

**CENTER FOR DRUG EVALUATION AND
RESEARCH**

APPLICATION NUMBER:

205572Orig1s000

MEDICAL REVIEW(S)

Medical Officer Review

Date	March 17, 2015
From	Yuliya Yasinskaya, M.D.
Medical Team Leader	John Alexander M.D., MPH
Subject	Medical Officer Review
NDA #	205-572 Class 2 resubmission
Applicant	Fresenius Kabi
Date of Submission	October 3, 2014
PDUFA Goal Date	April 3, 2015
Proprietary Name / Established (USAN) names	Moxifloxacin Injection
Dosage forms / Strength	400 mg/250 mL
Proposed Indication(s)	<ol style="list-style-type: none"> 1. Acute Bacterial Sinusitis, 2. Acute Bacterial Exacerbation of Chronic Bronchitis 3. Community Acquired Pneumonia, 4. Uncomplicated Skin and Skin Structure Infections (SSSI), 5. Complicated SSSI 6. Complicated Intra-Abdominal Infections
Recommended:	<i>Approval contingent on the CMC, Biopharmaceutics, and Pharmacology-Toxicology review findings</i>

The submission is a class 2 resubmission following an April 4, 2014 complete response letter to the original 505(b)(2) New Drug Application for Moxifloxacin Injection 400 mg/250 mL submission dated June 6, 2013. The applicant submitted their responses to the deficiencies identified in the complete response letter and supporting information. The reference listed drug (RLD) for this application is Avelox[®], NDA 21,277 held by Bayer Healthcare.

The submission does not contain clinical data. Therefore, this clinical review is limited to the proposed product labeling. For the determination of adequacy of the applicant responses to the deficiencies listed in the complete response letter dated April 4, 2014 and approvability of this application please refer to the detailed reviews by the following disciplines: Chemistry Manufacturing and Controls (Milton Sloan, Ph.D.), Biopharmaceutics (Vidula Kolhatkar, Ph.D.), and Pharmacology-Toxicology (Terry Miller, Ph.D.).

Since the NDA is relying on FDA's previous findings of safety and effectiveness for the RLD, the labeling for this product should be based on the PLR labeling for Avelox[®], except for removal of some text that is relevant only to the oral formulation of moxifloxacin. However, the proposed formulation of moxifloxacin intravenous injection 400mg/250ml contains sodium acetate trihydrate and disodium sulfate to adjust tonicity and sulfuric acid to adjust pH, while the RLD contains sodium chloride to adjust tonicity and hydrochloric acid and/or sodium hydroxide to adjust pH. As such, the proposed formulation in a single 60 minute daily infusion dose delivers 52.5 mEq (1207 mg) of sodium, whereas RLD delivers 34.2 mEq (787 mg). The amount of sodium in the proposed formulation is high (AHA recommended daily sodium

intake for an elderly person is 1500 mg and for a healthy young adult is 2300 mg) and significantly higher than the RLD. An abrupt high sodium load from a single moxifloxacin dose delivered over 1 hour and as well as persistent additional high sodium exposure over the course of treatment (up to 21 days) constitutes a safety concern for individuals with sodium sensitivity: elderly, patients with underlying comorbidities, such as congestive heart failure, high blood pressure, metabolic syndrome, and chronic kidney disease, leading to vascular volume overload.

Given the differences in the sodium content between the RLD and moxifloxacin injection by Fresenius Kabi, this reviewer proposes to add a new language about high sodium load and additional safety language to the Warnings and Precautions, Use in Specific Populations, and Description Sections, as well as to the MedGuide:

5.9 High Sodium Load

Each unit dose of moxifloxacin injection contains 52.5 mEq (1207 mg) of sodium. Avoid use of moxifloxacin injection in patients with congestive heart failure, elderly, and those with restricted sodium intake. [see Use in Specific Populations (8) (b) (4) Description (11)].

8.5 Geriatric Use

Geriatric patients are at increased risk for developing severe tendon disorders including tendon rupture when being treated with a fluoroquinolone such as moxifloxacin. This risk is further increased in patients receiving concomitant corticosteroid therapy. Tendinitis or tendon rupture can involve the Achilles, hand, shoulder, or other tendon sites and can occur during or after completion of therapy; cases occurring up to several months after fluoroquinolone treatment have been reported. Caution should be used when prescribing moxifloxacin to elderly patients especially those on corticosteroids. Patients should be informed of this potential side effect and advised to discontinue moxifloxacin and contact their healthcare provider if any symptoms of tendinitis or tendon rupture occur [see Boxed Warning, Warnings and Precautions (5.1), and Adverse Reactions (6.4)].

Moxifloxacin injection contains 1207 mg (52.5 mEq) of sodium per unit dose. The geriatric population may respond with a blunted natriuresis to salt loading. This may be clinically important with regard to such diseases as congestive heart failure. [see Warnings and Precautions (5.9) (b) (4)].

11 DESCRIPTION

Moxifloxacin is a synthetic broad spectrum antibacterial agent for intravenous administration. Moxifloxacin, a fluoroquinolone, is available as a buffered salt of 1-cyclopropyl-7-[(S,S)-2,8-diazabicyclo[4.3.0]non-8-yl]-6-fluoro-8-methoxy-1,4-dihydro-4-oxo-3 quinoline carboxylic acid.

Moxifloxacin injection contains approximately 52.5 mEq (1207 mg) of sodium in 250 mL.

MEDICATION GUIDE

Moxifloxacin Injection, solution for Intravenous use

Tell your healthcare provider about all your medical conditions, including if you:

- Have tendon problems
- Have a disease that causes muscle weakness (myasthenia gravis)
- Have central nervous system problems (such as epilepsy)
- Have nerve problems
- Have or anyone in your family has an irregular heartbeat, especially a condition called “QT prolongation”
- Have low blood potassium (hypokalemia)
- Have a slow heartbeat (bradycardia)
- Have congestive heart failure
- Have a history of seizures
- Have kidney problems
- Have rheumatoid arthritis (RA) or other history of joint problems
- Are on salt- restricted diet
- Are pregnant or planning to become pregnant. It is not known if moxifloxacin will harm your unborn child
- Are breast-feeding or planning to breast-feed. It is not known if moxifloxacin passes into breast milk. You and your healthcare provider should decide whether you will ^{(b) (4)} moxifloxacin or breast-feed.
- Have diabetes or problems with low blood sugar (hypoglycemia)

What are the possible side effects of moxifloxacin?

• Changes in blood sodium

^{(b) (4)} blood sodium can happen in people who ^{(b) (4)} moxifloxacin injection. Tell your ^{(b) (4)} if you are on a salt-restricted diet or have congestive heart failure. Your antibiotic medicine may need to be changed.

Recommendation

- Recommended Regulatory Action

Approval, contingent on the approval recommendations from CMC, Biopharmaceutics, and Pharmacology-Toxicology reviewers and on the sponsor’s agreement to the reviewer-proposed labeling changes, is recommended.

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/s/

YULIYA I YASINSKAYA
03/17/2015

JOHN J ALEXANDER
03/17/2015

Division Director Decisional Memo

Date	(electronic stamp)
From	Sumathi Nambiar MD MPH
Subject	Division Director Decisional Memo
NDA #	205572
Applicant Name	Fresenius Kabi USA, LLC
Date of Submission	June 6, 2013
PDUFA Goal Date	April 7, 2014
Established (USAN) Name	Moxifloxacin Injection
Dosage Forms / Strength	Intravenous Solution, 400 mg/250 mL
Proposed Indications	Acute Bacterial Sinusitis Acute Bacterial Exacerbation of Chronic Bronchitis Complicated Intra-abdominal Infections Complicated and Uncomplicated Skin and Skin Structure Infections Community Acquired Pneumonia
Recommended Action:	Complete Response

Material Reviewed/Consulted	Names of Discipline Reviewers
Action Package including:	
Pharmacology Toxicology Review	Terry Miller PhD
Chemistry Manufacturing and Controls Review	Milton Sloan PhD
Biopharmaceutics Review	Kareen Riviere PhD
Cross-Discipline Team Leader Review	Dorota Matecka PhD
Medical Officer Review	Yuliya Yasinskaya MD
Statistical Review	Christopher Kadoorie PhD
Product Quality Review	Neal Sweeney PhD
Microbiology Review	Kerry Snow MS
Clinical Pharmacology Review	Seong Jang PhD
Labeling Review	Aleksander Winiarski Pharm D

1.0 Introduction

NDA 205572, Moxifloxacin Injection 400 mg/250 mL submitted by Fresenius Kabi, USA, LLC provides for a new formulation of injectable moxifloxacin to be used for the treatment of the same indications as listed in the drug labeling for Avelox® (moxifloxacin hydrochloride) Injection. This NDA was submitted as a 505(b)(2) application and the listed drug is Avelox® (moxifloxacin hydrochloride) Injection, 400 mg/250 mL (NDA 21277), held by Bayer HealthCare Pharmaceutical. Avelox® (moxifloxacin hydrochloride) Injection is approved for the treatment of the following infections:

- Acute Bacterial Sinusitis
- Acute Bacterial Exacerbation of Chronic Bronchitis
- Community Acquired Pneumonia
- Uncomplicated Skin and Skin Structure Infections
- Complicated Skin and Skin Structure Infections
- Complicated Intra-abdominal Infections

2.0 Background

The proposed drug product, Moxifloxacin Injection, 400 mg/250 mL, is a new formulation of moxifloxacin hydrochloride intravenous solution supplied in a 300 mL **freeflex**® bag. The drug product differs from the listed drug in the excipients used in the formulation, specifically, the tonicity and pH adjusters. No clinical data have been submitted in this application. The majority of the information submitted in the NDA relates to the chemistry, manufacturing and controls used in the manufacture of the proposed moxifloxacin drug product. The applicant has requested a waiver for conducting in-vivo bioequivalence studies based on 21 CFR 320.22 (b).

A 74-day filing letter was issued on 08/15/2013. The filing letter included an information request to provide data/justification that the human physiological disposition (i.e. metabolism and excretion) of the proposed and listed products are similar, despite the differences in the inactive ingredients. An information request pertaining to nonclinical and product quality data was sent to the applicant on 10/22/2013. The applicant responded to the information requests on 02/11/2014. This submission was not reviewed in this review cycle.

The review team has completed their reviews of this application. For a detailed discussion of NDA 205572, please refer to discipline specific reviews and the Cross-Discipline Team Leader Review.

3.0 Product Quality

The Chemistry, Manufacturing and Controls (CMC) reviewer for this application is Milton Sloan, Ph.D., and the product quality microbiology reviewer is Neal Sweeney, Ph.D.

Moxifloxacin hydrochloride drug substance is manufactured by (b) (4). (b) (4) For all drug substance information, reference is made to Drug Master File (DMF) (b) (4) held by (b) (4). The DMF has been previously reviewed and is adequate to support this NDA.

The proposed drug product Moxifloxacin Injection, 400 mg/250 mL, supplied in **freeflex**[®] bags contains moxifloxacin hydrochloride (b) (4) and sodium acetate trihydrate, disodium sulfate, sulfuric acid, and water for injection. All excipients used in the manufacture of the drug product meet the requirements of the current USP/NF.

The drug product is manufactured at the Fresenius Kabi Norge AS facility in Norway. In addition, several other facilities are involved (and are listed in the NDA) in chemical and microbiological testing of the proposed drug product. An overall recommendation of “Acceptable” has been issued by the FDA Office of Compliance for all facilities involved in manufacture of the drug substance and the drug product.

The applicant has proposed a (b) (4)-month expiration period based on the stability data of three pilot batches at 6 months accelerated (40 °C/≤ 25 % RH) and 12 months long-term (25°C/40 % RH). No determination has been made on the proposed expiration period at this time.

The **freeflex**[®] container closure system for Moxifloxacin Injection consists of three components: (b) (4). Details about the composition and component manufacturing methods are provided in the referenced type III DMF (b) (4) (same as DMF (b) (4) filed with CBER). The proposed container closure system was evaluated by the applicant for safety and suitability for the proposed drug product.

A number of deficiencies were identified by Dr. Sloan regarding the extractable/leachable studies reported in the NDA. Specifically, Dr. Sloan noted that the extractable assessment studies were not adequately designed to establish the maximum accumulation values of extractables. In addition, inadequate information was provided on levels of leachables observed in batches of the proposed drug product to demonstrate the quality or purity of drug product is not altered by the container closure system. These deficiencies were communicated to the applicant on October 22, 2013.

The drug product specification, which includes tests for appearance, clarity, degree of coloration, visible particles, particle contamination (USP <788>), extractable volume (USP <1>), pH,

osmolality, identification, assay, impurities, bacterial endotoxins, sterility, and residual solvents has been evaluated in detail. Dr. Sloan has identified a number of deficiencies with the drug product and these will be communicated to the applicant in the complete response letter.

Dr. Sloan concluded that sufficient information has not been provided in the NDA to assure identity, strength, purity, and quality of the drug product. He recommended that the NDA not be approved for the following reasons:

1. Insufficient information was submitted to evaluate the requested bioequivalence waiver for the proposed product.
2. The DMF (b) (4) referenced for the 300 mL **freeflex**[®] bag packaging system to support the NDA is deficient.
3. Safety of the observed leachables from the proposed container closure system has not been established.

The sterilization validation, bioburden specification and endotoxin specification were reviewed by Dr. Neal Sweeney, the Product Quality Microbiology Reviewer and found to be acceptable. Dr. Sweeney recommended that the NDA be approved from a product quality standpoint.

4.0 Pharmacology/Toxicology

The pharmacology/toxicology reviewer for this application is Terry Miller PhD. Dr. Miller does not recommend approval of this application, as adequate safety information was not provided regarding three leachables (b) (4) identified in 6-month migration studies with moxifloxacin in the proposed **freeflex**[®] container system. The applicant also needs to provide data on potential leachables with longer term studies. The data submitted thus far were based on 6-month stability studies.

Dr. Miller conducted an evaluation of the DMF for the **freeflex**[®] IV bag (b) (4) Migration studies showed leachables from the container closure system, including (b) (4) No toxicology data were provided to support the safety of these leachables. These deficiencies were communicated to the DMF holder on 06/24/2013. The DMF holder has not yet responded to these deficiencies.

The proposed formulation contains two excipients, sodium acetate and trihydrate and disodium sulfate, that are not included in the listed drug. Both excipients have been approved for use in several intravenous products and hence no new pharmacology/toxicology information was necessary to support the proposed formulation. All impurities are within the USP and/or API specifications of NMT (b) (4) %.

I agree with Dr. Miller's recommendation that the application not be approved as adequate information has not been submitted to assess the safety of the three leachable compounds

(b) (4)

5.0 Biopharmaceutics

Kareen Riviere, PhD is the biopharmaceutics reviewer for this application. The applicant had requested a waiver of the requirement for submission of data from an in vivo bioequivalence study. Dr. Riviere concluded that the biowaiver request cannot be granted due to inadequate information. To support the approval of the biowaiver request, Dr. Riviere recommended that the applicant provide the following information:

1. A side -by-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 listed products are similar, despite the differences in the inactive ingredients.

This information was also requested in the 74-day letter sent to the applicant on 08/15/2013.

I agree with Dr. Riviere's recommendation for a complete response as the applicant has not submitted adequate data to support the biowaiver request.

6.0 Clinical Microbiology

Kerry Snow, MS, is the clinical microbiology reviewer for this application. No new clinical microbiology information was submitted in this application. Mr. Snow stated that no recommendation is made regarding approval of this application and no labeling changes are proposed at this time.

7.0 Clinical Pharmacology

Seong Jang, PhD, is the clinical pharmacology reviewer for this application. A clinical pharmacology review was not performed as no new clinical pharmacology data were submitted with this application.

8.0 Clinical Efficacy/Safety

Yuliya Yasinskaya, MD, is the clinical reviewer for this application. No new clinical or statistical information was submitted in this NDA. Dr. Yasinskaya recommends a complete response due to lack of biopharmaceutic information to support a biowaiver and the lack of toxicology information for the identified leachables in the proposed container closure system.

Christopher Kadoorie, PhD, is the statistical reviewer for this application. No new clinical data were submitted with this application. Dr. Kadoorie deferred a decision on this application to other review disciplines.

9.0 Labeling

Robin Duer, MBA, BSN, RN from the Division of Medical Policy Programs (DMPP) is the patient labeling reviewer. Review of the Medication Guide was deferred during this review cycle as a complete response action is being taken on the application. Christine Corser, PharmD, from the Office of Prescription Drug Products (OPDP) will provide labeling comments during the subsequent review cycle as a complete response action is being taken at this time. Aleksander Winiarski, PharmD, from the Division of Medication Error Prevention and Analysis (DMEPA) has provided a review of the labeling has provided some recommendations to improve the proposed labeling. As the application is not being approved during this review cycle, labeling discussions with the applicant will take place during the next review cycle and recommendations provided by Dr. Winiarski were communicated to the applicant on 04/04/2014.

10.0 Pediatrics

Under the Pediatric Research and Equity Act (PREA), all applications for new active ingredients, new indications, new dosage forms, new dosing regimens, or new routes of administration are required to contain an assessment of the safety and effectiveness of the product for the claimed indication(s) in pediatric patients unless the requirement is waived, deferred or inapplicable. As none of these criteria are applicable, this NDA is exempt from PREA requirements.

11.0 Other Regulatory Issues

The reference listed drug, NDA 21277 Avelox® (moxifloxacin hydrochloride) Injection, 400 mg/250 mL, has the following unexpired patents listed in the Orange Book:

- US Patent No. 5,607,942 - Expiry Date: March 4, 2014
- US Patent No. 5,849,752 - Expiry Date: December 5, 2016
- US Patent No. 6,548,079 - Expiry Date: July 25, 2020

Fresenius Kabi USA, LLC has submitted a Paragraph III certification [per 21 CFR 314.50(i)(1)(i)(A)(3)] and stated that “according to the Orange Book, U.S. Patent No. 5,607,942, which is assigned on its face to Bayer Aktiengesellschaft and listed in the Orange Book for the reference listed drug, will expire on March 4, 2014. Fresenius Kabi is not currently seeking approval of this NDA for Moxifloxacin Injection, 400 mg/250 mL, until after the expiration of this patent”. Fresenius Kabi also submitted Paragraph IV certifications [per 21 CFR

314.50(i)(1)(i)(A)(4)] regarding the other two patents (No. 5,8497,52 and No. 6,5480,79) stating that they are invalid, unenforceable, and/or will not be infringed by the manufacture, use, or sale of Moxifloxacin Injection, 400 mg/250 mL, which is the subject of the current application.

To comply with 21 CFR 314.52(b), Fresenius Kabi notified Bayer on August 7, 2013 that they had submitted an NDA under Section 505(b)(2) of the Federal Food, Drug, and Cosmetic Act along with a certification under Section 505(b)(2)(A)(iv) ("Paragraph IV"), requesting approval to market Moxifloxacin Injection, 400 mg/250 mL. In an amendment dated November 12, 2013, the applicant certified that Bayer Pharmaceuticals had not filed suit against Fresenius Kabi for patent infringement.

This application was not presented to the Anti-Infective Drugs Advisory Committee (AIDAC) as there were no issues requiring input from the AIDAC.

12.0 Recommended Regulatory Action

I agree with the recommendations made by the review team that a complete response action should be taken as the applicant has not submitted adequate information to assess the safety and effectiveness of the product. The key deficiencies are listed below:

Biopharmaceutics:

1. Provide adequate comparative physicochemical property data such as comparison of API solubility, osmolality, and pH of the proposed drug product and the listed product using at least 3 production lots (if available) of the proposed drug product and three commercial lots of the listed drug product. The measurements should be done in triplicate for each lot tested.
2. Provide adequate data/justification demonstrating that the human physiological disposition (i.e., metabolism and excretion) of the proposed drug product and the listed drug product is similar, despite the formulation differences between these drug products. You may include published literature references to support your justification.

Pharmacology-Toxicology:

3. Provide additional toxicity information for each of the three identified leachables (b) (4) and the "related" compounds from nonclinical studies you may have conducted, from studies described in published literature, or from public toxicity databases. Provide a more detailed rationale for your selection of "related" compounds used to determine the Permitted Daily Exposure (PDE) for each of the identified leachables for which no toxicity information is available.

Product Quality:

4. A DMF deficiency letter was sent to the DMF holder on June 24, 2013. Please follow-up with the DMF holder to ensure that the deficiencies have been addressed.
5. Leachable data on one batch at six months is insufficient to justify the exclusion of leachable testing in the drug product specification. Establish tentative acceptance criteria for four leachables, (b) (4) in the drug product specification and provide justification for the proposed acceptance criteria. Include monitoring leachable levels on stability until end of shelf-life for the three ongoing registration stability batches, and for each annual batch as part of post-approval stability protocol. Test the leachable levels in the three registration stability batches and the batch for which the six month leachable data were provided. If data from a sufficient number of commercial scale batches show negligible levels of leachables or data are generated to provide accurate PDE for each leachable you may propose to eliminate the leachable test.
6. The conditions used for extraction testing of 300 mL *free/flex* bags are not adequate to establish appropriate acceptance criteria for leachables in the container closure raw material. Specifically, you did not conduct studies in alcohol and at pH 2 solution, and studies were done only over 1 hour. Using methods that meet or exceed USP, determine total extractables for drug product contact materials (b) (4) in a one-time extraction study in water for injection (WFI), pH 2, pH 8.0, and alcohol. Continue refluxing in the extraction media at hourly intervals until the extractables are exhausted from material and calculate new safety factors for each using these values. Report these data to your type III DMF (b) (4).
7. The proposed drug product specification includes one identification test by HPLC. Per ICH Q6A, identification solely by a single chromatographic retention time is not regarded as being specific. Include a second chromatographic procedure where the separation is based on different principles, or include a combination of tests into a single procedure (e.g. HPLC/UV diode array, HPLC/MS, etc.). If a single method is used, propose a specific identification test such as infrared spectroscopy.
8. You have indicated that at your drug product formulation pH, moxifloxacin exists as moxifloxacin hydrogen sulfate, not as moxifloxacin HCl, but have not demonstrated that the moxifloxacin hydrogen sulfate salt form is functionally equivalent to Avelox I.V. (moxifloxacin HCl in (b) (4) injection). In addition to pH and osmolality, the side by side comparison between Moxifloxacin Injection and the listed drug product, Avelox I.V. should include a comparison of sodium content, chloride content, hydrogen sulfate content, and isotonicity calculations.

9. You have indicated that at pH 4.0-6.0, the sulfuric acid is (b) (4). Provide information on acid base equilibria over the 4.0-6.0 pH range (and in particular over the 4.1-4.6 pH range) to substantiate the above claim.
10. You have indicated that precipitation occurs in the drug product at pH (b) (4), but have specified a pH range of (b) (4) 6.0 for the drug product formulation. The lower limit of the pH range should be revised to pH 4.5 or higher to prevent precipitation. As this could result in a different pH range from that of the listed drug product, additional justification should be provided to support the comparability of your product to the listed product.
11. The exhibit batches show an underage. Provide the target fill volume, target fill weight and formulation density. Provide the target assay for each drug product unit (as a percentage of label claim) and additional clarification on weight loss determination.
12. You have submitted an in-house analytical method (b) (4) test for the identification, assay at release, and assay at stability for moxifloxacin and impurities of moxifloxacin in the finished drug product. Provide the complete analytical method with details of the method and any modifications to the use for identification, release and stability. Details such as sampling procedure for release testing, detector sensitivity, flow rate, sample preparation, standard preparation, assay preparation, injection volume, etc. should be included. The limits of detection (LOD) and quantitation (LOQ) should also be described in the method. The LOD and LOQ should be measured with respect to the label. Additionally, the analytical calculations appear to be based on a moxifloxacin hydrochloride conversion factor which may be a less precise determination than with moxifloxacin hydrogen sulfate.
13. Include specifications for specified degradants. Revise the term (b) (4) to “Any unspecified degradations product”, and revise your acceptance criterion for any unspecified degradation product to NMT (b) (4) %.
14. Replace the term of “total impurities” with “total degradants” and revise your acceptance criterion for total degradation product to NMT (b) (4) %. Explain why degradants less than (b) (4) % are not included in the total degradant calculation.
15. Revise the acceptance criterion for Extractable Volume in Container to the actual nominal value. The specification should state: NLT (b) (4) mL complies with current USP <1> of NLT labeled volume.

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/s/

SUMATHI NAMBIAR
04/04/2014

Cross-Discipline Team Leader Review

Date	(electronic stamp)
From	Dorota Matecka, Ph.D.
Subject	Cross-Discipline Team Leader Review
NDA #	205572
Applicant	Fresenius Kabi, Inc.
Date of Submission	June 6, 2013
PDUFA Goal Date	April 7, 2014
Proprietary Name / Established (USAN) names	Moxifloxacin Injection* (moxifloxacin)
Dosage forms/Strength	Intravenous Solution, 400 mg/250 mL
Proposed Indication(s)	1. Acute Bacterial Sinusitis, 2. Acute Bacterial Exacerbation of Chronic Bronchitis 3. Community Acquired Pneumonia 4. Uncomplicated Skin and Skin Structure Infections (SSSI) 5. Complicated SSSI 6. Complicated Intra-Abdominal Infections
Recommended:	Complete Response

* No proprietary/trade name was proposed for the drug product

1. Introduction

This 505(b)(2) NDA submitted by Fresenius Kabi, Inc. provides for a new injectable formulation of moxifloxacin to be used for the treatment of the same infections as listed in the listed drug labeling. The listed drug for this 505(b)(2) NDA is Avelox® (moxifloxacin) Injection, 400 mg/250 mL, manufactured by Bayer HealthCare Pharmaceuticals and approved in 2001 via NDA 21277. The drug product proposed via the current NDA, Moxifloxacin Injection, 400 mg/250 mL, is a new formulation of moxifloxacin hydrochloride intravenous solution supplied in a 300 mL freeflex® bag. Fresenius Kabi's Moxifloxacin Injection differs from the listed drug in the excipients used in the formulation, specifically, the tonicity and pH adjusters.

There is no IND associated with the application and no clinical data have been submitted. The applicant is relying on previous findings of efficacy and safety for Avelox® Injection for approval of this product. The majority of the submitted information submitted in the NDA relates to the chemistry, manufacturing and controls used in the manufacture of the proposed moxifloxacin drug product. In view of the similarities between the proposed and listed drugs, a biowaiver for conducting in-vivo bioequivalence studies was requested by the applicant on the basis of 21 CFR 320.22 (b): "a drug product's in vivo bioavailability or bioequivalence may be considered self-evident".

2. Background

Moxifloxacin hydrochloride is a synthetic fluoroquinolone antibacterial drug that can be administered orally or intravenously. The bactericidal action of moxifloxacin results from inhibition of the topoisomerase II (DNA gyrase) and topoisomerase IV required for bacterial DNA replication, transcription, repair, and recombination. It appears that the C8-methoxy moiety contributes to enhanced activity and lower selection of resistant mutants of Gram-positive bacteria compared to the C8-H moiety. The presence of the bulky bicycloamine substituent at the C-7 position prevents active efflux, associated with the *NorA* or *pmrA* genes seen in certain Gram-positive bacteria.

Moxifloxacin hydrochloride has been previously approved in a variety of dosage forms, such as tablets, IV solution and ophthalmic solution. The current 505(b)(2) NDA provides for a new IV formulation of moxifloxacin hydrochloride to be used for the treatment of the same infections as listed in the listed drug labeling. As discussed above, the proposed drug product by Fresenius Kabi, Moxifloxacin Injection, 400 mg/250 mL, has the same drug substance, concentration, dosage form, route of administration, and indications as Avelox[®] Injection. Due to the difference in the formulation (i.e., a change in the excipients not permitted per 314.94(a)(9)(iii)), this application was submitted as 505(b)(2) application and not as a 505(j) application.

3. CMC/Device

The CMC reviewer was Milton Sloan, Ph.D., and the product quality microbiology reviewer was Neal Sweeney, Ph.D. Their findings are summarized below.

Moxifloxacin hydrochloride drug substance is manufactured by (b) (4).
For all drug substance information reference is made to DMF (b) (4) held by (b) (4). A letter of authorization (LOA) is included in the NDA submission. The DMF was previously reviewed and is adequate to support this NDA.

The proposed drug product is a new formulation of moxifloxacin injection solution. Moxifloxacin Injection, 400 mg/250 mL, supplied in **freeflex**[®] bags contains moxifloxacin hydrochloride (b) (4) as a drug substance/active ingredient and the following excipients: sodium acetate trihydrate, disodium sulfate, sulfuric acid, and water for injection. All excipients used in the manufacture of Fresenius Kabi's drug product meet the requirements of the current USP/NF.

The manufacturing process consists of (b) (4)

(b) (4)

(b) (4)

(b) (4) were reviewed by the Product Quality Microbiology Reviewer, Dr. Neal Sweeney who recommended this NDA for approval from the product quality microbiology standpoint (review dated February 10, 2014 in DARRTS).

The drug product is manufactured at the Fresenius Kabi Norge AS facility in Norway. In addition, several other facilities will be involved (and are listed in the NDA) in chemical and microbiological testing of the proposed drug product. An overall recommendation of “Acceptable” has been issued by the Office of Compliance for all those facilities involved in manufacture of the drug substance and the drug product.

The drug product specification, which includes tests for appearance, clarity, degree of coloration, visible particles, particle contamination (USP <788>), extractable volume (USP <1>), pH, osmolality, identification, assay, impurities, bacterial endotoxins, sterility, residual solvents has been evaluated in detail and a number of deficiencies identified. These deficiencies and requests for further clarifications will be included in the Complete Response letter.

Fresenius Kabi has proposed a (b) (4) month expiration period based on the stability data of three pilot batches at 6 months accelerated (40 °C/≤ 25 % RH) and 12 months long-term (25°C/40 % RH). Based on their proposed test attributes and acceptance criteria, the drug product remained relatively stable. No determination has been made on the proposed expiration period at this time. The proposed storage condition in the NDA states (b) (4) however, the USP controlled room storage statement is “Store at 20-25°C (68-77°F)”. (b) (4) [see USP Controlled Room Temperature] will be recommended to be used in all parts of labeling.

The **freeflex**® container closure system for Moxifloxacin Injection consists of (b) (4)

(b) (4)

The 300 mL infusion bag is manufactured without (b) (4) latex or PVC material. The labeling information is printed directly on the primary bag using the (b) (4)

The detailed composition of the components and component manufacturing methods are provided in the referenced type III DMF (b) (4) (which is the same as DMF (b) (4) filed with CBER). The proposed container closure system was evaluated by the applicant for safety and suitability for the proposed drug product. A number of deficiencies were identified by Dr. Sloan regarding the extractable/leachable studies reported in the NDA. Specifically, Dr. Sloan

noted that the extractable assessment studies were not adequately designed to establish the maximum accumulation values of extractables. In addition, inadequate information was provided on levels of leachables observed in batches of the proposed drug product. These deficiencies were communicated to the Applicant on October 22, 2013; however, they have not been addressed.

Dr. Sloan concluded that sufficient information has not been provided in this NDA to assure identity, strength, purity, and quality of the drug product and, therefore, is not recommended for approval from CMC perspective. The list of deficiencies to be included in the Complete Response letter is included in the CMC review (dated February 13, 2014 in DARRTS).

4. Nonclinical Pharmacology/Toxicology

Terry Miller, Ph.D. was the pharmacology/toxicology reviewer for this application. The pharmacology/toxicology review focused on a safety assessment of the proposed new injectable formulation of moxifloxacin and suitability and safety of the proposed container closure system. Dr. Miller's findings and recommendations are summarized below.

Fresenius Kabi's moxifloxacin for injection is intended to be a near copy of the listed drug, Avelox® Injection, with an identical active ingredient (moxifloxacin), drug strength (1.6 mg/mL) and route of administration. However, in comparison with the listed drug, the proposed drug formulation will include two additional excipients ((b) (4) mg of sodium acetate trihydrate, and (b) (4) mg of disodium sulfate), and eliminate one excipient (sodium chloride) from the final drug formulation. Both sodium acetate and disodium sulfate have been approved for use in several intravenous drug products (as identified in the FDA "Inactive Ingredient Search for Approved Drug Products" database). No new pharmacology or toxicology information was submitted, or necessary in support of this new formulation. At this time, no new drug substance impurities have been identified. All impurities were within USP and/or API specifications of NMT (b) (4) %.

The proposed container closure system for the proposed moxifloxacin formulation **freeflex**® IV bag has been used/approved for several other drugs such as Zyvox® injection (linezolid; NDA 21131; Pfizer, Inc.) and Reclast® injection (zoledronic acid; NDA 21817), and several other approved generic drugs including Levofloxacin in 5% dextrose injection (ANDA 200674; APP Pharmaceuticals). In addition, this bag also been approved for use with Voluven® infusion (hydroxyethyl starch; NDA BN070012) for plasma replacement in hypovolemic patients. Despite its use in several approved drugs, a concern for the systemic safety of four leachables found in at least two drug products packaged within **freeflex**® bags has emerged within the Division of Anesthesia, Analgesics and Addiction Products (DAAAP) in 2012/2013, leading their reviewing toxicologists to recommend that applications not be approved because of the presence of unqualified leachable compounds of unknown toxicologic risk within the drug products [Naropin® Injection (NDA 20533/S-026) and Acetaminophen Injection (NDA 204767)]. The reviewing toxicologists for these applications, required the applicant to conduct additional whole animal, repeat dose toxicology study(ies) to determine the toxicology profile for each of these leachables (via an Information Request forwarded to

the DMF (b) (4) holder). To date, none of the required information or completed study reports have been submitted to DMF (b) (4). Because 3 of the 4 unqualified leachables ((b) (4)) also appear in migration studies with the currently proposed drug product, Moxifloxacin Injection, the required toxicology studies also pertain to the current NDA and should be completed and submitted to the DMF or NDA for review before any approval decision for this NDA can be considered. Detailed comments requesting these data were forwarded to Fresenius Kabi on October 22, 2013; however, they were not addressed at the time of the pharmacology/toxicology review.

Based on the above evaluation, Dr. Terry Miller has concluded that from the nonclinical pharmacology standpoint, the NDA cannot be recommended for approval at this time until all the deficiencies are adequately addressed (for details refer to the review dated February 4, 2014 in DARRTS).

5. Clinical Pharmacology/Biopharmaceutics

Kareen Riviere, Ph.D., was the biopharmaceutics reviewer and Seong Jang, Ph.D., was the clinical pharmacology reviewer for this application. Their findings and recommendations are summarized below.

This NDA includes a bioequivalence (BE) waiver request for the proposed drug product (referring to the listed drug, Avelox® Injection approved under NDA 21277). The focus of the biopharmaceutics review is on the evaluation and acceptability of the data supporting the approval of the BE waiver request.

ONDQA-Biopharmaceutics has evaluated the information provided in the current NDA for Moxifloxacin Injection and concludes that a waiver of the CFR 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; and
- 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.

Dr. Riviere noted that the above information was requested in the 74-Day letter; however, the Applicant did not provide this information. It was also 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. Therefore, Dr. Riviere recommended Complete Response to be issued for this NDA (refer to the review dated January 27, 2014).

The Clinical Pharmacology Reviewer, Dr. Seong Jang, stated that since no new clinical pharmacology data were submitted by the Applicant in this NDA, no formal Clinical Pharmacology review was necessary for this 505(b)(2) NDA, and, in addition, a review of the Applicant's proposed labeling was not conducted under this review cycle (review dated February 4, 2014 in DARRTS).

6. Clinical Microbiology

Kerry Snow, MS, was the clinical microbiology reviewer for this application.

No new clinical microbiology information was submitted with this application; therefore, Mr. Snow stated that no recommendation is made regarding approval of this application and no labeling changes are proposed at this time (refer to the microbiology dated February 5, 2014 in DARRTS).

7. Clinical/Statistical – Efficacy

Yuliya Yasinskaya, MD, was the clinical reviewer, and Christopher Kadoorie, Ph.D., was the statistical reviewer for this NDA.

Dr. Yasinskaya stated that there were no Clinical Pharmacology, Clinical Microbiology, or Clinical/Statistical information/data submitted in this NDA. In addition, she noted that the biopharmaceutics and pharmacology toxicology reviewers did not recommend approval due to incomplete information submitted in the NDA and inadequate information regarding safety risk assessment for leachables from the proposed **freeflex**[®] container.

Therefore, from a clinical standpoint, Dr. Yasinskaya recommended Complete Response for this application due to the lack of supporting information for a biopharmaceutics waiver and toxicology safety risk assessment for the identified leachables in the proposed container closure system (refer to review dated February 5, 2014 in DARRTS).

Dr. Kadoorie stated that there were no statistical issues identified for this application as there were no clinical studies submitted in this NDA (review dated March 19, 2014 in DARRTS).

8. Safety

The applicant is relying on the previous findings of safety for the listed drug, Avelox[®] Injection. However, as stated above, the clinical reviewer of this NDA, Dr. Yasinskaya, recommended Complete Response for this application due to the lack of supporting information for a biopharmaceutics waiver and toxicology safety risk assessment for the identified leachables in the proposed container closure system (review dated February 5, 2014 in DARRTS).

9. Advisory Committee Meeting

There was no Advisory Committee Meeting for this application (the product is not an NME).

10. Pediatrics

The drug product proposed via this 505(b)(2) NDA does not contain a new active ingredient and is not a new dosage form. No new indication is proposed and no new dosing regimen is proposed. There is no new route of administration associated with the new product. For these reasons, the Pediatric Research Equity Act (PREA) (21 U.S.C. 355c), does not apply to this application. No pediatric studies will be required as a condition of approval.

11. Other Relevant Regulatory Issues

No clinical studies/trials were conducted in support of this NDA. Therefore, no inspection request was sent to the Office of Scientific Investigations (OSI).

The reference listed application, NDA 21277 Avelox® (moxifloxacin) Injection, 400 mg/250 mL, has the following unexpired patents listed in the Orange Book:

- US Patent No. 5,607,942 - Expiry Date: March 4, 2014
- US Patent No. 5,849,752 - Expiry Date: December 5, 2016
- US Patent No. 6,548,079 - Expiry Date: July 25, 2020

Fresenius Kabi has submitted Paragraph III certification [per 21 CFR 314.50(i)(1)(i)(A)(3)] and stated that “according to the Orange Book, U.S. Patent No. 5,607,942, which is assigned on its face to Bayer Aktiengesellschaft and listed in the Orange Book for the reference listed drug, will expire on March 4, 2014. Fresenius Kabi is not currently seeking approval of this NDA for Moxifloxacin Injection, 400 mg/250 mL, until after the expiration of this patent”. Fresenius Kabi also submitted Paragraph IV certifications [per 21 CFR 314.50(i)(1)(i)(A)(4)] regarding the other two patents (No. 5,849,752 and No. 6,548,079) stating that they are invalid, unenforceable, and/or will not be infringed by the manufacture, use, or sale of Moxifloxacin Injection, 400 mg/250 mL, which is the subject of the current application.

To comply with 21 CFR 314.52(b), Fresenius Kabi, Inc. notified Bayer on August 7, 2013 that they had submitted an NDA to the FDA under Section 505(b)(2) of the Federal Food, Drug, and Cosmetic Act along with a certification under Section 505(b)(2)(A)(iv) (“Paragraph IV”), requesting approval to market Moxifloxacin Injection, 400 mg/250 mL [Fed Ex tracking receipt (by email dated August 7, 2013 was submitted to the NDA via amendment on November 12, 2013)]. In addition, in the amendment dated November 12, 2013, the Applicant

certified that Bayer Pharmaceuticals has not filed suit against Fresenius Kabi for patent infringement.

12. Labeling

The proposed labeling and labels for Moxifloxacin Injection, 400 mg/250 mL, were submitted in the NDA. No trade name was proposed for the drug product.

The Division of Medication Errors Prevention and Analysis (DMEPA) evaluated the proposed container and carton labels and package insert for areas of vulnerability that could lead to medication errors and provided several recommendations for the overwrap and bag labels (refer to the review dated December 17, 2013 in DARRTS).

The Office of Prescription Drug Promotion (OPDP) indicated they will provide comments regarding labeling for this application during a subsequent review cycle in the labeling (due to Complete Response being planned in this cycle). In addition, the Division of Medical Policy Programs (DMPP) also indicated that a final review of the patient labeling will be performed after the Applicant submits a complete response to the Complete Response letter.

Due to the Complete Response recommendation, a comprehensive review of the labeling and labels was not performed in this review cycle and no comments were forwarded to the Applicant at the time of this review.

13. Recommendations/Risk Benefit Assessment

- Recommended Regulatory Action

I concur with the recommendation of the review team that Complete Response should be issued for this NDA.

- Risk Benefit Assessment

The risk-benefit assessment for this application focused on the significant biopharmaceutics, CMC and safety toxicology issues identified during the review cycle, as follows:

- Insufficient information to evaluate the requested bioequivalence waiver for the proposed product has been submitted.
- DMF (b) (4) referenced for the 300 mL **freeflex**[®] bag packaging system to support this NDA remains deficient.
- Safety of the observed leachables from the proposed container closure system has not been established.

- The extractable assessment studies were not adequately designed to establish the maximum accumulation values of extractable and thereby the worst case potential to enable the safety evaluation/qualifications.
- A number of deficiencies regarding the drug product specification (tests, analytical procedures, and acceptance criteria) have been identified.

- Recommendation for Postmarketing Risk Evaluation and Management Strategies

Not applicable.

- Recommendation for other Postmarketing Study Commitments

Not applicable.

- Recommended Comments to Applicant

As stated above, the overall recommendation for this NDA is Complete Response. This conclusion is based on recommendations from all disciplines involved in the review of this application. The following deficiencies should be included in the Complete Response letter:

Deficiencies Previously Communicated to the Applicant:

Biopharmaceutics:

1. 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 product and the reference product is similar, despite the formulation differences between these drug products.

Pharmacology/Toxicology:

2. Your NDA does not contain adequate safety justification for the systemic toxicity of three identified leachables from your proposed drug product packaged in the **freeflex**[®] container system. The permissible daily exposure approach in the submitted toxicological risk assessment was deemed inadequate as there are insufficient data to support the extrapolation of safety from related compounds.
3. The referenced Master File (MF#: (b) (4)) contains a number of deficiencies that require additional information. These deficiencies were previously communicated to the Master File holder and will need to be addressed before any decision on approval can be considered.

CMC:

4. With respect to moxifloxacin injection in 300 mL *freeflex* bags, you have only provided leachable data on one batch at 6 months. The amount of data provided is insufficient to justify the exclusion of leachable testing in the drug product specification. Establish tentative acceptance criteria for four leachables, (b) (4) in the drug product specification and provide justification for the proposed acceptance criteria. Include monitoring leachable levels on stability until end of shelf-life for the 3 ongoing registration stability batches, and for each annual batch as part of post-approval stability protocol. If data from a sufficient number of commercial scale batches show negligible levels of leachables or data is generated to provide accurate PDE for each leachable as requested in the DMF deficiency letter, you may propose to eliminate the leachable test. It will be valuable to test the leachable levels in the 3 registration stability batches and the batch for which the 6 month leachable data was provided, and report the data to the NDA during this review cycle.
5. The conditions used for extraction testing of 300 mL *freeflex* bags do not appear to have been exhaustive to establish appropriate acceptance criteria for leachables in the container closure raw material. Specifically, you did not conduct studies in alcohol and at pH 2 solution, and studies were done only over 1 hour. Using methods that meet or exceed USP, determine total extractables for drug product contact materials (b) (4) in a one-time extraction study in water for injections (WFI), pH 2, pH 8.0, and alcohol. Reflux in the extraction media at hourly intervals until the extractables are exhausted from material. Calculate new safety factors for each using these values. Please also report these data to your type III DMF 26696.

Additional CMC Deficiencies and Comments:

6. The proposed drug product specification includes one identification test by HPLC. Per ICH Q6A, identification solely by a single chromatographic retention time is not regarded as being specific. Include a second chromatographic procedure where the separation is based on different principles, or include a combination of tests into a single procedure (e.g. HPLC/UV diode array, HPLC/MS, etc.). If a single method is used, propose a specific identification test such as infrared spectroscopy.
7. The applicant has claimed that at (b) (4) Provide information on acid base equilibria over the 4.0-6.0 pH range (and in particular over the 4.1-4.6 pH range) to substantiate the above claim.
8. The applicant has claimed that at their drug product formulation pH, moxifloxacin exists as moxifloxacin hydrogen sulfate, not as moxifloxacin HCl, but has not demonstrated that the moxifloxacin hydrogen sulfate salt form is functionally equivalent to Avelox® I.V. (moxifloxacin HCl in NaCl injection). In addition to pH and osmolality (see deficiency #1), the side by side comparison between Moxifloxacin

Injection and the RLD Avelox® I.V. (moxifloxacin HCl in NaCl injection) should also include a comparison of sodium content, chloride content, hydrogen sulfate content, and isotonicity calculations.

9. NDA submission states that precipitation occurs in the drug product at pH (b) (4) or lower, but has specified a pH range of (b) (4) 6.0 for the drug product formulation. The lower limit of the pH range should be revised to pH (b) (4) or higher to prevent precipitation. As this could result in a different pH range from the RLD, additional justification should be provided to support the comparability of your product to the RLD.
10. The exhibit batches show an underage. Please provide the target fill volume, target fill weight and formulation density. Clarify if the target assay for each drug product unit is less than 100% of label claim. Provide additional clarification on weight loss determination.
11. Fresenius Kabi has submitted an in-house analytical method FRD088 tests for the identification, assay at release and at stability for moxifloxacin and impurities of moxifloxacin in the finished drug product. Provide the complete analytical method with details of the method and any modifications to the use for identification, release and stability. Also such details as sampling procedure for release testing, detector sensitivity, flow rate, sample preparation, standard preparation, assay preparation, injection volume, etc. should be included. The limits of detection (LOD) and quantitation (LOQ) should also be described in the method. The LOD and LOQ should be measured with respect to the label. Additionally, the analytical calculations appear to be based on a moxifloxacin hydrochloride conversion factor which may be a less precise determination than with moxifloxacin hydrogen sulfate.
12. Please revise the term “Any other individual impurities” to “Any unspecified degradation products”, and revise your acceptance criterion for any unspecified degradation product to NMT (b) (4)%. Also include specifications for specified degradants.
13. Please replace term of “total impurities” with “total degradants”. Revise your acceptance criterion for total degradation product to NMT (b) (4)%. Please explain why degradants less than (b) (4)% are not included in the total degradant calculation.
14. Please revise the acceptance criterion for Extractable Volume in Container to the actual nominal value. The specification should state: NLT (b) (4) mL complies with current USP <1> of NLT labeled volume.
15. We recommend the labeling in the NDA resubmission include the following storage statement revised from (b) (4) to the USP controlled room storage statement “Store at 20-25°C (68-77°F) [see USP Controlled Room Temperature for full text]. Labeling will be evaluated further upon NDA resubmission.

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/s/

DOROTA M MATECKA
03/19/2014

Medical Officer Review

Date	February 4, 2014
From	Yuliya Yasinskaya, M.D.
Medical Team Leader	John Alexander M.D., MPH
Subject	Medical Officer Review
NDA #	205-572
Applicant	Fresenius Kabi
Date of Submission	June 6, 2013
PDUFA Goal Date	April 7, 2014
Proprietary Name / Established (USAN) names	Moxifloxacin Injection
Dosage forms / Strength	400 mg/250 mL
Proposed Indication(s)	<ol style="list-style-type: none"> 1. Acute Bacterial Sinusitis, 2. Acute Bacterial Exacerbation of Chronic Bronchitis 3. Community Acquired Pneumonia, 4. Uncomplicated Skin and Skin Structure Infections (SSSI), 5. Complicated SSSI 6. Complicated Intra-Abdominal Infections
Recommended:	<i>Complete Response</i>

The submission is a 505(b)(2) New Drug Application for Moxifloxacin Injection 400 mg/250 mL. The applicant submitted the information describing the chemistry, manufacturing and controls for Moxifloxacin Injection, 400 mg/250 mL. The reference listed drug (RLD) for this application is Avelox®, NDA 21,277 held by Bayer Healthcare. The application included 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, Kareen Riviere, Ph.D. Dr. Riviere concluded that the waiver request cannot be granted due to incomplete supportive information (see the ONDQA Review dated January 27, 2014).

Dr. Terry Miller, Pharmacology Toxicology Reviewer, did not recommend approval of the application during current review cycle due to inadequate information regarding safety risk assessment for three leachables (b)(4) identified in the migration studies with moxifloxacin in the proposed Freeflex® container system (see nonclinical review dated February 4, 2014). Proposed extrapolation of safety from the related compounds was deemed inadequate by the reviewer. Additional toxicity information was requested from the applicant during the review cycle and no response was received to date. This request remains outstanding and should be addressed in the NDA resubmission. Similar deficiencies should be addressed in the referenced Master file for Freeflex® container enclosure system. Alternatively the applicant may choose a different container enclosure system with appropriate supportive data.

There were no Clinical Pharmacology, Clinical Microbiology, or Clinical/Statistical information/data submitted in this NDA; thus, no detailed discipline reviews were necessary.

Review of the Applicant's proposed label, packaging and product labeling was conducted DMEPA reviewer, Aleksander Winiarski, PharmD. The reviewer concluded that proposed label and labeling can be improved to increase readability and prominence of important information on the label and package insert (for specific recommendations to the applicant see Dr. Winiarski's review dated December 17, 2013).

Recommendation

- Recommended Regulatory Action

Complete response is recommended for this application due to the lack of supporting information for a biopharmaceutics waiver (CMC) and toxicology safety risk assessment for the identified leachables in the proposed container closure system (Pharmacology/Toxicology).

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/s/

YULIYA I YASINSKAYA
02/05/2014

JOHN J ALEXANDER
02/05/2014