

**CENTER FOR DRUG EVALUATION AND  
RESEARCH**

*APPLICATION NUMBER:*

**204767Orig1s000**

**MEDICAL REVIEW(S)**

## Summary Review for Regulatory Action

<b>Date</b>	(electronic stamp)
<b>From</b>	Sharon Hertz, M.D.
<b>Subject</b>	Division Director Summary Review
<b>NDA/BLA #</b>	204767/000
<b>Applicant Name</b>	Fresenius Kabi USA, LLC
<b>Date of Submission</b>	September 28, 2012
<b>PDUFA Goal Date</b>	July 28, 2013
<b>Proprietary Name / Established (USAN) Name</b>	Acetaminophen injection
<b>Dosage Forms / Strength</b>	Injection, 10 mg/mL
<b>Proposed Indication(s)</b>	Management of mild to moderate pain; management of moderate to severe pain with adjunctive opioid analgesics; reduction of fever
<b>Action:</b>	Complete Response

<b>Material Reviewed/Consulted</b>	
OND Action Package, including:	
Medical Officer Review	N/A
Statistical Review	N/A
Pharmacology Toxicology Review	Carlic K. Huynh, Ph.D., R. Daniel Mellon, Ph.D.
CMC Review	Ying Wang, Ph.D., Prasad Peri, Ph.D.
Biopharmaceutics Review	Deepika Lakhani, Ph.D., John Duan, Ph.D.
Product Quality Microbiology Review	Denise A. Miller, Bryan S. Riley, Ph.D.
Clinical Pharmacology Review	N/A
OSE/DMEPA	Denise V. Baugh, Pharm.D., BCPS, Lubna Merchant, Pharm.D., M.S.
OPDP/DCDP	Eunice Chung-Davies, Pharm.D.
Other	

OND=Office of New Drugs  
 OSE= Office of Surveillance and Epidemiology  
 DMEPA=Division of Medication Errors Prevention  
 DSI=Division of Scientific Investigations  
 CDTL=Cross-Discipline Team Leader  
 OPDP=Office of Prescription Drug Promotion  
 DCDP=Division of Consumer Drug Promotion

# Signatory Authority Review Template

## 1. Introduction

This is a 505(b)(2) application for an acetaminophen injection, 10 mg/mL, relying on the Agency's prior findings of safety and efficacy for Ofirmev (Cadence Pharmaceuticals, NDA 22450). (b) (4) packaging configurations (b) (4) 1000 mg in 100 mL in a 100 mL (b) (4). The differences in this application, compared to the referenced drug, are that this product utilizes a different container closure system than the listed drug. (b) (4)

## 2. Background

The Applicant had not requested any meetings with FDA prior to submission of the NDA. The product is comparable to the referenced product in concentration and tonicity, and contains no novel excipients. No new toxicology studies, clinical pharmacology, clinical efficacy or safety studies were submitted in support of this application, nor are any required. The support for the safety of the container closure system, the FreeFlex (b) (4) was located in a CBER Master File (MF) referenced by the Applicant. The reviewers in CDER do not have ready access to MFs in CBER, so in order to access the information in the MF, the Applicant agreed to submit a master file to CDER.

Ofirmev was approved on November 2, 2010 and has exclusivity that expires on November 2, 2013. There are also two active patents listed in the Orange Book due to expire on August 5, 2017 and June 6, 2021.

## 3. CMC/Device

The drug substance MF and specifications were found acceptable. The drug product is an injection with a strength of 10 mg/mL, packaged in a 100 mL proprietary FreeFlex plastic (b) (4) container closure system (b) (4)

Upon filing, the Applicant was asked to lower the drug product specification for the degradant, (b) (4) also known as (b) (4) to as low as possible. The Applicant committed to a stability limit for (b) (4) of NMT (b) (4)%. The release limit remains at NMT (b) (4)%.

A Type III MF for the freeflex packaging system was compiled according to the CDER Guideline for Drug Master Files (September 1989) and the CDER/CBER guidance for

Industry – Container Closure Systems for Packaging Human Drugs and Biologics – CMC Documentation (May 1999). The original version of the MF was submitted by Fresenius Kabi Deutschland GmbH (MF holder) to CDER on December 26, 2012. The MF was acceptable except for inadequate qualification of leachables. The leachable study data submitted were from data collected at 6 months for three different storage conditions and from 12 months at one storage condition (b)(4) fill volume. As described in the Pharmacology/Toxicology section below, additional safety qualification is required for the evaluation of leachables including additional data at 18-month and 24-month time points for all stability batches at the long-term storage condition for the 100 mL fill volume of the Freeflex (b)(4) container closure system.

The Applicant provided adequate support for a 24-month expiry for the drug product when stored at controlled room temperature conditions (b)(4) for all parameters except leachables. The expiry will be re-evaluated once more information is available about the leachable impurity.

A product quality microbiology review found no deficiencies from a quality microbiology standpoint. The drug substance was tested for microbial bioburden and bacterial endotoxin. The drug product is preservative free. (b)(4) Manufacturing site inspections were acceptable.

I concur with the conclusions reached by the chemistry reviewer, and once additional leachable data are submitted the requested 24-month expiry will be re-evaluated.

## 4. Nonclinical Pharmacology/Toxicology

As described in the primary review by Dr. Huynh and secondary review by Dr. Mellon, There are no safety concerns associated with the proposed drug substance or drug product specifications. However, upon review of the MF for the FreeFlex (b)(4) several leachable compounds were identified. At the levels detected in the stability studies, the safety of two of the leachables, (b)(4)

(b)(4) which appear to arise from the (b)(4) container closure (b)(4) is not adequately supported by data.

The Applicant initiated a 4-week IV toxicology study to support the safety of (b)(4), but the study has not been completed. The toxicology risk assessment for (b)(4) is based on the safety of the two main metabolites (b)(4). As the rate of (b)(4) in vivo is not known and the extent of exposure to the parent is unknown, but there is likely to be some exposure to the parent compound, additional toxicology studies were recommended. To support the safety of (b)(4) the Applicant must either conduct a 28-day IV toxicology study or provide convincing evidence that, upon infusion, (b)(4) fast enough that there is no meaningful systemic exposure. Additionally, Dr. Mellon notes that the risk assessments on the leachables completed were based on the highest levels detected from the available stability testing, which is limited. Additional stability data are required to confirm that the levels of the

leachables do not increase further over time and the nonclinical review team agrees with the CMC review team that data from at least three batches over the entire course of stability are necessary in order to fully characterize the potential leachables that may accumulate in this product. Once the maximum levels of the leachables are confirmed, Dr. Mellon notes that a re-evaluation of the toxicological risk assessments will be performed.

The Applicant has proposed to complete in vitro bacterial reverse mutation studies (Ames tests) for [REDACTED] (b) (4) and another leachable, [REDACTED] (b) (4) which was also found in the drug product. While the results are not required for approval, if the studies are completed, the information should be submitted to the NDA.

I concur with the conclusions reached by the nonclinical pharmacology/toxicology reviewers that there are outstanding pharmacology/toxicology issues with the leachable data that preclude approval.

## **5. Clinical Pharmacology/Biopharmaceutics**

No new clinical pharmacology data were submitted in support of this application. The Applicant has requested a waiver for in-vivo bioavailability/ bioequivalence studies. The proposed drug product is identical to the referenced drug with the exception of the concentration of the inactive ingredients and the elimination of the buffer from the product under review. The information submitted in support of the request was found adequate and the biowaiver is granted.

I concur with the conclusions reached by the biopharmaceutics reviewers that there are no outstanding biopharmaceutical issues that preclude approval.

## **6. Clinical Microbiology**

No clinical microbiology review was required for this application.

## **7. Clinical/Statistical-Efficacy**

No clinical efficacy studies were submitted in support of this application. As a 505(b)(2) application for an acetaminophen solution of the same concentration and tonicity as the referenced product and with no novel or unusual excipients, there was no need for additional clinical efficacy studies.

## **8. Safety**

No clinical safety studies were submitted in support of this application. As a 505(b)(2) application for an acetaminophen solution of the same concentration and tonicity as the referenced product and with no novel or unusual excipients, there was no need for additional clinical safety studies.

## **9. Advisory Committee Meeting**

No advisory committee was held for this application. There were no scientific or regulatory issues that required discussions from an AC.

## **10. Pediatrics**

This NDA does not trigger any of the requirements of the Pediatric Research Equity Act.

## **11. Other Relevant Regulatory Issues**

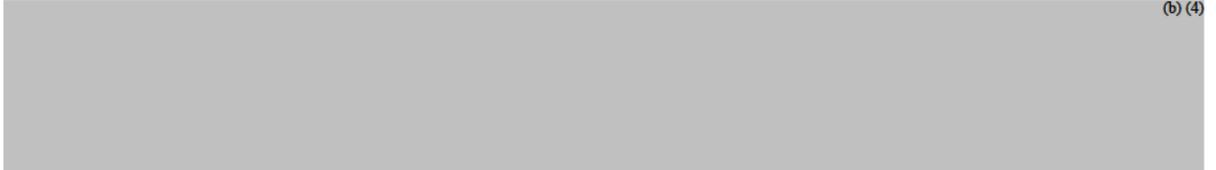
Ofirmev was approved on November 2, 2010 and has exclusivity that expires on November 2, 2013. There are also two active patents listed in the Orange Book due to expire on August 5, 2017 and June 6, 2021. The Applicant filed the application under 21 CFR 314.50(i)(1)(i)(A)(4): The patent is invalid, unenforceable, or will not be infringed by the manufacture, use, or sale of the drug product for which the application is submitted (Paragraph IV certification). The Applicant notified the owners of the referenced product, Ofirmev, that this b(2) application was filed [21 CFR 314.52(b)] and submitted documentation showing that the NDA holder and patent owner(s) received the notification [21 CFR 314.52(e)]. In response, the Applicant has been sued for patent infringement.

## 12. Labeling

The Division of Medication Error Prevention and Analysis conducted a review of the proposed container label, carton and full prescribing information. The product is dosed by weight above or below 50 kg, and by age from 2 to 12 years of age according to the following table:



The Applicant proposed  (b) (4) 1000 mg/100 mL in a 100 mL flexible plastic container. This is problematic as described in Dr. Baugh's review:



The flexible plastic  (b) (4) (container) implies the product is 'ready to use' (e.g., ready for dispensing or administration) without removing or adding product to the  (b) (4). However, the DOSAGE AND ADMINISTRATION section provides for doses of 1000 mg, 650 mg or less depending on the patient's age and weight.  (b) (4)

(b) (4)

A request to (b) (4) was accepted by the Applicant. The following labeling changes were also accepted by the Applicant:

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

DMEPA has conducted several reviews of domestic and foreign medication error reports associated with IV acetaminophen, including the preparation for a presentation at the September 11, 2012 meeting of the Pediatric Advisory Committee. The details are described in Dr. Baugh’s review. [REDACTED] (b) (4)

[REDACTED] DMEPA recommended labeling changes that were conveyed to the Applicant.

Additional labeling comments were conveyed to the Applicant from the Office of Professional Drug Promotion.

### 13. Decision/Action/Risk Benefit Assessment

- Regulatory Action – Complete response
- Risk Benefit Assessment

Inadequate safety qualification was provided for two leachable compounds identified [REDACTED] (b) (4) which appear to arise from the [REDACTED] (b) (4) container closure [REDACTED] (b) (4)

The following deficiencies must be addressed prior to approval of this NDA:

1. Adequate safety justification for the levels of [REDACTED] (b) (4) leachables from the container closure system has not been provided. To resolve this deficiency:
  - a. Submit the results of the proposed 4-week IV toxicology study of [REDACTED] (b) (4) and a revised toxicological risk assessment.

- b. Conduct and submit the results of a 4-week IV toxicology study of (b) (4) and a revised toxicological risk assessment for this compound. Alternatively, provide adequate data to support your conclusion that (b) (4) is virtually instantaneous in vivo such that exposure to the parent compound, when the product is used as directed, does not occur.
2. The leachable study data that you have submitted, 6 months at three different storage conditions and 12 months at one storage condition (b) (4) fill volume, are inadequate to support the safety of your drug product. To resolve this deficiency, submit additional leachable data at 18-month and 24-month time points for all stability batches at long-term storage condition for the 100 mL fill volume of the freeflex (b) (4) container closure system.
3. Your application referenced the Master File (MF) 26696. This MF was found to be inadequate to support your submission and a deficiency letter was sent to the MF holder on June 24, 2013. These deficiencies must be adequately addressed before this application can be approved. As part of your response to this letter, include the date the MF holder amended their MF to address the deficiencies.
- Recommendation for Postmarketing Risk Management Activities  
None
  - Recommendation for other Postmarketing Study Commitments  
None

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/s/

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SHARON H HERTZ  
07/25/2013





## CLINICAL FILING CHECKLIST FOR NDA/BLA or Supplement

	Content Parameter	Yes	No	NA	Comment
24.	Has the applicant adequately evaluated the safety issues that are known to occur with the drugs in the class to which the new drug belongs?			XX	
25.	Have narrative summaries been submitted for all deaths and adverse dropouts (and serious adverse events if requested by the Division)?			XX	
<b>OTHER STUDIES</b>					
26.	Has the applicant submitted all special studies/data requested by the Division during pre-submission discussions?			XX	
27.	For Rx-to-OTC switch and direct-to-OTC applications, are the necessary consumer behavioral studies included ( <i>e.g.</i> , label comprehension, self selection and/or actual use)?			XX	
<b>PEDIATRIC USE</b>					
28.	Has the applicant submitted the pediatric assessment, or provided documentation for a waiver and/or deferral?			XX	This application does not trigger PREA.
<b>ABUSE LIABILITY</b>					
29.	If relevant, has the applicant submitted information to assess the abuse liability of the product?			XX	
<b>FOREIGN STUDIES</b>					
30.	Has the applicant submitted a rationale for assuming the applicability of foreign data in the submission to the U.S. population?			XX	
<b>DATASETS</b>					
31.	Has the applicant submitted datasets in a format to allow reasonable review of the patient data?			XX	
32.	Has the applicant submitted datasets in the format agreed to previously by the Division?			XX	
33.	Are all datasets for pivotal efficacy studies available and complete for all indications requested?			XX	
34.	Are all datasets to support the critical safety analyses available and complete?			XX	
35.	For the major derived or composite endpoints, are all of the raw data needed to derive these endpoints included?			XX	
<b>CASE REPORT FORMS</b>					
36.	Has the applicant submitted all required Case Report Forms in a legible format (deaths, serious adverse events, and adverse dropouts)?			XX	
37.	Has the applicant submitted all additional Case Report Forms (beyond deaths, serious adverse events, and adverse drop-outs) as previously requested by the Division?			XX	
<b>FINANCIAL DISCLOSURE</b>					
38.	Has the applicant submitted the required Financial Disclosure information?	XX			
<b>GOOD CLINICAL PRACTICE</b>					
39.	Is there a statement of Good Clinical Practice; that all clinical studies were conducted under the supervision of an IRB and with adequate informed consent procedures?			XX	

as needed; however, if it is submitted as a PDF document, it should be submitted in both directions (verbatim -> preferred and preferred -> verbatim).

File name: 5\_Clinical Filing Checklist for NDA\_BLA or Supplement 010908

# CLINICAL FILING CHECKLIST FOR NDA/BLA or Supplement

**IS THE CLINICAL SECTION OF THE APPLICATION FILEABLE? \_\_\_ Yes \_\_\_**

If the Application is not fileable from the clinical perspective, state the reasons and provide comments to be sent to the Applicant.

Please identify and list any potential review issues to be forwarded to the Applicant for the 74-day letter.

Sharon Hertz, M.D.	11/20/16	
Reviewing Medical Officer		Date
Sharon Hertz, M.D.	11/20/16	
Clinical Team Leader		Date

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**This is a representation of an electronic record that was signed electronically and this page is the manifestation of the electronic signature.**  
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/s/  
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SHARON H HERTZ  
11/20/2012