDA Adverse Event Reporting System (FAERS)*	N/A E
Other	N/A F
Labels and Labeling	G

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

3 OVERALL ASSESSMENT OF THE MATERIALS REVIEWED

DMEPA performed a risk assessment of the proposed Prescribing Information, container labels (b) (4) for Acetaminophen Injection to identify areas of vulnerability that may lead to medication errors. We reviewed the labels and labeling in OSE review # 2012-2519[1] dated June 4, 2013 and found the proposed labels unacceptable from a medication error perspective. As part of the Class 2 resubmission dated April 30, 2015, Fresenius Kabi indicated in their cover letter that the labels (b) (4) submitted on December 12, 2014 are the current proposed labels and labeling.

The revisions requested in OSE 2012-2519 were fully implemented. However, we found some additional changes to the container labels (b) (4). On the container labe (b) (4) Fresenius Kabi included the statement "1,000 mg" to the right of the

[1] Baugh D. Label, Labeling and Packaging Review for Acetaminophen Injection (NDA 204767). Silver Spring (MD): Food and Drug Administration, Center for Drug Evaluation and Research, Office of Surveillance and Epidemiology, Division of Medication Error Prevention and Analysis (US); 2013 JUN 04. 35 p. OSE RCM No.: 2012-2519.

strength statement. (b) (4) See Appendix G for a side by side comparison. We find the addition of the red color background acceptable. (b) (4) We provide recommendations to improve communication of important information to minimize confusion and improve readability in sections 4.1.

4 CONCLUSION & RECOMMENDATIONS

We conclude that the proposed labels and labeling can be improved to increase the readability and prominence of important information and to promote the safe use of the product.

4.1 RECOMMENDATIONS FOR FRESENIUS KABI

We recommend the following be implemented prior to approval of this NDA:

(b) (4)

APPENDICES: METHODS & RESULTS FOR EACH MATERIALS REVIEWED

APPENDIX A. PRODUCT INFORMATION/PRESCRIBING INFORMATION

Table 2 presents relevant product information for Acetaminophen Injection that Fresenius Kabi submitted on April 30, 2015.

Table 2. Relevant Product Information for Acetaminophen Injection	
Initial Approval Date	N/A
Active Ingredient	Acetaminophen
Indication	Pain management
Route of Administration	Intravenous Infusion
Dosage Form	Injection for Intravenous Infusion
Strength	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:** • 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.
How Supplied/Container Closure	In a 100 mL flexible bag (b) (4)
Storage	USP Controlled room temperature

APPENDIX B. PREVIOUS DMEPA REVIEWS

B.1 Methods

On June 4, 2015, we searched the L:drive using the terms, Acetaminophen Injection and Fresenius Kabi to identify reviews previously performed by DMEPA.

B.2 Results

Our search identified one previous review,[2] and we confirmed that our previous recommendations were implemented or considered.

[2] Baugh D. Label, Labeling and Packaging Review for Acetaminophen Injection (NDA 204767). Silver Spring (MD): Food and Drug Administration, Center for Drug Evaluation and Research, Office of Surveillance and Epidemiology, Division of Medication Error Prevention and Analysis (US); 2013 JUN 04. 35 p. OSE RCM No.: 2012-2519.

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,[3] along with postmarket medication error data, we reviewed the following Acetaminophen labels and labeling submitted by Fresenius Kabi on December 12, 2014 and April 30, 2015.

- Container label December 12, 2014
- Overwrap labeling December 12, 2014
- Prescribing Information April 30, 2015 - No Image

G.2 Label and Labeling Images

Container Label

(b) (4)

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

1 Page(s) of Draft Labeling have been Withheld in Full as b4 (CCI/TS) immediately following this page

---

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

/s/

JAMES H SCHLICK
06/11/2015

BRENDA V BORDERS-HEMPHILL
06/11/2015

Department of Health and Human Services
Public Health Service
Food and Drug Administration
Center for Drug Evaluation and Research
Office of Surveillance and Epidemiology
Office of Medication Error Prevention and Risk Management

Label, Labeling and Packaging Review

Date	June 4, 2013
Reviewer	Denise V. Baugh, PharmD, BCPS Division of Medication Error Prevention and Analysis
Team Leader	Lubna Merchant, PharmD, MS Division of Medication Error Prevention and Analysis
Associate Director	Scott Dallas, R.Ph. Division of Medication Error Prevention and Analysis
Drug Name	Acetaminophen Injection
Strength	1000 mg/100 mL (b) (4)
Application Type/Number	NDA 204767
Applicant	Fresenius Kabi USA, LLC
OSE RCM #	2012-2519

*** This document contains proprietary and confidential information that should not be released to the public.***

Contents

1 INTRODUCTION

This review evaluates the proposed container label, carton and Full Prescribing Information for Acetaminophen Injection (NDA 204767) for areas of vulnerability that could lead to medication errors.

1.1 REGULATORY HISTORY

The applicant submitted the Acetaminophen Injection NDA as a 505(b)(2) application. The reference listed drug (RLD) is Ofirmev (Acetaminophen Injection), NDA 022450, which was approved November 2, 2010.

1.2 PRODUCT INFORMATION

The applicant provided the following product information in their September 28, 2012 submission.

- Active Ingredient: Acetaminophen
- Indication of Use: management of mild to moderate pain, management of moderate to severe pain with adjunctive opioid analgesics, and for the reduction of fever
- Route of Administration: intravenous
- Dosage Form: sterile, (b) (4) solution for intravenous infusion
- Strength: 10 mg/mL
- Dose and Frequency are as follows (All doses should be administered as a 15 minute infusion):

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 2 years old up to 12 years old	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

- How Supplied: (b) (4) 1000 mg/100 mL in a 100 mL flexible plastic container
- Storage and Handling: 20°C to 25°C (68°F to 77°F). For single use only. (b) (4) Use within six hours after opening.
- Container and Closure System: (b) (4) 100 mL in a 100 mL flexible plastic container (b) (4)

2 METHODS AND MATERIALS REVIEWED

This section describes the methods used to search the FDA Adverse Event Reporting System (FAERS) for Ofirmev medication error reports, and to evaluate the Acetaminophen Injection label, outer pouch labeling, and Full Prescribing Information submitted by the Applicant.

2.1 SELECTION OF MEDICATION ERROR CASES

We searched the FAERS database using the strategy listed in Table 1. Appendix 1 provides a description of FAERS.

Table 1: FAERS Search Strategy to Identify Medication Error Cases Associated with Ofirmev

Date	January 29, 2013 (from July 12, 2012 to January 29, 2013) from the last FAERS search cited in OSE Review# 2012-1016 dated August 8, 2012[1]
Drug Names	Trade Name: Ofirmev
MedDRA Search Strategy	Medication Errors HLGT Product Packaging Issues HLT Product Label Issues HLT Product Quality Issues (NEC) HLT

2.2 LABELS AND LABELING

Using the principles of human factors and Failure Mode and Effects Analysis[2], along with post marketing medication error data, we evaluated the:

- Container Labels (inner pouch) submitted September 28, 2012 (Appendix 2 provides the Acetaminophen Injection proposed container label, and the Ofirmev container label and carton labeling)
- Full Prescribing Information submitted September 28, 2012

Samples of the flexible plastic container with the label were received March 2, 2013. The samples did not include the outer pouch. Therefore, we based our review of the outer pouch upon the description of information in the Applicant's September 28, 2012 submission.

2.3 PREVIOUSLY COMPLETED REVIEWS

We considered previous recommendations[1,3,4,5,6] we made to revise the label and labeling for the reference listed drug (Ofirmev) so the Acetaminophen Injection label and labeling would be consistent with those recommendations.

3 RESULTS

This section provides the results for the search of medication error cases, the label and labeling review, and a summary of our previous reviews.

3.1 MEDICATION ERROR CASES

Using the criteria specified in Section 2.1, we did not retrieve any medication error cases from FAERS. However, the Office of Surveillance and Epidemiology approved a postmarket waiver for Cadence Pharmaceuticals to submit Ofirmev non-serious expected events to the FDA, so there may be medication error cases that have not been submitted to the FDA or entered into the FAERS database.

3.2 LABELS AND LABELING

This section provides the results of our review of the proposed container label, outer pouch labeling and Full Prescribing Information. The applicant did not provide a copy of the aluminum outer pouch.

3.2.1 Container Label Review

The Acetaminophen Injection label contains unnecessary information such as "free flex container" and extraneous numbers irrelevant to the user. In addition, the label contains italicized text (i.e., '*Injection*') that provides unneeded prominence, as well as statements that should be relocated. Section 5.B provides our specific findings and recommendations.

3.2.2 Proposed Full Prescribing Information

Table 2 highlights key differences in the proposed product information for Acetaminophen Injection with the referenced listed drug (RLD), Ofirmev.

Table 2. Key Differences in the Proposed Product Information for Acetaminophen Injection with the Reference Listed Drug (RLD), Ofirmev

Proprietary Name	None proposed	Ofirmev
Application #	NDA 204767	NDA 022450*
Drug Content Per Unit	(b) (4) – 1000 mg/100 mL	1000 mg/100 mL
Container Size	100 mL (b) (4) 1000 mg/100 mL units)	100 mL
Container Type	Flexible plastic container (b) (4)	Glass vial

*Ofirmev, NDA 022450 is the reference listed drug

3.3 PREVIOUSLY COMPLETED REVIEWS AND COMMUNICATIONS

We have performed four label and labeling reviews and one postmarket medication error review for Ofirmev. A summary of the medication error review and the most recent recommendations to revise the Full Prescribing Information is as follows:

On August 8, 2012, in accordance with the Pediatric Research Equity Act, we reviewed 29 postmarket reports of pediatric and adult medication errors associated with the reference listed drug (RLD), Ofirmev and its foreign counterpart, Perfalgan. We presented our findings at the September 11, 2012 Meeting of the Pediatric Advisory Committee.[7]

Twelve of the twenty-nine medication error reports involved pediatric patients. All twelve pediatric patients were administered an overdose of acetaminophen (paracetamol), of which half (n=6) received a 10 fold overdose. For the seventeen adult reports, 94 percent (n=16) reported an overdose, of which 11 of the 16 patients received more than the recommended four grams of acetaminophen within 24 hours. One pediatric and two adult deaths were reported (all associated with overdose). The case narratives suggested that the overdoses were attributed to confusion between the prescription of acetaminophen issued in milligrams (mg) and then administered in milliliters (mL), pump mis-programming errors in which the mg amount of acetaminophen was transposed into a mL volume, and incorrect dose adjustments based on patient weight. DMEPA recommended revising the Ofirmev labeling to describe the risk of hepatic injury with the maximum daily dose of 4000 mg, importance of prescribing based on patient weight, and the occurrence of dosing errors that have occurred in the pediatric and adult population. DMEPA also asked the Committee to comment on whether the labeling should be revised to recommend dosing in both mg and mL, and if smaller vial sizes or different concentrations should be available for the pediatric or lower weight adult population.

After considering comments from the Pediatric Advisory Committee meeting, we recommended the following revisions to the Ofirmev Full Prescribing Information:

1) There should be a clear link between exceeding the maximum recommended dose and the risk of hepatic injury

2) Communicate that the maximum recommended Ofirmev dose includes all sources of acetaminophen (e.g., all routes of administration and multi-ingredient products containing acetaminophen)

3) Caution against potential medication errors that may occur with this product

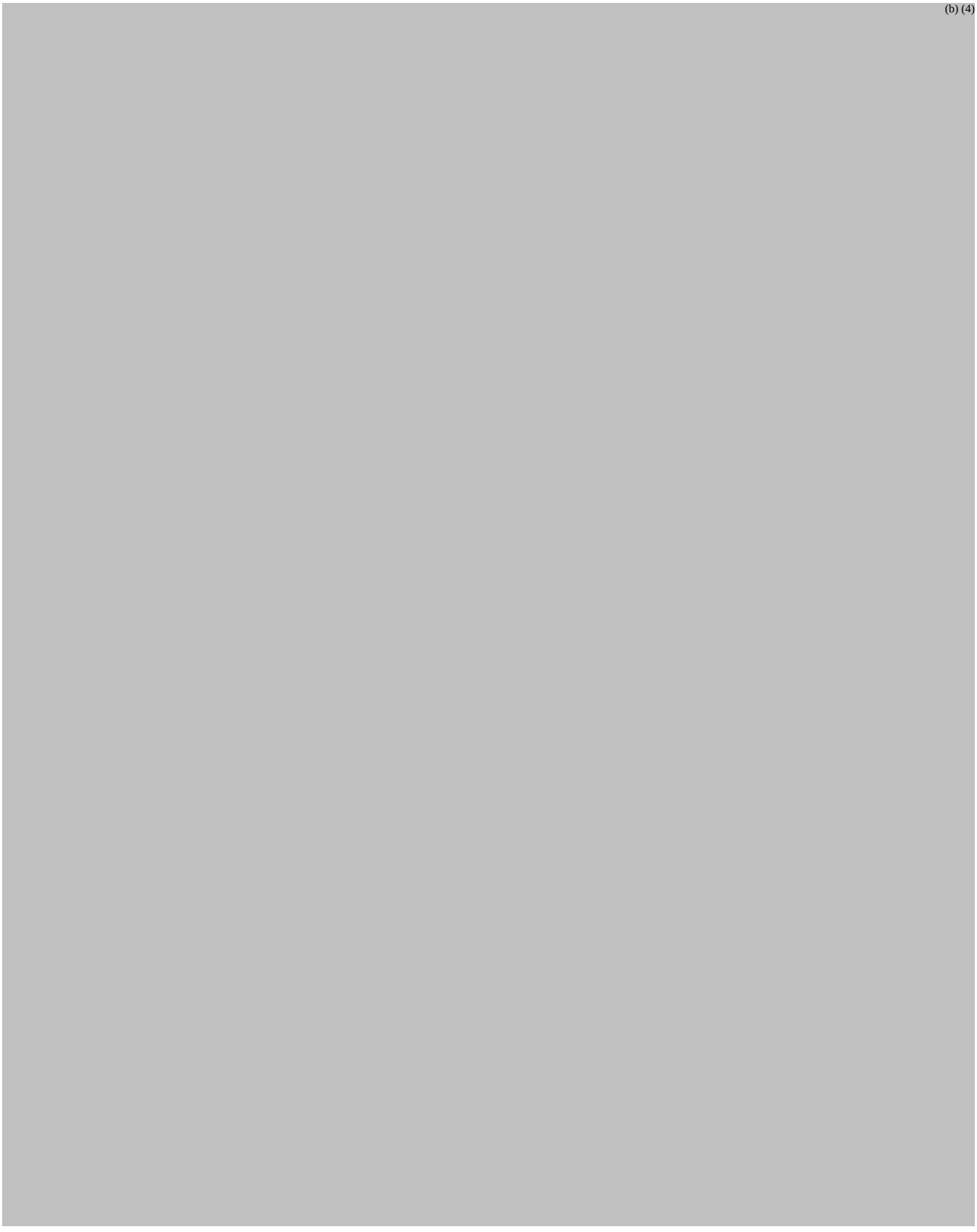
4) Prescribers should be aware that the acetaminophen (Ofirmev) injection dose can be weight based for some adult populations (those adults less than 50 kg)

5) Present the pediatric dosing in a separate table and include the pediatric maximum dose.

Additionally, on May 9, 2013 the Division communicated their desire to increase the prominence of the above statements consistent with the approved product as morphine sulfate oral solution.

This decision was based upon the significance of the adverse outcomes associated with Ofirmev and Perfalgan.

(b) (4)



(b) (4)

6 RECOMMENDATIONS

DMEPA provides the following comments for consideration by the Division prior to the approval of this NDA:

A. Comments to the Division

1. (b) (4)

2. We revised the proposed Full Prescribing Information to be consistent with the recent changes proposed for the reference listed drug, Ofirmev. Appendix 4 provides the specific revisions.

B. Comments to the Applicant

Container Label and Outer pouch Labeling

1. Delete the following statements to minimize clutter and to improve the overall readability of the label: (b) (4)

2. Delete the extraneous numbers from the container label. These numbers clutter the label and are not useful to the user (b) (4) If the numbers cannot be deleted, then attempt to decrease their prominence, and relocate the number directly to the right of the NDC to the lower portion of the label.

3. Relocate the inactive ingredient list to appear directly following the "Single Use Only, Discard Unused Portion" statements on the principal display panel.

4. Relocate the statements which begin with "Single Use Only, Discard Unused Portion" to appear just below the boxed statement "For Intravenous Use Only".

5. Delete the [redacted] (b) (4)

6. Add the following statement on the 1000 mg per 100 mL label "Doses less than 1000 mg require aseptic transfer to a separate container prior to dispensing". Locate this after the Usual Dosage statement.

7. Revise the statement "Injection" to the same font style as the active ingredient, Acetaminophen. The italics give unnecessary prominence to this dosage form.

8. Revise the strength presentation to appear in a stacked format as follows:

1000 mg/100 mL
(10 mg/mL)

If you have further questions or need clarifications, please contact Teena Thomas, OSE Project Manager, at 301-796-0549.

REFERENCES

---

[1] OSE Review # 2012-1016. Post-marketing Medication Error Review for Acetaminophen Injection. Baugh, D. August 8, 2012.

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

[3] OSE Review # 2009-1010. Label and Labeling Review for Acetaminophen Injection 1000 mg/100 mL vial. Abate, R. October 6, 2009.

[4] OSE Review # 2009-2204. Label and Labeling Review for Ofirmev (Acetaminophen) Injection 1000 mg/100 mL vial. Abate, R. December 17, 2009.

[5] OSE Review # 2009-1118. Label and Labeling Review for Ofirmev (Acetaminophen) Injection 1000 mg/100 mL vial. Abate, R. September 13, 2010.

[6] OSE Review # 2013-329. Label and Labeling Memorandum for Ofirmev (Acetaminophen Injection). Baugh, D. March 15, 2013.

[7] Advisory Committees: 2012 Meeting Materials, Pediatric Advisory Committee to the Food and Drug Administration [Internet]. Silver Spring (MD): U.S. Food and Drug Administration; [updated 2013 Feb]. Available from: http://www.fda.gov/AdvisoryCommittees/CommitteesMeetingMaterials/PediatricAdvisoryCommittee/ucm283814.htm

[8] ISMP, Fatal overdose uncovers need to rethink where pediatric IV medications are dispensed and administered; ISMP Medication Safety Alert; Vol 13, Issue 2; January 31, 2008.

APPENDICES

APPENDIX 1. DESCRIPTION OF THE FDA ADVERSE EVENT REPORTING SYSTEM (FAERS)

OSE Review # 2012-1016. Postmarketing Medication Error Review for Acetaminophen Injection, Baugh, D. August 8, 2012.

The FDA Adverse Event Reporting System (FAERS) is a database that contains information on adverse event and medication error reports submitted to FDA. The database is designed to support the FDA's post-marketing safety surveillance program for drug and therapeutic biologic products. The informatic structure of the database adheres to the international safety reporting guidance issued by the International Conference on Harmonisation. Adverse events and medication errors are coded to terms in the Medical Dictionary for Regulatory Activities (MedDRA) terminology. The suspect products are coded to valid tradenames or active ingredients in the FAERS Product Dictionary (FPD).

FDA implemented FAERS on September 10, 2012, and migrated all the data from the previous reporting system (AERS) to FAERS. Differences may exist when comparing case counts in AERS and FAERS. FDA validated and recoded product information as the AERS reports were migrated to FAERS. In addition, FDA implemented new search functionality based on the date FDA initially received the case to more accurately portray the follow up cases that have multiple receive dates.

FAERS data have limitations. First, there is no certainty that the reported event was actually due to the product. FDA does not require that a causal relationship between a product and event be proven, and reports do not always contain enough detail to properly evaluate an event. Further, FDA does not receive reports for every adverse event or medication error that occurs with a product. Many factors can influence whether or not an event will be reported, such as the time a product has been marketed and publicity about an event. Therefore, FAERS data cannot be used to calculate the incidence of an adverse event or medication error in the U.S. population.

23 Page(s) of Draft Labeling have been Withheld in Full as b4 (CCI/TS) immediately following this page

---

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

/s/

DENISE V BAUGH
06/04/2013

LUBNA A MERCHANT
06/04/2013

SCOTT M DALLAS
06/05/2013

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

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

Memorandum

Date: May 17, 2013

To: Diana Walker
Senior Regulatory Project Manager
Division Anesthesia, Analgesia, and Addition Products (DAAAP)

From: Eunice Chung-Davies, PharmD., Regulatory Review Officer
Office of Professional Drug Promotion (OPDP)

Subject: OPDP's comments for NDA 204767
Acetaminophen injection

On November 21, 2012, OPDP received a consult request from DAAAP to review the proposed package insert for Acetaminophen injection

OPDP has reviewed the proposed labeling using the following version of the proposed package insert:

- NDA 204767 APAP-Working-draft-pi 26apr13-to OPDP.doc (emailed from Diana Walker on April 26, 2013)

Upon review of the proposed labeling, OPDP offers the following comments.

If you have any questions regarding the package insert, please contact Eunice Chung-Davies at 301-796-4006 or eunice.chung-davies@fda.hhs.gov .

Enclosure:
Marked up Package Insert

17 Page(s) of Draft Labeling have been Withheld in Full as b4 (CCI/TS) immediately following this page

---

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

/s/

EUNICE H CHUNG-DAVIES
05/17/2013

RPM FILING REVIEW

(Including Memo of Filing Meeting)

To be completed for all new NDAs, BLAs, and Efficacy Supplements [except SE8 (labeling change with clinical data) and SE9 (manufacturing change with clinical data]

Application Information		
NDA # 204767 BLA#	NDA Supplement #:S- BLA Supplement #	Efficacy Supplement Type SE-
Proprietary Name: N/A Established/Proper Name: Acetaminophen for Injection Dosage Form: Sterile (b) (4) Solution for Infusion Strengths: 10 mg/mL		
Applicant: Fresenius Kabi USA, LLC Agent for Applicant (if applicable): N/A		
Date of Application: September 28, 2012 Date of Receipt: September 28, 2012 Date clock started after UN: N/A		
PDUFA Goal Date: July 28, 2013	Action Goal Date (if different):	
Filing Date: November 27, 2012	Date of Filing Meeting: November 15, 2012	
Chemical Classification: (1,2,3 etc.) (original NDAs only) : Type 5 – New Formulation or New Manufacturer		
Proposed indications: management of mild to moderate pain, management of moderate to severe pain with adjunctive opioid analgesics, reduction of fever		

Type of Original NDA: AND (if applicable) Type of NDA Supplement: ***If 505(b)(2): Draft the "505(b)(2) Assessment" review found at: http://inside.fda.gov:9003/CDER/OfficeofNewDrugs/ImmediateOffice/UCM027499 and refer to Appendix A for further information.***	☐ 505(b)(1) ☒ 505(b)(2) ☐ 505(b)(1) ☐ 505(b)(2)
Review Classification: ***If the application includes a complete response to pediatric WR, review classification is Priority.*** ***If a tropical disease priority review voucher was submitted, review classification is Priority.***	☒ Standard ☐ Priority ☐ Tropical Disease Priority Review Voucher submitted
Resubmission after withdrawal? ☐	Resubmission after refuse to file? ☐
Part 3 Combination Product? ☐ ***If yes, contact the Office of Combination Products (OCP) and copy them on all Inter-Center consults***	☐ Convenience kit/Co-package ☐ Pre-filled drug delivery device/system (syringe, patch, etc.) ☐ Pre-filled biologic delivery device/system (syringe, patch, etc.) ☐ Device coated/impregnated/combined with drug ☐ Device coated/impregnated/combined with biologic ☐ Separate products requiring cross-labeling ☐ Drug/Biologic ☐ Possible combination based on cross-labeling of separate products ☐ Other (drug/device/biological product)

☐ Fast Track ☐ Rolling Review ☐ Orphan Designation ☐ Rx-to-OTC switch, Full ☐ Rx-to-OTC switch, Partial ☐ Direct-to-OTC Other:	☐ PMC response ☐ PMR response: ☐ FDAAA [505(o)] ☐ PREA deferred pediatric studies [21 CFR 314.55(b)/21 CFR 601.27(b)] ☐ Accelerated approval confirmatory studies (21 CFR 314.510/21 CFR 601.41) ☐ Animal rule postmarketing studies to verify clinical benefit and safety (21 CFR 314.610/21 CFR 601.42)

Collaborative Review Division (*if OTC product*):

List referenced IND Number(s): N/A for IND
RLD = NDA 022450, Ofirmev (Cadence Pharmaceuticals), Acetaminophen for Injection

Goal Dates/Product Names/Classification Properties	**YES**	**NO**	**NA**	**Comment**
PDUFA and Action Goal dates correct in tracking system? ***If no, ask the document room staff to correct them immediately. These are the dates used for calculating inspection dates.***	**XX**			
Are the proprietary, established/proper, and applicant names correct in tracking system? ***If no, ask the document room staff to make the corrections. Also, ask the document room staff to add the established/proper name to the supporting IND(s) if not already entered into tracking system.***		**XX**		Requested corrections on 10/4/2012. Currently correct.
Is the review priority (S or P) and all appropriate classifications/properties entered into tracking system (e.g., chemical classification, combination product classification, 505(b)(2), orphan drug)? ***For NDAs/NDA supplements, check the New Application and New Supplement Notification Checklists for a list of all classifications/properties at:*** ***http://inside.fda.gov:9003/CDER/OfficeofBusinessProcessSupport/ucm163969.htm*** ***If no, ask the document room staff to make the appropriate entries.***	**XX**			
Application Integrity Policy	**YES**	**NO**	**NA**	**Comment**
Is the application affected by the Application Integrity Policy (AIP)? ***Check the AIP list at:*** ***http://www.fda.gov/ICECI/EnforcementActions/ApplicationIntegrityPolicy/default.htm***		**XX**		
If yes, explain in comment column.				
If affected by AIP, has OC/OMPQ been notified of the submission? **If yes,** date notified:				
User Fees	**YES**	**NO**	**NA**	**Comment**
Is Form 3397 (User Fee Cover Sheet) included with authorized signature?	**XX**			

User Fee Status ***If a user fee is required and it has not been paid (and it is not exempted or waived), the application is unacceptable for filing following a 5-day grace period. Review stops. Send Unacceptable for Filing (UN) letter and contact user fee staff.***	Payment for this application: ☒ Paid ☐ Exempt (orphan, government) ☐ Waived (e.g., small business, public health) ☐ Not required
If the firm is in arrears for other fees (regardless of whether a user fee has been paid for this application), the application is unacceptable for filing (5-day grace period does not apply). Review stops. Send UN letter and contact the user fee staff.	Payment of other user fees: ☒ Not in arrears ☐ In arrears

505(b)(2) **(NDAs/NDA Efficacy Supplements only)**	**YES**	**NO**	**NA**	**Comment**
Is the application for a duplicate of a listed drug and eligible for approval under section 505(j) as an ANDA?		**XX**		No, due to inactive ingredients and presentation.
Is the application for a duplicate of a listed drug whose only difference is that the extent to which the active ingredient(s) is absorbed or otherwise made available to the site of action is less than that of the reference listed drug (RLD)? **[see 21 CFR 314.54(b)(1)].**		**XX**		
Is the application for a duplicate of a listed drug whose only difference is that the rate at which the proposed product's active ingredient(s) is absorbed or made available to the site of action is unintentionally less than that of the listed drug **[see 21 CFR 314.54(b)(2)]?** ***If you answered yes to any of the above questions, the application may be refused for filing under 21 CFR 314.101(d)(9). Contact the 505(b)(2) review staff in the Immediate Office of New Drugs***		**XX**		
Is there unexpired exclusivity on the active moiety (e.g., 5-year, 3-year, orphan, or pediatric exclusivity)? ***Check the Electronic Orange Book at:*** ***http://www.accessdata.fda.gov/scripts/cder/ob/default.cfm*** **If yes**, please list below:	**XX**			3-year

Application No.	Drug Name	Exclusivity Code	Exclusivity Expiration
NDA 22450	Ofirmev	NP	November 2, 2013

If there is unexpired, 5-year exclusivity remaining on the active moiety for the proposed drug product, a 505(b)(2) application cannot be submitted until the period of exclusivity expires (unless the applicant provides paragraph IV patent certification; then an application can be submitted four years after the date of approval.) Pediatric exclusivity will extend both of the timeframes in this provision by 6 months. 21 CFR 314.108(b)(2).Unexpired, 3-year exclusivity will only block the approval, not the submission of a 505(b)(2) application.

Exclusivity	**YES**	**NO**	**NA**	**Comment**
Does another product (same active moiety) have orphan exclusivity for the same indication? ***Check the Orphan Drug Designations and Approvals list at:***		**XX**		

http://www.accessdata.fda.gov/scripts/opdlisting/oopd/index.cfm				

APPEARS THIS WAY ON ORIGINAL

If another product has orphan exclusivity, is the product considered to be the same product according to the orphan drug definition of sameness **[see 21 CFR 316.3(b)(13)]**? ***If yes, consult the Director, Division of Regulatory Policy II, Office of Regulatory Policy***			**XX**	
Has the applicant requested 5-year or 3-year Waxman-Hatch exclusivity? ***(NDAs/NDA efficacy supplements only)*** **If yes**, # years requested: ***Note:*** *An applicant can receive exclusivity without requesting it; therefore, requesting exclusivity is not required.*		**XX**		
Is the proposed product a single enantiomer of a racemic drug previously approved for a different therapeutic use (***NDAs only***)?		**XX**		
If yes, did the applicant: (a) elect to have the single enantiomer (contained as an active ingredient) not be considered the same active ingredient as that contained in an already approved racemic drug, and/or (b): request exclusivity pursuant to section 505(u) of the Act (per FDAAA Section 1113)? ***If yes, contact Mary Ann Holovac, Director of Drug Information, OGD/DLPS/LRB.***			**XX**	

Format and Content				
Do not check mixed submission if the only electronic component is the content of labeling (COL).	☐ All paper (except for COL) ☒ All electronic ☐ Mixed (paper/electronic) ☒ CTD ☐ Non-CTD ☐ Mixed (CTD/non-CTD)			
If mixed (paper/electronic) submission, which parts of the application are submitted in electronic format?				
Overall Format/Content	**YES**	**NO**	**NA**	**Comment**
If electronic submission, does it follow the eCTD guidance?[1] **If not,** explain (e.g., waiver granted).	**XX**			
Index: Does the submission contain an accurate comprehensive index?	**XX**			
Is the submission complete as required under 21 CFR 314.50 (*NDAs/NDA efficacy supplements*) or under 21 CFR 601.2 (*BLAs/BLA efficacy supplements*) including:	**XX**			

[1] http://www fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/ucm072349.pdf

☒ legible ☒ English (or translated into English) ☒ pagination ☒ navigable hyperlinks (electronic submissions only) **If no**, explain.				
BLAs only: Companion application received if a shared or divided manufacturing arrangement? **If yes**, BLA #			**XX**	
Applications in "the Program" (PDUFA V) (NME NDAs/Original BLAs)	**YES**	**NO**	**NA**	**Comment**
Was there an agreement for any minor application components to be submitted within 30 days after the original submission?			**XX**	
• If yes, were all of them submitted on time?			**XX**	
Is a comprehensive and readily located list of all clinical sites included or referenced in the application?			**XX**	
Is a comprehensive and readily located list of all manufacturing facilities included or referenced in the application?			**XX**	
Forms and Certifications				
Electronic *forms and certifications with electronic signatures (scanned, digital, or electronic – similar to DARRTS, e.g., /s/) are acceptable. Otherwise,* ***paper*** *forms and certifications with hand-written signatures must be included.* ***Forms*** *include: user fee cover sheet (3397), application form (356h), patent information (3542a), financial disclosure (3454/3455), and clinical trials (3674);* ***Certifications*** *include: debarment certification, patent certification(s), field copy certification, and pediatric certification.*				
Application Form	**YES**	**NO**	**NA**	**Comment**
Is form FDA 356h included with authorized signature per 21 CFR 314.50(a)? ***If foreign applicant, a U.S. agent must sign the form [see 21 CFR 314.50(a)(5)].***	**XX**			
Are all establishments and their registration numbers listed on the form/attached to the form?	**XX**			
Patent Information (NDAs/NDA efficacy supplements only)	**YES**	**NO**	**NA**	**Comment**
Is patent information submitted on form FDA 3542a per 21 CFR 314.53(c)?		**XX**		The applicant has no patents.
Financial Disclosure	**YES**	**NO**	**NA**	**Comment**
Are financial disclosure forms FDA 3454 and/or 3455 included with authorized signature per 21 CFR 54.4(a)(1) and (3)?		**XX**		There were no studies done for this NDA, so there is no financial disclosure.

Forms must be signed by the APPLICANT, not an Agent [see 21 CFR 54.2(g)]. ***Note:*** *Financial disclosure is required for bioequivalence studies that are the basis for approval.*				
Clinical Trials Database	**YES**	**NO**	**NA**	**Comment**
Is form FDA 3674 included with authorized signature? ***If yes, ensure that the application is also coded with the supporting document category, "Form 3674."*** ***If no, ensure that language requesting submission of the form is included in the acknowledgement letter sent to the applicant***	**XX**			
Debarment Certification	**YES**	**NO**	**NA**	**Comment**
Is a correctly worded Debarment Certification included with authorized signature? ***Certification is not required for supplements if submitted in the original application; If foreign applicant, <u>both</u> the applicant and the U.S. Agent must sign the certification [per Guidance for Industry: Submitting Debarment Certifications].*** ***Note:*** *Debarment Certification should use wording in FD&C Act Section 306(k)(1) i.e., "[Name of applicant] hereby certifies that it did not and will not use in any capacity the services of any person debarred under section 306 of the Federal Food, Drug, and Cosmetic Act in connection with this application." Applicant may not use wording such as, "To the best of my knowledge…"*	**XX**			
Field Copy Certification (NDAs/NDA efficacy supplements only)	**YES**	**NO**	**NA**	**Comment**
For paper submissions only: Is a Field Copy Certification (that it is a true copy of the CMC technical section) included? ***Field Copy Certification is not needed if there is no CMC technical section or if this is an electronic submission (the Field Office has access to the EDR)*** ***If maroon field copy jackets from foreign applicants are received, return them to CDR for delivery to the appropriate field office.***			**XX**	This is an electronic CTD submission

Controlled Substance/Product with Abuse Potential	**YES**	**NO**	**NA**	**Comment**
<u>For NMEs:</u> Is an Abuse Liability Assessment, including a proposal for scheduling, submitted per 21 CFR 314.50(d)(5)(vii)? ***If yes,*** *date consult sent to the Controlled Substance Staff:* <u>For non-NMEs</u>: *Date of consult sent to Controlled Substance Staff*:			**XX**	

Pediatrics	**YES**	**NO**	**NA**	**Comment**

PREA Does the application trigger PREA? ***If yes, notify PeRC RPM (PeRC meeting is required)***[2] ***Note**: NDAs/BLAs/efficacy supplements for new active ingredients, new indications, new dosage forms, new dosing regimens, or new routes of administration trigger PREA. All waiver & deferral requests, pediatric plans, and pediatric assessment studies must be reviewed by PeRC prior to approval of the application/supplement.*		**XX**		This is not a new active ingredient, new indication, new dosage form, new dosing regimen, or new route of administration.
If the application triggers PREA, are the required pediatric assessment studies or a full waiver of pediatric studies included?			**XX**	
If studies or full waiver not included, is a request for full waiver of pediatric studies OR a request for partial waiver and/or deferral with a pediatric plan included? ***If no, request in 74-day letter***			**XX**	
If a request for full waiver/partial waiver/deferral is included, does the application contain the certification(s) required by FDCA Section 505B(a)(3) and (4)? ***If no, request in 74-day letter***			**XX**	
BPCA (NDAs/NDA efficacy supplements only): Is this submission a complete response to a pediatric Written Request? ***If yes, notify Pediatric Exclusivity Board RPM (pediatric exclusivity determination is required)***[3]		**XX**		
Proprietary Name	**YES**	**NO**	**NA**	**Comment**
Is a proposed proprietary name submitted? ***If yes, ensure that the application is also coded with the supporting document category, "Proprietary Name/Request for Review."***		**XX**		
REMS	**YES**	**NO**	**NA**	**Comment**
Is a REMS submitted? ***If yes, send consult to OSE/DRISK and notify OC/ OSI/DSC/PMSB via the CDER OSI RMP mailbox***		**XX**		
Prescription Labeling	☐ **Not applicable**			
Check all types of labeling submitted.	☒ Package Insert (PI) ☐ Patient Package Insert (PPI) ☐ Instructions for Use (IFU) ☐ Medication Guide (MedGuide) ☒ Carton labels			

[2] http://inside fda.gov:9003/CDER/OfficeofNewDrugs/PediatricandMaternalHealthStaff/ucm027829.htm
[3] http://inside fda.gov:9003/CDER/OfficeofNewDrugs/PediatricandMaternalHealthStaff/ucm027837.htm

	☒ Immediate container labels ☐ Diluent ☐ Other (specify)			
	YES	**NO**	**NA**	**Comment**
Is Electronic Content of Labeling (COL) submitted in SPL format? ***If no, request applicant to submit SPL before the filing date.***	**XX**			
Is the PI submitted in PLR format?[4]	**XX**			
If PI not submitted in PLR format, was a waiver or deferral requested before the application was received or in the submission? **If requested before application was submitted**, what is the status of the request? ***If no waiver or deferral, request applicant to submit labeling in PLR format before the filing date.***			**XX**	
All labeling (PI, PPI, MedGuide, IFU, carton and immediate container labels) consulted to OPDP?	**XX**			Consult requested November 21, 2012.
MedGuide, PPI, IFU (plus PI) consulted to OSE/DRISK? (*send WORD version if available*)			**XX**	
Carton and immediate container labels, PI, PPI sent to OSE/DMEPA and appropriate CMC review office (OBP or ONDQA)?	**XX**			Consult requested October 25, 2012.
OTC Labeling	☒ **Not Applicable**			
Check all types of labeling submitted.	☐ Outer carton label ☐ Immediate container label ☐ Blister card ☐ Blister backing label ☐ Consumer Information Leaflet (CIL) ☐ Physician sample ☐ Consumer sample ☐ Other (specify)			
	YES	**NO**	**NA**	**Comment**
Is electronic content of labeling (COL) submitted? ***If no, request in 74-day letter.***				
Are annotated specifications submitted for all stock keeping units (SKUs)? ***If no, request in 74-day letter.***				
If representative labeling is submitted, are all represented SKUs defined? ***If no, request in 74-day letter.***				

[4] http://inside fda.gov:9003/CDER/OfficeofNewDrugs/StudyEndpointsandLabelingDevelopmentTeam/ucm025576.htm

All labeling/packaging, and current approved Rx PI (if switch) sent to OSE/DMEPA?				
Other Consults	**YES**	**NO**	**NA**	**Comment**
Are additional consults needed? (e.g., IFU to CDRH; QT study report to QT Interdisciplinary Review Team) ***If yes, specify consult(s) and date(s) sent:***	**XX**			Quality Microbiology-requested by ONDQA 10/25/12.
Meeting Minutes/SPAs	**YES**	**NO**	**NA**	**Comment**
End-of Phase 2 meeting(s)? **Date(s):** ***If yes, distribute minutes before filing meeting***		**XX**		
Pre-NDA/Pre-BLA/Pre-Supplement meeting(s)? **Date(s):** ***If yes, distribute minutes before filing meeting***		**XX**		
Any Special Protocol Assessments (SPAs)? **Date(s):** ***If yes, distribute letter and/or relevant minutes before filing meeting***		**XX**		

ATTACHMENT

MEMO OF FILING MEETING

DATE: November 15, 2012

NDA #: 204767

PROPRIETARY NAME: N/A

ESTABLISHED/PROPER NAME: Acetaminophen for Injection

DOSAGE FORM/STRENGTH: Sterile (b) (4) Solution for Infusion, 10 mg/mL

APPLICANT: Fresenius Kabi USA, LLC

PROPOSED INDICATIONS: management of mild to moderate pain, management of moderate to severe pain with adjunctive opioid analgesics, reduction of fever

BACKGROUND: There was no previous communication and there were no IND meetings with this Sponsor concerning this product.

REVIEW TEAM:

Discipline/Organization	Names		Present at filing meeting? (Y or N)
Regulatory Project Management	RPM:	Diana Walker	Yes
	CPMS/TL:	Parinda Jani	No
Cross-Discipline Team Leader (CDTL)	Sharon Hertz		Yes
Clinical	Reviewer:	Sharon Hertz	Yes
	TL:	N/A	N/A

Clinical Pharmacology	Reviewer:	Ying Fan	No
	TL:	Yun Xu	Yes
Nonclinical (Pharmacology/Toxicology)	Reviewer:	Carlic Huynh	Yes
	TL:	Daniel Mellon	Yes
Product Quality (CMC)	Reviewer:	Ying Wang	Yes
	TL:	Danae Christodoulou	Yes
Quality Microbiology *(for sterile products)*	Reviewer:	Denise Miller	No, but Filing review completed.
	TL:	Stephen Langille	No
Facility Review/Inspection	Reviewer:	Derek Smith	No, but sent email updating status, and no Filing Issues.
	TL:	N/A	N/A
OSE/DMEPA	Reviewer:	Vicky Borders-Hemphill	No
	TL:	Jamie Wilkins-Parker	No

Biopharmaceutics	Reviewer:	Deepika Lakhani	Yes
	TL:	Anjelica Dorantes	No
Other reviewers	Alister Rubenstein, OSE		
Other attendees	Bob Rappaport, DAAAP Director Teena Thomas, OSE RPM Art Shaw, ONDQA		

FILING MEETING DISCUSSION:

GENERAL • 505(b)(2) filing issues? **If yes,** list issues: None discussed	☐ Not Applicable ☐ YES ☒ NO
• Per reviewers, are all parts in English or English translation? **If no**, explain:	☒ YES ☐ NO
• Electronic Submission comments **List comments**: None	☐ Not Applicable
CLINICAL **Comments**:	☐ Not Applicable ☒ FILE ☐ REFUSE TO FILE ☐ Review issues for 74-day letter
• Clinical study site(s) inspections(s) needed? **If no,** explain: No studies were conducted by the Sponsor in support of this NDA.	☐ YES ☒ NO
• Advisory Committee Meeting needed? **Comments**: ***If no, for an NME NDA or original BLA , include the reason. For example:*** o ***this drug/biologic is not the first in its class*** o ***the clinical study design was acceptable*** o ***the application did not raise significant safety or efficacy issues***	☐ YES Date if known: ☒ NO ☐ To be determined Reason:

○ ***the application did not raise significant public health questions on the role of the drug/biologic in the diagnosis, cure, mitigation, treatment or prevention of a disease***	
• Abuse Liability/Potential **Comments**:	☒ Not Applicable ☐ FILE ☐ REFUSE TO FILE ☐ Review issues for 74-day letter
• If the application is affected by the AIP, has the division made a recommendation regarding whether or not an exception to the AIP should be granted to permit review based on medical necessity or public health significance? **Comments**:	☒ Not Applicable ☐ YES ☐ NO
CLINICAL MICROBIOLOGY **Comments**:	☒ Not Applicable ☐ FILE ☐ REFUSE TO FILE ☐ Review issues for 74-day letter
CLINICAL PHARMACOLOGY **Comments**: Biowaiver requested so nothing for Clin-Pharm to review.	☐ Not Applicable ☒ FILE ☐ REFUSE TO FILE ☐ Review issues for 74-day letter
• Clinical pharmacology study site(s) inspections(s) needed?	☐ YES ☒ NO
BIOSTATISTICS **Comments**:	☒ Not Applicable ☐ FILE ☐ REFUSE TO FILE ☐ Review issues for 74-day letter
NONCLINICAL (PHARMACOLOGY/TOXICOLOGY) **Comments**: Comments regarding tightening impurity specs and osmolality comparison	☐ Not Applicable ☒ FILE ☐ REFUSE TO FILE ☒ Review issues for 74-day letter

IMMUNOGENICITY (BLAs/BLA efficacy supplements only) **Comments**:	☒ Not Applicable ☐ FILE ☐ REFUSE TO FILE ☐ Review issues for 74-day letter
PRODUCT QUALITY (CMC) **Comments**: Comments on DMF, clarification of batch size needed, samples and description of bags needed, osmolality comparison (Biopharm)	☐ Not Applicable ☒ FILE ☐ REFUSE TO FILE ☒ Review issues for 74-day letter
Environmental Assessment • Categorical exclusion for environmental assessment (EA) requested? **If no**, was a complete EA submitted? **If EA submitted**, consulted to EA officer (OPS)? **Comments**:	☐ Not Applicable ☒ YES ☐ NO ☐ YES ☐ NO ☐ YES ☐ NO
Quality Microbiology (for sterile products) • Was the Microbiology Team consulted for validation of sterilization? (**NDAs/NDA supplements only**) **Comments**: No Filing issues noted.	☐ Not Applicable ☒ YES ☐ NO
Facility Inspection • Establishment(s) ready for inspection? ▪ Establishment Evaluation Request (EER/TBP-EER) submitted to OMPQ? **Comments**:	☐ Not Applicable ☒ YES ☐ NO ☒ YES ☐ NO

Facility/Microbiology Review (BLAs only) **Comments**:	☒ Not Applicable ☐ FILE ☐ REFUSE TO FILE ☐ Review issues for 74-day letter
CMC Labeling Review **Comments**: Not at this time	 ☐ Review issues for 74-day letter

REGULATORY PROJECT MANAGEMENT

Signatory Authority: TBD

Date of Mid-Cycle Meeting (for NME NDAs/BLAs in "the Program" PDUFA V): N/A

21st Century Review Milestones (see attached) (listing review milestones in this document is optional):
74-day letter: December 11, 2012
Mid-Cycle: February 27, 2013
Wrap-Up: June 13, 2013
Primary Reviews due: June 23, 2012
PDUFA Date: July 28, 2013
Comments: 505(b)(2) assessment due May 28, 2013. Label and PMR comments to the Sponsor due June 30, 2013.

REGULATORY CONCLUSIONS/DEFICIENCIES

☐	The application is unsuitable for filing. Explain why:
☒	The application, on its face, appears to be suitable for filing. Review Issues: ☐ No review issues have been identified for the 74-day letter. ☒ Review issues have been identified for the 74-day letter. List (optional): see above under disciplines. Review Classification: ☒ Standard Review ☐ Priority Review

ACTIONS ITEMS

☒	Ensure that any updates to the review priority (S or P) and classifications/properties are

	entered into tracking system (e.g., chemical classification, combination product classification, 505(b)(2), orphan drug).
N/A ☐	If RTF, notify everybody who already received a consult request, OSE PM, and Product Quality PM (to cancel EER/TBP-EER).
N/A ☐	If filed, and the application is under AIP, prepare a letter either granting (for signature by Center Director) or denying (for signature by ODE Director) an exception for review.
N/A ☐	BLA/BLA supplements: If filed, send 60-day filing letter
N/A ☐	If priority review: • notify sponsor in writing by day 60 (For BLAs/BLA supplements: include in 60-day filing letter; For NDAs/NDA supplements: see CST for choices) • notify OMPQ (so facility inspections can be scheduled earlier)
☒	Send review issues/no review issues by day 74
☒	Conduct a PLR format labeling review and include labeling issues in the 74-day letter
N/A ☐	Update the PDUFA V DARRTS page (for NME NDAs in "the Program")
N/A ☐	BLA/BLA supplements: Send the Product Information Sheet to the product reviewer and the Facility Information Sheet to the facility reviewer for completion. Ensure that the completed forms are forwarded to the CDER RMS-BLA Superuser for data entry into RMS-BLA one month prior to taking an action [These sheets may be found in the CST eRoom at: http://eroom.fda.gov/eRoom/CDER2/CDERStandardLettersCommittee/0_1685f]
☐	Other

Appendix A (NDA and NDA Supplements only)

NOTE: The term "original application" or "original NDA" as used in this appendix denotes the NDA submitted. It does not refer to the reference drug product or "reference listed drug."

An original application is likely to be a 505(b)(2) application if:

(1) it relies on published literature to meet any of the approval requirements, and the applicant does not have a written right of reference to the underlying data. If published literature is cited in the NDA but is not necessary for approval, the inclusion of such literature will not, in itself, make the application a 505(b)(2) application,
(2) it relies for approval on the Agency's previous findings of safety and efficacy for a listed drug product and the applicant does not own or have right to reference the data supporting that approval, or
(3) it relies on what is "generally known" or "scientifically accepted" about a class of products to support the safety or effectiveness of the particular drug for which the applicant is seeking approval. (Note, however, that this does not mean *any* reference to general information or knowledge (e.g., about disease etiology, support for particular endpoints, methods of analysis) causes the application to be a 505(b)(2) application.)

Types of products for which 505(b)(2) applications are likely to be submitted include: fixed-dose combination drug products (e.g., heart drug and diuretic (hydrochlorothiazide) combinations); OTC monograph deviations (see 21 CFR 330.11); new dosage forms; new indications; and, new salts.

An efficacy supplement can be either a (b)(1) or a (b)(2) regardless of whether the original NDA was a (b)(1) or a (b)(2).

An efficacy supplement is a 505(b)(1) supplement if the supplement contains all of the information needed to support the approval of the change proposed in the supplement. For example, if the supplemental application is for a new indication, the supplement is a 505(b)(1) if:

(1) The applicant has conducted its own studies to support the new indication (or otherwise owns or has right of reference to the data/studies),

(2) No additional information beyond what is included in the supplement or was embodied in the finding of safety and effectiveness for the original application or previously approved supplements is needed to support the change. For example, this would likely be the case with respect to safety considerations if the dose(s) was/were the same as (or lower than) the original application, and.

(3) All other “criteria” are met (e.g., the applicant owns or has right of reference to the data relied upon for approval of the supplement, the application does not rely

for approval on published literature based on data to which the applicant does not have a right of reference).

An efficacy supplement is a 505(b)(2) supplement if:

(1) Approval of the change proposed in the supplemental application would require data beyond that needed to support our previous finding of safety and efficacy in the approval of the original application (or earlier supplement), and the applicant has not conducted all of its own studies for approval of the change, or obtained a right to reference studies it does not own. For example, if the change were for a new indication AND a higher dose, we would likely require clinical efficacy data and preclinical safety data to approve the higher dose. If the applicant provided the effectiveness data, but had to rely on a different listed drug, or a new aspect of a previously cited listed drug, to support the safety of the new dose, the supplement would be a 505(b)(2),

(2) The applicant relies for approval of the supplement on published literature that is based on data that the applicant does not own or have a right to reference. If published literature is cited in the supplement but is not necessary for approval, the inclusion of such literature will not, in itself, make the supplement a 505(b)(2) supplement, or

(3) The applicant is relying upon any data they do not own or to which they do not have right of reference.

If you have questions about whether an application is a 505(b)(1) or 505(b)(2) application, consult with your OND ADRA or OND IO.

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

/s/

DIANA L WALKER
11/23/2012