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APPLICATION NUMBER:

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PHARMACOLOGY REVIEW(S)

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

PHARMACOLOGY/TOXICOLOGY NDA REVIEW AND EVALUATION

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Product: Dexmedetomidine HCl Injection
Indication: Sedation of non-intubated patients prior to and/or during surgical and other procedures
Applicant: HQ Specialty Pharma Corp.
Review Division: Division of Anesthesia, Analgesia, and Addiction Products (DAAAP)
Reviewer: Newton H. Woo, PhD
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1 Executive Summary

1.1 Introduction

The Applicant is submitting NDA 206638 via the 505(b)(2) regulatory pathway with Precedex® (NDA 21038) as the referenced product. The proposed product is not a generic product because two preservatives, namely methylparaben and propylparaben, were added to the drug product formulation. The Applicant is relying on the Agency's previous findings of safety and the relevant pharmacology, pharmacokinetics, and toxicology information in the label of the referenced product.

1.2 Brief Discussion of Nonclinical Findings

There were no nonclinical pharmacology or toxicology studies submitted in support of this NDA application. The excipients in the aqueous dexmedetomidine HCl injection formulation can be found in equal or higher amounts in approved intravenous aqueous products and do not pose any novel toxicologic concerns. All impurities in the drug substances and degradants in the drug product are controlled at acceptable levels and within the range of the referenced drug product, with the exception of (b) (4) (b) (4) is controlled at a specification of (b) (4)% of the total amount of preservatives, which is deemed acceptable because this compound is a significant metabolite of the paraben preservatives.

A post-marketing requirement will be requested to conduct a leachables assessment of Dexmedetomidine HCl Injection and its container closure system over the course of stability. This leachables assessment is deemed acceptable as a PMR because the (b) (4) stopper (b) (4) is used in several FDA-approved aqueous injectable drug products and the submitted extractables data do not raise any significant cause for concern.

1.3 Recommendations

1.3.1 Approvability

From a pharmacology toxicology perspective, NDA 206628 may be approved with a post-marketing requirement.

1.3.2 Additional Non Clinical Recommendations

The following nonclinical study is recommended as a post-marketing requirement (PMR) should this NDA be approved:

Conduct an adequate leachable safety assessment for your drug product and container closure system. This assessment must include leachable data from long-term stability studies (taking into consideration the proposed shelf-life) to determine if the identified/specified extractables also leach into the drug product over time, and a

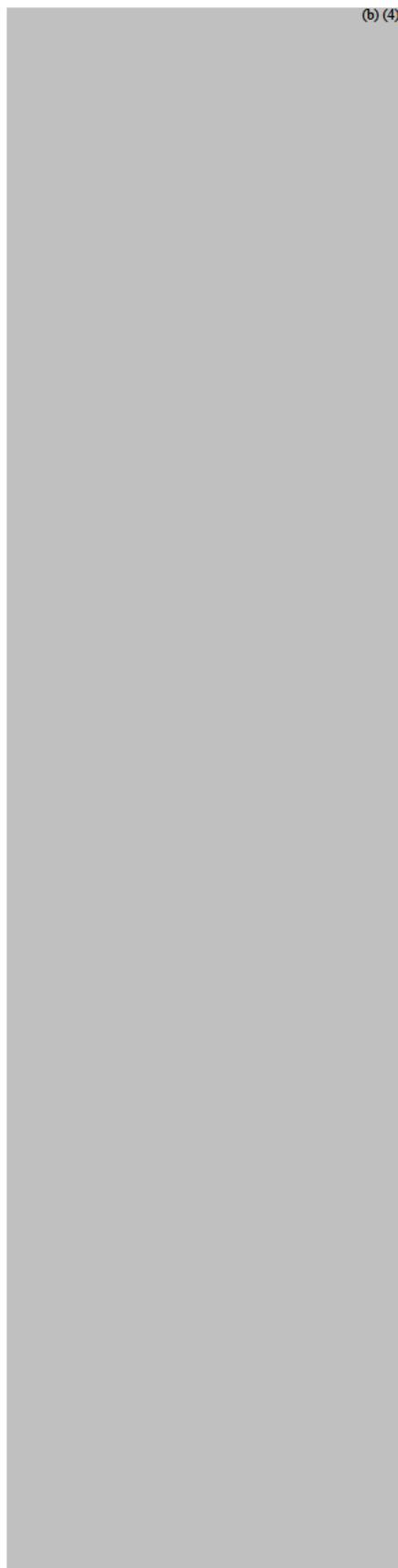
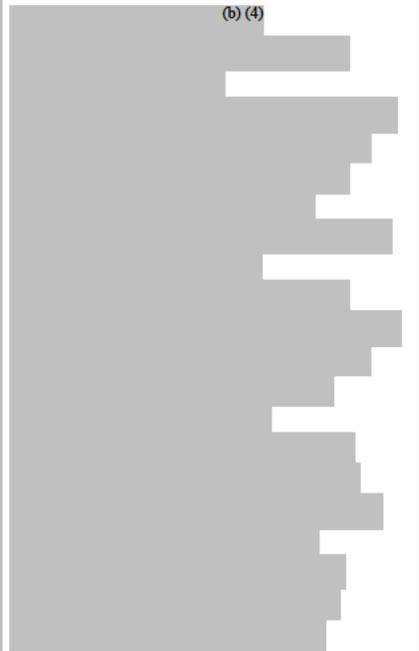
toxicological risk assessment justifying the safety of the leachables taking into consideration the maximum daily dose of the identified materials for this drug product. For your toxicological risk assessment, any leachable that contains a structural alert for mutagenicity should not exceed (b) (4) mcg/day total daily exposure or be adequately qualified for safety. A toxicological risk assessment should be provided for any non-genotoxic leachable that exceeds (b) (4) mcg/day.

1.3.3 Labeling

The table below contains the draft labeling proposed by the Applicant with the changes proposed by this reviewer and the rationale for the proposed changes. The labeling recommendations below have not been discussed with the entire review team or the Applicant. The reader is referred to the final action letter for final drug product labeling.

Table 1. Labeling Review

Applicant's Proposed Labeling	Reviewer's Proposed Changes	Rationale for Changes
<p>HIGHLIGHTS OF PRESCRIBING INFORMATION</p> <p>-----</p> <p>INDICATIONS AND USAGE-----</p> <p>-----</p> <p>Dexmedetomidine Hydrochloride Injection is a (b) (4)</p> <p>(b) (4)</p> <ul style="list-style-type: none"> Sedation of non-intubated patients prior to and/or during surgical and other procedures. (Error! Reference source not found.) 	<p>HIGHLIGHTS OF PRESCRIBING INFORMATION</p> <p>-----</p> <p>INDICATIONS AND USAGE-----</p> <p>-----</p> <p>Dexmedetomidine Hydrochloride Injection is a (b) (4) central alpha-2 adrenergic agonist indicated for:</p> <p>(b) (4)</p> <ul style="list-style-type: none"> Sedation of non-intubated patients prior to and/or during surgical and other procedures. (Error! Reference source not found.) 	<p>Established Pharmacologic Class: Central alpha-2 adrenergic agonist</p>
<p>8 USE IN SPECIFIC POPULATIONS</p> <p>8.1 Pregnancy</p> <p>(b) (4)</p> <p>There are no (b) (4) studies (b) (4) dexmedetomidine hydrochloride in pregnant women. (b) (4)</p>	<p>8 USE IN SPECIFIC POPULATIONS</p> <p>8.1 Pregnancy</p> <p>(b) (4)</p> <p>[INSERT PREGNANCY EXPOSURE REGISTRY INFORMATION IF AVAILABLE]</p>	<p>To convert to PLLR format, several changes will be made:</p> <p>(b) (4)</p>

<p>(b) (4)</p> 	<p><u>Risk Summary</u> [For clinical Risk Summary, refer to Pediatric and Maternal Health Consult for clinical risk summary.] Rats subcutaneously administered dexmedetomidine during organogenesis showed pregnancy loss and pup mortality at doses equivalent to the maximal recommended human intravenous dose. Reduced fetal weights were observed in rats administered subcutaneously dexmedetomidine at a dose that is less than one-half of the maximal recommended human intravenous dose during gestation and lactation. In this study, elevated fetal and embryocidal toxicity and delayed motor development was observed in second generation offspring. No fetal malformations were observed in animal reproduction studies with subcutaneous administration of dexmedetomidine during organogenesis in rats and rabbits at doses approximately equal to and one-half the maximal recommended human intravenous dose, respectively [see Data].</p> <p>(b) (4)</p> 	<p>(b) (4) addition of several sections with a risk summary inserted, and nonclinical findings will be under Subheading Animal Data. This section will require input from the maternal health and various review disciplines.</p> <p>The reader is referred to the final action letter for the final drug product labeling</p>
<p>Animal Data</p>		

	<p>(b) (4) Teratogenic effects were not observed in rats following subcutaneous administration of dexmedetomidine during the period of fetal organogenesis (from gestation day 5 to 16) with doses up to 200 mcg/kg (representing a dose approximately equal to the maximum recommended human intravenous dose based on body surface area) or in rabbits following intravenous administration of dexmedetomidine during the period of fetal organogenesis (from gestation day 6 to 18) with doses up to 96 mcg/kg (representing approximately half the human exposure at the maximum recommended dose based on plasma area under the time-curve comparison). However, fetal toxicity, as evidenced by increased post-implantation losses and reduced live pups, was observed in rats at a subcutaneous dose of 200 mcg/kg. The no-effect dose in rats was 20 mcg/kg (representing a dose less than the maximum recommended human intravenous dose based on a body surface area comparison). In another reproductive toxicity study when dexmedetomidine was administered subcutaneously to pregnant rats at 8 and 32 mcg/kg (representing a dose less than the maximum recommended human intravenous dose based on a body surface area comparison) from gestation day 16 through weaning, lower offspring weights were observed. Additionally, when offspring of the 32 mcg/kg group were allowed to mate, elevated fetal and embryocidal toxicity and delayed motor development was observed in second generation offspring.</p> <p>8.2 Lactation</p> <p>[INSERT RISK SUMMARY]</p> <p>It is not known whether dexmedetomidine hydrochloride is excreted in human milk. Radio-labeled dexmedetomidine</p>	
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<p>(b) (4)</p>	<p>administered subcutaneously to lactating female rats was excreted in milk. Because many drugs are excreted in human milk, caution should be exercised when dexmedetomidine hydrochloride is administered to a nursing woman.</p>	
<p>13 NONCLINICAL TOXICOLOGY</p> <p>13.1 Carcinogenesis, Mutagenesis, Impairment of Fertility Animal carcinogenicity studies have not been performed with dexmedetomidine. Dexmedetomidine was not mutagenic <i>in vitro</i>, in either the bacterial reverse mutation assay (<i>E. coli</i> and <i>Salmonella typhimurium</i>) or the mammalian cell forward mutation assay (mouse lymphoma). Dexmedetomidine was clastogenic in the <i>in vitro</i> human lymphocyte chromosome aberration test with, but not without, rat S9 metabolic activation. In contrast, dexmedetomidine was not clastogenic in the <i>in vitro</i> human lymphocyte chromosome aberration test with or without human S9 metabolic activation. Although dexmedetomidine was clastogenic in an <i>in vivo</i> mouse micronucleus test in NMRI mice, there was no evidence of clastogenicity in CD-1 mice. Fertility in male or female rats was not affected after daily subcutaneous injections of dexmedetomidine at doses up to 54 mcg/kg (less than the maximum recommended human intravenous dose on a mcg/m² basis) administered from 10 weeks prior to mating in males, and 3 weeks prior to mating and during mating in females.</p>	<p>13 NONCLINICAL TOXICOLOGY</p> <p>13.1 Carcinogenesis, Mutagenesis, Impairment of Fertility Carcinogenesis: Animal carcinogenicity studies have not been performed with dexmedetomidine. Mutagenesis: Dexmedetomidine was not mutagenic <i>in vitro</i>, in either the bacterial reverse mutation assay (<i>E. coli</i> and <i>Salmonella typhimurium</i>) or the mammalian cell forward mutation assay (mouse lymphoma). Dexmedetomidine was clastogenic in the <i>in vitro</i> human lymphocyte chromosome aberration test with, but not without, rat S9 metabolic activation. In contrast, dexmedetomidine was not clastogenic in the <i>in vitro</i> human lymphocyte chromosome aberration test with or without human S9 metabolic activation. Although dexmedetomidine was clastogenic in an <i>in vivo</i> mouse micronucleus test in NMRI mice, there was no evidence of clastogenicity in CD-1 mice. Impairment of Fertility: Fertility in male or female rats was not affected after daily subcutaneous injections of dexmedetomidine at doses up to 54 mcg/kg (less than the maximum recommended human intravenous dose on a mcg/m² basis) administered from 10 weeks prior to mating in males, and 3 weeks prior to mating and during mating in females.</p>	<p>No changes from the referenced product, Precedex®. Headers were added to assist the reader.</p>

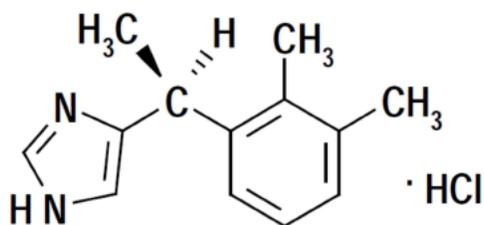
<p>13.2 Animal Pharmacology and/or Toxicology There were no differences in the adrenocorticotrophic hormone (ACTH)-stimulated cortisol response in dogs following a single dose of dexmedetomidine compared to saline control. However, after continuous subcutaneous infusions of dexmedetomidine at 3 mcg/kg/hr and 10 mcg/kg/hr for one week in dogs (exposures estimated to be within the clinical range), the ACTH-stimulated cortisol response was diminished by approximately 27% and 40%, respectively, compared to saline-treated control animals indicating a dose-dependent adrenal suppression.</p>	<p>13.2 Animal Pharmacology and/or Toxicology There were no differences in the adrenocorticotrophic hormone (ACTH)-stimulated cortisol response in dogs following a single dose of dexmedetomidine compared to saline control. However, after continuous subcutaneous infusions of dexmedetomidine at 3 mcg/kg/hr and 10 mcg/kg/hr for one week in dogs (exposures estimated to be within the clinical range), the ACTH-stimulated cortisol response was diminished by approximately 27% and 40%, respectively, compared to saline-treated control animals indicating a dose-dependent adrenal suppression.</p>	
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2 Drug Information

2.1 Drug

CAS Registry Number:	113775-47-6 (base); 145108-58-3 (HCl salt)
Generic Name:	dexmedetomidine
Code Name:	Dexmedetomidine hydrochloride (HCl) injection
Chemical Name:	1H-Imidazole, 4-[1-(2,3-dimethylphenyl) ethyl]-, monohydrochloride 4-((S)-alpha,2,3-trimethylbenzyl)imidazole monohydrochloride
Molecular Formula/MW:	C ₁₃ H ₁₆ N ₂ • HCl / 236.74

Structure of Dexmedetomidine



Pharmacologic Class:	Central alpha-2 adrenergic agonist (FDA Established Pharmacological Class)
Mechanism of Action:	Adrenergic alpha2-agonists
Physiological Effect:	General Anesthesia

2.2 Relevant INDs, NDAs, and DMFs

The Agency has approved one NDA application for dexmedetomidine as the API, which is the referenced product, and is listed below. The Table below contains the IND and DMFs referenced by the Applicant in this NDA submission.

Table 2. Referenced NDA, IND and DMFs

IND/NDA/DMF	Drug/Compound/Product	Sponsor	Division	Status
NDA 21038	Precedex	Hospira	DAAAP	Approved, 505(b)(2) reference product
PIND 119008	Dexmedetomidine	HQ Specialty Pharma	DAAAP	Presubmission

DMF (b) (4)	Dexmedetomidine drug substance	(b) (4)	DRM	The DMF is referenced by a FDA-approved drug product. From a CMC perspective, the DMF has been deemed adequate (see latest quality review dated January 26, 2015).
DMF (b) (4)	Vials	(b) (4)	DRM	Active
DMF (b) (4)	Stopper	(b) (4)	DRM	Active
DMF (b) (4)	Stopper	(b) (4)	DRM	Active

2.3 Drug Formulation

The composition of the Sponsor’s Dexmedetomidine HCl Injection is identical with the same concentration as the referenced product, Precedex, with the exception for the addition of two preservatives, methylparaben and propylparaben. The Sponsor has developed two presentations of the drug product, which is offered in 4 mL and 10 mL vials (Shown below are the Sponsor’s Tables exhibiting the composition of the two configurations).

Table 3. Composition of the 4 mL Vial Drug Product

Name of Ingredients	Composition	
	mg /mL	mg per 4 ml vial (4.0 ml)*
Dexmedetomidine (base) weighed as: Dexmedetomidine hydrochloride	0.100 mg (base) 0.118 mg	(b) (4)
Methylparaben	1.6	(b) (4)
Propylparaben	0.2	(b) (4)
Sodium Chloride	9.0	(b) (4)
WFI	qs (b) (4)	(b) (4)
Total	1004.92 mg	(b) (4)

Table 4. Composition of the 10 mL Vial Drug Product

Name of Ingredients	Composition	
	mg /mL	mg per 10 ml vial (10.0 ml)*
Dexmedetomidine (base)	0.100 mg (base)	(b) (4)
weighed as: Dexmedetomidine hydrochloride	0.118 mg	
Methylparaben	1.6	
Propylparaben	0.2	
Sodium Chloride	9.0	
WFI	qs (b) (4)	
Total	1004.92 mg	

The maximum daily intake of dexmedetomidine is 1177 mcg (see Determination of Maximum Daily Dose in Section 2.6).

2.4 Comments on Novel Excipients

There are no novel excipients in the formulation. All of the excipients are listed in the FDA Inactive Ingredients Database (IID) and are used in several approved FDA drug products at levels greater than those in the proposed dexmedetomidine drug product when calculated for the concentration and maximum daily dose.

Table 5. Excipients Included in the Drug Product and Qualification Status

Ingredients	Function	Amount (mg/mL)	Maximum exposure (mg/day)	Acceptable? (Rationale)
Methylparabe (b) (4)	Preservative	1.6	18.8	YES (IID)
Propylparabe (b) (4)	Preservative	0.2	2.35	YES (IID)
Sodium Chloride	(b) (4)	9.0	106	YES (IID)

IID: FDA Inactive Ingredients Database

2.5 Comments on Impurities/Degradants of Concern

Drug Substance Impurities

The drug substance impurity specifications are presented in the table below. The

identification threshold according to ICH Q3A(R2) for a MDD of ≤ 2 g/day is 0.10% or 1.0 mg/day intake, whichever is lower. The qualification threshold according to ICH Q3A(R2) for a MDD of ≤ 2 g/day is 0.15% or 1 mg/day intake, whichever is lower. The Applicant is referencing (b) (4) DMF (b) (4) for the dexmedetomidine drug substance. The drug substance impurity specifications are presented in the table below. The Applicant has set a specification of NMT (b) (4) % for any unspecified individual impurity, which is deemed acceptable.

Table 6. Drug Substance Impurities and Qualification Status

Impurity	Structure	Proposed Specification	Comment
(b) (4)	(b) (4)	NMT (b) (4) %	Acceptable. The proposed specification is within the range of the referenced drug product.
Heavy Metals		NMT (b) (4) ppm	Acceptable. This specification would result in a total daily intake of (b) (4) mcg/day, which is lower than the parenteral PDE for any Class 1 elemental impurity described in ICH Q3D.

Residual Solvents

The Sponsor has proposed specifications for (b) (4) of NMT (b) (4) %, respectively, which are compliant to ICH guidelines (See Table below).

Table 7. Residual Solvents and Qualification Status

Residual Solvent	Specifications	Reviewer's Comments
(b) (4)	NMT (b) (4) %	Acceptable, meets ICH Q3C threshold of 0.5% for a Class 3 residual solvent
(b) (4)	NMT %	Acceptable, meets ICH Q3C threshold of 0.5% for a Class 3 residual solvent

Drug Product Degradants

To characterize drug product degradants dexmedetomidine HCl was exposed to acidic, alkaline, oxidative, accelerated humidity and temperature conditions. No significant degradation was observed in any condition tested. Amounts of (b) (4) after stress testing were not increased.

As the maximum daily intake of dexmedetomidine is 1177 mcg, the identification threshold according to ICH Q3B(R2) for a maximum daily dose of a drug product that is 1 mg – 10 mg is 0.5% or 20 mcg intake, whichever is lower. The qualification threshold according to ICH Q3B(R2) for a MDD of a drug product administered per day between < 10 mg is 1% or 50 mcg total daily intake, whichever is lower. The Applicant has set a

specification of NMT (b) (4)% for any unspecified individual impurity, which is deemed acceptable. The Sponsor has set a specification for the degradation product of (b) (4) (b) (4) of NMT (b) (4)% (calculated against the total amount of the preservative in the product). It was agreed at a Pre-IND meeting that a specification that resulted in the level of (b) (4) that exceeds (b) (4)% in the drug product would require additional nonclinical qualification studies.

Table 8. Drug Product Degradants and Qualification Status

Degradant	Structure	Proposed Specification	Comment
(b) (4)			The drug product specification is acceptable. Refer to body text for justification that details how (b) (4) (b) (4) is a human metabolite.

In the NDA submission, the Sponsor has set the (b) (4) specification based on the total amount of preservatives in the drug product and not based on the API. Although the Division stated to the Sponsor that this specification must adhere to ICH Q3B(R2) threshold levels, the specification exceeds the respective qualification threshold. The Sponsor justifies the safety of this specification by stating that parabens are hydrolyzed to (b) (4) in mammals.

Upon review of literature, this reviewer agrees with the Sponsor that (b) (4) is a human metabolite (b) (4) and also notes that (b) (4) is not mutagenic (b) (4). Parabens are metabolized through hydrolysis by esterases, i.e., carboxylesterases 1 and 2, and undergo glucuronidation prior to being excreted in the urine. As noted before, both (b) (4) parabens are in several marketed parenteral solutions for bolus and infusion administration at comparable levels. Taken together, given it is a significant human metabolite of parabens that are used in marketed products and is non-mutagenic, the impurity specification of (b) (4)% of the total preservatives amount for (b) (4) does not appear to pose

an additional risk for adverse toxicities when dexmedetomidine is used under normal therapeutic conditions.

Figure 1. Metabolic Routes for Parabens in Humans

(b) (4)



Container Closure System

The container closure system consists of a glass vial (two sizes 5 mL and 10 mL), 20 mm (b) (4) rubber stopper and a 200 mm aluminum over seal (see Sponsor's Table below).

In the NDA submission the Sponsor, stated the components of the container closure system was chosen because they are conventional, widely used for storage of parenteral products. This reviewer notes that the (b) (4) rubber stopper is also found in several FDA approved aqueous intravenous drug products.

Table 9. Constituents of the Container Closure System

Component	Description	Supplier	DMF Number
5 mL vial	Clear, tubular type I glass	(b) (4)	(b) (4)
10 mL vial	Clear, tubular type I glass		(b) (4)
Rubber Stopper (20 mm)	Grey, (b) (4) rubber with (b) (4)		(b) (4)
Over Seal (20 mm)	20 mm aluminum over seal with plastic lid		N/A

In a preIND meeting held in 2013, the Division communicated to the Applicant to provide adequate justification for the safety of the container closure system of this drug product. The Sponsor did not include a leachable/extractable assessment for the container closure system in the initial NDA submission; rather they noted that the (b) (4) grey (b) (4) rubber stopper with a (b) (4) coating provided by (b) (4) has been used in many other aqueous drug products. In an Information Request the Sponsor was asked to address the following:

Leachable/Extractable testing of the drug product must be included in the stability. Provide leachable testing on batches of drug product you currently have on stability, to demonstrate, the leachable profile through to expiry of the drug product. Further, provide a commitment to continue to monitor batches of drug product, for leachable testing, on stability through to expiry. Also provide the leachable/extractables methods along with their validation reports.

In response to the information request, the Applicant submitted justification that stated the vial and stopper were tested in Biological Reactivity tests according to the USP <88> and ISO 10993-5 with results supporting the materials safety. The study report and the raw data obtained from these test were not included in the NDA submission. In addition the Sponsor submitted results from an extractables study (TE140572) under exaggerated conditions. The extraction study was performed using several different extraction conditions, including the use of the following solvents:

1. UltraPureWater (UPW) pH as is
2. UPW pH 3
3. isopropanol (IPA).

Use of multiple solvents with different polarities is consistent with best-practice recommendations (USP <1663>). For the extractables study, the vials were closed with the proposed rubber stopper, placed upside down and (b) (4). It is noted that the drug product is an aqueous based solution with a pH range of (b) (4). Given the drug product is aqueous based with a pH in between the two pH conditions tested and use of a pH range that

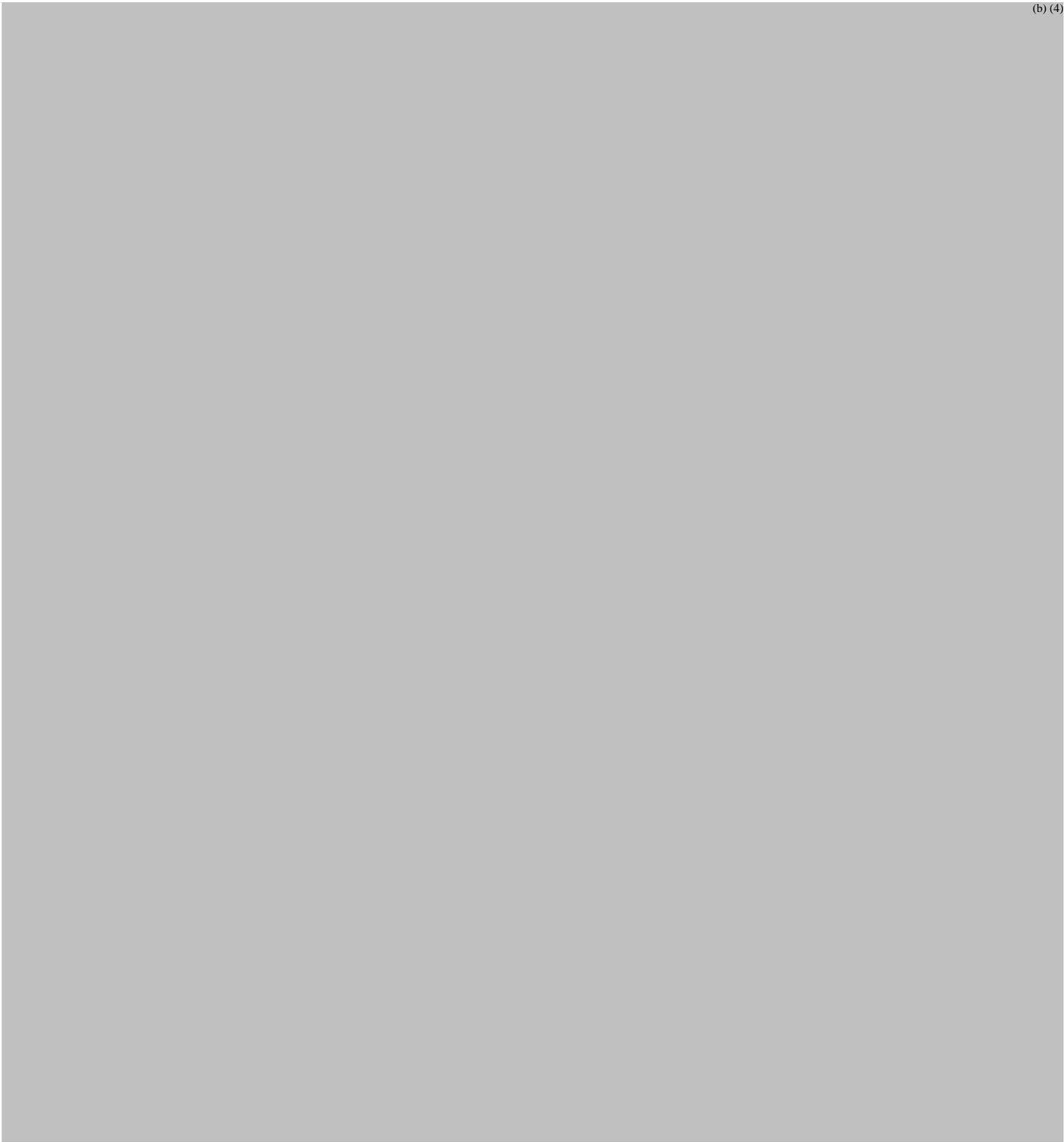
encompasses and slightly exceeds the pH limits of the product addresses the potential effect of pH, the use of aqueous extraction conditions appear adequate (USP <1663>). For the third extraction condition, isopropanol was used as the extracting medium and is ^{(b) (4)} capabilities. Extraction with IPA, likely ^{(b) (4)} represents an ^{(b) (4)} vial rubber stopper with an aqueous based formulation (USP <1663>).

Altogether 12 theoretical leachables were identified that were higher than the 1.5 mcg/day (see Table below that was adapted from the Sponsor's submission). According to the Sponsor, the identified extractables did not contain structural alerts for DNA reactivity as tested in an *in silico* Derek Nexus 3.0 analyses.

Table 10. Summary of Detected Extractable Compounds and Qualification Status

Extractables	CAS	Maximum daily intake* (mcg/day)			Reasonable? (Rationale)
		UPW	UPW pH 3	IPA	
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2.6 Proposed Clinical Population and Dosing Regimen

The Applicant plans to pursue one of two indications that are approved for the referenced product, Precedex®, which is sedation of non-intubated patients prior to and/or during surgical and other procedures. The proposed clinical population is non-

intubated patients who require sedation prior to and/or during surgical and other procedures.

The dosing regimen for the indication is summarized below:

Figure 2. Dosage Information in the Proposed Label

INDICATION	DOSAGE AND ADMINISTRATION
Initiation of Procedural Sedatio	(b) (4)
Maintenance of Procedural Sedatio	(b) (4)

(b) (4)

2.7 Regulatory Background

This is a 505(b)(2) application referencing the Agency’s previous findings of safety and efficacy to Precedex® (NDA 21038).

A preIND meeting with the Applicant under IND 119008 was scheduled for September 24, 2013. However the meeting was cancelled at the request of the Sponsor as the Division’s preliminary comments did not require further clarification or discussion. Excerpts of the nonclinical comments that were communicated to the Sponsor are shown below:

3. Does the FDA concur with the difference in packaging material, which has been

previously approved for other products, will not require additional nonclinical studies to support the filing and review for approvability of HQ Dexmedetomidine HCl (b) (4) Injection NDA?

FDA Response: No, we cannot agree at this time that additional nonclinical studies for the (b) (4) injection formulation will not be required, since safety information regarding the new container closure system was not provided in the meeting package. You will need to provide adequate support from the use of these container closure systems in approved aqueous drug products. Otherwise, submit information on potential leachables and extractables for your drug products as soon as it is available so that, if necessary, the Agency can provide additional guidance on what qualification studies may be required for the NDA submission.

4. Is the proposed nonclinical approach based up the review of the data from published literature, reference to FDA's previous determination of nonclinical safety and efficacy by reference to the Precedex Injection NDA 021038, sufficient to support a 505(b)(2) NDA filing for HQ's proposed Dexmedetomidine Hydrochloride Injection, for the proposed indication?

FDA Response: Yes, your nonclinical approach based upon published literature and reference to the Agency's previous determination of safety and efficacy of the referenced drug appears sufficient to support a 505(b)(2) NDA filing for your drug product. However, additional nonclinical data may be necessary to support the safety of the drug product formulation. Your NDA must include adequate information to support the safety of the drug substance impurities, drug product degradants, and the safety of the container closure system via an appropriate extractables and leachables safety assessment (see additional comments below).

5. Does the FDA agree that the proposed levels of (b) (4) will not require additional nonclinical studies for approvability of HQ Dexmedetomidine HCl Pharmacy Bulk Solution NDA?

FDA Response: We agree additional nonclinical qualification studies are not required provided the level of (b) (4) does not exceed 1% in the drug product (see additional comment #2 below). However, any impurity or degradation product that exceeds ICH thresholds as per ICH Q3A(R2), ICH Q3B(R2) must be adequately qualified for safety or be demonstrated to be within the specifications of the referenced drug used for approval through the 505(b)(2) pathway. Guidance for Industry: *Q3A Impurities in New Drug Substances*, available at

<http://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/ucm073385.pdf>

Guidance for Industry: *Q3B (R2) Impurities in New Drug Products*, available at <http://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/ucm073389.pdf>

3.0 Additional Comments

1. For your NDA submission:

- a. In Module 2 of your NDA (2.6.6.8 Toxicology Written Summary/Other Toxicity), include a table listing the drug substance and drug product impurity specifications, the maximum daily exposure to these impurities based on the maximum daily dose of the product and how these levels compare to ICH Q3A(R2) and ICH Q3B(R2) qualification thresholds and determination if the impurity contains a structural alert for mutagenicity. Any proposed specification

that exceeds the qualification thresholds should be adequately justified for safety from a toxicological perspective and include:

- i. *a genetic toxicology assessment*
- ii. *a repeat-dose toxicology study of appropriate duration to support the proposed indication*

NOTE: We may refuse to file your application if your NDA submission does not contain adequate safety qualification data for any identified impurity or degradant that exceeds the ICH qualification thresholds.

b. Provide extractables and leachables evaluations for all container closure components that contact the drug product solution. These evaluations should include specific assessments for residual monomers, solvents, polymerizers etc. Based on identified leachables you will need to provide a toxicological evaluation to determine the safe level of exposure. The approach for toxicological evaluation of the safety of leachables must be based on good scientific principles and take into account the specific container closure system drug product formulation, dosage form, route of administration, and dose regimen. As many residual monomers are known genotoxic agents, your safety assessment must take into account the potential that these leachables may either be known or suspected highly reactive and/or genotoxic compounds. The safety assessment should be specifically discussed in Module 2.6.6.8 (Toxicology Written Summary/Other Toxicity) of the NDA submission. For your toxicological risk assessment, any leachable that contains a structural alert for mutagenicity should not exceed 1.5 mcg/day total daily exposure or be adequately qualified for safety. A toxicological risk assessment should be provided for any non-genotoxic leachable that exceeds 5 mcg/day. The risk assessment should be based on the levels of leachables detected in long-term stability samples that include any intended secondary container closure system(s) unless otherwise justified.

For reference in how to design an extractables and leachables study, we refer you to the following PQRI publication:

http://www.pqri.org/pdfs/LE_Recommendations_to_FDA_09-29-06.pdf

3 Studies Submitted

There were no nonclinical studies submitted in this NDA.

4 Pharmacology

There were no primary, secondary or safety pharmacology studies with dexmedetomidine submitted in this NDA.

5 Pharmacokinetics/ADME/Toxicokinetics

There were no pharmacokinetic, ADME, or toxicokinetic studies/data with dexmedetomidine submitted in this NDA.

6 General Toxicology

There were no general toxicology studies with dexmedetomidine submitted in this NDA.

7 Genetic Toxicology

There were no genetic toxicology studies with dexmedetomidine submitted in this NDA. The following information on the genetic toxicology (mutagenesis) of dexmedetomidine is from the referenced Precedex® label (Hospira, November 2014):

Dexmedetomidine was not mutagenic *in vitro*, in either the bacterial reverse mutation assay (*E. coli* and *Salmonella typhimurium*) or the mammalian cell forward mutation assay (mouse lymphoma). Dexmedetomidine was clastogenic in the *in vitro* human lymphocyte chromosome aberration test with, but not without, rat S9 metabolic activation. In contrast, dexmedetomidine was not clastogenic in the *in vitro* human lymphocyte chromosome aberration test with or without human S9 metabolic activation. Although dexmedetomidine was clastogenic in an *in vivo* mouse micronucleus test in NMRI mice, there was no evidence of clastogenicity in CD-1 mice.

8 Carcinogenicity

As the proposed drug product is for acute use, a carcinogenicity evaluation with dexmedetomidine is not required. The following information on the carcinogenicity of dexmedetomidine is from the referenced Precedex® label (Hospira, November 2014):

Animal Carcinogenicity studies have not been performed with dexmedetomidine.

9 Reproductive and Developmental Toxicology

There were no fertility studies with dexmedetomidine submitted in this NDA. The following information on the impairment of fertility of dexmedetomidine is from the referenced Precedex® label (Hospira, November 2014):

Fertility in male or female rats was not affected after daily subcutaneous injections of dexmedetomidine at doses up to 54 mcg/kg (less than the maximum recommended human intravenous does on a mcg/m² basis) administered from 10 weeks prior to mating in males, and 3 weeks prior to mating and during mating in females.

There were no further reproductive and developmental toxicology studies with dexmedetomidine submitted in this NDA. The following information on the reproductive and developmental toxicology of acetaminophen is from the pregnancy section of the referenced Precedex® label (Hospira, November 2014):

Pregnancy Category C

There are no adequate and well-controlled studies of Precedex use in pregnant women. In an *in vitro* human placenta study, placental transfer of dexmedetomidine occurred. In a study in the pregnant rat, placental transfer of dexmedetomidine was observed when radiolabeled dexmedetomidine was administered subcutaneously. Thus, fetal exposure should be expected in humans, and Precedex should be used during pregnancy only if the potential benefits justify the potential risk to the fetus.

Teratogenic effects were not observed in rats following subcutaneous administration of dexmedetomidine during the period of fetal organogenesis (from gestation day 5 to 16)

with doses up to 200 mcg/kg (representing a dose approximately equal to the maximum recommended human intravenous dose based on body surface area) or in rabbits following intravenous administration of dexmedetomidine during the period of fetal organogenesis (from gestation day 6 to 18) with doses up to 96 mcg/kg (representing approximately half the human exposure at the maximum recommended dose based on plasma area under the time-curve comparison). However, fetal toxicity, as evidenced by increased post-implantation losses and reduced live pups, was observed in rats at a subcutaneous dose of 200 mcg/kg. The no-effect dose in rats was 20 mcg/kg (representing a dose less than the maximum recommended human intravenous dose based on a body surface area comparison). In another reproductive toxicity study when dexmedetomidine was administered subcutaneously to pregnant rats at 8 and 32 mcg/kg (representing a dose less than the maximum recommended human intravenous dose based on a body surface area comparison) from gestation day 16 through weaning, lower offspring weights were observed. Additionally, when offspring of the 32 mcg/kg group were allowed to mate, elevated fetal and embryocidal toxicity and delayed motor development was observed in second generation offspring.

10 Special Toxicology Studies

There were no special toxicology studies with dexmedetomidine submitted in this NDA.

11 Integrated Summary and Safety Evaluation

There were no new toxicology studies submitted or required to support this NDA as the drug product is identical to the referenced product with the exception of two excipients, methylparaben and propylparaben, which were added to the drug product formulation as preservatives. These excipients are not novel excipients as they exist in FDA approved injectable aqueous drug products at comparable concentrations and maximum total daily intake. The drug substance and drug product specifications are acceptable.

An extractables/leachables assessment was not included in the initial NDA submission and as a result the Division requested this assessment in an Information Request. The Sponsor responded and provided extractables data under three extraction conditions, water, water pH 3, and isopropanol. A risk assessment was conducted on those extractable compounds that exceeded a daily intake level of 5 mcg/day and it was noted that none of these detected compounds contained structural alerts. These extractables were associated with daily intake levels of less than (b) (4) mcg/day, which is an acceptable intake level for a mutagenic impurity. It is also noted that the same (b) (4) stopper are used in FDA-approved intravenous drug products. Therefore by taking a weight-of-evidence approach, the lack of leachable profile does not appear to be an approval issue for this NDA but it is recommended that a leachables assessment on stability samples be requested as a Postmarketing Requirement.

Taken together, from a nonclinical pharmacology toxicology perspective, this application may be approved with the recommended PMR.

APPEARS THIS WAY ON ORIGINAL

12 Appendix/Attachments

References

1.  (b) (4)
2. CIR (1987) Final report of the safety assessment for oleic acid, lauric acid, palmitic acid, myristic acid, stearic acid. Prepared by the Expert Panel of the Cosmetic Ingredient Review, Washington D.C.
3. Japan Chemical Industry Ecology- Toxicology and Information Center, Japan (2000) Mutagenicity Test Data of Existing Chemical Substances Based on the Toxicity Investigation of the Industrial Safety and Health Law (Suppl. 2), 2000.
4.  (b) (4)
5. Mortelmans K, Haworth S, Lawlor T, Speck W, Tainer B and Zeiger E (1986) Salmonella Mutagenicity Tests II. Results from the Testing of 270 Chemicals. Environ. Mutagen. 8(Suppl. 7):1-119.
6. Trumbo P, Sutherland-Smith M, Kitchell B, Tove SB (1987) The result of feeding palmitoyl glycerol on lymph and plasma lipids, Lipids 22(12): 1009-1015.
7. USP <1663> Assessment of extractables associated with Pharmaceutical Packaging/Delivery Systems.
8. Zeiger R, Anderson B, Haworth S, Lawlor T and Mortelmans K (1992) Salmonella Mutagenicity Tests V. Results from the Testing of 311 Chemicals. Environ. Mol. Mutagen. 19(Suppl.21): 2-141.

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/s/

NEWTON H WOO
02/06/2015

RICHARD D MELLON
02/06/2015

I concur with Dr. Woo's recommendation that from a nonclinical pharmacology toxicology perspective, NDA 206628 may be approved. I also concur with the recommended PMR and labeling adjustments.

**PHARMACOLOGY/TOXICOLOGY FILING CHECKLIST FOR
NDA/BLA or Supplement**

	Content Parameter	Yes	No	Comment
9	Are the proposed labeling sections relative to pharmacology/toxicology appropriate (including human dose multiples expressed in either mg/m2 or comparative serum/plasma levels) and in accordance with 201.57?	X		505(b)(2)
10	Have any impurity – etc. issues been addressed? (New toxicity studies may not be needed.)	X		
11	Has the applicant addressed any abuse potential issues in the submission?		X	
12	If this NDA/BLA is to support a Rx to OTC switch, have all relevant studies been submitted?			N/A

IS THE PHARMACOLOGY/TOXICOLOGY SECTION OF THE APPLICATION FILEABLE? YES

If the NDA/BLA is not fileable from the pharmacology/toxicology perspective, state the reasons and provide comments to be sent to the Applicant.

N/A

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

None.

Reviewing Pharmacologist Date

Team Leader/Supervisor Date

File name: 5_Pharmacology_Toxicology Filing Checklist for NDA_BLA or Supplement
010908

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/s/

NEWTON H WOO
07/14/2014

ADAM M WASSERMAN
07/14/2014