CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

204767Orig1s000

CLINICAL PHARMACOLOGY AND BIOPHARMACEUTICS REVIEW(S)

MEMO

This memo is about NDA 204767, Acetaminophen injection 10 mg/mL, submitted on 9/28/2012. Reference is also made to the filing review in Darrts on 11/15/2012.

The sponsor is requesting biowaiver for *in-vivo* bioavailability/bioequivalence requirements for Acetaminophen Injection. The Sponsor stated the drug product's self-evident *in-vivo* bioavailability or bioequivalence is based on the fact that the drug product is a sterile (b) (4) solution intended solely for administration by intravenous administration. The Sponsor submitted a biowaiver request for the *in-vivo* bioavailability/bioequivalence study. Based on the biopharmaceutics review in Darrts on 6/17/2013, biowaiver is granted for the product.

There is no clinical pharmacology study or data submitted in this application to be reviewed. The application is acceptable from clinical pharmacology perspective providing a mutual agreement on the labeling language is reached.

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/s/

YUN XU
06/21/2013

BIOPHARMACEUTICS FILING REVIEW

Office of New Drugs Quality Assessment

Application No.:	NDA 204-767	**Reviewer:** Deepika Arora Lakhani, PhD	
Submission Date:	Sep 28, 2012 Feb 04, 2013		
Division:	DAAAP	**Team Lead (Acting):** John Duan, PhD	
Sponsor:	Fresenius Kabi USA, LLC	**Supervisor (Acting):** Rik Lostritto, PhD	
Trade Name:	Acetaminophen Injection for Intravenous Infusion	**Date Assigned:**	Oct 05, 2012
Generic Name:	Acetaminophen Injection	**Date of Review:**	June 13, 2013
Indication:	management of mild to moderate pain, management of moderate to severe pain with adjunctive opioid analgesics and reduction of fever	**Type of Submission:** New Drug Application	
Formulation/ strengths	Sterile (b) (4) Solution, 10 mg/mL		
Route of Administration	Intravenous, Infusion		
Type of Review	BIOWAIVER REQUEST		

SUBMISSION:

On 28-SEP-2013, Fresenius Kabi USA, LLC submitted NDA 204-767 for Acetaminophen Injection for Intravenous Infusion 10 mg/mL under 505(b)(2) of the Federal Food, Drug, and Cosmetic Act. This 505 (b)(2) application relies for approval on the FDA's findings of safety and effectiveness for the Cadence Pharmaceuticals's Ofirmev™, 100 mL under the approved NDA 22-450.
NDA 204-767 for Acetaminophen Injection, 10 mg/mL (a sterile (b) (4) solution for intravenous administration) provides a request for waiver for in-vivo bioavailability/ bioequivalence studies.

BIOPHARMACEUTICS:

Formulation: The proposed drug product (b) (4) The comparative description of the proposed formulation and the RLD formulation is given in the Table below:

Comparative Formulations of the Proposed Product and Reference product		
Ingredients	**Ofirmev™**	**Acetaminophen Injection**
	Cadence Pharmaceuticals	**Fresenius Kabi USA, LLC**
	100 mL fill	**100 mL fill**
Acetaminophen, USP	1000 mg	1000 mg
Mannitol, USP	3850 mg	3670 mg
Cysteine Hydrochloride (monohydrate), USP	25 mg	-
Cysteine (b) (4)	-	10 mg
Dibasic Sodium Phosphate (b) (4), USP	10.4 mg	-
(b) (4)		
Hydrochloric Acid	As required to adjust pH	As required to adjust pH
Sodium Hydroxide	As required to adjust pH	As required to adjust pH

(b) (4)

The proposed change is in accordance with 21 CFR § 314.94 (a)(9)(iii) that states that "…an applicant may seek approval of a drug product that differs from the reference listed drug in preservative, buffer, or antioxidant provided that the applicant identifies and characterizes the differences and provides information demonstrating that the differences do not affect the safety or efficacy of the proposed drug product." The Applicant was sent the following IR on 4-DEC-2012, to provide comparative osmolalities of the two products as there were slight changes in the mannitol concentration. ***IR (dated 4-DEC-2012):***

Provide osmolalities of your proposed product and the referenced drug to ensure that the change in mannitol composition in the proposed product formulation with respect to the referenced drug has no significant impact on relative bioavailability. If the solution is not isotonic, provide justification for why any differences in osmolality between your drug product and the referenced drug product do not represent a safety concern.

The Applicant responded on 4-FEB-2013. The comparative osmolality data is shown below:

Osmolality Results for FK Finished Product

Lot no.	Manufacturing Date	Osmolality (mOsm/kg)
12EGU94	July 2011	275
12EGU95	July 2011	276
12EGU96	July 2011	275
12EGU97	July 2011	275

Osmolality Results for Ofirmev® Finished Product

Lot no.	Expiration Date	Osmolality (mOsm/kg)
V005710	May 2012	286
2B70898	February 2014	281
2G71267	July 2014	282
2H60284	August 2014	282

As can be seen from the comparative osmolality data, there is less than 3% difference between the osmolalities of the two formulations supporting that the (b) (4) change in mannitol should not impact the osmolality of the proposed product when compared with the reference drug.

The Applicant conducted other physicochemical tests for their proposed Acetaminophen Injection product and for the reference product Offirmev® (subject of CMC review).

BIOWAIVER REQUEST:

In this NDA submission, Fresenius Kabi USA, LLC is requesting that the Agency waive the CFR's requirement to provide in vivo bioavailability/bioequivalence (BA/BE) data for their product In accordance with 21 CFR § 320.22(a).

Reviewer Comments:

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.*

3. Acetaminophen Injection for intravenous infusion is a dosage form intended solely for IV administration and is a true solution.

4. The route of administration, dosage form and indications of the proposed product are the same as the reference drug product.

5. No other in vitro pharmacodynamic activity comparison was provided or required by the Office of Clinical Pharmacology for this product.

§ 320.22 Criteria for waiver of evidence of in vivo bioavailability or bioequivalence.

Any person submitting a full or abbreviated new drug application, or a supplemental application proposing any of the changes set forth in §320.21(c), may request FDA to waive the requirement for the submission of evidence measuring the in vivo bioavailability or demonstrating the in vivo bioequivalence of the drug product that is the subject of the application. An applicant shall submit a request for waiver with the application., FDA shall waive the requirement for the submission of evidence of in vivo bioavailability or bioequivalence if the drug product meets any of the provisions of paragraphs (b), (c), (d), or (e) of this section.

(b) For certain drug products, the in vivo bioavailability or bioequivalence of the drug product may be self-evident. FDA shall waive the requirement for the submission of evidence obtained in vivo measuring the bioavailability or

demonstrating the bioequivalence of these drug products. A drug product's in vivo bioavailability or bioequivalence may be considered self-evident based on other data in the application if the product meets one of the following criteria:

(1) The drug product:
(i) Is a parenteral solution intended solely for administration by injection, or an ophthalmic or otic solution; and
(ii) Contains the same active and inactive ingredients in the same concentration as a drug product that is the subject of an approved full new drug application or abbreviated new drug application.

RECOMMENDATION:

The Office of New Drugs Quality Assessment (ONDQA)-Biopharmaceutics has reviewed the information included in NDA 204-767 for Acetaminophen Injection, 10 mg/ml. Based on the provided information, ONDQA-Biopharmaceutics considers that Fresenius Kabi USA, LLC's request for a waiver of the CFR's requirement to provide in vivo BA/BE data to support the approval of their product is acceptable and the biowaiver for the proposed Acetaminophen Injection is granted. From the Biopharmaceutics perspective, an approval is recommended.

Deepika Arora Lakhani, Ph.D.
Biopharmaceutics Reviewer
Office of New Drugs Quality Assessment

John Duan, Ph.D.
Biopharmaceutics Team Lead (Acting)
Office of New Drugs Quality Assessment

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/s/

DEEPIKA LAKHANI
06/17/2013
Recommend Approval from Biopharmaceutics perspective.

JOHN Z DUAN
06/17/2013

ONDQA – BIOPHARMACEUTICS
NDA 204-767
Initial Product Quality Assessment and Filing Review

NDA Number	204-767
Submission Date	Sep 28, 2012
Product name, generic name of the active	Acetaminophen Injection for Intravenous Infusion
Dosage form and strength	Sterile (b) (4) Solution, 10 mg/mL
Applicant	Fresenius Kabi USA, LLC
Clinical Division	DAAAP
Type of Submission	NDA 505(b)(2)
Biopharmaceutics Primary Reviewer	Deepika Arora Lakhani, Ph.D.
Biopharmaceutics Team Leader (Acting)	John Duan, Ph.D.

BIOPHARMACEUTICS INITIAL ASSESSMENT

Biopharmaceutics Summary

NDA 204-767 for Acetaminophen Injection, 10 mg/mL (a sterile (b) (4) solution for intravenous administration) provides a request for waiver for in-vivo bioavailability/ bioequivalence studies.

(b) (4)

The comparison of the two products is provided below:

Table 1. Comparison of FK USA's and Innovator's Formulation

(b) (4)

Dibasic S

Hydrochl

Sodium I

ONDQA – BIOPHARMACEUTICS
NDA 204-767
Initial Product Quality Assessment and Filing Review

BIOPHARMACEUTICS INITIAL ASSESSMENT
Biopharmaceutics Summary
The Biopharmaceutics review will focus on reviewing the request for waiver for in-vivo bioavailability/ bioequivalence studies.
Critical Review Issues
As seen in Table 1, the two formulations have slight differences in formulation composition (b) (4) The review will focus on evaluating the impact of the formulation differences, if any. The application contains supportive information comparing quality attributes of the proposed formulation with the RLD, for e.g., pH, impurities etc. however, lacks information regarding the osmolality of the proposed formulation with respect to the RLD. The applicant will be asked to provide the same.
Comments for Day 74-Letter
The following comment should be conveyed to the Applicant: – Provide osmolalities of your proposed product and the RLD to ensure that the change in mannitol composition in the proposed product formulation with respect to the RLD has no significant impact.

ONDQA – BIOPHARMACEUTICS
NDA 204-767
Initial Product Quality Assessment and Filing Review

The following parameters for the ONDQA's Product Quality-Biopharmaceutics filing checklist are necessary in order to initiate a full biopharmaceutics review (i.e., complete enough to review but may have deficiencies).

ONDQA-BIOPHARMACEUTICS **A. INITIAL** OVERVIEW OF THE NDA APPLICATION FOR FILING				
	PARAMETER	**YES**	**NO**	**COMMENT**
1.	Does the application contain dissolution data?		x	
2.	Is the dissolution test part of the DP specifications?		x	
3.	Does the application contain the dissolution method development report?		x	
4.	Is there a validation package for the analytical method and dissolution methodology?		x	
5.	Does the application include a biowaiver request?	x		
6.	Does the application include an IVIVC model?		x	
7.	Is information such as BCS classification mentioned, and supportive data provided?		x	
8.	Is information on mixing the product with foods or liquids included?		x	
9.	Is there any in *vivo* BA or BE information in the submission?		x	
10.	Is there a modified-release claim? If yes, address the following: a.) Is there information submitted to support the claim in accordance with 320.25(f)? b.) Is there information on the potential for alcohol-induced dose dumping?		x x	

ONDQA – BIOPHARMACEUTICS
NDA 204-767
Initial Product Quality Assessment and Filing Review

B. FILING CONCLUSION				
	Parameter	**Yes**	**No**	**Comment**
11.	**IS THE BIOPHARMACEUTICS SECTIONS OF THE APPLICATION FILEABLE?**	x		
12.	If the NDA is not fileable from the product quality-biopharmaceutics perspective, state the reasons and provide **filing** comments to be sent to the Applicant.			Not applicable.
13.	Are there any **potential review** issues to be forwarded to the Applicant for the 74-day letter?	x		Please convey the comment described in page 2 of this IQA and filing review.

Administrative Block: *{See appended electronic signature page}*

Deepika Arora Lakhani, Ph.D.
Biopharmaceutics Primary Reviewer
Office of New drug Quality Assessment

John Duan, Ph.D.
Acting Biopharmaceutics Team Leader
Office of New drug Quality Assessment

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/s/

DEEPIKA LAKHANI
11/27/2012
NDA is fileable. Comments for 74 day letter are on Page 2 of review.

JOHN Z DUAN
11/27/2012

Office of Clinical Pharmacology

New Drug Application Filing Form

General Information About the Submission

	Information		Information
NDA Number	**20-4767**	**Brand Name**	**TBA**
OCP Division	**DCP2**	**Generic Name**	**Acetaminophen injection 10 mg/mL**
Medical Division	**DAAAP (OND-170)**	**Drug Class**	**Analgesics and antipyretics**
OCP Reviewer	**Ying Fan**	**Proposed Indication(s)**	**Management of mild to moderate pain, management of moderate to severe pain with adjunctive opioid analgesics, and reduction of fever**
OCP Team Leader	**Yun Xu**	**Dosage Form**	**(b) (4) solution for infusion**
		Dosing Regimen	**See details in Introduction section**
Date of Submission	**September 28, 2012**	**Route of Administration**	**Intravenous infusion**
Estimated Due Date of OCP Review	**April 28, 2013**	**Sponsor**	**Fresenius Kabi USA, LLC**
PDUFA Due Date	**July 28, 2013**	**Priority Classification**	**Standard**
Division Due Date	**June 28, 2013**		

Clin. Pharm. and Biopharm. Information

	"X" if included at filing	**Number of studies submitted**	**Number of studies reviewed**	**Critical Comments If any**
STUDY TYPE				
Table of Contents present and sufficient to locate reports, tables, data, etc.	**x**			
Tabular Listing of All Human Studies				
HPK Summary				
Labeling	**x**			
Reference Bioanalytical and Analytical Methods				
I. Clinical Pharmacology				
Mass balance:				
Isozyme characterization:				
Blood/plasma ratio:				
Plasma protein binding:				
Pharmacokinetics (e.g., Phase I) -				
1 Healthy Volunteers-				
single dose:				
multiple dose:				
2 Patients-				
single dose:				
multiple dose:				
Dose proportionality -				
fasting / non-fasting single dose:				
fasting / non-fasting multiple dose:				
Drug-drug interaction studies -				
In-vivo effects on primary drug:				
In-vivo effects of primary drug:				
In-vitro:				
Subpopulation studies -				

ethnicity:				
gender:				
pediatrics:				
geriatrics:				
renal impairment:				
hepatic impairment:				
PD:				
Phase 2:				
Phase 3:				
PK/PD:				
Phase 1 and/or 2, proof of concept:				
Phase 3 clinical trial:				
Population Analyses -				
Data rich:				
Data sparse:				
II. Biopharmaceutics				
Absolute bioavailability:				
Relative bioavailability -				
solution as reference:				
alternate formulation as reference:				
Bioequivalence studies -				
traditional design; single / multi dose:				
replicate design; single / multi dose:				
Food-drug interaction studies:				
Dissolution:				
(IVIVC):				
Bio-wavier request based on BCS				
BCS class				
III. Other CPB Studies				
Genotype/phenotype studies:				
Chronopharmacokinetics				
Pediatric development plan				
Literature References				
Total Number of Studies		**0**		
3				

4 Filability and QBR comments

5	**"X" if yes**	**6 Comments**
Application filable?	**x**	**The Sponsor submitted a biowaiver request for the *in-vivo* bioavailability/bioequivalence study. There is no clinical pharmacology study or data submitted in this application for review. The application is filable from clinical pharmacology perspective. We do not plan to write a review for this NDA.**
Comments sent to firm?		**None.**
QBR questions (key issues to be considered)		

Introduction
The sponsor is submitting new drug application through 505(b)(2) pathway to seek marketing clearance for Acetaminophen injection 10 mg/mL. Acetaminophen injection 10 mg/mL is a sterile (b) (4) solution for intravenous administration. Each (b) (4) 100 mL flexible plastic container has 1000 mg acetaminophen (10 mg/mL). The proposed indication is management of mild to moderate pain, management of moderate to severe pain with adjunctive opioid analgesics, and reduction of fever. The Listed Drug, Ofirmev (NDA 22450), is manufactured by Cadence Pharmaceuticals.

The proposed dosing regimen is as follows (same as Ofirmev):

Acetaminophen injection may be given as a single or repeated dose.
Acetaminophen injection should be administered only as a 15 minute intravenous 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:** Children ≥ 2 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*

Regulatory History
There are no previous meetings or communications between the sponsor and the Agency related to this submission.

Clinical Pharmacology Finding
The sponsor is requesting for the waiver for *in-vivo* bioavailability/bioequivalence requirements for Acetaminophen Injection. This request is based on 21 CFR § 320.22(b), which states that for certain drug products, the *in*-vivo bioavailability or bioequivalence of the drug product may be self-evident. The Sponsor stated the drug product's self-evident *in*-vivo bioavailability or bioequivalence is based on the fact that the drug product is a sterile (b) (4) solution intended solely for administration by intravenous administration.

The Sponsor submitted a biowaiver request for the *in-vivo* bioavailability/bioequivalence study. There is no clinical pharmacology study or data submitted in this application to be reviewed from a Clinical Pharmacology perspective. The application is filable from clinical pharmacology perspective. We do not plan to write a review for this NDA.

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/s/

YUN XU
11/15/2012
Dr. Ying Fan, the primary reviewer is on medical leave. So I Darrts the review for her.