CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

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PHARMACOLOGY REVIEW(S)

DEPARTMENT OF HEALTH AND HUMAN SERVICES
FOOD AND DRUG ADMINISTRATION
CENTER FOR DRUG EVALUATION AND RESEARCH

PHARMACOLOGY/TOXICOLOGY NDA REVIEW AND EVALUATION

DATE: 3/09/2015

Application number:	205572 (Class 2 Resubmission)
Supporting document/s:	6
Sponsor's letter date:	10/03/2014
CDER stamp date:	10/03/2014
Product:	Moxifloxacin for Injection
Indication:	Antibacterial indicated for treating infections
Sponsor:	Fresenius Kabi USA LLC
Review Division:	Division of Anti-Infective Products
Reviewer:	Terry J. Miller, Ph.D.
Supervisor/Team Leader:	Wendelyn Schmidt, Ph.D.
Division Director:	Sumathi Nambiar, M.D.
Project Manager:	Fariba Izadi, Pharm.D.

Disclaimer

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Recommendations:

The pharmacology/toxicology reviewer has no objection to the approval of NDA 205572 (Class 2 resubmission) for Moxifloxacin for Injection. There are no nonclinical recommendations or comments to be sent to the Applicant.

Labeling:

Applicant Suggested Labeling: (From Module 1.14 Draft Annotated Package Insert of the NDA application submitted on 8/29/2014 for NDA 205572.

The Applicant's proposed labeling and my recommended labeling changes for the relevant pharmacology/toxicology sections can be found below. The Applicant proposed very minor labeling changes for the pharm/tox relevant sections of the approved labeling for Avelox. The Applicants recommended changes from the RLD are underlined. My recommended changes to the Applicant's proposed changes and/or the approved labeling for the RLD contain a strikethrough and are in bold.

5 WARNINGS AND PRECAUTIONS

5.9 Arthropathic Effects in Animals

The oral administration of moxifloxacin caused lameness in immature dogs. Histopathological examination of the weight-bearing joints of these dogs revealed permanent lesions of the cartilage. Related quinolone-class drugs also produce erosions of cartilage of weight-bearing joints and other signs of arthropathy in immature animals of various species. *[See Animal Toxicology and/or Pharmacology (13.2).]*

(Reviewer's comment: The Applicant proposed a change of Avelox to moxifloxacin in Section 5.9. There are no recommendations for changes by the pharm/tox reviewer for this section of the labeling).

8. USE IN SPECIFIC POPULATIONS

8.1 Pregnancy: Category C

Pregnancy Category C. Because no adequate or well-controlled studies have been conducted in pregnant women, moxifloxacin should be used during pregnancy only if the potential benefit justifies the potential risk to the fetus.

Moxifloxacin was not teratogenic when administered to pregnant rats during organogenesis at oral doses as high as 500 mg/kg/day or 0.24 times the maximum recommended human dose based on systemic exposure (AUC), but decreased fetal body weights and slightly delayed fetal skeletal development (indicative of fetotoxicity) were observed. Intravenous administration of 80 mg/kg/day (approximately 2 times the maximum recommended human dose based on body surface area**)** (b) (4) to pregnant rats resulted in maternal toxicity and a marginal effect on fetal and placental weights and the appearance of the placenta. There was no evidence of teratogenicity at intravenous doses as high as 80 mg/kg/day. Intravenous administration of 20 mg/kg/day (approximately equal to the maximum recommended human oral dose based upon systemic exposure) to pregnant rabbits

during organogenesis resulted in decreased fetal body weights and delayed fetal skeletal ossification. When rib and vertebral malformations were combined, there was an increased fetal and litter incidence of these effects. Signs of maternal toxicity in rabbits at this dose included mortality, abortions, marked reduction of food consumption, decreased water intake, body weight loss and hypoactivity. There was no evidence of teratogenicity when pregnant cynomolgus monkeys were given oral doses as high as 100 mg/kg/day (2.5 times the maximum recommended human dose based upon systemic exposure). An increased incidence of smaller fetuses was observed at 100 mg/kg/day. In an oral pre- and postnatal development study conducted in rats, effects observed at 500 mg/kg/day included slight increases in duration of pregnancy and prenatal loss, reduced pup birth weight and decreased neonatal survival. Treatment-related maternal mortality occurred during gestation at 500 mg/kg/day in this study.

(Reviewer's comment: The Applicant proposed a change of Avelox to moxifloxacin in Section 8.1. There is a minor changes recommended by the pharm/tox reviewer for this section of the labeling above).

8.3 Nursing Mothers

Moxifloxacin is excreted in the breast milk of rats. Moxifloxacin may also be excreted in human milk. Because of the potential for serious adverse reactions in infants who are nursing from mothers taking moxifloxacin, a decision should be made whether to discontinue nursing or to discontinue the drug, taking into account the importance of the drug to the mother.

(Reviewer's comment: The Applicant proposed no changes to Section 8.3. There are no recommendations for changes by the pharm/tox reviewer for this section of the labeling above).

10 OVERDOSAGE

Single oral overdoses up to 2.8 g were not associated with any serious adverse events. In the event of acute overdose, the stomach should be emptied and adequate hydration maintained. ECG monitoring is recommended due to the possibility of QT interval prolongation. The patient should be carefully observed and given supportive treatment. The administration of activated charcoal as soon as possible after oral overdose may prevent excessive increase of systemic moxifloxacin exposure. About 3% and 9% of the dose of moxifloxacin, as well as about 2% and 4.5% of its glucuronide metabolite are removed by continuous ambulatory peritoneal dialysis and hemodialysis, respectively.

(b) (4)

13 NONCLINICAL TOXICOLOGY

13.1 Carcinogenesis, Mutagenesis, Impairment of Fertility

Long term studies in animals to determine the carcinogenic potential of moxifloxacin have not been performed.

Moxifloxacin was not mutagenic in 4 bacterial strains (TA 98, TA 100, TA 1535, TA 1537) used in the Ames *Salmonella* reversion assay. As with other quinolones, the positive response observed with moxifloxacin in strain TA 102 using the same assay may be due to the inhibition of DNA gyrase. Moxifloxacin was not mutagenic in the CHO/HGPRT mammalian cell gene mutation assay. An equivocal result was obtained in the same assay when v79 cells were used. Moxifloxacin was clastogenic in the v79 chromosome aberration assay, but it did not induce unscheduled DNA synthesis in cultured rat hepatocytes. There was no evidence of genotoxicity *in vivo* in a micronucleus test or a dominant lethal test in mice.

Moxifloxacin had no effect on fertility in male and female rats at oral doses as high as 500 mg/kg/day, approximately 12 times the maximum recommended human dose based on body surface area**)** (b) (4) or at intravenous doses as high as 45 mg/kg/day, approximately equal to the maximum recommended human dose based on body surface area**)** (b) (4). At 500 mg/kg orally there were slight effects on sperm morphology (head-tail separation) in male rats and on the estrous cycle in female rats.

(Reviewer's comment: The Applicant proposed no changes to Section 13.1. There are minor changes recommended by the pharm/tox reviewer for this section of the labeling above).

13.2 Animal Toxicology and/or Pharmacology

Quinolones have been shown to cause arthropathy in immature animals. In studies in juvenile dogs oral doses of moxifloxacin ≥ 30 mg/kg/day (approximately 1.5 times the maximum recommended human dose based upon systemic exposure) for 28 days resulted in arthropathy. There was no evidence of arthropathy in mature monkeys and rats at oral doses up to 135 and 500 mg/kg/day, respectively.

Moxifloxacin at an oral dose of 300 mg/kg did not show an increase in acute toxicity or potential for CNS toxicity (for example, seizures) in mice when used in combination with NSAIDs such as diclofenac, ibuprofen, or fenbufen. Some quinolones have been reported to have proconvulsant activity that is exacerbated with concomitant use of non-steroidal anti-inflammatory drugs (NSAIDs).

A QT-prolonging effect of moxifloxacin was found in dog studies, at plasma concentrations about five times the human therapeutic level. The combined infusion of sotalol, a Class III antiarrhythmic agent, with moxifloxacin induced a higher

degree of QTc prolongation in dogs than that induced by the same dose (30 mg/kg) of moxifloxacin alone. Electrophysiological *in vitro* studies suggested an inhibition of the rapid activating component of the delayed rectifier potassium current (I_{Kr}) as an underlying mechanism.

No signs of local intolerability were observed in dogs when moxifloxacin was administered intravenously. After intra-arterial injection, inflammatory changes involving the peri-arterial soft tissue were observed suggesting that intra-arterial administration of AVELOX should be avoided.

(Reviewer's comment: The Applicant proposed no changes to Section 13.2. There are no recommendations for changes by the pharm/tox reviewer for this section of the labeling).

Regulatory Background:

Fresenius Kabi (FK) USA, LLC, submitted a Class 2 Resubmission of a 505(b)(2) New Drug Application (NDA) to obtain marketing approval for Moxifloxacin for Injection (400 mg/250 mL). FK, USA submitted the original 505(b)(2) NDA on June 6, 2013, and after a standard review, received a Complete Response from the Division denying marketing approval on April 4, 2014. Multiple disciplines including the Biopharmaceutics, Pharmacology / Toxicology, and Product Quality review teams noted several deficiencies the Applicant needed to address before marketing approval could be granted. In particular, Pharmacology/Toxicology requested additional toxicity information for three identified leachables (b) (4) from the Free*flex*® I.V. bag of unknown toxicological risk (referenced MF No. 26696; Fresenius Kabi AG, Germany). Despite the approved use of this container enclosure system in several marketed drugs, the absence of adequate safety information for these three commonly detected leachables was noted in multiple pharm/tox reviews, including the review of the original submission of NDA 205572 (in DARRTS 2/04/2014), in the pharm/tox NDA reviews for at least 2 other products in another review Division, and in a pharm/tox review of the MF for the Free*flex*® I.V. bag itself (MF No. 26696) by Dr. Carlic Huyhn .[1] In response to a communication sent by the Division on 10/22/2013 requesting additional toxicity information for the unqualified leachables, the Applicant submitted a single study report for a 3-month oral toxicology study with (b) (4) on 2/14/2014, late in the original review cycle. In the Complete Response (CR) Letter submitted to the Applicant from the Division on April 4, 2014, the Applicant was asked to provide the following:

[1] In a prior review of MF 26696 (in DARRTS 6/20/2013), Dr. Carlic K. Huynh concluded the toxicological risk assessments for three leachables were inadequate and required the MF holder of the Freeflex I.V. bag to submit the following: 1) Final study report for the proposed 3 month toxicology study for (b) (4) and updated toxicological risk assessment; 2) Final study report for the proposed 28-day i.v. toxicology study for (b) (4) and updated toxicological risk assessment; 3) final study report for the proposed 28-day i.v. toxicology study for (b) (4) and updated toxicological risk assessment; and 4) long-term stability data > 6 months.

"Provide additional toxicity information for each of the three identified leachables [redacted] *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."*

The Applicant resubmitted their 505(b)(2) NDA Application on 8/20/2014, including both the final study reports for the toxicology studies and updated toxicology risk assessments for each of the three unqualified leachables. Although the Applicant submitted all of the requested nonclinical information to address the pharmacology/toxicology deficiencies noted in the CR Letter of 4/4/2014, continued product quality issues, particularly with the Free*flex*® I.V. bag, resulted in the Applicant receiving an "Acknowledge Incomplete Response" Letter on 9/12/2014.

FK, USA submitted the current Class 2 resubmission of the 505(b)(2) NDA on 10/21/2014 requesting marketing approval for Moxifloxacin for Injection. Since that time, the Applicant has submitted responses to several information requests from the Division for additional information on product quality.

(Please refer to the pharmacology/toxicology review of the original NDA application by Dr. Terry Miller (in DARRTS 2/4/2014) for additional information.)

Nonclinical Studies Submitted in this NDA Application

1. 90-day rat oral toxicology study with [redacted]
2. 28-day rat intravenous toxicology study with [redacted]
3. 28-day rat intravenous toxicology study with [redacted]
4. Bacteria reverse mutation assay (AMES) with [redacted]
5. Bacteria reverse mutation assay (AMES) with [redacted]
6. Updated toxicological risk assessment for [redacted]
7. Updated toxicological risk assessment for [redacted]
8. Updated toxicological risk assessment for [redacted]

Product Information

Moxifloxacin for Injection is intended to be a near copy of the reference listed drug (RLD) Avelox® (moxifloxacin hydrochloride, Bayer Healthcare, NDA #021277), with an identical active ingredient, drug strength (1.6 mg/mL) and route of administration. However, in comparison with the RLD product, the generic drug formulation will include two additional excipients (Sodium Acetate Trihydrate, USP – [redacted] mg and Disodium Sulfate, USP - [redacted] mg), and eliminate sodium chloride from the final drug formulation (Table 1). 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). A side-by-side comparison of the RLD and proposed drug

formulation can be found in (Table 2) below. The pre-mixed packaging will contain (6) 250-mL flexible plastic containers each with 400 mg of moxifloxacin in water for injection. No new pharmacology or toxicology information was submitted, or necessary in support of this new drug 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) %.

Table 1. Component Composition of Drug Product (Moxifloxacin, 400 mg/250 mL Solution for Infusion)

Strength	1.6 mg/mL		
Packaging Configuration	400 mg/250 ml fill in a 300-mL **free***flex*® bags		
Freeflex Primary Film	(b) (4)		
Ports	Administration port (infusion port) and addition port (injection port)		
Overpouch	Aluminum (secondary packaging)		
Drug Product Name	**Content**	**Function**	**Quality of Ingredient**
Moxifloxacin Hydrochloride	(b) (4) (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		solvent	USP
Sulphuric Acid		pH adjuster	NF

(Table 2.3.P-1 on page 4 of Section 2.3.P Quality Overall Summary of Drug Product, Original Submission 6/7/2013)

Table 2. Side-by-Side Comparison of the Reference Listed Drug and 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 (monohydrate)	Moxifloxacin Hydrochloride (anhydrous)
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		
Bioequivalence	Refer to SECTION 1.12.15	Refer to SECTION 1.12.15
Labeling	Refer to Section 1.14	Refer to Section 1.14

* The RLD does not list Water for Injection on the labeling, however it must be employed in the compounding of the drug product.

(Table 1.12.12-1, page 3 of Section 1.12.12: Comparison of the generic drug and RLD)

The Sponsor plans to package the current drug product in a Free*flex*® I.V. bag consisting of a (b) (4) container for parenteral solutions. The Free*flex*® I.V. bag is manufactured by Fresenius Kabi AG (Germany), and is currently used with approved innovator drugs such as Zyvox® injection (NDA-021131; Pfizer, Inc.) and Reclast® injection (NDA 21817, Novartis Pharmaceuticals Corp.), and several approved generic drugs including Levofloxacin in 5% dextrose injection (ANDA 200674; APP Pharmaceuticals). The FK, USA Free*flex*® bag has also been approved for use with Voluven® (NDA BN070012, FK, USA, LLC) infusion for plasma replacement in hypovolemic patients. The Sponsor included a Letter of Authorization (LOA) from the MF Holder of the Free*flex*® packaging system (MF 26696; FK, Deutschland GmbH) in the current application authorizing FK, USA to reference information contained within the MF, and for the FDA to examine the entire contents of the MF in review of the current NDA application.

(Reviewer comment*: The extraction and migration studies for Moxifloxacin for Injection and the* Freeflex® *container system were evaluated in the Pharm/Tox review of the original NDA application (in DARRTS 2/4/2014). Only the updated information from: 1) requested extraction studies of the* Freeflex® *i.v. bag with Ethanol* (b) (4) *% (submitted to MF 26696 on 3/6/2015); and 2) requested extended migration/stability studies to determine leachable compounds up to 24 months will be included in the current review).*

Extraction Studies with the Free*flex*® I.V. Bag (Updated)

The focus of the recently submitted extraction study to MF 26696 (in DARRTS 3/6/2015) was the (b) (4) in ethanol (b) (4) % (v/v) (Figure 1)

Figure 1. Schematic Drawing of the Free*flex*® Container Closure System

(b) (4)

(Figure 3.2.P.2-1 on page 30 of Module 3.2.P.2.4 in the original NDA application)

A comparison of the extractables detected from the (b) (4) (Table 3) in the ethanol ((b) (4) %) extraction media are shown below. After a 60 minute incubation period, several extractables were identified as an extractable products from the container. No new extractables were detected in ethanol compared to WFI (water for injection) tested previously. The detected extractables were monitored in the migration studies as possible leachables. All leachables were toxicologically evaluated (see the Migration studies section below for the toxicology risk assessment for (b) (4)).

Table 3. Results of Extraction Studies in Ethanol (b) (4)% (v/v), Batch U1893

(b) (4)

(Table 1 from DARRTS submission to MF (b) (4) 3/6/2015)

(Reviewer's comment: Although the concentrations of (b) (4) were detected at significantly greater levels (3 and 15 times, respectively) in the extraction study of (b) (4) in ethanol compared to the levels in the migration studies with Moxifloxacin for injection in the Freeflex I.V. bag, the very large safety margins of 4340 and 678, respectively, above the maximum levels detected in the migration study easily encompass the increased levels of each solvent detected in the extraction study. There does not appear to be any significant safety risk from the increased levels of either extractable noted in the extraction studies with the (b) (4))

Migration Studies with Moxifloxacin for Injection in the Free*flex* i.v. bag

The recently submitted migration studies conducted with Moxifloxacin for Injection within the complete Free*flex*® container system examined the stability of the drug product for up to 24 months (batches: 12FCU92, 12FCU93, 12FCU94) under various storage conditions at different time intervals (Table 4). (Only batch 12FCU92 was analyzed at 6 and 12 months; all 3 batches were analyzed at 18 and 24 months). All packaging materials (b) (4) were considered in these studies. The size of the Free*flex*® bag is 300 mL filled with 250 mL of Moxifloxacin for Injection.

Table 4. Storage Intervals for Migration Studies with Moxifloxacin

Storage Condition	Interval in Months				
	6	12	18	24	36
25 °C ± 2 °C/ 40 % RH ± 5 %	x *	x *	x	x	x
30 °C ± 2 °C/ 35 % RH ± 5 %		x *	x	x	x
40 °C ± 2 °C/ NMT 25 % RH	x *				

* only available for batch 12FCU92

Table 3.2.P.2.4-3 on page 7 of Section 3.2.P.2. Pharmaceutical Development

Samples of the exhibit and annual drug product batches contained within the Free*flex*® packaging system were sampled at different time intervals and analyzed using high performance liquid chromatography (HPLC) or gas chromatography (GC) [Table 5].

Table 5. Analytical Methods Used to Determine Extractables/Migrants

Method No.	Type of Method	Title
(b) (4)	High Performance Liquid Chromatography (HPLC)	(b) (4)
	Headspace Gas Chromatography Gas Chromatography (HS-GC)	
	Gas Chromatography Mass Spectrometry (GC-MS)	

(Table 3.2.P.2-32 on page 45 of Module 3.2.P.2.4 – Container Closure System)

The results of the 6, 12, 18, and 24-month migration study with batch#: 12FCU92 of Moxifloxacin for Injection are shown in (Table 6).

Table 6. Moxifloxacin for Injection - Migration Study (Batch: 12FCU92) in 300 mL (250 mL filling) Free*flex*®Bags

(b) (4)

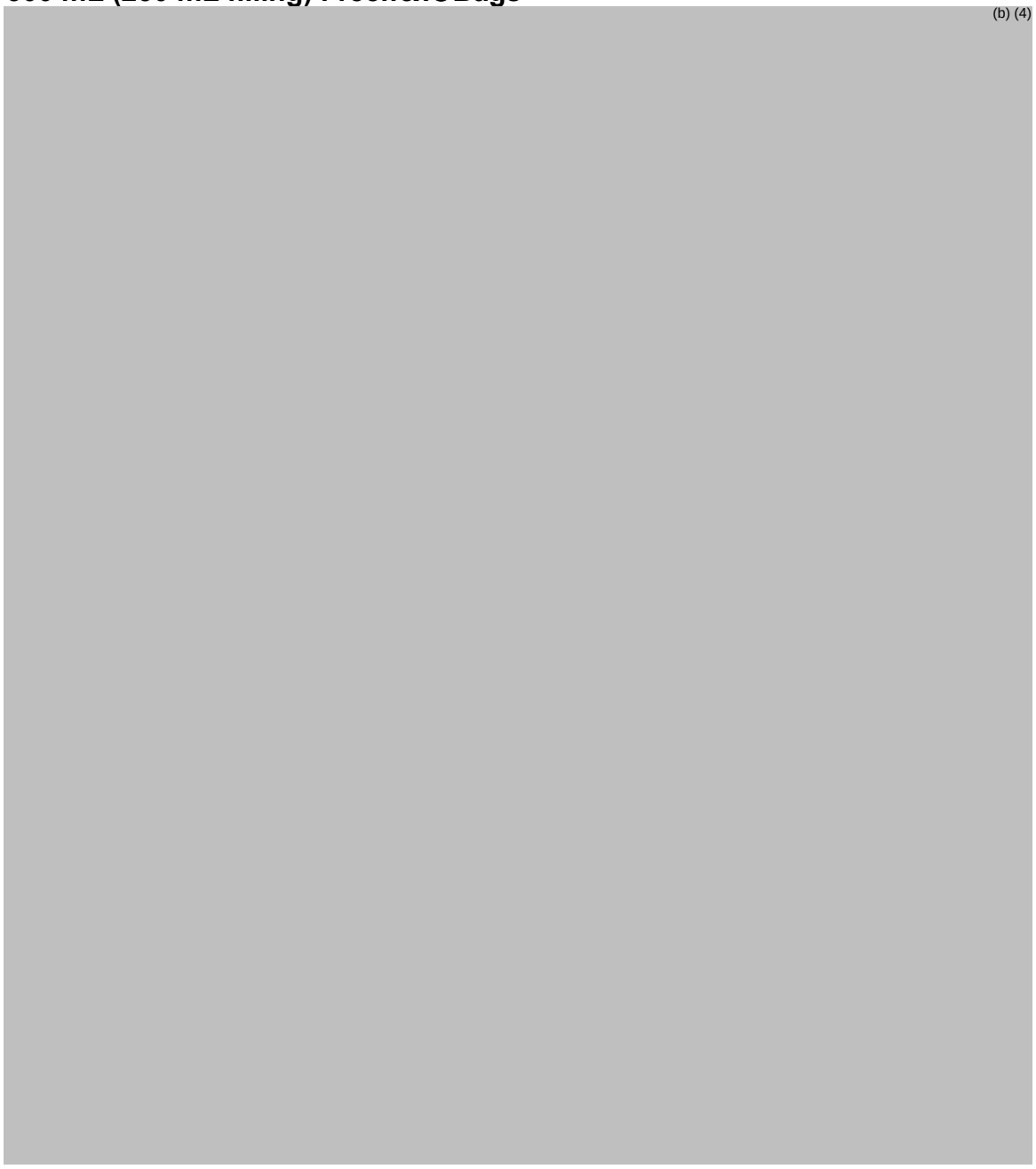


Table 6. Moxifloxacin for Injection - Migration Study, Batch #: 12FCU92 in 300 mL (250 mL filling) Free*flex* Bags (cont.)

(b) (4)

Table 6. Moxifloxacin for Injection - Migration Study, Batch #: 12FCU92 in 300 mL (250 mL filling) Freeflex Bags (cont.)

(Table 3.2.P.2.4.4 on pages 8-10 of Section 3.2.P.2 Pharmaceutical Development)

The primary leachables from the Free*flex*® container detected in the drug product after 24 months includes the following:

The Sponsor conducted a toxicologic evaluation of each of these detected leachables/extractable using standard toxicology reference literature, and public toxicology databases including ECHAS, RTEC, TOXLINE CORE, TOXLINE

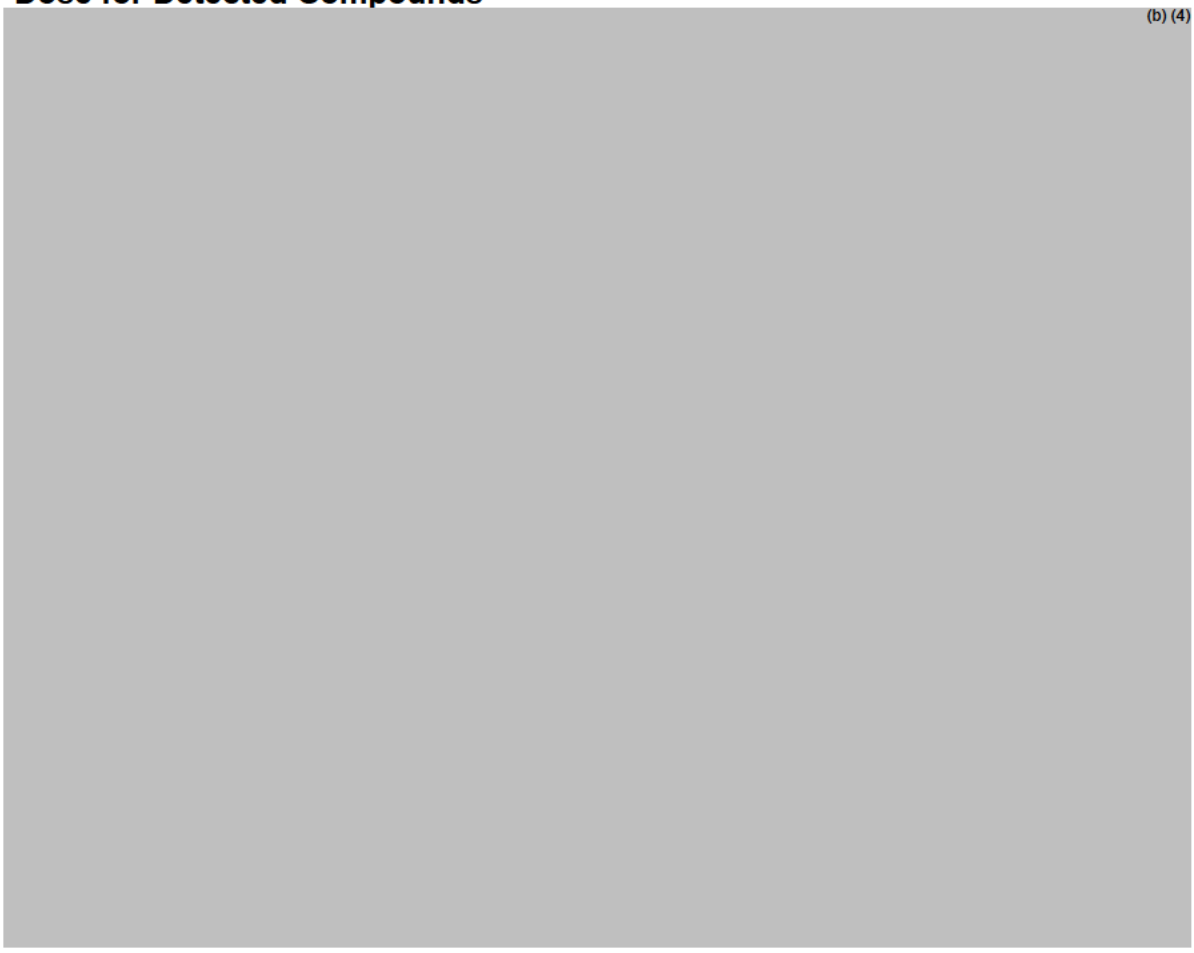
SPECIAL, TOXBIO, and TOXCAS, as well as a general internet search. The focus of this search were based on defining the no-observed-effect-level (NOEL) or lowest-observed-effect-level (LOEL) derived from existing pharmacokinetic, single- and repeat-dose toxicity, genotoxicity, carcinogenicity, and reproductive and developmental toxicology studies. When no toxicologic data for an extractable/leachable was available, the Applicant conducted new toxicology study(ies) with the unqualified leachable and/or examined "related" compounds (i.e. parent compound or individual components of a complex compound) for which toxicology data were available. The "permitted daily exposure" (PDE) for each extractable was calculated as described in ICH Q3C(R5) Guideline on Impurities: Residual Solvents (1997), and represent values estimated from toxicologic assessments and worst case maximum daily doses.

PDE = [NOEL (mg/kg/day) x Weight adjustment (50 kg)] / [F1 x F2 x F3 x F4 x F5]
Where
F1 is a factor for extrapolation between species
F2 is a factor of 10 for variability between individuals
F3 is a factor for short-term toxicity studies
F4 is a factor for severe toxicity
F5 is a variable factor if the NOEL was not established

Internal specifications for extractable compounds were established by the Applicant using maximum values observed during all extractable testing of Free*flex*® components and during migration studies with a variety of aqueous product solutions packaged in Free*flex*® bags. The maximum total daily intake (TDI), PDE estimations, internal specification limits, and calculated safety margins of each leachable/extractable are shown in (Table 7) below.

Table 7. Safety Margins for Upper Specification Limits and Maximum Daily Dose for Detected Compounds

(b) (4)



(Table 3.2.P.2.4-7 of Section 3.2.P.2 Pharmaceutical Development)

The results of the migration studies with Moxifloxacin in the Free*flex*® bag showed that after 24 months of storage, that 3 leachables of unknown toxicologic risk for which the Applicant was required to conduct additional toxicology studies were detected in the Moxifloxacin drug product (Table 8). The three leachable compounds are (b) (4) was not detected in any of the migration studies conducted with Moxifloxacin for Injection.

Table 8. Leachable Concentrations in Migration Studies with Moxifloxacin

(b) (4)

[redacted]

(Table in Section 3.2.P.8.1 Stability Summary and Conclusion)

(Reviewer's comments: The highest level of the three leachables in Moxifloxacin Injection from the Freeflex (b) (4) [redacted] (b) (4) [redacted] *as well. Note that Table 7 and Table 8 were updated with the new PDE values from toxicology studies the Applicant conducted with the leachables). Data for the toxicologic evaluations of the commonly found leachables are included in the referenced Master File (MF) for the* Freeflex® *polyolefin bags (MF 26696, FK, Deutschland GmbH). The current NDA contains a LOA from FK, Deutschland GmbH authorizing FK, USA to reference information from this MF, and for the FDA to review the MF during review of the current NDA).*

Due to concerns for systemic safety of unqualified leachables found to migrate from the Free*flex* I.V. bag, the Applicant reviewed the available nonclinical studies conducted with each leachable and related compounds, and conducted several toxicology studies evaluate the risk of toxicity for the maximum levels of leachables detected in the final drug product. Using the analytical information obtained in the migration studies with Moxifloxacin for Injection, the Applicant calculated the permitted daily exposure (PDE) values for each leachable in accordance with ICH Guideline Q3C(R5) generally used for solvents.[2]

A review of the nonclinical toxicology studies evaluated for each of the 3 leachables (b) (4) [redacted] and updated toxicology risk assessment conducted by the Applicant appears in the section below. (Note that because (b) (4) [redacted] was not detected in the migration studies (LOQ= (b) (4) [redacted] mcg/L)), no risk assessment was conducted for this compound).

[2] ICH Q3C(R5): IMPURITIES: GUIDELINE FOR RESIDUAL SOLVENTS

Toxicology Evaluation of Leachables from the Free*flex*® I.V. bag

A. (b) (4)

(b) (4)

(b) (4)

(b) (4) was detected as a leachable from the Free*flex*® container at a maximal concentration of (b) (4) mcg/L; (b) (4) was not detected in the migration studies. Only limited toxicological data was available in the literature and internet databases for (b) (4). (b) (4) was qualified toxicologically by the Applicant in the evaluation below.

Figure 2. Structural Formula for (b) (4)

(b) (4)

Toxicity data for the risk assessment for (b) (4) consists primarily of a repeat dose toxicology study in rats from which a permitted data exposure (PDE) value was calculated. In addition, the Applicant conducted an AMES test with (b) (4) to evaluate its mutagenic potential. The Applicant submitted both the 90 day oral toxicology study in rats and the bacterial reverse mutation assay in this NDA application.

(b) (4) showed no mutagenic potential when evaluated in a GLP compliant, bacterial reverse mutation assay (AMES; Study No. HKQ0015) using 4 Salmonella strains (TA98, 100, 1535, 1537) and an E.coli strain (WP2 uvrA), with and without S9 metabolic activation (S9 mix from Aroclor-induced liver of male SD rats).

Data from a single, 13-week repeat dose, rat toxicity study (Study No. 810895) was used by the Applicant to calculate the PDE for (b) (4). In this study, groups of 20 adult rats/sex were administered (b) (4) in 0.5 % carboxymethyl-cellulose/0.1% Tween 80 by oral gavage at doses of 0, 3, 10, 30, and 100 mg/kg/day for 90 consecutive days. The No Observed Effect Level

(NOEL) in this study was determined to be 3 mg/kg/day, based on a slight increase in absolute (8-13%) and relative (6-14%) mean liver weight in male and female rats treated with 10 mg/kg/day. The No Observed Adverse Effect Level (NOAEL) dose was determined to be 30 mg/kg/day. The PDE for (b) (4) was calculated with the formula used for Solvents in ICH Guidance Q3C(R5).

$$PDE = \frac{NOEL\ (mg/kg/day) \times Weight\ Adjustment\ (50\ kg)}{F1 \times F2 \times F3 \times F4 \times F5}$$

F1 = factor for extrapolation between species
F2 = factor of 10 for variability between individuals
F3 = factor for short-term toxicity studies
F4 = factor for severe toxicity
F5 = variable factor if the no-effect level was not established

For (b) (4), the PDE was calculated with factors (F1-F5) (Table 9).

Table 9. Calculation of PDE for (b) (4)

Reference	Study Type	Species	NOEL mg/kg/day	Modifying Factors	PDE mg
Ciba Geigy 1983	90 day repeated dose oral toxicity study	Rat	(b) (4)	F1=5, F2=10, F3=5, F4=1, F5=1	(b) (4)

Based on the findings from the 90 day repeated dose oral toxicity study in the rats, the calculated PDE for (b) (4) mg. Although the plasma levels and PK parameters of (b) (4) were not determined in this study, it appears likely that systemic absorption had occurred based on the dose proportionality of increased liver weights and histological findings (e.g. liver hypertrophy). Therefore, a systemic absorption of (b) (4) was assumed by the Applicant resulting in a proposed PDE of (b) (4) mg. A comparison of the estimated PDE ((b) (4) mg) to the maximum possible posure of (b) (4) from the migration dies ((b) (4) mg/day in 250 mL of Moxifloxacin Injection administered daily; Table 6 above), showed the calculated permitted daily exposure to be **12.5** times greater than the maximum daily exposure. Therefore, assuming the orally administered drug is at least 50% absorbed, the calculated safety margin of 12.5 times above the expected maximum exposure levels is adequate and no significant safety risk is expected from (b) (4) as a leachable from the Freeflex bag containing Moxifloxacin for Injection.

(Reviewer's comment: Results from the recently submitted extraction study with the (b) (4) (from the Freeflex® i.v. bag) in ethanol (b) (4)% (v/v) showed a higher concentration of (b) (4) of 199 mcg/L, compared to 95 mcg/L detected in the migration studies with Moxifloxacin. The near doubling of the

concentration of (b) (4) *detected in the extraction studies (as a worst case scenario) would reduce the safety margin to approximately 6.25 above maximum exposure levels which remains adequate in the toxicological risk assessment for this leachable compound.)*

A review of the study design and summary of findings from both the 90 day oral rat toxicology study and the AMES test conducted with (b) (4) is included below:

1) <u>Bacterial Reverse Mutation Test (Study No. HKQ0015; GLP)</u>

- **Objective**: GLP compliant study tested (b) (4) (Batch I2012; Purity: > (b) (4) %) for the ability to induce reverse mutations at the histidine locus in several strains of *S.typhimurium* and at the tryptophan locus of *E.coli*, in the presence/absence of a mammalian metabolic activation system (rat liver S9).
- Experimental Start Date: 2/27/2014
- Test Facility: (b) (4)
- Strains: *S.typhimurium* (TA1535, TA1537, TA98, TA100); *E.coli* (WP2 *uvr*A)
- Positive Control: (-S9: Sodium azide, 9-AA, 2-NF, 4-nitroquinoline-1-oxide), (+S9: 2-AA, Benzo[a]pyrene)
- First Test with (b) (4) (50 mg/mL) in 7 concentrations (5-5000 mcg/plate) in DMSO ± S9 at 37°C for 72 hours showed toxicity at the highest doses; precipitate of test article at 5000 mcg/plate; and no increase in numbers of revertant colonies compared to assay and historical controls, for any tester strains up to 5000 mcg/plate of (b) (4) in the presence or absence of S9 mix.
- Second Test with (b) (4) (50 mg/mL, 30 minute incubation before agar overly) in 5 concentrations (5-5000 mcg/plate) in DMSO ± S9 at 37°C for 72 hours showed toxicity at highest doses; precipitate of test article at 5000 mcg/plate; and no increase in numbers of revertant colonies compared to assay and historical controls, for any tester strains up to 5000 mcg/plate of (b) (4), in the presence or absence of S9 mix.
- The negative vehicle and positive control articles confirmed the adequacy of the test system.
- Conclusion: (b) (4) showed no evidence of mutagenic activity in this bacterial system under these test conditions.

2) Study title: 3 Month Oral Toxicity Study in Rats (with [redacted])

Study no.:	810895
Study report location:	EDR
Conducting laboratory and location:	[redacted]
Date of study initiation:	5/24/1982
GLP compliance:	Yes (OECD GLP)
QA statement:	Yes
Drug, lot #, and % purity:	TK 10797 ([redacted]), batch #: T 9820, [redacted]% pure

Methods

Doses:	0, 3, 10, 30, 100 mg/kg/day b.w.
Frequency of dosing:	Once daily for 90 consecutive days
Route of administration:	Oral gavage
Dose volume:	10 mL/kg b.w.
Formulation/Vehicle:	Carboxymethyl-cellulose 0.5%/Tween 80 0.1%
Species/Strain:	Rat (Tif:RAIf, a Sprague-Dawley derived strain), SPF
Number/Sex/Group:	20/sex/group (total: n=200)
Age:	Males and females, ≈ 6 weeks old
Weight:	M: 165-169 g; F: 135-141 g
Satellite groups:	None.
Deviation from study protocol:	None that was noteworthy.

Study Design:

Animal No. (cage no.)	Group 1 0 mg/kg	Group 2 3.0 mg/kg	Group 3 10 mg/kg	Group 4 30 mg/kg	Group 5 100 mg/kg
MALES	1-20 (1-20)	21-40 (21-40)	41-60 (41-60)	61-80 (61-90)	81-100 (81-100)
FEMALES	101-120 (101-120)	121-140 (121-140)	141-160 (141-160)	161-180 (161-180)	181-200 (181-200)

Observations and Results

Mortality (2x daily)

Three rats died during the 3 month test period (Male No. 84 in group 5, 100 mg/kg; Female No. 196 in group 5, 100 mg/kg; Male No. 51 in group 3, 10 mg/kg). All mortalities were caused by gavage errors.

Clinical Signs (pre-test, Daily):

None observed.

Body Weight (Pre-test, weekly, and at necropsy):

Mean body weight gains were similar for all treated male and female groups compared to the respective control groups.

Food Consumption (Pre-test, weekly, and at necropsy):

Mean food consumption was similar for all treated male and female groups compared to the respective control groups.

Water Consumption (Pre-test, weekly, and at necropsy):

A slight trend towards increased water consumption was observed in treated males and females in groups 5 (100 mg/kg/day b.w.) after Week 5 of treatment until the end of the study. Mean water consumption of all other groups was similar to the respective control groups.

Hearing Test (Pre-test, towards end of treatment period)

No treatment related effects on auditory perception.

Ophthalmologic Examination (Pre-study, and toward end of treatment period)

Findings from the ophthalmological examination were not reported in the study report. No reason for its exclusion from the report was provided.

Hematology / Coagulation (blood samples collected pre-test and at necropsy – orbital sinus bleed under ether anesthesia)

A slight increase in thrombocytes and leukocytes were noted in both male and female rats treated with (b) (4) compared with the respective controls. A slight increase in prothrombin time was detected in female rats only compared to controls. All changes were minimal, appeared greatest at the lowest doses, lacked a dose response, and/or were within the reported historical range for normal physiological variation for this rat strain.

Clinical Chemistry (blood samples collected pre-test and at necropsy – orbital sinus bleed under ether anesthesia)

Slight increase in plasma GGT, inorganic phosphate, cholesterol, and gamma globulins were noted in both male and female rats treated with (b) (4) compared with the respective controls. All plasma chemistry changes were considered minimal, appeared greatest at the lowest doses, lacked a dose response, and/or were within the reported historical range for normal physiological variation for this rat strain.

Gross Necropsy (at necropsy)

Two of three (2/3) animals that died showed perforation of the esophagus, purulent content and fibrinous adhesions in the thoracic cavity due to faulty administration of the test article. In the third animal that died, no gross anatomical changes were observed at necropsy. All other macroscopic changes in other treated animals were comparable to controls or were considered incidental in nature.

Organ Weights (at necropsy; brain, heart, liver, kidneys, adrenals, thymus, and gonads weighed)

Mean absolute liver weight in treated male and female groups 3, 4, and 5 (10, 30, and 100 mg/kg b.w.) increased 7.5%, 27%, and 41%, respectively, in males, and 13%, 21%, and 36% in females, respectively, in comparison to the respective control groups. Similarly, mean relative liver/body weight increased 6%, 22%, and 43% for males, respectively, and 14%, 21%, and 36% in females, respectively, in comparison to the respective controls. A slight, but significant decrease of 14-17% for both absolute and relative weights of adrenals was observed in female groups 4 and 5 (30 and 100 mg/kg b.w.).

Histopathology (at necropsy)

Adequate Battery: Yes
Routine Tissues Collected:

Adrenal glands*	Lymph nodes	Spinal cord
Aorta	Mammary area	Spleen
Bone (femur/sternum)	Nerves, sciatic	Stomach
Brain*	Ovaries*	Testes*
Epididymis*	Pancreas	Thymus*
Esophagus	Pituitary gland	Thyroid glands
Eyes/optic nerve	Prostate	Trachea
Heart*	Salivary glands	Urinary bladder
Kidneys*	Seminal vesicles	Uterus*
Large Intestine	Skeletal muscle	Orbital gland
Liver *	Skin	
Lungs	Small intestine	

*Organ weights collected

Peer Review: not reported

Histological Findings:

Histopathological findings were noted in the lungs, esophagus, liver, and kidneys. In all three rats that died, there was marked purulent inflammation and foreign body present in the mediastinum and on the pleura, chronic inflammation in the esophagus and in the trachea, congestion and hemorrhage in the lung and kidneys.

Six of 20 (6/20) male and (5/20) female rats in the 30 mg/kg/day group and 20/20 male and 14/20 female rats in the 100 mg/kg/day group showed slight hypertrophy of hepatocytes. A slight focal accumulation of foamy cells were noted in the lung alveoli of 13/20 males and 7/20 females in the highest (100 mg/kg/day) dose group. All other microscopic changes were comparable among treated and control animals and were considered incidental and not related to the test compound.

Dosing Solution Analysis:

Dose solutions were prepared fresh each day and were administered within 2 hours. Prior to initiation of the study, pretest samples of the dose suspension were analyzed for stability over 4 hours. Results revealed after 4 hours a concentration of 96-100% of the nominal value, whereas the initial concentration ranged 85-107%.

(Reviewer's comments: Repeat oral, daily dosing of rats for 90 days with (b) (4) *at 0, 3, 10, 30, and 100 mg/kg/day caused very minimal effects, with no significant clinical observations or systemic toxicity reported. Body weight and food consumption of treated animals were similar to controls, and there was a slight trend toward increased water consumption in the highest male and female dose group (100 mg/kg). Only minor changes on hematological and clinical chemistry parameters were noted, however these changes typically appeared minimal, lacked a dose response, or were within reported historical ranges for this strain. The investigator did not examine blood levels of test article and the ADME characteristics of* (b) (4) *were not determined in this study. Dose related increase in liver weights were noted in both sexes of rats treated with* (b) (4) *at 10 mg/kg/day, associated with slight hypertrophy of hepatocytes occurring with increased frequency at higher doses ≥ 30 mg/kg/day. A slight accumulation of foamy cells were noted in the alveoli of the lungs of nearly half the males and females in the highest dose group (100 mg/kg). The investigator reported a NOEL for* (b) (4) *administered daily for 90 days of 3.0 mg/kg bodyweight. The NOAEL for this study was 30 mg/kg/day under these study conditions).*

The clinical relevance of drug-induced liver changes caused by orally administered (b) (4) to the proposed intravenous route of administration of moxifloxacin remains unknown. Drugs administered intravenously often show greater systemic toxicity at lower doses when compared to oral administration. However, as this leachable was administered orally for 90 consecutive days to rats; perhaps a reduction of dose duration to 4 weeks similar to the other submitted nonclinical studies may offset some risk of toxicity by the intravenous route. In either case, without comparative plasma levels and toxicokinetic data, systemic delivery of (b) (4) could provide a lower NOEL and NOAEL dose when compared to this oral study leading to a reduced calculated PDE value for this compound.

In addition to the lack of plasma levels and toxicokinetic data for (b) (4) in this study, the lack of comparative ADME information (e.g. rate and extent of absorption; metabolism including first-pass effects; extent of tissue distribution; and tissue clearance and excretion properties) after oral and intravenous administration makes it difficult to compare between routes. Liver toxicity may be associated with first pass metabolism and distribution.

B. [redacted]

[redacted] hese compounds are reportedly commonly detected in migration and extraction studies of plastic containers. [redacted] was detected as a leachable from the Free*flex*® container in Moxifloxacin at a maximal concentration of [redacted] mcg/L; [redacted] was not detected in the migration studies. According to specifications, [redacted] contains [redacted] is not typically detected in migration studies [redacted] igure 3). Very little toxicology data are available in the literature and internet databases for [redacted]. [redacted] was qualified toxicologically in the evaluation below:

Figure 3. Degradation of [redacted]

Toxicity data for the risk assessment for [redacted] consists primarily of a repeat dose toxicology study in rats from which a PDE value was calculated. In addition, the Applicant conducted an AMES test with [redacted] to evaluate its mutagenic potential. The Applicant submitted both the 4-week i.v. toxicology study in rats and the bacterial reverse mutation assay in this NDA application. [redacted] showed no mutagenic potential when evaluated in a GLP compliant, bacterial reverse mutation assay (AMES, Study No. HKQ0016) in 4 Salmonella strains (TA98, 100, 1535, 1537) and an E.coli strain (WP2 uvrA) with and without metabolic activation (S9 mix from Aroclor-induced liver of male SD rats).

Data from the 4-week repeated, i.v. dose, rat toxicity study with (b) (4) was used by the Applicant to calculate its PDE value. In this study, groups of 10 rats/sex were administered (b) (4) i.v. in 0.9% saline at doses of 0, 12.5, 25, and 50 mg/kg/day. The NOEL for (b) (4) in rats was determined to be 12.5 mg/kg/day, based on minor incidences of vascular irritation in the lateral tail vein of a few animals observed at doses ≥ 25 mg/kg/day. The NOAEL dose was 50 mg/kg/day in this study. PDE for (b) (4) was calculated with the formula used for Solvent in accordance with ICH Guidance Q3C(R5).

$$PDE = \frac{NOEL\ (mg/kg/day) \times Weight\ Adjustment\ (50\ kg)}{F1 \times F2 \times F3 \times F4 \times F5}$$

F1 = factor for extrapolation between species
F2 = factor of 10 for variability between individuals
F3 = factor for short-term toxicity studies
F4 = factor for severe toxicity
F5 = variable factor if the no-effect level was not established

For (b) (4), the PDE was calculated with the factors (F1-F5) (Table 10).

Table 10. Calculation of PDE for (b) (4)

Reference	Study Type	Species	NOEL mg/kg/day	Modifying Factors	PDE mg
HLS HKQ0012, 2014	4-week repeated dose i.v. toxicity study	Rat	(b) (4)	F1=5, F2=10, F3=10, F4=1, F5=1	(b) (4)

(Reviewer's Comment: The Applicant proposed use of the NOAEL dose of 50 mg/kg/day for use in PDE calculation instead of the established NOEL dose of 25 mg/kg/day in the 4 week rat i.v. study, because the primary finding of vascular irritation in the tail vein observed with repeated administration of the test article occurred in a few animals at the highest dose. In addition, all other drug related effects observed at this high dose, including changes in body weight or hematology parameters lacked clinical relevance, occurred in a few animals of one sex, were mild in severity, lacked dose dependence, or were without any histological evidence of change. Although it is likely that the minor incidence of drug-related toxicity observed in the lateral tail vein of rats lacks clinical relevance, the established NOEL from that study was determined to be 25 mg/kg/day. In this case, the NOEL dose from the 4-week rat toxicity study with (b) (4) should be used in the PDE calculation as described in ICH Guidance Q3C(R5)).

Based on the findings from the 28 day repeated dose i.v. toxicity study in the rat, the calculated PDE for [(b) (4)] mg. A comparison of the estimated PDE ([(b) (4)] mg) to the maximum possible exposure of [(b) (4)] from the migration studies (7.783 mcmoles/L or 1334.7 mcg/L; or 0.334 mg/day in 250 mL of Moxifloxacin Injection administered daily; Table 6 above), showed the permitted daily exposure to be approximately **7.5** times greater than the maximum daily exposure. If it is assumed that the 2 rats that showed vascular irritability from repeated tail vein injections with the highest dose of [(b) (4)] (50 mg/kg/day) lacked clinical relevance, the use of this NOAEL dose in the calculation would increase the permitted PDE to 5 mg or 15 times greater than the maximum daily exposure. Therefore, it is agreed that in either case, the safety margin above the maximum possible exposure to [(b) (4)] is adequate, and there is no significant safety risk posed by exposure to [(b) (4)] as a leachable from the Freeflex i.v. bag containing Moxifloxacin.

(Reviewer's comment: Results from the recently submitted extraction study with the [(b) (4)] (from the Freeflex® i.v. bag) in ethanol [(b) (4)]% (v/v) showed a higher concentration of [(b) (4)] (11 mcmol/L) than in the migration studies with Moxifloxacin for Injection (7.783 mcmol/L). A revision of the calculated PDE with approximately a 1.5 times greater concentration of [(b) (4)] detected in the extraction studies (as a worst case scenario) would reduce the safety margin to approximately 5 times greater the maximum exposure levels which remains adequate in the toxicological risk assessment for this leachable compound.)

A review of the study design and summary of findings from both the 4-week i.v. rat toxicology study and the AMES test conducted with [(b) (4)] is included below:

1) **<u>Bacterial Reverse Mutation Test (Study No. HKQ0016; GLP)</u>**
   - **Objective**: GLP compliant study tested [(b) (4)] (Batch 047S-052S-EH; Purity: > [(b) (4)]%) for the ability to induce reverse mutations at the histidine locus in several strains of *S.typhimurium* and at the tryptophan locus of *E.coli* strain, in the presence/absence of a mammalian metabolic activation system (rat liver S9).
   - Experimental Start Date: 2/25/2014
   - Test Facility: [(b) (4)]
   - Strains: *S.typhimurium* (TA1535, TA1537, TA98, TA100); *E.coli* (WP2 *uvr*A)
   - Positive Control: (-S9: Sodium azide, 9-AA, 2-NF, 4-nitroquinoline-1-oxide), (+S9: 2-AA, Benzo[a]pyrene)
   - First Test with [(b) (4)] (50 mg/mL) in 7 concentrations (5-5000 mcg/plate) in DMSO ± S9 at 37°C for 72 hours showed toxicity at 5000 mcg/plate; no precipitate of test article detected up 5000 mcg/plate; and no increase in numbers of revertant colonies compared to assay and

historical controls for any tester strains up to 5000 mcg/plate of [redacted] in presence and absence of S9 mix.

- Second Test with [redacted] (50 mg/mL; 30 minute incubation before agar overly) in 5 concentrations (5-5000 mcg/plate) in DMSO ± S9 at 37°C for 72 hours showed toxicity at highest doses; precipitate of test article at 5000 mcg/plate; and no significant increase in numbers of revertant colonies compared to assay and historical controls for any tester strains up to 5000 mcg/plate [redacted], in the presence and absence of S9 mix.
- The negative vehicle and positive control articles confirmed the adequacy of the test system.
- Conclusion: [redacted] showed no evidence of mutagenic activity in this bacterial system under these test conditions.

2) Study title: [redacted]: Toxicity Study by Intravenous Infusion to CD Rats for 4 Weeks

Study no.:	HKQ0012
Study report location:	EDR
Conducting laboratory and location:	[redacted]
Date of study initiation:	3/5/2014
GLP compliance:	Yes (OECD GLP)
QA statement:	Yes
Drug, lot #, and % purity:	[redacted] batch #: 047S-052S-EH, [redacted]% pure; batch #: 053054S-EH, [redacted]% pure; batch #: 055/4-6S-A, [redacted]% pure.

Methods

Doses:	0, 12.5, 25, 50 mg/kg/day b.w.
Frequency of dosing:	Once daily for 28 consecutive days
Route of administration:	Intravenous
Dose volume:	1.25 to 5 mL/kg (rate: 2.5 mL/kg/min, 5 mL/kg saline flush to 1 mL max. volume)
Formulation/Vehicle:	0.9% saline solution
Species/Strain:	Rat (Crl:CD(SD))
Number/Sex/Group:	10/sex/group (total: n=80)
Age:	Males and females, ≈ 6 weeks old
Weight:	M: 206-257 g; F: 167-199 g
Satellite groups:	None.
Deviation from study protocol:	None that was noteworthy.

Study Design:

Group	Treatment	Dose level (mg/kg/day)#	Dose con. (mg/mL)	Dose volume (mL/kg)	Number of animals Male	Number of animals Female
1	Control	0	0	5	10	10
2	(b) (4)	12.5	10	1.25	10	10
3		25	10	2.5	10	10
4		50	10	5	10	10

As supplied.
Saline flush was administered as 5 mL/kg; up to a maximum of 1 mL saline.

Group	Treatment	Number of animals Male	Number of animals Female	Cage numbers Male	Cage numbers Female	Animal numbers Male	Animal numbers Female
1	Control	10	10	1-2	9-10	1-10	51-60
2	(b) (4)	10	10	3-4	11-12	11-20	61-70
3		10	10	5-6	13-14	21-30	71-80
4		10	10	7-8	15-16	31-40	81-90

Observations and Results

Mortality (2x daily)

None.

Clinical Signs (pre-test, 2x Daily):

No systemic test article related effects were observed at any dose level. Erythema and eschar formation was noted at the dose injection site on the tails from Days 4-6 in 1-3 males and in several females at 25 and 50 mg/kg/day. There were no similar incidences noted in controls or in animals administered 12.5 mg/kg/day. Pale areas on the tail associated with loss of flexibility, ulceration, and reddening of the tail were noted in one male at 25 mg/kg/day and one female at 25 and 50 mg/kg/day.

Several animals missed their scheduled daily dose of (b) (4) or saline flush on more than one occasion. The incidence appeared to be dose and volume related however the since the number of incidences was relatively few, this likely had minimal to no impact on study outcome (Table 11).

Table 4. Animal No. and Time of Missed Doses

Treatment	Day No.	Group/Sex/ Animal No.	Other information
0 mg/kg/day	25	1M 59	Had no flush as the needle flicked out at the end of dosing as the flush was about to be administered
12.5 mg/kg/day	2	2M 20	No flush given animal flicked needle out
	2	2F 63	No flush given animal flicked needle out
	2	2F 64	No flush given animal flicked needle out
	21	2F 63	Not dosed; unable to locate vein
	21	2F 68	No flush given animal flicked needle out
	26	2M 13	No flush given animal flicked needle out
25 mg/kg/day	4	3F 79	Not dosed due to signs seen on tail and unable to locate vein
	15	3F 77	No flush given animal flicked needle out
	19	3F 79	Not dosed; unable to locate vein
	21	3F 79	Not dosed; unable to locate vein
	22	3F 72	Not dosed; unable to locate vein
	26	3M 24	No flush given as cannula removed in error
50 mg/kg/day	7	4M 33	Small amount of dose appeared to be administered subcut
	7	4M 39	Small amount of dose appeared to be administered subcut
	8	4F 81	Not dosed; unable to locate vein
	14	4F 81	Not dosed; unable to locate vein
	18	4F 81	Not dosed; unable to locate vein
	19	4F 84	Not dosed; unable to locate vein
	21	4F 84	Not dosed; unable to locate vein
	21	4F 89	Not dosed; unable to locate vein
	22	4F 84	Not dosed; unable to locate vein
	24	4M 36	Not dosed; unable to locate vein
	25	4M 40	Had no flush given at the end of dosing as some dose noted to have gone subcut
	25	4F 82	Had no flush as the needle flicked out at the end of dosing as the flush was about to be administered
	27	4F 84	Not dosed; unable to locate vein
	28	4F 90	No flush given animal flicked needle out

(Table 1 on page 33 of the study report)

Body Weight (Pre-test, weekly, and at necropsy):

Overall mean body weight gains (Week 1-4) were significantly lower (-23%) in females receiving 50 mg/kg/day when compared to controls. Males at 50 mg/kg/day showed a trend toward slightly lower body weight gain than controls over the 4 weeks of treatment, although this body weight gain was not significant or statistically relevant. Group mean body weight at lower doses was similar between treated and control groups.

Food Consumption (Pre-test, weekly, and at necropsy):

Mean food consumption was unaffected by treatment.

Ophthalmologic Examination (Pre-study, and Week 4)

There were no ophthalmic changes observed related to treatment.

Hematology / Coagulation (blood samples collected pre-test and in Week 4 – blood collected from sublingual vein)

Male rats administered 50 mg/kg/day showed a 63% greater monocyte count compared with controls but females were not similarly affected. There was also a statistically significant 12% higher platelet count in the highest

dose males compared to controls, with no corresponding change in prothrombin time or activated partial thromboplastin time. Females were once again unaffected. There were no other significant differences in hematology parameters noted between treated and control animals.

Clinical Chemistry (blood samples collected pre-test and in Week 4 – blood collected from sublingual vein)

Male rats at 50 mg/kg/day showed a 12% higher serum glucose level, a 43% higher serum triglyceride level, and a 23% higher inorganic phosphate level compared to controls on Week 4. No changes in serum glucose, triglyceride, or phosphate levels were noted in female rats at any dose. There was a small reduction in the albumin to globulin (A/G) ration in males receiving 50 mg/kg/day; however no change in albumin or total protein levels were detected. Females were not similarly affected. The significance of these findings in males to treatment with (b) (4) remains unknown.

Urinalysis (Pre-test and in Week 4)

Female rats in the 50 mg/kg/day treatment group showed significantly higher urinary sodium (+23%) and total chloride (+42%) concentrations compared to controls. Males were not similarly affected. The relationship between (b) (4) treatment and these findings remains unclear.

Gross Necropsy (at necropsy)

Macroscopic findings were limited to injection site changes including depression of tissue at the injection site in 2 males and 1 female rat, and scabs that showed perivascular necrosis, epidermal ulceration observed by light microscopy. The nature and incidence of all other findings were consistent with commonly observed macroscopic changes and were considered unrelated to treatment.

Bone Marrow Smears (at necropsy)

Bone marrow smears appeared similar to controls.

Organ Weights (at necropsy; brain, heart, liver, kidneys, adrenals, thymus, and gonads weighed)

There were no organ weight differences attributable to treatment.

Histopathology (at necropsy)

Adequate Battery: Yes

Routine Tissues Collected:

Adrenal glands*	Ileum	Skeletal muscle
Aorta	Jejunum	Skin
Bone marrow smear	Kidneys*	Spinal cord
Brain*	Liver *	Spleen*
Caecum	Lungs	Stomach*
Colon	Lymph nodes	Testes*
Duodenum	Ovaries*	Thymus*
Epididymis*	Pancreas	Thyroid glands*
Esophagus*	Parenteral Site	Trachea
Eyes/optic nerve	Pituitary gland*	Urinary bladder
Femur	Prostate*	Uterus*
Harderian glands	Salivary glands	Vagina
Head	Sciatic nerves*	
Heart*	Seminal vesicles	

*Organ weights collected

Peer Review: not reported

Histological Findings:

Histopathological findings were limited to the injection sites in the lateral caudal vein of the tail (Table 12). The injection site showed slight to moderate epidermal ulceration and scabs at the highest dose in a few animals, and recanalized thrombi were present in many animals in all dose groups. Similar findings of thrombi related to repeated i.v. injections were present in control animals. The nature and incidence of all other findings were consistent with background microscopic changes commonly observed, and were considered incidental and unrelated to treatment.

Table 12. Histopathologic Findings at the Injection Site

Group/sex	1M	2M	3M	4M	1F	2F	3F	4F
Dose (mg/kg/day)	0	12.5	25	50	0	12.5	25	50
Thrombus, Recanalised								
Present	0	1	5	3	1	0	6	4
Proliferation, Vascular Intimal								
Minimal	1	2	1	1	0	3	1	1
Slight	1	1	3	0	2	2	2	2
Moderate	0	1	0	0	0	0	2	1
Marked	0	0	0	0	0	0	0	1
Total	2	4	4	1	2	5	5	5
Ulceration, Epidermal								
Minimal	0	0	0	0	0	0	0	0
Slight	0	0	0	1	0	0	0	0
Moderate	0	0	0	1	0	0	0	1
Total	0	0	0	2	0	0	0	1
Scabs								
Present	0	0	0	2	0	0	0	1
Number of tissues examined	10	10	10	10	10	10	10	10

Dosing Solution Analysis:

Dose solutions were prepared every 7 days in advance. Prior analysis of test article preparations showed (b) (4) to be stable in 0.9% saline for approximately 35 days at ambient temperature. No further testing of the dose solutions was performed. A sample of each dose solution prepared weekly for this study was archived with the bulk material.

(Reviewer's comments: Repeat, daily i.v. dosing of rats for 28 days with (b) (4) caused very minimal effects, with no significant clinical observations or systemic toxicity reported. Erythema and reddening at the injection site, associated with scan formation was reported for 4 animals total in the mid and highest dose groups. Several animals missed their scheduled daily dose of (b) (4) or saline flush, however, this appear to have had no impact on the study results. Body weight gain was moderately decreased (-23%) in females at the highest dose (50 mg/kg/day) compared to controls, and although males showed a similar trend towards decreased body weight gain at this dose, this decrease was not statistically significant. Food consumption appeared unaffected by treatment in either sex at all doses. Hematology and clinical chemistry changes relative to controls was limited to the 50 mg/kg/day dose group only, and generally appeared only in male rats. Increased levels of monocytes and platelets in male rats was unaccompanied by similar changes in other immune cell counts or in any coagulation parameters tested in this study. Similarly, greater levels of serum glucose, triglycerides, and inorganic phosphates in male rats at 50 mg/kg/day were unaccompanied by any changes in serum AST or ALT levels, or albumin or total protein. A slight decrease in albumin to globulin (A/G) ratios was observed in males of unknown toxicological relevance. In

all cases, female rats appeared generally unaffected in hematology and clinical chemistry test parameters. There were no corresponding microscopic changes in liver, or any other systemic tissues. Hematology and clinical chemistry changes observed in males lacked dose response and had no histological correlates, and therefore its relevance to the test article is unknown. Macroscopic and microscopic changes were limited to the injection site, indicative of a slight vascular irritation, in a few animals. The NOEL for (b) (4) *administered daily for 28 days was 25 mg/kg/day. The NOAEL for this study was 50 mg/kg/day under these study conditions.*

C. (b) (4)

(b) (4) Figure 4). (b) (4) was detected as a leachable from the Free*flex*® container in Moxifloxacin at a maximal concentration of (b) (4) mcg/L. (b) (4) eachable levels were not measured in the migration studies, their toxicity profile is well known; all three compounds were qualified in the toxicology evaluation below.

Figure 4. Degradation of (b) (4)

(b) (4)

Overview of toxicity data (provided in the Application)

1. (b) (4)

- **ECHA (European Chemical Agency). Registered Substances**. Last update July 29, 2013. (http://echa.europa.eu/information-on-chemicals/registered-substances)
- **OECD Existing Chemicals Databse/SIDS Report** (http://webnet.oecd.org/HPV/UI/SIDS_Details.aspx?key=d72b39a1-f434-42cd-be2d-d7232b27fc31&idx=0)

- LD_{50} rat oral: 5560 mg/kg
- 3 months rat oral feed study (1953): NOEL=200 mg/kg, PDE = (b) (4) mg
- Negative for genetic toxicity in vitro (e.g. AMES, human lung embryonic fibroblast cells), and in vivo (e.g. chromosomal aberration and dominant lethal assays)

A comparison of the estimated PDE ((b) (4) mg) to the maximum possible exposure of adipic acid (from (b) (4)) from the migration studies (606 mcg/L, or 0.152 mg/day in 250 mL of Moxifloxacin Injection administered daily; Table 6 above), assuming worst case where all of the (b) (4) showed the PDE value to be approximately 263 times greater than the maximum daily exposure. Therefore, there is no significant safety risk posed by exposure to (b) (4) degradant of the (b) (4) leachable compound from the Free*flex* bag containing Moxifloxacin.

2. (b) (4)

- **ECHA (European Chemical Agency). Registered Substances**. Last update July 29, 2013. (http://echa.europa.eu/information-on-chemicals/registered-substances)
- **OECD Existing Chemicals Database/SIDS Report** (http://webnet.oecd.org/HPV/UI/SIDS_Details.aspx?key=eaeb01d3-7ac1-421a-b361-a44c1559f833&idx=0)

- LD_{50} rat oral: 25 g/kg
- 225 days rat oral study: NOEL=50 mg/kg, **PDE =(b) (4) mg**
- Negative for genetic toxicity in vitro (e.g. AMES, chromosomal aberration assay) and in vivo (e.g. 2-year rat carcinogenicity study)

A comparison of the estimated PDE (b) (4) mg) to the maximum possible exposure of (b) (4) to patients from the migration studies (606 mcg/L, or 0.152 mg/day in 250 mL of Moxifloxacin Injection administered daily; Table 6 above), assuming worst case where all of the (b) (4), showed the permitted daily exposure to be approximately 164 times greater than the maximum daily exposure. Therefore, there is no significant safety risk posed by exposure to (b) (4) degradant of the (b) (4) leachable compound from the Freeflex bag containing Moxifloxacin.

3. (b) (4)

Toxicity data for the risk assessment for the parent compound, (b) (4) consists primarily of a repeat dose i.v. toxicology study in rats from which a PDE value was calculated. In addition, the Applicant provides summary data from an in vitro bacterial mutagenicity assay (AMES test) conducted with (b) (4) contained on the ECHA (European Chemicals Agency) Registered

substances database website.[3] The Applicant submitted the 28 day day oral toxicology study in rats and findings from the in vitro bacterial reverse mutation assay conducted to evaluate the mutagenic property of (b) (4). (b) (4) showed no mutagenic potential when evaluated in a GLP (OECD) compliant, AMES bacterial reverse mutation assay (2000) in 4 Salmonella strains (TA98, 100, 1535, 1537) and an E.coli strain (WP2 uvrA) with and without metabolic activation (S9 mix from Aroclor-induced liver of male SD rats) (ECHA 2013).

Data from the 4-week repeated, i.v. dose, rat toxicity study (HKQ0014) was evaluated by the Applicant to calculate the PDE of (b) (4). In this study, groups of 10 rats/sex were administered (b) (4) i.v. in (10% DMSO/1% HP-β-CD) at doses of 0, 7.5, 15, and 25 mg/kg/day. All of the animals in the 25 mg/kg/day treatment group were euthanized early due to significant toxicity to the tail including discoloration, reddening, thickening, and eschar formation observed at the injection site. In addition, no NOEL dose could be determined for (b) (4) in this study because most of the effects and nearly all of the histological findings, including significant tail vein irritation and inflammation, were also observed in the DMSO/HP-β-CD vehicle control group. Because the frequency and severity of the tail effects were slightly greater at 15 mg/kg/day compared to the vehicle control, it's likely that (b) (4) also shows toxicity to the vasculature of the tail vein. Therefore, a conservative NOAEL would be 7.5 mg/kg/day (and not 15 mg/kg/day as determined by the study director). The PDE for (b) (4) was calculated with the formula generally used for Solvents in accordance with ICH Q3C(R5). The use of the NOAEL of 7.5 mg/kg/day in this calculation as the NOEL dose by the Applicant assumes that the vascular effects in tail vein lack clinical relevance, and are likely caused by the vehicle and not the direct toxicity of the test article itself.

$$\text{PDE} = \frac{\text{NOEL (mg/kg/day)} \times \text{Weight Adjustment (50 kg)}}{F1 \times F2 \times F3 \times F4 \times F5}$$

F1 = factor for extrapolation between species
F2 = factor of 10 for variability between individuals
F3 = factor for short-term toxicity studies
F4 = factor for severe toxicity
F5 = variable factor if the no-effect level was not established

For (b) (4), the PDE was calculated with the factors (F1-F5) (Table 13).

[3] ECHA 2013 (http://echa.europa.eu/web/guest/information-on-chemicals/registered-substances).

Table 5. Calculation of PDE for (b) (4)

Reference	Study Type	Species	NOEL mg/kg/day	Modifying Factors	PDE mg
HLS HKQ0014, 2014	4-week repeated dose i.v. toxicity study	Rat	(b) (4)	F1=5, F2=10, F3=10, F4=1, F5=1	(b) (4)

Based on the findings from the 28 day repeated dose i.v. toxicity study in the rat, the calculated PDE for (b) (4) **mg**. A comparison of the estimated PDE ((b) (4) mg) to the maximum possible exposure of (b) (4) to patients from the migration studies (606 mcg/L, or 0.152 mg/day in 250 mL of Moxifloxacin Injection administered daily; Table 6 above), showed the permitted daily exposure to be approximately 5 times greater than the maximum daily exposure. Therefore, there is no significant safety risk posed by exposure to (b) (4) as a leachable from the Freeflex i.v. bag containing Moxifloxacin.

(Reviewer's comment: Results from the recently submitted extraction study with the (b) (4) *(from the Freeflex® i.v. bag) in ethanol* (b) (4) *% (v/v) showed no change in the concentration of* (b) (4) *detected in the migration studies with Moxifloxacin for Injection.)*

The Applicant submitted a standard 28 day intravenous toxicology study with (b) (4) in rats, and findings from a bacterial reverse mutation assay to evaluate the mutagenic property of (b) (4).[4] A description of the study design and summary of findings from both the 28 day i.v. rat toxicology study and the AMES assay with (b) (4) are included below:

A. <u>Bacterial Reverse Mutation Test (GLP)</u>

- **Objective**: GLP compliant study tested (b) (4) (Batch B74; Purity: (b) (4) %) for the ability to induce reverse mutations at the histidine locus in several strains of *S.typhimurium* and at the tryptophan locus of *E.coli* strain, in the presence/absence of a mammalian metabolic activation system (rat liver S9).
- Experimental Start Date: 2000
- Test Facility: (b) (4)
- Strains: *S.typhimurium* (TA1535, TA1537, TA98, TA100); *E.coli* (WP2 *uvr*A)
- Positive Control: (-S9: N-methyl-N'-nitro-N-nitrosoguanidine, 9-aminoacridine, 4-nitro-o-phenylendiamine, 4-nitroquinoline-1-oxide), (+S9: 2-aminoanthracene)

[4] ECHA 2013: (http://echa.europa.eu/web/guest/information-on-chemicals/registered-substances)

- First Test with (b) (4) in 7 concentrations (2-2500 mcg/plate) in DMSO ± S9 at 37°C for 48-72 hours showed toxicity at > 500 mcg/plate; no precipitate information was provided; and no significant increase in numbers of revertant colonies compared to assay and historical controls for any tester strains up to 2500 mcg/plate of (b) (4), in presence and absence of S9 mix.
- Second Test with (b) (4) in 5 concentrations (0-5000 mcg/plate) in DMSO ± S9 at 37°C for 48-72 hours showed toxicity at highest doses; no precipitate information was provided; and no significant increase in numbers of revertant colonies compared to assay and historical controls for any tester strains up to 5000 mcg/plate of (b) (4), in the presence and absence of S9 mix.
- The negative vehicle and positive control articles confirmed the adequacy of the test system.
- Conclusion: (b) (4) showed no evidence of mutagenic activity in this bacterial system under these test conditions.

B. Study title: cyclic diethyleneglycol adipate (cDEGA): Toxicity Study by Intravenous (Bolus) Administration to CD Rats for 4 Weeks

Study no.:	HKQ0014
Study report location:	EDR
Conducting laboratory and location:	(b) (4)
Date of study initiation:	2/12/2015
GLP compliance:	Yes (OECD GLP)
QA statement:	Yes
Drug, lot #, and % purity:	cDEGA, batch #: 9-EQJ-134-2, (b) (4)%

Methods

Doses:	0, 7.5, 15, 25 mg/kg/day b.w.
Frequency of dosing:	Once daily for 28 consecutive days
Route of administration:	Intravenous
Dose volume:	5 mL/kg (1 mL/min), 0.5 mL saline flush
Formulation/Vehicle:	10% DMSO in 1% HP-β-CD
Species/Strain:	Rat (Crl:CD(SD))
Number/Sex/Group:	10/sex/group, except saline control: 5/sex/group (total: n=90)
Age:	Males and females, ≈ 7-8 weeks old
Weight:	M: 244-313 g; F: 158-210 g
Satellite groups:	0.9% Saline control group
Deviation from study protocol:	Group 5 animals were not dosed on SD 12, 13. Group 5 (25 mg/kg/day) was terminated early on SD 15 due to adverse test article effects at the injection site and poor condition of the tails.

Study Design:

Group	Treatment	Dose (mg/kg/day)*#	Number of animals		Cage numbers		Animal numbers	
			Male	Female	Male	Female	Male	Female
1	Saline Control	0	5	5	1	10	1-5	51-55
2	Vehicle Control	0	10	10	2-3	11-12	6-15	56-65
3	(b) (4)	7.5	10	10	4-5	13-14	16-25	66-75
4		15.0	10	10	6-7	15-16	26-35	76-85
5		25.0	10	10	8-9	17-18	36-45	86-95

As supplied.
* Dose (mg/kg/day) selected in conjunction with the Sponsor.

Observations and Results

Mortality (2x daily)

One male (No. 26) in the 15 mg/kg/day group was found dead on Study Day (SD) 7. The rat had exhibited rapid respiration and dull eyes on SD 6, and elevated gait, hunched posture, piloerection, and lachrymation immediately after dosing on SD 7, and was found dead one hour later. There were no macroscopic or microscopic changes that could indicate a cause of death. This particular animal had no tail lesion.

Group 5 (25 mg/kg/day) was terminated early on SD 15 due to the poor condition of their tails after repeated daily administration of (b) (4). The tails of many animals became discolored (reddened/whitened) during or immediately after administration on SD 5 and increasing numbers of animals in this group were not dosed because of difficulty locating the tail vein. Treatment was stopped on SD 12 and 13 and three males (No 40, 41, 43) and two females (Nos. 86 and 92) were euthanized on Day 14 due to the condition of their tails (dark/black color at distal end, thickening, loss of flexibility, pale/white areas, reddening, bruising, swollen, eschar formation). Twelve of 15 animals scheduled for dosing on Day 14 could not be dosed. Group 5 was terminated on SD 15.

Clinical Signs (pre-test, 2x daily):

Rats in the highest dose group (25 mg/kg/day) showed transient, rapid respiration after dosing, observed in a few animals on SD 1 and 2, and in a majority of animals on SD 3 to 7. Most animals had a dull appearance of the eyes on SD 5-7 and 2 animals showed an unsteady gait on SD 3, 4, and 7. Decreased activity was noted in several animals in the high dose group during the first four days of treatment. Three female rats showed pallor on SD 4 and red tinged urine was noted in two animals on SD 4 or 6.

Dark, pale areas and/or scabs were noted on the tails from a majority of the animals in Group 5. Several animals had tails that appeared flaccid, or rigid, or swollen. Dark and pale areas correlated microscopically with soft tissue inflammation and/or venous thrombosis in most animals.

Group/sex Dose (mg/kg/day)	5M 25.0	5F 25.0
Dark area(s)	7	7
Pale area(s)	6	2
Scab(s)	4	6
Flaccid	1	1
Rigid	1	1
Swollen	1	0
Number of animals examined	[a]10	[a]10

[a] includes unscheduled decedents and animals terminated early, on Day 15

Enlarged lumbar lymph nodes were noted in two males and two females at 25 mg/kg/day. Enlarged axillary and inguinal lymph nodes were observed in one female each at 25 mg/kg/day. Lumbar and inguinal lymph node enlargement correlated microscopically with sinus histiocytosis and was considered secondary to tail inflammation or bacterial infection.

There were several incidences of missed doses in rats from the 7.5 and 15 mg/kg/day dose groups because of difficulty finding the tail vein. However the investigator noted all males and 7/10 females at 15 mg/kg/day were successfully dosed on at least 26 occasions. There were few incidences of reddening of the tip of the tail in 2 females on Day 6 and a bruised tail was reported in one female on SD 8 and 8. Red tinged urine was noted in a few animals on SD 5, 6, 18, and 25.

At 7.5 mg/kg, 17/20 rats were administered their scheduled daily dose. No changes were noted in the tails of any animals in this group. Similarly, no changes were noted in the tails of animals treated with the vehicle (10% DMSO in 1% HP-β-CD) or with saline; all control animals were successfully dosed on a daily basis.

Rapid breathing was commonly observed in many animals after dosing at 7.5 and 15 mg/kg/day during the first few days of dosing. Females at 15 mg/kg/day occasionally showed decreased activity, irregular, shallow or slow respiration; whole body pallor; piloerection; hunched or flat posture; prostration; and red tinged urine.

Body Weight (Pre-test, weekly, and at necropsy):

Overall mean body weight gains were similar between vehicle control and saline control groups. Overall mean body weight gains (Week 1-4) for males and females treated at 7.5 and 15 mg/kg/day were similar to vehicle and saline control groups. In Week 1, male and female rats at 25 mg/kg/day showed a markedly reduced body weight gain approximately 50% that of vehicle and saline control animals. By the end of the second week of dosing, mean body weight gains of females in the 25 mg/kg/day group were 50% greater than in the vehicle and saline control groups. Male rats at 25 mg/kg/day showed similar weight gain as the vehicle control.

Food Consumption (Pre-test, weekly, and at necropsy):

Overall food consumption was similar between vehicle and saline control groups. Overall mean food consumption (Weeks 1-4) for males and females treated at 7.5 and 15 mg/kg/day appeared marginally lower than vehicle controls, but lacked a dose relationship and statistical relevance. Mean food consumption in male rats in the highest dose group showed a slight 12% reduction compared to vehicle controls; females were similar to controls.

Ophthalmologic Examination (Pre-study, and Week 4)

There were no ophthalmic changes related to treatment.

Hematology / Coagulation (blood samples collected pre-test, Day 15 (Group 5 early termination), and in Week 4 – blood collected from sublingual vein)

Blood samples taken prior to termination of animals in the 25 mg/kg/day showed relatively high counts for reticulocytes and neutrophils as well as variations in red blood cell size and red cell distribution width. These values were not reported in the tables.

Male and female rats administered 15 mg/kg/day showed slight, but statistically significant reductions in hemoglobin levels (- 7-10%), red blood cell counts (-14%), and mean cell hemoglobin concentration (-3-4%); with statistically relevant increases in reticulocyte number (+ 172% and +63%, respectively), mean cell hemoglobin (+ 6-8%), mean cell volume (+9-13%); and red cell distribution (+ 11-12%). Similarly, increased WBC counts (+31-38%), lymphocyte number (+26-29%), and platelets (+12-26%) were observed in males and females in this group compared to vehicle control.

Male and female rats in the 7.5 mg/kg group showed a similar pattern of statistically relevant reductions and increases for many of the same parameters as the higher dose, however these differences were very slight (< 10%) and likely not biologically relevant.

There were slight differences (increases and decreases) in the group mean values for nearly every hematology parameter tested between the vehicle and saline control animals. It's likely that many of the changes included effects of the vehicle that were magnified in a dose related manner by treatment with (b) (4) at 15 mg/kg/day. All comparisons reported for statistical significance were in comparison with hematology values from the vehicle control animals. There were no other differences in hematology or coagulation parameters that were considered attributable to (b) (4)

(Reviewer comment: The effect of (b) (4) on several red blood cell parameters is likely a drug related effect, associated microscopically with extramedullary hematopoiesis in the spleen. Dose related increase in WBC and lymphocyte counts may be a response to chronic inflammation and perhaps bacterial infection in the tails and lungs observed microscopically in the affected animals. Increased platelet counts may also be secondary to inflammation as mild to moderate elevated platelet counts are commonly

observed when chronic inflammation is present. Extramedullary hematopoiesis can also occur during infection or inflammation.)

Clinical Chemistry (blood samples collected pre-test, Day 15 (Group 5 early termination), and in Week 4 – blood collected from sublingual vein)

(b) (4) had no significant effect on any clinical chemistry parameters in any treated animals in the 7.5 and 15 mg/kg/day groups compared to the saline and vehicle controls.

Blood chemistry samples from animals in the 25 mg/kg/day group showed slightly increased ALT, glucose and triglyceride levels, and low urea and creatinine concentrations. The applicant believes that these changes reflect the overall poor general health of the animals rather than an effect of treatment with (b) (4) The serum chemistry data for the animals in the 25 mg/kg/day were not included in the report.

(Reviewer's comment: Since these animals were euthanized early and these values are not included in the report, it is difficult to conclude that these changes are not attributable to treatment with (b) (4) The Applicant should have included the data for the high dose animals in the tables).

Urinalysis (Pre-test and in Week 4; Groups 1-4)

There were no differences in urinalysis parameters between any groups that were considered attributable to treatment with (b) (4)

Gross Necropsy (at necropsy)

There were no test-article related macroscopic findings in any control or treated animals that were administered (b) (4) for 4 weeks. Gross necropsy findings from animals in the 25 mg/kg/day group were not included in this report.

Bone Marrow Smears (at necropsy)

Bone marrow smears for treated animals appeared similar to saline and vehicle controls. Bone marrow smears of animals in the 25 mg/kg/day were not included in this report.

Organ Weights (at necropsy; brain, heart, liver, kidneys, adrenals, thymus, and gonads weighed)

Mean absolute and body weight adjusted spleen weights were higher in males (≈ 37) and females (≈ 13%) in the 15 mg/kg/day group compared to the vehicle control, but were only statistically different in males in this group. Very slight increase in body weight adjusted kidney and liver weights were noted in females in this group; males appeared similar to vehicle control. Organ weights for high dose animals in the 25 mg/kg/day were not included in this report.

Histopathology (at necropsy; Groups 1, 2, 4, and 5 full tissue list; Group 3 – Spleen, liver, lungs, and injection site only)

Adequate Battery: Yes
Routine Tissues Collected:

Adrenal glands*	Ileum	Skeletal muscle
Aorta	Jejunum	Skin
Bone marrow smear	Kidneys*	Spinal cord
Brain*	Liver *	Spleen*
Caecum	Lungs	Stomach*
Colon	Lymph nodes	Testes*
Duodenum	Ovaries*	Thymus*
Epididymis*	Pancreas	Thyroid glands*
Esophagus*	Parenteral Site	Trachea
Eyes/optic nerve	Pituitary gland*	Urinary bladder
Femur	Prostate*	Uterus*
Harderian glands	Salivary glands	Vagina
Head	Sciatic nerves*	
Heart*	Seminal vesicles	

*Organ weights collected

Peer Review: not reported

Histological Findings:

Histopathological findings were limited to spleen, lungs, and the injection sites in the lateral caudal vein of the tail. Extramedullary hematopoiesis was noted in the spleen of animals in all groups included controls, but was of dose-related increase in incidence and severity in males at 7.5 mg/kg/day and in both sexes at 15 mg/kg/day groups when compared to both controls.

The injection site showed acute and chronic thrombi present in many animals in all dose groups. Similar findings of thrombi related to repeated i.v. injections were present in the vehicle control animals, but not in the saline control animals. Perivascular inflammation in the tail was seen in all treatment groups and in the vehicle control, but not in saline control animals. Slightly greater incidence and severity of inflammation was noted at 15 mg/kg/day (b) (4) compared to vehicle control. Inflammation was chronic in nature, characterized by presence of mononuclear inflammatory cells cuffing the lateral veins and infiltrating surrounding tissue. Perivascular hemorrhage was noted in many animals from all treatment and control groups, however a notable increase in incidence and severity was observed in females administered 15 mg/kg/day (b) (4)

Minimal to slight thickening of pulmonary arterioles and intra-alveolar foamy cell macrophages were observed in lungs in both sexes in all treatment groups and in the vehicle control, but no in the saline controls. In the absence of a clear relationship to the test article, it's possible that these

findings may be related to the vehicle. Similarly, perivascular inflammatory cell infiltrates and granulomas were observed in the lungs of both sexes in all groups, including both controls, but were of greater incidence and severity in vehicle and (b) (4) groups. This finding may also be related to the vehicle or i.v. dosing procedure.

There were no other histological changes attributed to treatment. Histology findings in Group 5 (25 mg/kg/day) were not included in the final report.

(Reviewer's Comment: Complete histopathology evaluation was scheduled to be conducted on all animals that die or are euthanized early, for both control groups and Group 4 (15 mg/kg/day); and on spleen, lung, and injection site for Group 3; and for abnormalities only in Group 5. Histopathology findings from Group 5 or any of the animals that died or were euthanized early were not included in this report. Histopathology was noted in all 3 tissues evaluated in animals from Group 3. All tissues from Groups 3 and 5 should have been evaluated for histopathology to provide a more comprehensive evaluation of systemic toxicity. However, because the findings in the tissues evaluated in animals from Group 4 (15 mg/kg/day) showed fairly minor findings often indistinguishable from the toxicity of the vehicle control, it is likely that a complete evaluation of the tissues from the lower dose group may not have provided useful information).

Dosing Solution Analysis:

Dose solutions were prepared within 9 days in advance for use. Prior analysis of the test article preparations showed (b) (4) to be stable in 10% DMSO in 1% HP-β-CD for approximately 9 days at 2-8°C. A sample of each dose solution prepared for this study on Weeks 1-4 were analyzed for achieved concentration of the test article. The mean concentration of (b) (4) in test formulations analyzed for this study was between +0.3% and -6.0% of nominal concentrations.

(Reviewer's comments: Repeat, daily i.v. dosing of rats for 28 days with (b) (4) dissolved in 10% DMSO in 1% (HP-β-CD) showed this formulation to be a vascular irritant and fairly toxic to the lateral tail vein when administered intravenously. The Applicant believes that the vascular toxicity observed in the rat tail of animals treated with 15 and 25 mg/kg/day that led to the unscheduled euthanization of all Group 5 (25 mg/kg/day) animals, was primarily due to the vehicle and was exacerbated with (b) (4), particularly at the highest dose (25 mg/kg/day). DMSO is a well-known vascular toxicant that can cause vasospasms and vascular wall irritation. Despite the slow bolus injection reported for this study (1 mL/min), it's possible that the DMSO/HP-β-CD vehicle alone could have caused sufficient vascular toxicity, enhanced by whatever vascular irritation (b) (4) may cause. Regardless, it was often difficult to distinguish (b) (4) toxicity from that of the vehicle itself and likely was not a good choice of a vehicle to use in this study. Nearly all

of the lowest dose animals (7.5 mg/kg/day), and all of the controls were administered all of the scheduled doses over the 4 week treatment period.

Other than body weight information, none of the data obtained from the high dose treatment group (25 mg/kg/day) was included in this report. It's likely this data would have provided added value in determining the systemic toxicity profile of (b) (4) *even after just 14 days of dosing.*

Intravenous treatment with (b) (4) *showed slight effects on several hematology parameters, including effects on red blood cells (hemoglobin, RBC counts, mean hemoglobin concentration, reticulocyte number, mean cell volume, and red cell distribution); white blood cells, lymphocytes, and platelets. It is not clear if* (b) (4) *causes direct toxicity to the red blood cell itself, but RBC counts and hemoglobin do decrease in a dose dependent fashion and the red tinged urine observed in the bedding may be related to this effect. Also, the increase in reticulocyte number (correlating with extramedullary splenic hematopoiesis (EH) microscopically) appears independent of any bone marrow changes as bone marrow smears appeared similar to controls. WBC and lymphocyte counts increased in a dose dependent fashion, either in a systemic response to the test article, to inflammation detected microscopically in the lung, or secondary to injury to the tail and possible infection. Increased platelet count and EH are often observed with inflammation and infection.*

There were no changes in any clinical chemistry parameters in animals administered (b) (4) *i.v. up to 15 mg/kg/day or in both controls. There does not appear to be any direct organ toxicity noted in any of these parameters and other than the vascular toxicity and inflammation observed at the injection site, there does not appear to be any histopathological findings that could be attributed to treatment in animals dosed i.v. for 4 weeks. Again, the animals in the highest dose group euthanized early were not evaluated for histopathology.*

Overall (b) (4) *appeared to be fairly well tolerated at 7.5 and 15 mg/kg/day, though there was local toxicity at the site of injection, and a mild test article related inflammation and anemia associated with an expected hematopoietic response. At higher doses, the poor condition of the tail from repeated treatment of the test article required early euthanization of all high dose animals. The NOEL for* (b) (4) *could not be determined from this study, particularly because the vehicle control often showed evidence of toxicity compared to the saline control. The Applicant determined the NOAEL to be 15 mg/kg/day. However, in light of the test article related changes to several hematology parameters in the 15 mg/kg/day group for both RBC cells and leukocytes, associated with histological evidence of extramedullary hematopoiesis and increased spleen organ weight observed in this treatment group, the NOAEL likely should be 7.5 mg/kg/day under these study conditions.*

Integrated Summary and Safety Evaluation

The current submission from FK, USA, is a Class 2 resubmission of a 505(b)(2) NDA Application for Moxifloxacin for Injection (400 mg/250 mL), as a general antibiotic indicated in the treatment of infections. The Sponsor's current formulation of the proposed drug product is nearly identical to the RLD Avelox® (moxifloxacin hydrochloride, Bayer Healthcare, NDA #021277), with identical active ingredient, drug strength (1.6 mg/mL) and route of administration; however, the new drug formulation will include two additional excipients (sodium acetate trihydrate and disodium sulfate), and eliminate sodium chloride from the final drug formulation. At this time, no new drug substance impurities have been identified and there are no safety concerns with the proposed drug substance or drug product specifications. The pharmacology/toxicology relevant sections of the labeling shall remain identical to the RLD, except in replacement of the drug name (e.g. Avelox® to moxifloxacin) and product description.

The original NDA application submitted 6/6/2013 by FK, USA received a Complete Response from the Division on 4/4/2014 primarily due to deficiencies in CMC product quality, and deficiencies noted in the referenced Master File for the Free*flex*® container system (MF 26696). Long-term stability studies of Moxifloxacin in the Free*flex*® bag identified 3 leachables (b) (4)) of unknown toxicological risk. In response to a requirement for additional toxicity data for these leachables, the Applicant conducted GLP-compliant, repeated dose toxicology and/or genetic toxicology studies with the leachable compounds. Findings from these nonclinical studies and safety information obtained from various toxicology databases were used to revise the calculated the permitted daily exposure (PDE) values, provide updated safety margins for each leachable to the maximum possible exposure, and reassess the toxicological risk of detected concentrations of leachables to patients to be administered the drug product. The Applicant conducted a 90-day, repeated dose, oral toxicology rat study with (b) (4); 4-week, repeated dose i.v. toxicology rat studies with (b) (4); and AMES tests with (b) (4). The Sponsor referenced published genetic toxicology information for (b) (4), and complete toxicology information the 2 hydrolysis products of (b) (4)

Animal toxicology studies conducted with all three leachables showed these compounds to be generally well tolerated at concentrations that far exceed levels detected in the drug product from the Free*flex*® container. Repeated oral administration of (b) (4) (in 0.5% carboxymethyl-cellulose/0.1% Tween-80) for 90 days up to 100 mg/kg/day showed minimal effects with no significant clinical observations or systemic toxicity reported. A slight accumulation of foamy cells in the lung alveoli at 100 mg/kg/day of unknown cause or toxicological consequence established the NOAEL for this study at 30 mg/kg/day. The NOEL for this study was determined to be 3 mg/kg/day, due to dose related increase in liver weights associated with microscopic evidence of slight hypertrophy of hepatocytes at doses ≥ 30 mg/kg/day. Although the investigator did not determine the systemic drug levels of (b) (4), systemic absorption of at least 50% of the administered dose was assumed due to dose related

changes in liver weights and histology of the liver. The permitted daily exposure (PDE) level incorporating the NOEL dose from this study results in a PDE of (b) (4) mg (or (b) (4) mg assuming 50% oral absorption), with an approximate safety margin of 12.5 times the maximum daily exposure of (b) (4) detected in the migration studies. In addition, (b) (4) showed no mutagenic potential in the AMES assay. The toxicological risk assessment for (b) (4) was deemed adequate, and no significant safety risk is expected from (b) (4) as a leachable in Moxifloxacin for Injection in the Free*flex* i.v. bag.

Repeated i.v. administration of (b) (4) in 0.9% saline for 4 weeks for up to 50 mg/kg/day similarly showed minimal effects with no significant clinical observations or systemic toxicity reported. The primary toxicity was observed at the injection site in only 4 animals at 25 and 50 mg/kg/day, with observations of erythema and reddening, along with histological evidence of vascular irritation of low incidence and severity in a few animals. All other changes including a slight decrease in body weight gain noted in females at the highest dose, or increased monocyte and platelet counts observed in males at the highest dose, occurred in only one sex, lacked dose dependence, or were without histological correlates. The NOAEL for this study was determined to be 50 mg/kg/day; the NOEL was 25 mg/kg/day due to the slight effects noted in the tail with repeated injection for 28 days. Although it's likely the minor vascular irritability noted at the injection site on the in the lateral tail vein lacks clinical relevance, the established NOEL dose of 25 mg/kg/day was used to calculate a PDE value for (b) (4) mg. A comparison of the calculated PDE value to the maximum daily exposure to (b) (4) detected in the migration studies reveals a safety margin of approximately 7.5. The Applicants proposed use of the NOAEL dose of 50 mg/kg/day further increases the safety margin to 15 times above the maximum exposure level of (b) (4) detected in the migration studies. As (b) (4) I showed no mutagenic potential in the AMES assay, the toxicological risk assessment for (b) (4) I was deemed adequate, and no significant safety risk is expected from this leachable in Moxifloxacin for Injection in the Free*flex* i.v. bag.

The risk assessment for (b) (4) incorporated an evaluation of both (b) (4) and its two hydrolysis products, (b) (4). A search of the various toxicology databases including ECHA (2013) showed (b) (4) to be well tolerated in rat feed studies up to 90 days and 225 days, with reported NOEL doses determined to be 200 mg/kg and 50 mg/kg respectively. In addition, neither degradants was found to have mutagenic potential in multiple in vitro and in vivo genetox studies. A comparison of the calculated PDE values of 40 mg and 25 mg to the maximum daily exposure values (worst case assuming 100% conversion of (b) (4) to each hydrolysis product) showed the PDE to be 263 and 164 times greater than the potential maximum daily exposure, respectively. The toxicological risk assessments for adipic acid and diethylene glycol were deemed adequate, and no significant safety risk is expected from this potential leachables in Moxifloxacin for Injection in the Free*flex* i.v. bag.

Repeated i.v. administration of (b) (4) (in 10% DMSO in 1% HP-β-CD) for 4 weeks for up to 25 mg/kg/day showed vehicle related toxicity to the injection site on the lateral tail vein of most animals at all doses, included the vehicle control. DMSO is a well-known vascular toxicant, and when administered repeatedly by i.v. injection at high concentrations in a bolus dose, it's not uncommon to observe injection site toxicity. Saline control animals did not show tail vein toxicity. In addition, adverse effects on the tail observed at 15 and 25 mg/kg/day appeared to be exacerbated by (b) (4), leading to unscheduled euthanization of all high dose animals on SD 15. Isolated incidences of missed doses were noted for few animals in most groups because of the difficulty in finding the tail vein. It is not clear if (b) (4) is a direct RBC toxicant, however (b) (4) administration at 25 mg/kg/day caused a decrease in RBC counts and hemoglobin, associated with a significant increase in reticulocyte number and histological evidence of extramedullary splenic hematopoiesis (EH). WBC and lymphocyte counts also increased in a dose dependent fashion, either in systemic response to the test article, or in response to mild lung inflammation, tail injury, or related infection. Increased platelet counts and EH noted in animals at 25 mg/kg/day are often associated with inflammation and infection. (b) (4) was generally well tolerated at 7.5 and 15 mg/kg/day; the NOAEL of this study was determined to be 15 mg/kg/day. Because the NOEL could not be determined because of the toxicity attributed to the vehicle itself, the lowest dose tested (7.5 mg/kg/day) was used to calculate a PDE value for (b) (4) mg. A comparison of the calculated PDE value to the maximum daily exposure to (b) (4) detected in the migration studies reveals a safety margin of approximately 5. As (b) (4) reportedly has no mutagenic potential in several in the AMES assay (ECHA 2013), the toxicological risk assessment for (b) (4) was deemed adequate, and no significant safety risk is expected from this leachable in Moxifloxacin for Injection in the Free*flex* i.v. bag.

Recommendation: From a pharmacology/toxicology perspective, NDA 205572 (Class 2 resubmission) for Moxifloxacin for Injection is approvable. None of the leachables detected in long-term stability studies with Moxifloxacin for Injection in the Freeflex® i.v. bag likely pose any significant risk to patient safety when the final drug product is administered as described in the proposed labeling. There are no further nonclinical recommendations or comments to be sent to the Applicant.

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/s/

TERRY J MILLER
03/18/2015

WENDELYN J SCHMIDT
03/19/2015
I concur with Dr. Miller's assesment of the completeness and interpretation of the data provided.

DIVISION OF ANTI-INFECTIVE PRODUCTS
PHARMACOLOGY/TOXICOLOGY REVIEW

DATE: 2/04/2014

Application number:	205572
Supporting document/s:	1
Sponsor's letter date:	6/6/2013
CDER stamp date:	6/7/2013
Product:	Moxifloxacin for Intravenous Injection
Indication:	Antibacterial indicated for treating infections
Sponsor:	Fresenius Kabi USA LLC
Review Division:	Division of Anti-Infective Products
Reviewer:	Terry J. Miller, Ph.D.
Supervisor/Team Leader:	Wendelyn Schmidt, Ph.D.
Division Director:	Sumathi Nambiar, M.D.
Project Manager:	Fariba Izadi, Pharm.D.

Recommendations:

The nonclinical reviewer does not recommend approval of NDA 205572 for Moxifloxacin for Intravenous Injection due to inadequate safety information to justify the potential local and systemic effects of several leachables identified in migration studies with moxifloxacin in the proposed free*flex*® container system.

There are no labeling recommendations at this time. All labeling recommendations will be deferred until a later time.

Comments to the Sponsor:
Based on inadequate information to justify the systemic safety of the following identified leachable compounds: (b) (4) ; from a nonclinical pharmacology/toxicology perspective, we cannot recommend approval of this NDA at this time. The following deficiencies and recommendations will need to be addressed before any decision on approval can be considered.

Deficiencies:

1. Your NDA application does not contain adequate safety justification for the systemic toxicity of three identified leachables from your proposed drug product packaged in the free*flex*® 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.

2. 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.

Information Needed to Resolve Deficiencies:

1. Provide a written response to the information request sent to you on 10/22/2013 that requested additional toxicity information for each of these 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. Also, include a more detailed rationale for your selection of "related" compounds used to determine the PDE for each of the identified leachables for which no toxicity information is available.
2. You and/or the Master File Holder (Fresenius Kabi Deutschland GMBH) must adequately address the deficiencies noted in the Master File (MF# 26696) for the free*flex*® container enclosure system. Alternatively, you may propose using a different container enclosure system with your drug product; we defer to the CMC review team to determine the necessary studies to support a change in the container.

Background:

The Sponsor, Fresnius Kabi (FK) USA, LLC, has submitted a 505(b)(2) New Drug Application (NDA) to obtain marketing approval for moxifloxacin for intravenous injection, 400 mg/250 mL. FK's moxifloxacin for injection is intended to be a near copy of the reference listed drug (RLD) Avelox® (moxifloxacin hydrochloride, Bayer Healthcare, NDA #021277), with an identical active ingredient, drug strength (1.6 mg/mL) and route of administration. However, in comparison with the RLD product, the generic drug formulation will include two additional excipients (Sodium Acetate Trihydrate, USP – (b) (4) mg and Disodium Sulfate, USP - (b) (4) mg), and eliminate one excipient (sodium chloride) from the final drug formulation (Table 1). 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). A side-by-side comparison of the RLD and proposed drug formulation can be found in Table 2 below. The pre-mixed packaging will contain (6) 250-mL flexible plastic containers each with 400 mg of moxifloxacin in 0.8% saline. 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)%.

Table 1. Component Composition of Drug Product (Moxifloxacin, 400 mg/250 mL Solution for Infusion)

Strength	1.6 mg/mL		
Packaging Configuration	400 mg/250 ml fill in a 300-mL **free***flex*® bags		
Freeflex Primary Film	(b) (4)		
Ports	Administration port (infusion port) and addition port (injection port)		
Overpouch	Aluminum (secondary packaging)		
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		solvent	USP
Sulphuric Acid		pH adjuster	NF

(Taken from Table 2.3.P-1 on page 4 of Section 2.3.P Quality Overall Summary of Drug Product)

Table 2. Side-by-Side Comparison of the Reference Listed Drug and 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 (monohydrate)	Moxifloxacin Hydrochloride (anhydrous)
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		
Bioequivalence	Refer to SECTION 1.12.15	Refer to SECTION 1.12.15
Labeling	Refer to Section 1.14	Refer to Section 1.14

* The RLD does not list Water for Injection on the labeling, however it must be employed in the compounding of the drug product.

(Table 1.12.12-1,page 3 of Section 1.12.12: Comparison of the generic drug and RLD)

The Sponsor plans to package the current drug product in a free*flex*® IV bag consisting of a (b) (4) multilayer container for parenteral solutions. The free*flex*® I.V. bag is manufactured by Fresenius Kabi AG (Bad Homburg, Germany), and is currently used with approved drugs such as Zyvox® injection (linezolid; NDA-021131; 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). The FK free*flex*® bag has also been approved for use with Voluven® (hydroxyethyl starch; NDA BN070012) infusion for plasma replacement in hypovolemic patients. The Sponsor included a Letter of Authorization (LOA) from the DMF Holder of the free*flex*® packaging system (Fresnius Kabi Deutschland GmbH; DMF No. 26696) in the current application authorizing Fresenius Kabi USA to reference information contained within the DMF, and for the FDA to examine the entire contents of the DMF in review of the current NDA.

Evaluation of the Master File (MF #26696) and FDA Enterprise Search for the free*flex*® IV bag

As part of my review of this NDA application, I conducted both an evaluation of the Master File for the free*flex*® IV bag (MF #26696) and a search of an internal FDA database for pharmacology/toxicology reviews of NDA applications for drugs packaged in the free*flex*® IV bag. 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 free*flex*® 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. In two specific cases, Naropin® injection (NDA 20533; NDA Supplement-26) and Acetaminophen injection (NDA 204767; New NDA), migration studies showed a large number of identical leachables at similar levels from the container closure system, including (b) (4) for which no direct toxicology data exists. In both cases, the Sponsors referenced DMF 26696 (Kabi Deutschland GmbH) for information from toxicological risk assessments performed on "related" compounds (ie. parent compound for which the unknown compound is a metabolite or degradant; individual chemical components of a complex compound, or structurally similar compounds) to help qualify the detected leachables. For these applications, the reviewing toxicologists, Dr. Jay Chang (NDA #20533; MF #26696) and Dr Carlie Huynh (NDA 204767, MF #26696), each disagreed with the Sponsor's risk assessment of these 4 compounds and required the Sponsor to conduct additional whole animal, repeat dose toxicology study(ies) to determine the toxicology profile for each of these leachables. (Please see Dr. Huynh's Pharmacology/Toxicology Memo to MF 26696 (6/20/2013) and Dr. Jay Chang's Pharmacology/Toxicology Memo to NDA 20,533 (4/15/2013) in DARRTS for additional information). In an information request communicated to the DMF holder on 6/24/2013 and submitted to MF 26696 (in DARRTS), Dr. Huynh (DAAAP) stated the following:

> "*Based upon the results of the migration studies conducted to date and review of the toxicological risk assessments provided in the Master File, there are inadequate safety justifications for the systemic safety of four of the leachables from the container closure system. Specifically, from a systemic toxicity perspective, there is inadequate safety justification for the following four identified leachables:* (b) (4) *(and related substance)".*
>
> *The Division required the following information to address the deficiency for the IV APAP NDA (NDA 204767) :*
>
> 1. *Submit a final study report for the proposed 3-month oral toxicology study for* (b) (4) *to the MF and update the toxicological risk assessment accordingly.*

2. *Submit the final study report for the proposed 28-day IV toxicology study for* (b) (4) *(to the MF) and update the toxicological risk assessment accordingly.*
3. *Conduct and submit the final study report for a 4-week IV toxicology study of CDEGA (to the MF) and update the toxicological risk assessment accordingly. Alternatively, … provide adequate data to support your conclusion* (b) (4) *hydrolysis is instantaneous in vivo such that exposure to the parent compound would not occur and your assessment based on major metabolites alone is adequate to address the safety of the parent compound.*
4. *Submit long-term stability data to the MF to demonstrate that* (b) (4) *(and related substances) are not present in IV APAP NDA through the duration of the intended shefl-life or complete a repeat-dose IV toxicology study of adequate duration to support the IV APAP NDA (at least 14-days duration). If* (b) (4) *(and related substances) are not detectable in the IV APAP product, submit a discussion of why this compound has been detected in migration studies using comparable solutions but not the IV APAP product.*

To date, none of the required information or completed study reports have been submitted to MF 26696 as required for NDA 204767. Because 3 of the 4 unqualified leachables (b) (4) also appear in migration studies with IV moxifloxacin (see below), the required toxicology studies (#1-3) described in the letter also pertain to the current NDA and should be completed and submitted to the MF or NDA for review before any approval decision for this NDA application can be considered. Since (b) (4) was not detected in the migration studies with moxifloxacin, there is less concern that this unqualified leachable will be detected at levels that may pose any toxicological risk in the current drug preparation. Because on the lack of adequate safety qualification of three leachables identified in IV moxifloxacin packaged within the free*flex*® bags, combined with the unresolved nonclinical deficiencies previously noted in a communication in the MF (6/24/2013), it is our recommendation that the current NDA application not be considered for approval until all of the required nonclinical studies to address these described deficiencies in the MF are completed and submitted for review.

Evaluation of Moxifloxacin IV in the free*flex*® **Container Closure System:**
In the current application, the Sponsor has conducted and referenced (DMF #26696) extraction and migration studies, as well as biologic reactivity tests, and risk assessment of leachables found within drug product (Moxifloxacin for injection, 250 mL). The analytical methods for determining extractables and migrants are described in Table 3.

Table 3. Analytical Methods Used to Determine Extractables and Migrants

Method No.	Type of Method	Title
(b) (4)	High Performance Liquid Chromatography (HPLC)	(b) (4)
	Headspace Gas Chromatography Gas Chromatography (HS-GC)	
	Gas Chromatography Mass Spectrometry (GC-MS)	

(Table 3.2.P.2-32 on page 45 of Module 3.2.P.2.4 – Container Closure System)

- **Extraction Study**
  The focus of the extraction studies were the two components of the carton in direct contact with the drug product, mainly the (b) (4) and the injection molded tubing (Figure 1)

(b) (4)

Figure 1. Schematic Drawing of the Container Closure System
(Figure 3.2.P.2-1 on page 30 of Module 3.2.P.2.4 – Container Closure System)

Kabi Fresnius placed 0.27 m^2 of the film and 20 injection molded tubes into a glass bottle and examined the extractables in three different extraction media (water for injection (WFI) at neutral pH, WFI buffered to pH 3.5, and WFI buffered to pH 8.0). The samples were extracted at 123°C for 60 minutes to mimic stress conditions, under the worst case volume:surface ratios, and resulting extractables were identified using validated analytic methods.

(Reviewer's comment: The contact surface of the film to the solution in the bag is 0.027 m^2 in a 50 mL bag. To represent worst case conditions, 0.027 m^2 was multiplied by a safety margin of 10. Hence, 0.27 m^2 of the film used in the study includes the 10 fold safety factor. Likewise, since 2 tubes are

present in one bag, use of 20 tubes provides for a 10 fold safety factor to represent a worst case condition for this extraction study).

A comparison of the extractables detected from the (b) (4) (Table 4) and injection molded tubing (Table 5) in the three extraction media are shown below. After a 60 minute incubation period, several extractables were identified to be mostly degradation products of the container in a sub ppm concentration range. (b) (4) were three notable extractables detected in media from the (b) (4) (b) (4), a plastic additive, was detected under all extraction conditions, from both the (b) (4) at similar levels. A comparison of the extractables between the three different extraction media showed that pH significantly impacted extract levels.

Table 4. Detected Extractables of the (b) (4)

(b) (4)

(Table 3.2.P.2-27 on page 40 of Module 3.2.P.2.4 – Container Enclosure System)

Table 5. Detected Extractables (b) (4)

(b) (4)

(Table 3.2.P.2-28 on page 40 of Module 3.2.P.2.4 – Contain Enclosure System)

- **Migration Study**

Migration studies were performed with the complete free*flex*® packaging system containing Moxifloxacin Injection (Batch #: 12FCU92). All packaging materials (b) (4) were considered in these studies. The contents of the drug-filled package from a single registration batch were analyzed after storage at different temperatures for a 6 month period of time; additional analysis is planned for 24 and 36 months as described in Table 6.

Table 6. Planned Storage Intervals for Migration Studies of Moxifloxacin Injection

Storage Condition	Interval in Months			
	6	18	24	36
25 °C ± 2 °C/ 40 % RH ± 5 %	X			X
30 °C ± 2 °C/ 35 % RH ± 5 %			X	X
40 °C ± 2 °C/ NMT 25 % RH	X			

(Table 3.2.P.2-29 on page 42 of Module 3.2.P.2.4 – Contain Enclosure System)

(Reviewer's comment: There is no information on the stability or leachable content at timepoints greater than 6 months, and the submitted 6 month data comes from 1 registration batch. In a letter submitted to the Sponsor on 10/22/2013, CMC requested additional stability data (including leachables) for IV moxifloxacin in the freeflex® *bags over the entire proposed shelf life from at least 3 registration batches).*

The results of this 6-month migration study with a single batch of IV moxifloxacin for injection are shown in Table 7.

Table 7. Moxifloxacin Injection Migration Study (Batch: 12FCU92) in 300 mL (250 mL filling) free*flex*® Bags

(b) (4)

Table 7. Moxifloxacin Injection Migration Study (Batch: 12FCU92) in 300 ®

(b) (4)

(Table 3.2.P.2-30 pages 42-43 of Module 3.2.P.2.4 – Contain Enclosure System)

From table 7 above, the impurities/degradants from the container enclosure system detected in the drug product following 6 month storage include the following compounds:

(b) (4)

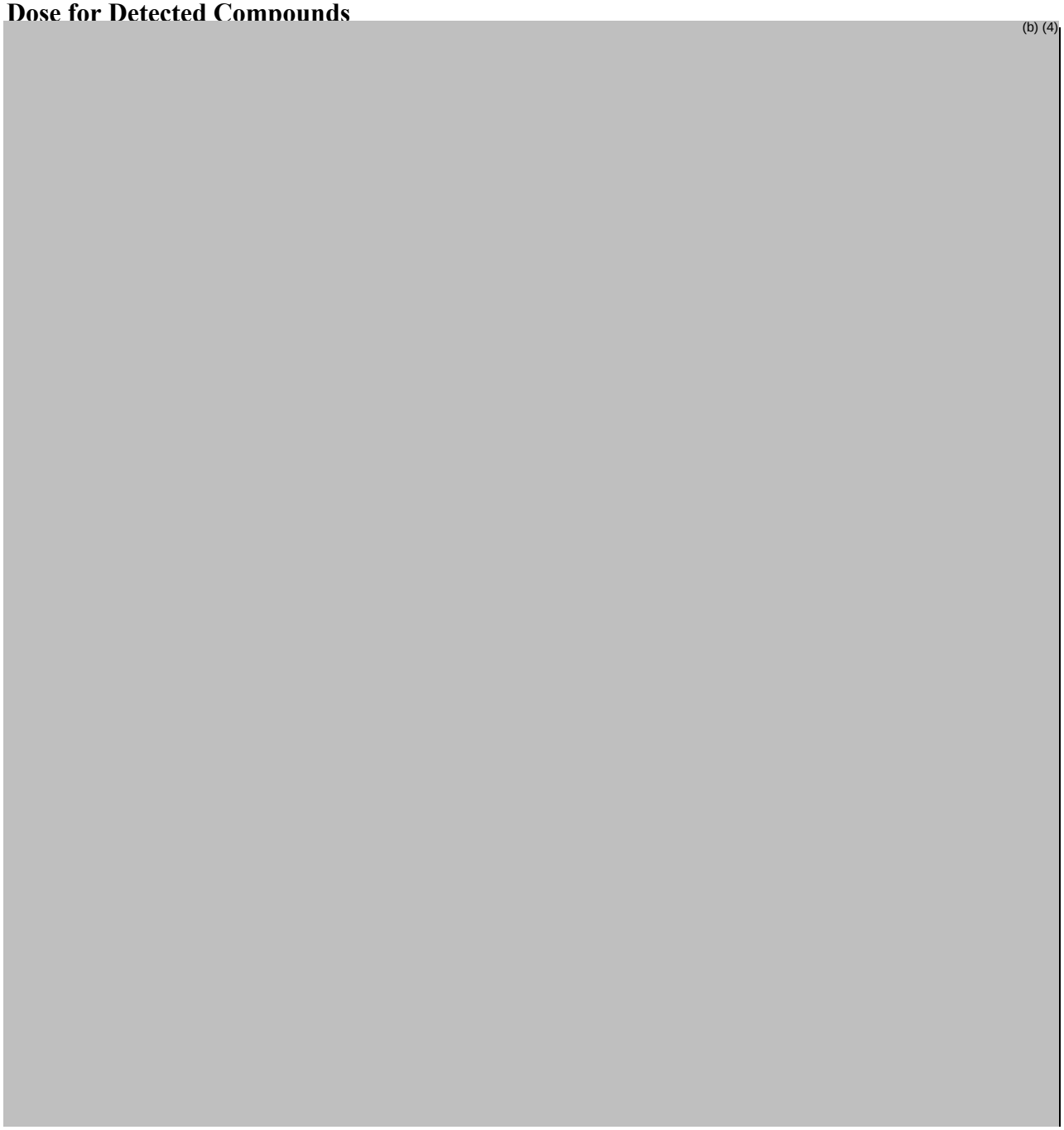
The Sponsor conducted a toxicologic evaluation of each of these detected extractables using standard toxicology reference literature, and public toxicology databases including RTEC, TOXLINE CORE, TOXLINE SPECIAL, TOXBIO, and TOXCAS, as well as a general internet search. The results of this search were based exclusively on the no-observed-effect-level (NOEL) or

lowest-observed-effect-level (LOEL) derived from existing pharmacokinetic, single- and repeat-dose toxicity, genotoxicity, carcinogenicity, and reproductive and developmental toxicology studies. When no toxicologic data for an extractable/leachable was available, a "related" compound (ie. parent compound for which the unknown compound is a metabolite or degradant, individual chemical components of a complex compound, or structurally similar compounds) for which toxicology data was available was used in this assessment. The "permitted daily exposure" (PDE) for each extractable was calculated as defined in ICH Q3C Guideline on Impurities: Residual Solvents (1997), and represent values estimated from toxicologic assessments and worst case maximum daily dose. Internal specifications for extractable compounds were established by the Sponsor using maximum values observed during all extractable testing of free*flex*® components and during migration studies with a variety of aqueous product solutions packaged in free*flex*® bags. The maximum total daily intake (TDI), PDE estimations, FK internal specification limits, and calculated safety margins from FK internal specification limits and TDI of each extractable are shown in Table 8 below.

PDE = [NOAEL (mg/kg/day) x Weight adjustment (50 kg)] / [F1 x F2 x F3 x F4 x F5]
Where
F1 is a factor for extrapolation between species
F2 is a factor of 10 for variability between individuals
F3 is a factor for short-term toxicity studies
F4 is a factor for severe toxicity
F5 is a variable factor if the NOEL was not established

(Reviewer's comment: The data for these toxicologic evaluations of the commonly found leachables are included in the referenced Drug Master File (DMF) No. 26696, for the free*flex*® (b) (4) *bags, currently held by Fresenius Kabi Deutschland GmbH. The current NDA contains a Letter of Authorization (LOA) from Fresenius Kabi Deutschland GmbH authorizing Fresenius Kabi USA to reference information from this DMF, and for the FDA to review the entire contents of the DMF during review of the current NDA).*

Table 8. Safety Margins for Upper Specification Limits and Maximum Daily Dose for Detected Compounds



(Table 3.2.P.2-31 on pages 44-45 of Module 2.3.P – QOS for Drug Product)

(Reviewer's comment: The Sponsor should submit the leachable levels in the drug product over the course of the entire intended shelf-life. The Sponsor should also plan to submit a revised risk assessment based on worst-case exposures based on long-term stability data of > 6 months when available).

The results of the migration studies with moxifloxacin (400 mg in a 250 mL) in the free*flex*® i.v. bag in Table 8, showed that after 6 months of storage within

the free*flex*® container, that 3 of the 4 leachables of unknown toxicologic risk (namely (b) (4)) detected in other drug products and for which additional toxicology studies in animals were required in a prior communication in the MF (6/24/2013), were similarly detected in the IV moxifloxacin drug product. Although the leachable levels are expected to be low and the Sponsor's PDE values appear to provide an adequate safety margin above the maximum levels observed in their extraction and migration studies, the Sponsor's calculation of PDE based on the toxicologic profile of "related" compounds to qualify levels of these leachables do not appear to be adequate without additional justification of the relevance of the "related" compounds to each leachable from the container closure system (Table 9).

Table 9. Unqualified Leachables and "Related" Compounds

(b) (4)

In summary, The Sponsor, Fresenius Kabi USA, has submitted a 505(b)(2) NDA for moxifloxacin for intravenous injection in 0.8% saline (400 mg/250 mL) as a general antibiotic indicated in the treatment of infections. The Sponsor's current formulation of the proposed drug product is nearly identical to the RLD Avelox® (moxifloxacin hydrochloride, Bayer Healthcare, NDA #021277), with identical active ingredient, drug strength (1.6 mg/mL) and route of administration; however, the generic drug formulation will include two additional excipients (sodium acetate trihydrate and disodium sulfate), and eliminate one excipient (sodium chloride) from the final drug formulation. At this time, no new drug substance impurities have been identified. No new pharmacology or toxicology information was submitted, and there are no safety concerns with the proposed drug substance or drug product specifications.

However, at the time of NDA submission, adequate information on the safety of the container closure system is not readily available. In 6 month migration studies conducted with Moxifloxacin for Injection, 3 leachable compounds ((b) (4)) were identified for which the Sponsor has not adequately demonstrated systemic safety in their toxicological risk assessment or nonclinical toxicology studies. In the pharmacology/toxicology review of the referenced MF #(b) (4) by Dr. Carlic Huynh (DAAAP) (6/20/2013), Dr. Huynh

noted an absence of available toxicology data to support the safety of three compounds identified as leachables from the container closure system; (b) (4) . In that same review, Dr. Huynh determined the Sponsor's toxicology risk assessment used to generate the permitted daily exposure (PDE) of these three leachables to be inadequate, as it based its calculations on toxicology data available for the "related" compounds, without justification or sufficient data to bridge the toxicity profiles of the two "related" compounds. In a communication sent to the MF holder on 6/24/13 Dr. Huynh, required that several nonclinical studies be conducted to support the safety of identified leachable compounds discovered in (b) (4) also packaged in a free*flex*® enclosure system. The MF holder (Fresenius Kabi Deutschland GMBH) of the referenced master file (MD #26696) has not submitted the required nonclinical studies to qualify these 3 shared leachables from migration studies conducted with IV acetaminophen (NDA #204767) in the free*flex*® bag. In addition, the current Sponsor has not responded to our information request sent on 10/22/2013 requesting additional toxicology information on the three identified leachables ((b) (4)) and more detailed rational for the selection of the "related" compounds used to determine the PDE for each of the identified leachables for which no toxicity information is available.

It should be noted that the toxicological risk assessments on the leachables completed to date were based on the highest levels detected after 6 month stability studies with the assumption that they would not increase with longer storage. The stability data to date is limited and CMC plans to recommend that adequate stability data from at least 3 stability batches, until end of the proposed shelf-life be evaluated for leachable content. Once the Sponsor has provided additional data on potential leachables with longer term-stability studies, it is recommended we revisit the toxicologic risk assessment based on definitive stability data prior to finalizing any decision on the approvability of this product.

Therefore, based on inadequate information to justify the systemic safety of the following identified leachable compounds: (b) (4) from a nonclinical pharmacology/toxicology perspective, we cannot recommend approval of this NDA at this time. The Sponsor and/or MF holder of the referenced Master File will need to address our information request of 10/22/2013 for additional information on these unqualified leachables and conduct the nonclinical toxicology studies described in the deficiency letter submitted to the MF on 6/24/2013, before any decision on approval can be considered.

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/s/

TERRY J MILLER
02/04/2014

WENDELYN J SCHMIDT
02/04/2014
I concur with Dr. Miller's assessment of the data.