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RESEARCH**

APPLICATION NUMBER:

205572Orig1s000

**CLINICAL PHARMACOLOGY AND
BIOPHARMACEUTICS REVIEW(S)**

BIOPHARMACEUTICS REVIEW Office of New Drug Products			
Application No.:	NDA 205572	Reviewer: Vidula R. Kolhatkar, Ph.D.	
Submission Date:	October 03, 2014		
Division:	Division of Anti-Infective Products	Quality Assessment Lead: Kelly M. Kitchens, Ph.D.	
Applicant:	Fresenius Kabi	Acting Supervisor: Tapash Ghosh, Ph.D.	
Trade Name:	Moxifloxacin Injection, 400 mg/250 mL	Date Assigned:	October 16, 2014
Established Name:	Moxifloxacin Injection	Date of Review:	March 2, 2014
Indication:	Treatment of infections in adults at least 18 years of age caused by designated, susceptible bacteria	Type of Submission: 505(b)(2) NDA Resubmission after April 04, 2014 Complete Response letter	
Formulation/strengths	Sterile injectable solution/400 mg/250 mL		
Route of Administration	Intravenous infusion		
Type of Review:	Biowaiver Request		
<u>SUMMARY:</u>			
<p>Background: Moxifloxacin is indicated for treatment of infections caused by designated, susceptible bacteria. On June 07, 2013, Fresenius Kabi USA, LLC submitted a new drug application for Moxifloxacin Injection and requested a waiver for in vivo bioavailability studies. The application cited Avelox as the reference listed drug (RLD) (NDA 21277, approved 11/30/2001).</p> <p>Submission: The applicant requested a biowaiver for Moxifloxacin Injection based on 21 CFR § 320.22(b). In the biopharmaceutics review dated January 27, 2014 by Dr. Karen Riviere, a Complete Response (CR) was recommended. The following summarizes the conclusion and recommendation in the review by Dr. Karen Riviere:</p> <p><i>ONDQA-Biopharmaceutics has evaluated the information provided in NDA 205572 for Moxifloxacin Injection and concludes that a waiver of the CFR's requirement for the submission of data from an in vivo bioequivalence study for the proposed product cannot be granted at this time due to incomplete supportive information.</i></p> <p><i>To support the approval of the biowaiver request the Applicant should provide the following information that is lacking:</i></p> <ul style="list-style-type: none"> • <i>A side to side comparison of the osmolality and pH values for the proposed and listed products,</i> 			

- *A justification that the human physiological disposition (i.e., metabolism and excretion) of the proposed and the listed products are similar, despite the differences in the inactive ingredients between these products.*

In the current resubmission (dated October 03, 2014), the Applicant responded to the CR letter (dated April 04, 2014) by providing the requested information: a side-by-side comparison of osmolality and pH values for the proposed drug and listed drug products; and a justification that the human physiological disposition of the proposed drug product does not differ from that of the listed drug product.

Review: Biopharmaceutics review is focused on the evaluation of the requested information to support the biowaiver request.

RECOMMENDATION:

The waiver for in vivo bioavailability/bioequivalence studies for Moxifloxacin Injection, 400 mg/250 mL, is granted. From the Biopharmaceutics perspective, NDA 205572 for Moxifloxacin Injection, 400 mg/250 mL, is recommended for approval.

Signature

Vidula R. Kolhatkar, Ph.D.
Biopharmaceutics Reviewer
Office of New Drug Products

Signature

Kelly M. Kitchens, Ph.D.
Biopharmaceutics Quality Assessment Lead
Office of New Drug Products

cc. TGhosh; PSeo.

Assessment of Biopharmaceutics information

- Moxifloxacin is a fluoroquinolone antibacterial that is sparingly soluble in water. Moxifloxacin is indicated for treating infections in adults at least 18 years of age caused by designated, susceptible bacteria, such as:
 - Acute Bacterial Sinusitis
 - Acute Bacterial Exacerbation of Chronic Bronchitis
 - Community Acquired Pneumonia
 - Skin and Skin Structure Infections: Uncomplicated and Complicated
 - Complicated Intra-Abdominal Infections

- A side-by-side comparison of the RLD, Avelox®, and the proposed drug is shown in Table 1:

Table 1. Side-by-side comparison of the RLD and the proposed drug product

	Reference Listed Drug	Proposed Drug Product
Name	Avelox®	Moxifloxacin Injection
Conditions of Use (Indications)	It is indicated for treatment of infections.	It is indicated for treatment of infections.
Dosage Form	Sterile Liquid	Sterile Liquid
Route of Administration	Intravenous Infusion	Intravenous Infusion
Active Ingredient	Moxifloxacin Hydrochloride (b) (4)	Moxifloxacin Hydrochloride (b) (4)
Strength	160 mg/100 mL (1.6 mg/mL)	400 mg/250 mL (1.6 mg/mL)
Excipients (per mL)	per mL	per mL
Sodium Acetate Trihydrate, USP	(b) (4)	
Sodium Chloride, USP		
Disodium Sulfate, USP (b) (4)		
Sodium Hydroxide		
Hydrochloric Acid		
Sulphuric Acid, NF		
Water for Injections, USP		

Table 1.12.15- 1 in the original submission (06/07/2013)

- The applicant was issued a CR letter dated April 04, 2014, and was recommended to provide:
 1. A side to side comparison of the osmolality and pH values for the proposed and listed products;
 2. A justification that the human physiological disposition (i.e. metabolism and excretion) of the proposed and the listed products are similar, despite the differences in the inactive ingredients between these products.

- The applicant resubmitted this NDA (October 03, 2014), which includes responses for the CR letter.
- In response to **CR comment #1**, the applicant provided comparative data between the listed drug (Avelox) and the proposed drug product (Table 2). This includes data from three exhibit batches for the proposed product (12FCU92, 12FCU93, and 12FCU94) and three lots of the RLD (BXA5U00, BXA5TZU and BXA5U02).

Table 2: Comparative physicochemical data between RLD and the proposed drug product

Tests [Unit]	Acceptance criteria	Avelox (Bayer) Storage Condition: Room temp, expiration: Sep 2016			Moxifloxacin Injection (FK USA) 24 months at 25°C Expiration: proposed (b) (4)		
		BXA5U00	BXA5TZU	BXA5U02	12FCU92	12FCU93	12FCU94
Clarity	clear	clear	clear	clear	clear	clear	clear
Degree of coloration	not more colored than (b) (4)	(b) (4)			conform	conform	conform
Sub-visible particles (b) (4)	(b) (4)	0 part/mL	0 part/mL	1 part/mL	0 part/mL	0 part/mL	0 part/mL
Sub-visible particles (b) (4)	(b) (4)	0 part/mL	0 part/mL	0 part/mL	0 part/mL	0 part/mL	0 part/mL
Visible particles	Essentially free from visible part.	conform	conform	conform	conform	conform	conform
Extractable volume	NLT (b) (4) mL	conform	conform	conform	conform	conform	conform
Osmolality [mOsmol]	260 - 330	260	260	259	284	286	284
pH	5.0 - 6.0	4.3	4.3	4.4	5.5	5.5	5.5
Moxifloxacin Assay	(b) (4)	(b) (4)			(b) (4)		
Any unspecified degradation product	NMT (b) (4)	(b) (4)			(b) (4)		
Total degradants	NMT	(b) (4)			(b) (4)		

Table 1 from response to CR letter 10/03/2014

- The proposed drug product has pH acceptance criterion 5.0 - 6.0 (compared to 4.0 - 6.0 in the original submission 06/07/2013). The three exhibit batches of the proposed product had pH 5.5, and the three exhibit batches of the RLD had pH 4.3-4.4. The applicant provided the following justification for the difference in the pH values: Buffer capacity of blood at physiologic pH values is 38.5 mEq/L/pH, and the effect of plasma buffering is almost immediate. Intravenous infusion of 250 mL of a solution with pH of 4.3 (RLD) or solution with pH of 5.5 (Fresenius Kabi (FK)'s proposed product) will not result in appreciable blood pH change, and consequently will have no effect on drug disposition. The applicant's justification for the different pH values is acceptable.
- The mean osmolality of the proposed drug product (285 mOsmol) is 9.63% greater than the osmolality of the RLD (260 mOsmol). The applicant stated that the osmolality is within isotonic range. Internal discussion with the Division of Anti-Infective Products clinical reviewer, Dr. Yuliya Yasinskaya, indicated that this difference in osmolality is acceptable.
- The proposed drug product and RLD have different excipients to adjust tonicity and pH. The RLD has sodium chloride to adjust tonicity and hydrochloric acid and/or

sodium hydroxide to adjust pH. The proposed product has sodium acetate trihydrate and disodium sulfate to adjust tonicity and sulfuric acid to adjust pH (Table 1 and Table 3). This will result in intake of sodium, sulfate and acetate from the proposed product, as opposed to intake of sodium and chloride for the RLD.

Table 3: Comparison of compositions for the RLD and the proposed drug product, the contents per mL

FK USA's Moxifloxacin Injection		RLD's Avelox®		Function
Ingredient	Content	Ingredient	Content	
Moxifloxacin hydrochloride	(b) (4) mg/ml (corresponding to 1.6 mg/ml moxifloxacin)	Moxifloxacin hydrochloride	(b) (4) mg/ml (corresponding to 1.6 mg/ml moxifloxacin)	Active pharmaceutical ingredient
Sodium acetate trihydrate	(b) (4)	Sodium chloride	(b) (4) mL	adjusting of tonicity
Disodium sulfate	(b) (4)	N/A	N/A	adjusting of tonicity
Sulfuric acid	(b) (4)	Hydrochloric acid	qs	pH adjusting agent
-	(b) (4)	Sodium hydroxide	qs	pH adjusting agent
Water for injections	(b) (4)	Water for injections	1 mL	(b) (4)
(b) (4)				
(b) (4)				
(b) (4)				

Table 3 from response to CR letter 10/03/2014

- In response to **CR comment #2**, the applicant stated that administration of the maximum daily dose (MDD) of the proposed drug product is not expected to elevate endogenous serum levels of sodium, sulfate, bicarbonate or chloride above normal physiological levels, and thereby is not expected to have an effect on physiological disposition of moxifloxacin. However, the Applicant did not provide any additional justification about the actual disposition of moxifloxacin. Overall, the justification was inadequate.
- The following Information Request (IR) was sent to the applicant on January 12, 2015:

You have not provided adequate supportive information demonstrating that the physiological disposition of your proposed and listed drug products are similar despite the differences in the inactive ingredients. To support the approval of the biowaiver, submit strong justification and evidence that with the inclusion of sodium acetate trihydrate and disodium sulfate, the physiological disposition (i.e. metabolism and excretion) of your proposed drug product is not different than that of the listed

drug product upon administration. You may include literature references to support your justification.

- The Applicant responded to the IR on February 09, 2015 with the following justification for the differences in the inactive ingredients:
- Moxifloxacin metabolism: moxifloxacin undergoes N-sulfate conjugation (38%), glucuronidation (14%) or is excreted as unchanged drug (45%) with 20% excreted in the urine and 25% excreted in feces.
- Sodium: In the response it is stated that the MDD of the proposed product will result in a maximum daily intake of 1207 mg sodium, whereas the MDD of the RLD will result in a maximum daily intake of (b) (4) mg sodium (Reviewer's Note: RLD label states that it contains approximately 787 mg of sodium in 250 mL). Further, it is stated that 1207 mg is significantly lower than the recommended daily sodium intake (1.5 g/day) and is not expected to elevate endogenous serum sodium levels above normal physiological levels. Citing literature references, the applicant stated that variability in sodium intake is known to alter renal elimination of some drugs that are predominantly cleared by the kidneys. Moxifloxacin clearance involves a combination of hepatic metabolism and unchanged excretion. 20% moxifloxacin is excreted unchanged in urine and increase in sodium intake is not expected to affect renal elimination of moxifloxacin. Existing pharmacokinetic drug-drug interaction studies with moxifloxacin suggest lack of renal elimination-based drug interactions. The applicant's justification is *acceptable*.
However, the applicant did not clarify if this amount of sodium intake is safe under disease condition. As per internal discussion with Dr. Yasinskaya, the MDD sodium intake in the proposed drug product may have the following potential safety concerns in:
 - Elderly patients;
 - Patients on sodium-restricted diet; and,
 - Patients with co-morbidities.

The drug product label proposed by the Applicant was updated to note these safety concerns.

- Sulfate: The applicant stated that the amount of sulfate, administered with the MDD of the proposed drug product equals (b) (4) mg and falls below typical sulfate dietary intake. According to the applicant, administration of the MDD of FK Moxifloxacin Injection is not expected to elevate endogenous serum levels of sulfate above normal physiological levels. Moxifloxacin undergoes N-sulfate conjugation (38%) and based on the literature references related to sulfation, rate of sulfation may decrease with sulfate deficiency but there is no effect when sulfate is above physiological level. The applicant's justification is *acceptable*.
- Based on the literature, the applicant stated that sodium, sulfate, or acetate derived bicarbonate are not known to have an effect on glucuronidation of moxifloxacin.

- Acetate: This is a source of hydrogen ion acceptor and is metabolically converted to bicarbonate in the liver, even in the presence of severe liver disease. Acetate from the proposed product is not expected to increase endogenous levels of acetate derived bicarbonate above normal physiological levels. The amount of sodium acetate trihydrate, administered in a single MDD of the proposed product is not expected to increase renal drug clearance. The applicant's justification is *acceptable*.
- The applicant stated that addition of sodium acetate trihydrate and disodium sulfate in the aforementioned amounts will not have an effect on metabolism and excretion of moxifloxacin. Based on the information provided in response to the IR, the justification is *acceptable*.

Recommendation:

The waiver for in vivo bioavailability/bioequivalence studies for Moxifloxacin Injection, 400 mg/250 mL, is granted. From the Biopharmaceutics perspective, NDA 205572 for Moxifloxacin Injection, 400 mg/250 mL, is recommended for approval.

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/s/

VIDULA R KOLHATKAR
03/12/2015

KELLY M KITCHENS
03/12/2015

CLINICAL PHARMACOLOGY REVIEW

NDA: 205-572	Submission Date(s): 10/03/2014
Drug	Moxifloxacin
Trade Name	Moxifloxacin Injection
OCP Reviewers	Seong H, Jang, Ph.D.
OCP Team Leader	Kimberly Bergman, Pharm.D.
OCP Division	DCP4
OND division	DAIP
Sponsor	Fresenius Kabi
Relevant IND(s)	NA
Submission Type; Code	505(b)(2); Resubmission/Class 2
Formulation; Strength(s)	Injection; 400 mg/250 mL
Indication	Acute Bacterial Sinusitis, Acute Bacterial Exacerbation of Chronic Bronchitis, Community Acquired Pneumonia, Uncomplicated Skin and Skin Structure Infections (SSSI), Complicated SSSI, and Complicated Intra-Abdominal Infections
Dosage and Administration	400 mg QD (60 minutes infusion). Duration of therapy is based on indication (5 to 21 days).

This is a 505(b)(2) New Drug Application resubmission for Moxifloxacin Injection 400mg/250 mL. The FDA sent a Complete Response letter on 04/14/2014 because a request for the waiver of *in vivo* bioequivalence studies could not be granted due to incomplete supportive information (see ONDQA Review dated on 01/27/2014). The sponsor resubmitted the NDA with response to the Complete Response letter on 08/29/2014. However, the FDA did not consider the sponsor's response dated 08/29/2014 to be complete because the DMF deficiency letter dated June 24, 2013 was not addressed. The sponsor resubmitted this NDA resubmission after they have confirmed that the DMF holder has amended DMF (b) (4) in response to the DMF deficiency letter.

This application contains the information required describing the chemistry, manufacturing and control of Moxifloxacin Injection, 400 mg/250 mL. The reference listed drug (RLD) for this submission is Avelox[®] approved under NDA 21,277 and held by Bayer Healthcare. The active pharmaceutical ingredient (API) of the proposed drug product is Moxifloxacin Hydrochloride which is the same as the RLD except the sponsor uses (b) (4) form and the RLD uses the monohydrate form of the API, Moxifloxacin Hydrochloride. The inactive ingredients of the proposed drug product differ from those

listed in the RLD package insert. Different agents for isotonicity are used in the formulation and the target pH value of the solution differs with regard to the RLD. All agents are in the FDA inactive ingredient database. This application includes a request for the waiver of *in vivo* bioequivalence studies and this request is being reviewed by the Office of New Drug Quality Assessment (ONDQA) reviewer.

There is no Clinical Pharmacology information/data in this 505(b)(2) NDA. Thus, no formal Clinical Pharmacology review was made for this 505(b)(2) NDA. The labeling should be revised from the Avelox[®] labeling because the Avelox labeling includes the information of moxifloxacin oral tablets as well as moxifloxacin IV injection. The labeling recommendation is attached at the end of this review.

Seong H. Jang, Ph.D.
Clinical Pharmacology Reviewer
OTS/OCP/DCP 4

Concurrence _____
Kimberly Bergman, Pharm.D.
Clinical Pharmacology Team Leader
OTS/OCP/DCP 4

Labeling Recommendation (As of 03/10/2015)

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

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/s/

SEONG H JANG
03/10/2015

KIMBERLY L BERGMAN
03/11/2015

CLINICAL PHARMACOLOGY REVIEW

NDA: 205-572	Submission Date(s): 06/06/2013
Drug	Moxifloxacin
Trade Name	Moxifloxacin Injection
OCP Reviewers	Seong H, Jang, Ph.D.
OCP Team Leader	Kimberly Bergman, Pharm.D.
OCP Division	DCP4
OND division	DAIP
Sponsor	Fresenius Kabi
Relevant IND(s)	NA
Submission Type; Code	505(b)(2)
Formulation; Strength(s)	Injection; 400 mg/250 mL
Indication	Acute Bacterial Sinusitis, Acute Bacterial Exacerbation of Chronic Bronchitis, Community Acquired Pneumonia, Uncomplicated Skin and Skin Structure Infections (SSSI), Complicated SSSI, and Complicated Intra-Abdominal Infections
Dosage and Administration	400 mg QD (60 minutes infusion). Duration of therapy is based on indication (5 to 21 days).

This is a 505(b)(2) New Drug Application for Moxifloxacin Injection 400mg/250 mL. This application contains the information required describing the chemistry, manufacturing and control of Moxifloxacin Injection, 400 mg/250 mL. The reference listed drug (RLD) for this submission is Avelox[®] approved under NDA 21,277 and held by Bayer Healthcare. This application includes a request for the waiver of *in vivo* bioequivalence studies and this request was reviewed by the Office of New Drug Quality Assessment (ONDQA) Biopharmaceutics reviewer. The ONDQA Biopharmaceutics reviewer concluded that the waiver request cannot be granted due to incomplete supportive information (see the ONDQA Review, January 27, 2014).

There is no Clinical Pharmacology information/data submitted in this 505(b)(2) NDA thus, no formal Clinical Pharmacology review was necessary for this 505(b)(2) NDA. Additionally, a review of the Applicant's proposed labeling was not conducted under this review cycle.

Seong H. Jang, Ph.D.

Clinical Pharmacology Reviewer
OTS/OCP/DCP 4

Concurrence _____.
Kimberly Bergman, Pharm.D.
Clinical Pharmacology Team Leader
OTS/OCP/DCP 4

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/s/

SEONG H JANG
02/04/2014

KIMBERLY L BERGMAN
02/04/2014

BIOPHARMACEUTICS REVIEW
Office of New Drug Quality Assessment

Application No.:	NDA 205-572	Reviewer: Kareen Riviere, Ph.D.	
Submission Date:	6/7/2013		
Division:	DAIP	Team Leader: Angelica Dorantes, Ph.D.	
Applicant:	Fresenius Kabi	Acting Supervisor: Richard Lostritto, Ph.D.	
Trade Name:	Moxifloxacin Injection,400mg/250 mL	Date Assigned:	6/23/2013
Generic Name:	Moxifloxacin Injection	Date of Review:	1/27/2014
Indication:	for treating infections	Type of Submission: 505(b)(2) NDA	
Formulation/strengths:	Injection; 400mg/250 mL (1.6 mg/mL)		
Route of Administration:	Intravenous infusion		

SUBMISSION:
This is a 505(b)(2) New Drug Application for Moxifloxacin Injection 400mg/250 mL. The proposed indication is for treating infections.

REVIEW:
This submission includes a bioequivalence (BE) waiver request for the proposed drug product. The reference listed drug (RLD) for this submission is Avelox® approved under NDA 21277 and held by Bayer Healthcare. The focus of the Biopharmaceutics review is on the evaluation and acceptability of the data supporting the approval of the BE waiver request.

RECOMMENDATION:
ONDQA-Biopharmaceutics has evaluated the information provided in NDA 205572 for Moxifloxacin Injection and concludes that a waiver of the CFR's requirement for the submission of data from an in vivo bioequivalence study for the proposed product **cannot be granted** at this time due to incomplete supportive information.

To support the approval of the biowaiver request the Applicant should provide the following information that is lacking:

- A side to side comparison of the osmolality and pH values for the proposed and listed products,
- A justification that the human physiological disposition (i.e., metabolism and excretion) of the proposed and the listed products are similar, despite the differences in the inactive ingredients between these products.

It is noted that the above information was already requested in the 74-Day letter and up to date the Applicant has not provided this information. Also, it is noted that if the above request cannot be adequately addressed, the Applicant will be required to provide data from an *in vivo* bioequivalence study to support the approval of the proposed product.

Overall, at this time in the review process (GRMP date), due to the lack of complete information supporting the biowaiver request, from the Biopharmaceutics perspective a **complete response** is recommended for NDA 205572. However, note that if the requested information is provided before the NDA's goal date, the Biopharmaceutics recommendation will be revised as appropriate under an Addendum to this Original Review.

Kareen Riviere, Ph.D.
Biopharmaceutics Reviewer
Office of New Drug Quality Assessment

Angelica Dorantes, Ph.D.
Biopharmaceutics Team Leader
Office of New Drug Quality Assessment

cc: Dr. Richard Lostritto

ASSESSMENT OF BIOPHARMACEUTICS INFORMATION

1. Background

Drug Substance

The structure of moxifloxacin hydrochloride is shown in Figure 1.

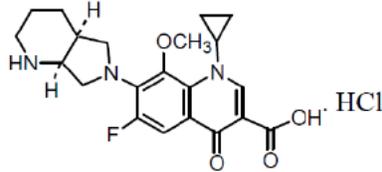


Figure 1. Chemical structure of moxifloxacin hydrochloride

Drug Product

The composition of the proposed product is displayed in Table 1.

Table 1. Composition of Moxifloxacin Injection 400mg/250 mL

Drug Product Name	Content	Function	Quality of Ingredient
Moxifloxacin Hydrochloride	1.75 mg (corresponding to 1.6 mg)	therapeutic agent	USP
Sodium Acetate Trihydrate	(b) (4)	adjusting of tonicity	USP
Disodium Sulfate (b) (4)		adjusting of tonicity	USP
Water for Injections		(b) (4)	USP
Sulfuric Acid		pH adjuster	NF

2. Biowaiver

A side-by-side comparison of the reference listed drug and the proposed drug is shown in Table 2.

Table 2. Side-by-Side Comparison of the Reference Listed and Proposed Drugs

	Reference Listed Drug	Proposed Drug Product
Name	Avelox [®]	Moxifloxacin Injection
Conditions of Use (Indications)	It is indicated for treatment of infections.	It is indicated for treatment of infections.
Dosage Form	Sterile Liquid	Sterile Liquid
Route of Administration	Intravenous Infusion	Intravenous Infusion
Active Ingredient	Moxifloxacin Hydrochloride (b) (4)	Moxifloxacin Hydrochloride (b) (4)
Strength	160 mg/100 mL (1.6 mg/mL)	400 mg/250 mL (1.6 mg/mL)
Excipients (per mL)	per mL	per mL
Sodium Acetate Trihydrate, USP	(b) (4)	(b) (4)
Sodium Chloride, USP		
Disodium Sulfate, USP (b) (4)		
Sodium Hydroxide		
Hydrochloric Acid		
Sulphuric Acid, NF		
Water for Injections, USP		

REVIEWER'S ASSESSMENT:

According to 21 CFR 320.22(b)(1), a waiver may be granted if the drug product under evaluation meets the following criteria:

- *It is a parenteral solution intended solely for administration by injection, or an ophthalmic or otic solution;*
- *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.*

The active ingredients and the concentration are similar for the reference and proposed proposed product; however, the excipients are different. Therefore, the following IR Comment was conveyed to the Applicant in the 74 day letter dated August 15, 2013:

FDA IR Comment

Provide data/justification (e.g. comparison of API solubility, drug product osmolality, and drug product pH) demonstrating that the human physiological disposition (i.e., metabolism and excretion) of the proposed products and the RLDs are similar, despite the formulation differences between these drug products.

Up to date, the Applicant has not provided a response to the above information request. Therefore, due to incomplete supportive information, the requested BE waiver for the proposed product cannot be granted at this time

To address this deficiency, the Applicant should provide a side to side comparison of the osmolality and pH values for the proposed and listed products, as well as a justification that the human physiological disposition (i.e., metabolism and excretion) of the proposed and the listed products are similar, despite the differences in the inactive ingredients between these products. If the above deficiency is not adequately addressed, the Applicant will be required to provide data from an in vivo bioequivalence study to support approval of the proposed product.

Thus at this time of the review process (GRMP date), from the Biopharmaceutics perspective, a complete response is recommended for NDA 205572 due to the lack of complete information. If the Applicant provides the requested information before the NDA's goal date, this recommendation will be revised as appropriate under an Addendum to this review.

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/s/

KAREEN RIVIERE
01/27/2014

ANGELICA DORANTES
01/27/2014