CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

217812Orig1s000

NON-CLINICAL 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

Application number:	217812
Supporting document/s:	01, 02
Applicant's letter date:	02/16/2023, 05/10/2023
CDER stamp date:	02/16/2023, 05/10/2023
Product:	Hydromorphone Hydrochloride Injection (b) (4) 40 mg/20 mL
Indication:	Management of pain severe enough to require an opioid analgesic and for which alternate treatments are inadequate
Applicant:	Hikma Pharmaceuticals
Review Division:	Division of Anesthesiology, Addiction Medicine, and Pain Medicine (DAAP)
Reviewer:	Jessica Hoffman, PhD
Supervisor/Team Leader:	Jay Chang, PhD / Misol Ahn, PhD
Division Director:	Rigoberto Roca, MD
Project Manager:	Cooma Asonye, PharmD

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1 Executive Summary

1.1 Introduction

NDA 217812 was submitted by Hikma Pharmaceuticals USA Inc. to seek marketing approval of Hydromorphone Hydrochloride Injection, an intravenous formulation of the opioid agonist for the management of pain severe enough to require an opioid analgesic and for which alternate treatments are inadequate.

The NDA was submitted by the 505(b)(2) pathway relying on the listed drug Dilaudid® Injection (hydromorphone hydrochloride) for intravenous, intramuscular, or subcutaneous use (NDA 019034 approved in 1984), which is indicated for the same indication as proposed with this NDA. Dilaudid is available in 0.5 mg/0.5 mL, 1 mg/mL, or 2 mg/mL single-dose prefilled syringes. For intramuscular or subcutaneous use, the recommended starting dose is 1 mg to 2 mg every 2 to 3 hours as necessary. For intravenous use, the recommended starting dose is 0.2 mg to 1 mg every 2 to 3 hours, given slowly, over at least 2 to 3 minutes. Therefore, the maximum theoretical daily dose is considered 24 mg per day.

Hikma's Hydromorphone Hydrochloride Injection drug product has the same indication, dosage form, dosing regimen, and the concentration of hydromorphone hydrochloride as the listed drug, Dilaudid®, but it is formulated with different inactive ingredients and is packaged in a multiple-dose vial compared to the single-dose prefilled syringes for Dilaudid®.

The Applicant also notes that the drug product is the same as a legacy marketed unapproved IV hydromorphone hydrochloride drug product under NDC 0641-2341-41 (originally marketed by Baxter), with no changes in the drug product formulation composition.

1.2 Brief Discussion of Nonclinical Findings

No new nonclinical studies were submitted with this NDA.

Information submitted with the NDA included a clinical literature review, a nonclinical literature review, drug substance and drug product stability data, an extractables and leachables assessment for the container closure system, and a biowaiver request in lieu of a human bioavailability study to establish a bridge to the systemic safety of the listed drug.

The CMC review team concluded that the methodologies for the extractable and leachable study were appropriate. See the CMC review for full details. The biopharmaceutics review team concluded that the formulation differences between the proposed drug product and the listed drug would not impact the PK or bioavailability of the API compared to the listed drug. See the Biopharmaceutics review for full details. Of

note, the biowaiver was granted; therefore, additional nonclinical studies to qualify hydromorphone from the systemic safety perspective were not needed.

There are no novel excipients in the proposed drug product formulation. The highest and most frequent dosing regimen is for the SC and IM routes of administration and results in a total maximum daily volume of 12 mL. Based on this daily exposure, the maximum daily exposure (MDE) as well as the concentration of all the excipients are adequately covered for systemic and local safety for all three proposed routes of administration by FDA-approved products based on MDEs listed in the Inactive Ingredient Database (IID).

Container Closure System
The proposed hydromorphone hydrochloride product (40 mg/20 mL) is a sterile aqueous solution in a multi-dose vial containing 40 mg of hydromorphone hydrochloride in 20 mL vial for subcutaneous, intramuscular and slow intravenous administration supplied as 1 vial per carton. The primary container closure system consists of a glass vial and rubber stopper. The Applicant conducted an extraction study and a leachable study on the container closure system and manufacturing process materials (Report BED-PN1314-2022-0376). The CMC review team noted that the extractable and leachable study methodologies were appropriate and adequate. The Applicant employed an appropriate Analytical Evaluation Threshold (AET) of (b) (4) ng/vial (or (b) (4) ng/mL) based on a maximum daily dose of 24 mg/day, a maximum daily volume of 12 mL/day, a safety concern threshold (SCT) of (b) (4) mcg/day, and an additional 50% uncertainty factor.

Under the conditions of the leachable study, from the pharmacology/toxicology perspective, there is no leachable safety concern from the container closure components or the process contact materials. For the glass vial, all the extracted element concentrations were found to be lower than 30% of the PDEs listed in ICH Q3D for all 24 elemental impurities. For the rubber stopper, no non-volatile, volatile, and semi volatile organic compounds were detected in any of the stability samples above the AET.

PLLR
An acceptable updated nonclinical literature search was conducted and we agree with the Applicant that there was no new information from this review that warrants any changes to the nonclinical sections of the labeling.

1.3 Recommendations

1.3.1 Approvability

From a nonclinical pharmacology/toxicology perspective, the NDA may be approved.

1.3.2 Additional Non-Clinical Recommendations

None

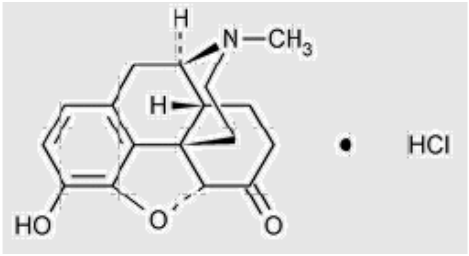
1.3.3 Labeling

The nonclinical sections of the proposed label are consistent with the listed drug. There is no new information that warrants changes to the nonclinical sections of the proposed labeling.

2 Drug Information

2.1 Drug

CAS Registry Number:	71-68-01
Generic Name:	Hydromorphone Hydrochloride, (b) (4)
Code Name:	Hydromorphone Hydrochloride injection, (b) (4)
Chemical Name:	4, 5α-epoxy-3-hydroxy-17-methylmorphinan-6-one hydrochloride
Molecular Formula:	$C_{17}H_{19}NO_3 \cdot HCl$
Molecular Weight:	321.80 g/mol
Structure or Biochemical Description:	A white or almost white crystalline powder that is freely soluble in water, very slightly soluble in ethanol (96%), and practically insoluble in methylene chloride.



Pharmacologic Class:	Opioid

2.2 Relevant INDs, NDAs, BLAs and DMFs

Application	Drug Product	Status	Notes
NDA 019034	Dilaudid® Hydromorphone Hydrochloride	Approved 01/11/1984 Active Applicant: Fresenius Kabi USA LLC	Listed Drug (LD)
PIND 157219	Hydromorphone Hydrochloride Injection, (b) (4) 40 mg/20 mL	Pre-submission, opened 10/14/2021	505(b0(2) pre-NDA advice WRO issued 03/24/2022

DMF	(b) (4)

2.3 Drug Formulation

The finished drug product, Hydromorphone Hydrochloride Injection, (b) (4) 40 mg/20 mL (2 mg/mL) is a sterile aqueous solution for injection in a multi-dose vial containing 40 mg of Hydromorphone Hydrochloride in 20 mL.

The Applicant provided the following table for the drug product formulation:

Table 1 Quantitative composition of proposed drug product

Composition of Hydromorphone Hydrochloride Injection (b) (4) 40 mg/20 mL (2 mg/mL) multiple-dose vial							
Component	**Function**	**Amount per mL**	**Amount per 20 mL vial**	**Unit (% w/v)**	**IID Levels**		
					Intravenous	**Intramuscular**	**Subcutaneous**
Hydromorphone HCl, USP	Active	2.0 mg	40 mg	0.2	Not Applicable	Not Applicable	Not Applicable
Edetate Disodium Dihydrate, USP	(b) (4)	0.5 mg	10 mg	0.05	10% w/v 19 mg/day	10 % w/v	0.2% w/v
Methylparaben, NF		1.8 mg	36 mg	0.18	5% w/v 54 mg/day	0.14% w/v 54 mg/day	0.44 % w/v
Propylparaben, NF		0.2 mg	4 mg	0.02	0.02% w/v 0.06 mg/day	0.02% w/v 0.06 mg/day	0.2% w/v
Hydrochloric Acid, NF	pH adjuster	As needed to adjust the pH			Not Applicable	Not Applicable	Not Applicable
Sodium Hydroxide, NF	pH adjuster	As needed to adjust the pH			Not Applicable	Not Applicable	Not Applicable
Water for Injection, USP	Diluent	QS to 1 mL	QS to 20 mL	QS to 100%	Not Applicable	Not Applicable	Not Applicable
(b) (4)							

Sponsor's table

Compared with the formulation of the LD, the proposed drug product formulation removes sodium citrate and citric acid, and adds edetate disodium dihydrate (b) (4), methylparaben, and propylparaben, as well as sodium hydroxide and hydrochloric acid for pH adjustment. The Applicant provided a comparison table of the formulations of the drug product and the LD, presented below:

Table 2 Side-by-side comparison of the proposed drug product formulation and listed drug product formulation

Component	Intended Function	Concentration in Proposed Hikma Product (mg/mL)	Concentration in Dilaudid (mg/mL)
Hydromorphone HCl, USP	Active Ingredient	2.0	2.0
Sodium Citrate, USP	Buffer	NA	2.0
Citric Acid, USP	Buffer	NA	2.0
Edetate Disodium Dihydrate	(b) (4)	0.5	NA
Methylparaben, NF		1.8[a]	NA
Propylparaben, NF		0.2[a]	NA
Sodium Hydroxide, NF	pH adjustor	pH adjustment (3.5 to 5.5)	NA
Hydrochloric Acid, NF	pH adjustor	pH adjustment (3.5 to 5.5)	NA
Water for Injection, USP	Aqueous Vehicle	q.s. ad 1 mL	q.s. ad 1 mL
(b) (4)			

HCl = hydrochloride; NA = not applicable; NF = National Formulary; q.s. ad = quantity sufficient to make; USP = United States Pharmacopeia.

Sponsor's table

According to the intended dosage labeling, for the subcutaneous (SC) or intramuscular (IM) routes of administration, the initial starting dose of Hydromorphone Hydrochloride Injection is 1 mg to 2 mg every 2 to 3 hours as necessary, for a maximum theoretical daily dose of 24 mg/day (12 mL based on 2 mg every 2 hours). For the intravenous route of administration, the initial starting dose is 0.2 to 1 mg every 2 to 3 hours, for a maximum theoretical daily dose of 12 mg/day (6 mL based on 1 mg every 2 hours). Systemic Maximum Daily Exposure (MDE) of excipients is thus based on the maximum proposed volumes (12 mL) via the proposed routes of administration (IV, SC, or IM).

As shown in the Reviewer's table below, all the excipients in the proposed drug product are covered by FDA-approved products in the Inactive Ingredient Database (IID) for the systemic MDE as well as the local concentration for each intended route of administration (IV, SC, and IM).

Table 3 Evaluation of proposed drug product excipient exposure

Component	Function	mg/mL	% w/v	MDE* mg/day	Maximum levels in IID	
					Systemic MDE mg/day	local concentration (% w/v)
Hydromorphone HCl, USP	API	2.0	0.2	24	-	-
Edetate Disodium Dihydrate, USP	(b) (4)	0.5	0.05	6	IV: 19	IV: 10
						IM: 10
						SC: 0.20
Methylparaben, NF	(b) (4)	1.8	0.18	21.6	IV: 54	IV: 5.00
						IM: 0.75
						SC: 0.44
Propylparaben, NF	(b) (4)	0.2	0.02	2.4	IV: 6	IV: 0.20
						IM: 0.40
						SC: 0.20
Hydrochloric Acid, NF	pH Adjuster	As needed to adjust pH			-	-
Sodium Hydroxide, NF	pH Adjuster	As needed to adjust pH			-	-
Water for injection, USP	Diluent	QS to 1 mL or 100% w/v			-	-
(b) (4)					-	-

*Maximum Daily Exposure (MDE) based on a maximum daily dosing volume of 12 mL

Of note, the Applicant's composition Table 1 includes the FDA IID-listed concentration of methylparaben for the IM route at 0.14% w/v, whereas the drug product formulation of 0.18 % w/v would not be covered for local safety; however, as shown in Table 3, the IID lists an FDA-approved product with a concentration of 0.75% w/v for the IM route, so this excipient is qualified for local safety for the IM route of administration. Additionally, the Applicant's composition Table 1 lists the MDE of propylparaben as 0.06 mg/day, which would not cover the maximum exposure of 2.4 mg/day of the proposed drug product; however, this appears to be a typo. As shown in Table 3, the MDE of propylparaben in an FDA-approved product listed in the IID for IV injection is 6 mg/day.

Additionally, the Applicant submitted a request for a waiver of the requirement to conduct in vivo bioavailability/bioequivalence studies in lieu of a New Drug Application (NDA) section describing the human pharmacokinetic data and human bioavailability data for Hikma's Hydromorphone Hydrochloride (HCl) injection formulation. See the

Biopharmaceutics review team review for additional details. We defer to their determination that the differences in formulation do not significantly impact the PK or bioavailability of the API.

Within this biowaiver, the Applicant also provided a table of comparative physiochemical properties between the proposed drug product and the listed drug product (Table 4 below).

Table 4 Comparative physiochemical properties between the proposed drug product and the LD product

Properties	Proposed Hikma Specification	Hikma MDV Submission Batches (Lots P110123, P110125, P110127)	Dilaudid Lot #6024409 Expiration Date 07/2023	Dilaudid Lot #6021709 Expiration Date 05/2024	Dilaudid Lot #6027316 Expiration Date 05/2024
pH	(b) (4) Shelf life: 3.5 to 5.5	(b) (4)	4.16	4.21	4.26
Osmolality	(b) (4)	23 mOsm/kg	49 mOsm/kg	49 mOsm/kg	58 mOsm/kg
Viscosity	Information Only	0.95 Cp at 25°C	1.23 Cp at 25°C	0.94 Cp at 25°C	0.96 at 25°C
Density	Information Only	0.99809 g/mL at 25.0°C	0.99988 g/mL at 25.0°C	0.99995 g/mL at 25.0°C	1.00025 g/mL at 25.0°C
Reference		Hydromorphone HCl Injection, (b) (4) 40 mg/20 mL (2 mg/mL); Exhibit Batch Stability Summary Report	WW-BED-0270 pages 94, 96	HI-BED-0370 pages 33-34	HI-BED-0357 pages 78-81

HCl = hydrochloride; MDV = multiple dose vial; USP = United States Pharmacopeia.

Sponsor's table

The Applicant indicated that the differences in excipients do not appear to significantly alter the pH, osmolality, or viscosity of the proposed formulation relative to the LD formulation. Of note, the osmolality of the proposed product has a specification of (b) (4) mOsm/kg, which is approximately 2-fold lower than the osmolality of the listed drug ((b) (4) mOsm/kg). Following discussion with the other review disciplines, the Clinical Reviewer agreed that this difference is insignificant considering plasma osmolality is approximately 300 mOsm/L. The Applicant noted that other approved products from the same Applicant have lower osmolality and have been approved. In addition, there is clinical experience with this formulation as it has been available as a marketed

unapproved product in the U.S. since 1972. Therefore, from the pharmacology/toxicology perspective, we do not have a safety concern for the difference in osmolality from the listed drug at this time.

2.4 Comments on Novel Excipients

There are no novel excipients.

2.5 Comments on Impurities/Degradants of Concern

There is no safety concern with impurities/degradants. Specifications for the Drug Substance and Drug Product, as shown in Tables 5 and 6 below, are within the appropriate ICH Q3A and Q3B thresholds based on the MTDD of 24 mg.

Table 5 Specifications for Drug Substance, Hydromorphone HCl

TEST	SPECIFICATION		TEST METHOD
Description	white to off-white powder.		APCHH15536
Identification A	Sample IR Spectrum corresponds to that of the standard.		USP <197>
Identification B	RT of the sample peak corresponds to that of the standard.		APCHH15576
Identification C	The sample responds to the test for Chloride.		USP <191>
Specific Rotation	-136° to -139° at 25°C in water		USP <781S>
Acidity	NMT 0.30 mL is required to produce a yellow color.		USP
Loss on Drying	NMT 1.5%		USP <731>
Residue on Ignition	NMT 0.3% w/w		USP <281>
Chloride Content	(b) (4)		APCHH15584
Hydromorphone Hydrochloride	98.0-102.0%w/w (dried basis)		APCHH15576
Related Compounds	Dihydromorphine	NMT (b) (4) %	APCHH15576
	Morphine	NMT 0.15%	
	Hydromorphone N-Oxide	NMT 0.15%	

TEST	SPECIFICATION		TEST METHOD
	2,2'-Bishydromorphone	NMT 0.15%	
	Hydromorphone Aldol Dimer	NMT (b) (4) %	
	(b) (4)		
	Any Unspecified Impurity	NMT 0.10%	
	Total Impurities	NMT 1.0%	
Residual Solvents	(b) (4)	NMT (b) (4) ppm	APCHH15582
		NMT ppm	
		NMT ppm	
Bioburden	Total Aerobic: NMT (b) (4) CFU/g		APCHH15145
	Total Yeasts and Molds: NMT (b) (4) CFU/g		
	E coli: (b) (4)		
	Ps. Aeruginosa: (b) (4)		
	Staphylococcus aureus: (b) (4)		
	Salmonella species: (b) (4)		
	Bile-tolerant, gram-negative bacteria: (b) (4)		
Bacterial Endotoxins	NMT (b) (4) EU/mg		APCHH15781
Vendor Protocol	Vendor's COA meets specifications		SOPCHH15064

Sponsor's table

Table 6 Specifications for Drug Product, Hydromorphone Hydrochloride Injectable

Test	Release Specifications		Stability Specifications		Method
Description	Clear, colorless liquid in a 20 ml colorless vial with a dark blue flip-off cap.		Clear, colorless liquid		Visual
Visible Particles	Essentially free of visible foreign matter		Essentially free of visible foreign matter		SOPCHH15295
Identification A	Sample IR spectrum corresponds to that of the standard.		N/A		USP
Identification B	(b) (4)		N/A		APCHH15580
pH	(b) (4)		3.5 – 5.5		USP<791>
APHA Color	NMT (b) (4) APHA		NMT (b) (4) APHA		WICHH15012
Osmolality	(b) (4) mOsm/Kg		(b) (4) mOsm/Kg		USP<785>
Volume in Container	NLT 20.0 mL		N/A		USP <697>
Hydromorphone Hydrochloride	(b) (4)				APCHH15580
Methylparaben					APCHH15580
Propylparaben					APCHH15580
Edetate Disodium, Dihydrate					APCHH15581
(b) (4					APCHH15580
Degradation Products	2,2'-Bishydromorphone	NMT (b) (4) %	2,2'-Bishydromorphone	NMT (b) (4) %	APCHH15580
	Hydromorphone N-Oxide	NMT %	Hydromorphone N-Oxide	NMT %	
	Any Unspecified Degradation Product	NMT (b) (4) %	Any Unspecified Degradation Product	NMT %	
	Total Degradation Product	NMT (b) (4) %	Total Degradation Product	NMT %	
Particulate Matter	Particles ≥ 10 µm: NMT (b) (4) Particles ≥ 25 µm: NMT		Particles ≥ 10 µm: NMT (b) (4) Particles ≥ 25 µm: NMT		USP<788>
Sterility	Meets USP<71> requirements.		Meets USP<71> requirements.		APCHH15139
Bacterial Endotoxins	NMT (b) (4) EU/mL (NMT 88.0 EU/mg)		NMT (b) (4) EU/mL (NMT 88.0 EU/mg)		APCHH15144

Test	Release Specifications	Stability Specifications	Method
(b) (4)			
Elemental Impurities	Meets USP <232> and ICH Q3D requirements	N/A	USP<232> Summation Option and ICH Q3D Option 2b
Other Requirements	Meets USP<1 > requirements.	N/A	USP<1>

N/A = Not Applicable; NLT = Not Less Than; NMT = Not More Than

Sponsor's table

The impurity hydromorphone N-oxide, a drug substance impurity, had a positive structural alert, so a request for (Q)SAR analysis was submitted to the CDER/OTS/OCP/DARS Computational Toxicology Consultation Service. Hydromorphone N-oxide is predicted to be negative for bacterial mutagenicity. The full consult summary and results table is below.

> Hydromorphone N-oxide, an impurity of the drug substance hydromorphone (API) from NDA 217812, was evaluated by the CDER/OTS/OCP/DARS Computational Toxicology Consultation Service for bacterial mutagenicity using (Q)SAR models. Three software programs were used: Derek Nexus 6.2.1 (DX), Leadscope Model Applier 2022.0.2-3 Bacterial Mut v2 model (LMA), and CASE Ultra 1.9.0.4 GT1_BMUT model 1.9.0.2 (CU). All (Q)SAR model outputs were reviewed with the use of expert knowledge in order to provide additional supportive evidence on the relevance of any positive, negative,

conflicting or inconclusive prediction and provide a rationale to support the final conclusion. The (Q)SAR assessment of mutagenic potential for the compound is consistent with recommendations described in the ICH M7(R1) guideline (i.e., prediction of bacterial mutagenicity using multiple complementary methodologies). Overall, hydromorphone N-oxide is predicted to be negative for bacterial mutagenicity.

No.	Chemical Name	Structure	Bacterial Mutagenicity Predictions[1]				Comments
			DX	*LMA*	*CU*	Overall Expert	
1	Hydromorphone *N*-oxide	(b) (4)					

[1] - = negative; NC = test chemical features are not adequately represented in the model training data set, leading to a no call.

2.6 Proposed Clinical Population and Dosing Regimen

The proposed clinical population is adults for which pain is severe enough to require an opioid analgesic and for which alternative treatments are inadequate.

For the subcutaneous or intramuscular routes of administration, the initial starting dose of Hydromorphone Hydrochloride Injection is 1 mg to 2 mg every 2 to 3 hours as necessary.

For the intravenous route of administration, the initial starting dose is 0.2 to 1 mg every 2 to 3 hours, for a maximum theoretical daily dose of 12 mg/day (6 mL based on 1 mg every 2 hours).

2.7 Regulatory Background

In December, 2021, the Applicant submitted a meeting request (PIND 157219) for input on data required to support the submission of a 505(b)(2) NDA for hydromorphone hydrochloride injection, 40 mg/20 mL. The request was granted and the WRO document sent 03/24/2022.

Briefly, the two nonclinical questions included in the PIND 157219 meeting package were regarding the Applicant's proposed nonclinical study designs for an in vitro hemolysis assay and a local irritation study in rabbit. In this WRO, the Division advised the Applicant that if the proposed formulation has comparable physiochemical properties compared to the reference product, a blood compatibility assessment and local tolerance rabbit study will not be needed. Additionally, the Applicant was advised that from a PK perspective, if a biowaiver/bio-bridge is granted for all the routes of administration, then no additional PK studies may be required to establish the scientific bridge between the proposed product and the listed drug. If, however, the biowaiver is not granted for all routes of administration, then additional nonclinical studies may be

warranted, noting that the acceptability of the biowaiver request would be made during the NDA submission review.

The NDA was submitted February 16, 2023 with a request for a waiver of the requirement to conduct in vivo bioavailability/bioequivalence studies in lieu of a New Drug Application (NDA) section describing the human pharmacokinetic data and human bioavailability data to support the new drug product formulation.

3 Studies Submitted

3.1 Studies Reviewed

No nonclinical studies were submitted with this NDA.

3.2 Studies Not Reviewed

No nonclinical studies were submitted with this NDA.

3.3 Previous Reviews Referenced

PIND 157219 – WRO Meeting Minutes (03/24/2022)

4 Pharmacology

No pharmacology studies were conducted by Hikma to support the NDA for hydromorphone hydrochloride injection. Hydromorphone is a full opioid agonist, relatively selective for the mu-opioid receptor and is able to bind to other opioid receptors at higher doses. The principal therapeutic action of hydromorphone is analgesia.

The Applicant is referencing the FDA's findings of clinical safety and efficacy for Dilaudid® according to the 505(b)(2) regulatory pathway.

5 Pharmacokinetics/ADME/Toxicokinetics

No pharmacokinetic (PK) studies were conducted by Hikma to support the NDA for hydromorphone hydrochloride injection. The PK profile of hydromorphone hydrochloride has been well-characterized based on extensive clinical experience with the legacy marketed unapproved product and 505(b)(2) to Dilaudid®. The Applicant is referencing the FDA's findings of clinical safety and efficacy for Dilaudid® according to the 505(b)(2) regulatory pathway.

6 General Toxicology

No single-dose or repeat-dose toxicology studies were conducted by Hikma to support the NDA for hydromorphone hydrochloride injection. The Applicant is referencing the FDA's findings of safety for Dilaudid® according to the 505(b)(2) regulatory pathway.

7 Genetic Toxicology

Additional genotoxicity studies were not conducted by Hikma to support the NDA for hydromorphone hydrochloride injection. The Applicant is referencing the FDA's findings of safety for Dilaudid® according to the 505(b)(2) regulatory pathway.

8 Carcinogenicity

Long-term studies evaluating the carcinogenic potential of hydromorphone or hydromorphone hydrochloride injection have not been conducted.

9 Reproductive and Developmental Toxicology

Additional reproductive and developmental toxicity studies were not conducted by Hikma. The Applicant is referencing the FDA's findings of clinical safety for Dilaudid® according to the 505(b)(2) regulatory pathway.

During the preliminary review of the submitted labeling, it was noted that the summary of available clinical published literature to support the changes in the Pregnancy, Lactation, and Females and Males of Reproductive Potential sections of labeling for hydromorphone were only provided for the years 2019-2022. An IR was sent to the Applicant on April 13, 2023, requesting additional information for a PLLR literature review. The IR also included a request for specific information for a review and summary of available nonclinical information from January 2015 to present. The Applicant provided a response to IR with the requested information on May 10, 2023.

Key Findings
The nonclinical literature search resulted in one publication that was relevant to the search criteria but did not provide relevant reproductive and development safety information that warrants safety-related changes to the nonclinical portions of the labeling for Hydromorphone HCl injection. There were relevant results in the clinical literature and pharmacovigilance database search that require changes to the labeling. See the clinical review for details.

PLLR Search Methods and Results
Literature search database: PubMed
Search date range: 01 January 2015 to 28 April 2023
PubMed access dates: 19 April 2023 and 28 April 2023

Table of Nonclinical PLLR Search Parameters and Hits:

Search #	Search Terms	# Hits
1	((Hydromorphone) OR (Hydromorphone HCl) OR (Dilaudid)) AND ((Reproduction) OR (Reproductive)) AND (Animal)	3
2	((Hydromorphone) OR (Hydromorphone HCl) OR (Dilaudid)) AND (Development) AND (Animal)	17
3	((Hydromorphone) OR (Hydromorphone HCl) OR (Dilaudid)) AND (Fertility) AND (Animal)	0
4	((Hydromorphone) OR (Hydromorphone HCl) OR (Dilaudid)) AND ((Female) OR (Male)) AND ((Reproduction) OR (Reproductive)) AND (Animal)	2
5	((Hydromorphone) OR (Hydromorphone HCl) OR (Dilaudid)) AND ((Reproduction) OR (Reproductive)) AND (Fertility) AND (Animal)	0
6	((Hydromorphone) OR (Hydromorphone HCl) OR (Dilaudid)) AND (Pregnancy) AND (Animal)	1
7	((Hydromorphone) OR (Hydromorphone HCl) OR (Dilaudid)) AND ((Female) OR (Male)) AND (Fertility) AND (Animal)	0
8	((Hydromorphone) OR (Hydromorphone HCl) OR (Dilaudid)) AND ((Female) OR (Male)) AND (Development) AND (Animal)	10
9	PubMed search #9: ((Hydromorphone) OR (Hydromorphone HCl) OR (Dilaudid)) AND (Lactation) AND (Animal)	0

Nine separate search term parameters were run. Nineteen unique articles were returned across all search results. One abstract was adjudicated as relevant and fully reviewed.

The relevant reference is summarized below:

Publication Title: Brief Hydromorphone Exposure During Pregnancy Sufficient to Induce Maternal and Neonatal Microbial Dysbiosis.

Publication Date: 2021
Authors: Abu Y, Tao J, Dutta R, Yan Y, Vitari N, Kolli U, Roy S.
Reference Info: *J Neuroimmune Pharmacol*. 2022 Jun;17(1-2):367-375. Doi: 10.1007/s11481-021-10019-2. Epub 2021 Sep 25. PMID: 34562195.

- Method: Female C57BL/6 mice were mated and received IP injection hydromorphone or saline once daily from Gestation Day (GD) 11-13 (10 mg/kg). Longitudinal changes in maternal gut microbiome (at 4 days post

exposure, birth, and weaning) and neonatal gut microbiome (at 2-, 3-, or 5-weeks postnatal) were evaluated.

- Result: Hydromorphone exposure resulted in induction of longitudinal changes in maternal and neonatal gut microbiota. Compared to control, significant changes in impact on beta-diversity, differences in microbial composition of fecal samples, and differences in gram-negative, gram-positive and potentially pathogenic bacterial phenotypes were observed, suggesting hydromorphone in breast milk may play a role in shaping the development of the neonatal gut microbiota.
- Applicant Conclusion and Justification: The publication is relevant based on search criteria but does not provide relevant reproductive and developmental safety information that warrants safety-related changes to the labeling.

Reviewer's Note: While this article reports intriguing findings of changes in maternal and neonatal gut microbiota from hydromorphone exposure, these data do not appear to be sufficient to warrant labeling changes on reproductive and development safety information; therefore, it does not appear to be appropriate to describe these data in the Hydromorphone Hydrochloride Injection label at this time.

The remaining 18 publications were considered not relevant because they were not relevant to evaluating the reproductive and developmental safety of hydromorphone. For each publication, the Applicant provided a short synopsis and justification for why it was not relevant. The references are listed below.

1. Cooper TE, Fisher E, Gray AL, Krane E, Sethna N, van Tilburg MA, Zernikow B, Wiffen PJ. Opioids for chronic non-cancer pain in children and adolescents. *Cochrane Database Syst Rev.* 2017 Jul 26;7(7):CD012538. doi: 10.1002/14651858.CD012538.pub2. PMID: 28745394; PMCID: PMC6477875.

2. Costa RS, Wetmore LA, Stein A. Randomized, blinded, controlled clinical trial to assess gastroesophageal reflux and regurgitation in dogs undergoing general anesthesia after hydromorphone premedication with or without acepromazine or dexmedetomidine. *Am J Vet Res*. 2021 Sep;82(9):695-700. doi: 10.2460/ajvr.82.9.695. PMID: 34432514.

3. Cox S, Bergman J, Hawkins S, Sladky K. Development of a method for the determination of hydromorphone in plasma by LC-MS. *Biomed Chromatogr*. 2018 Dec;32(12):e4357. doi: 10.1002/bmc.4357. Epub 2018 Aug 30. PMID: 30074252.

4. Divers SJ, Barbosa A, Ellis LE, Innis C, Gibbons P. Endoscopic sexing in turtles and tortoises: 467 cases (2007-2017). *Vet Rec.* 2022 Sep;191(5):e1795. doi: 10.1002/vetr.1795. Epub 2022 Jul 5. PMID: 35789491.

5. Han FY, Thurecht KJ, Lam AL, Whittaker AK, Smith MT. Novel polymeric bioerodable microparticles for prolonged-release intrathecal delivery of analgesic agents for relief of intractable cancer-related pain. *J Pharm Sci*. 2015 Jul;104(7):2334-44. doi: 10.1002/jps.24497. Epub 2015 May 19. PMID: 25990226.

6. Hornsey SJ, Carr AP, Loewen JM. Paroxysmal atrial fibrillation in a dog that was presented for neck wounds. *Can Vet J.* 2021 Jan;62(1):32-36. PMID: 33390596; PMCID: PMC7739399.

7. Jones TL, Calbay R, da Cunha AF, Hofmeister EH. Descriptive assessment of adverse events associated with midazolam-etomidate versus saline-etomidate in healthy hydromorphone premedicated dogs. *J Small Anim Pract*. 2021 Jun;62(6):437-441. doi: 10.1111/jsap.13304. Epub 2021 Feb 10. PMID: 33565094.

8. Kirkpatrick DL, Schmidt WK, Morales R, Cremin J, Seroogy J, Husfeld C, Jenkins T. In vitro and in vivo assessment of the abuse potential of PF614, a novel BIO-MD™ prodrug of oxycodone. *J Opioid Manag.* 2017 Jan/Feb;13(1):39-49. doi: 10.5055/jom.2017.0366. PMID: 28345745.

9. Martin-Flores M, Mostowy MM, Pittman E, Sakai DM, Mohammed HO, Gleed RD, Campoy L. Investigation of associations between preoperative acepromazine or dexmedetomidine administration and development of arterial hypotension or bradycardia in dogs undergoing ovariohysterectomy. *J Am Vet Med Assoc*. 2019 Jul 15;255(2):193- 199. doi: 10.2460/javma.255.2.193. PMID: 31260409.

10. Nystrom MR, Odunayo A, Okafor CC. Assessment of hydromorphone and dexmedetomidine for emesis induction in cats. *J Vet Emerg Crit Care* (San Antonio). 2019 Jul;29(4):360-365. doi: 10.1111/vec.12866. Epub 2019 Jun 25. PMID: 31240797.

11. Rasys AM, Divers SJ, Lauderdale JD, Menke DB. A systematic study of injectable anesthetic agents in the brown anole lizard (*Anolis sagrei*). *Lab Anim.* 2020 Jun;54(3):281-294. doi: 10.1177/0023677219862841. Epub 2019 Jul 26. PMID: 31345120; PMCID: PMC6982557.

12. Sanchez-Migallon Guzman D, Douglas JM, Beaufrère H, Paul-Murphy JR. Evaluation of the thermal antinociceptive effects of hydromorphone hydrochloride after intramuscular administration to orange-winged Amazon parrots (*Amazona amazonica*). *Am J Vet Res.* 2020 Oct;81(10):775-782. doi: 10.2460/ajvr.81.10.775. PMID: 32969733.

13. Shao J, Houghten RA, Dooley CT, Cazares M, McLaughlin JP, Eans SO, Ganno ML, Hoot MR, Giulianotti MA, Yu Y. A one-pot multicomponent approach to a new series of morphine derivatives and their biological evaluation. *Org Biomol Chem*. 2017 Sep 26;15(37):7796-7801. doi: 10.1039/c7ob01924f. PMID: 28875208.

14. Skrzypczak H, Reed R, Barletta M, Quandt J, Sakai D. A retrospective evaluation of the effect of perianesthetic hydromorphone administration on the incidence of postanesthetic signs of colic in horses. *Vet Anaesth Analg*. 2020 Nov;47(6):757-762. doi: 10.1016/j.vaa.2020.06.003. Epub 2020 Jul 23. PMID: 2830037.

15. Sulima A, Jalah R, Antoline JFG, Torres OB, Imler GH, Deschamps JR, Beck Z, Alving CR, Jacobson AE, Rice KC, Matyas GR. A Stable Heroin Analogue That Can Serve as a Vaccine Hapten to Induce Antibodies That Block the Effects of Heroin and Its Metabolites in Rodents and That Cross-React Immunologically with Related Drugs of Abuse. *J Med Chem*. 2018 Jan 11;61(1):329-343. doi: 10.1021/acs.jmedchem.7b01427. Epub 2017 Dec 29. PMID: 29236495; PMCID: PMC5767880.

16. Sylvestre FR, Monteiro BP, Simard MJ, Steagall PV. Anesthetic effects of ketamine-medetomidinehydromorphone in dogs during high-quality, high volume surgical sterilization program under field conditions. *Vet Anaesth Analg*. 2020 Nov;47(6):789- 792. doi: 10.1016/j.vaa.2020.08.001. Epub 2020 Aug 12. PMID: 32883624.

17. Thigpen JC, Odle BL, Harirforoosh S. Opioids: A Review of Pharmacokinetics and Pharmacodynamics in Neonates, Infants, and Children. *Eur J Drug Metab Pharmacokinet*. 2019 Oct;44(5):591-609. doi: 10.1007/s13318-019-00552-0. PMID: 31006834.

18. Weber L, Wang X, Ren R, Wei X, Zhao G, Yang J, Yuan H, Pang H, Wang H, Wang D. The Development of a Macromolecular Analgesic for Arthritic Pain. *Mol Pharm.* 2019 Mar

4;16(3):1234-1244. doi: 10.1021/acs.molpharmaceut.8b01197. Epub 2019 Feb 14. PMID: 30702897; PMCID: PMC6413733.

Reviewer's Conclusion
The search parameters were appropriate, and this Reviewer agrees with the determination of relevance and summaries for the publications that were identified in the search. This Reviewer also agrees that the relevant literature publication, while suggestive that hydromorphone HCl exposure from breast milk may have a role in shaping the neonatal gut microbiota, is insufficient to determine a clinical impact and safety margin; therefore, it does not warrant a change in the nonclinical data labeling.

10 Special Toxicology Studies

10.1 Extractable and Leachable Study

Title: Extractable and Leachable Assessment for the Container Closure System and Process Contact Hydromorphone Hydrochloride Injection, (b) (4) 40 mg/20 mL (2 mg/mL) Multi-Dose Vial

Study Number: BED-PN1314-2022-0376-00

Study Location: NDA217812 (217812 - 0001 - (1) - 2023-02-16 - ORIG-1 /Multiple Categories/Subcategories) - Extractables and Leachable Risk Assessment Report for CCS and Process Contact Parts

Testing Facility:
Hikma, Bedford Development Center
300 Northfield Road, Bedford, Ohio 44146

Key Findings:

- This risk assessment was performed for all contact materials during manufacturing and shelf-life storage (container closer system) of the Hydromorphone Hydrochloride Injection, (b) (4) 40 mg/20 mL (2mg/mL) multi-dose vial including, container closure, (b) (4)

- Extractable studies on the container closure system were followed and completed as per USP <1663>. For the glass vial, all the extracted element concentrations were found to be much lower than 30% of the permitted daily exposures (PDEs) listed in ICH Q3D for all 24 elementals. For the rubber stopper, a number of volatile, non-volatile, and semi-volatile organic compounds were identified above an appropriate AET (with additional 50% uncertainty factor) of (b) (4) ng/stopper and therefore were targeted in the leachable study.

- In the leachable studies for primary container closure components, no non-volatile, volatile, and semi volatile organic compounds were detected in any of the 3M, 6M, 15M and 18M inverted stability samples above the AET. None of the elementals of interest were detected in any of the 3M, 6M, 15M and 18M inverted stability samples above the PDE.

- Manufacturing process materials with potential contact with the drug product included (b) (4) valuation of these products determined a low risk of unsafe levels of impurities in bulk solution.

- **Conclusion:** The leachable screening studies confirmed that there is no leachable safety concern from process contact materials and container closure components from the Hydromorphone Hydrochloride Injection, (b) (4), 40 mg/20 mL (2 mg/mL).

For additional details and assessment of acceptability of the E&L study design and method validation, see the CMC review.

Purpose of Study:
The objective of this report is to perform the risk assessment on the extractables and leachables for the container closure system as per USP <1663>, USP<1664> and for product contact parts in the manufacturing process as per USP <1665>.

Note both the extractable and leachable assessments were submitted in a single report, and both are addressed in this section of the review.

The primary packaging components of the container closure system are listed in the table below:

Container Closure System Hydromorphone Hydrochloride Injection (b) (4) 40 mg/20 mL (2 mg/mL) multiple-dose vial			
Component	**Hikma Part #**	**Hikma Specifications #**	**Description**
Glass Vial	(b) (4)		20 mL Vial, (b) (4) (b) (4)
Stopper			(b) (4)
Seal			(b) (4)

Sponsor's table

Secondary packaging consists of 1 vial per carton with package insert.

The extraction study was performed for the following materials:

- Glass vial (Type (b) (4) 20 mL (b) (4) (b) (4) (b) (4) (b) (4)
- Stopper (b) (4) (b) (4) (b) (4)

Extraction Solvents used in the extraction study:

- Water (pH 2 and 10)
- 50% IPA in water

The hydromorphone hydrochloride drug product formulation consists of water making up more than (b) (4)% w/v, and the hydromorphone HCl making up 0.2% w/v, and an expected pH range of 3.5 to 5.5.

Extraction Methods

Type (b) (4) glass components are not considered an expected source of organic leachables and were analyzed for elemental impurities. Extractions were performed according to European Pharmacopeia 9.0 and American Pharmacopeia USP 39-NF 34: N.6 glass containers were filled with 34 mL of purified water and kept in an autoclave at 121 ±1°C for 60 ±1 min. The elemental concentration in the final extract was measured by Inductively Coupled Plasma Mass Spectrometry (ICP-MS) according to ISO 17294-2:2016.

Table 3: Summary of Container Closure System and Extraction Conditions

Component	Solvents	Type of extractions	Analytical Instruments used for Analysis	Reference Section
(b) (4) Vial: 20 mL. (b) (4) (b) (4)	• Water	121°C for 60mins	ICP-MS	Section 5.1
Stopper: (b) (4) (b) (4) (b) (4)	NA	115°C for 60mins	HS/GC-MS	Section 5.2
	• pH 2 Water • pH 10 Water • 50% IPA in water	Reflux for 12 hours	DI-GC/MS, LC-MS, ICP-MS	
20mm aluminum flip-off	NA	NA	NA	NA

Sponsor's table

Additionally, a glass delamination study was performed on stability samples of Hydromorphone Hydrochloride Injection, (b) (4) provided under "Examination of Hydromorphone vials for Delamination" (Reference a.3 of the E&L study report) and no

pitting or delamination was seen on any of the vial walls. See the CMC review for additional details.

For the rubber stoppers, (b) (4) are being used for Hydromorphone Hydrochloride Injection, (b) (4), whereas controlled extraction study was performed on (b) (4) stoppers. The Applicant applied a surface area correction in the MDI calculation and determined the substitution had no impact on the extractable studies. See the CMC review for additional details regarding the acceptability.

The extractable study design for the stoppers was conducted according to USP<1663> using several extraction solvents to bracket product pH and hydrophobicity. Stoppers were added into an extraction vessel and submerged with each extraction solvent at its boiling point for 12 hours. A control was generated by adding each extraction solvent into extraction vessel without a stopper. The SA/V ratios used in the extraction study are summarized in the table below. Solvents were analyzed for volatile organic compounds by HS-GC-FID/MS (reporting limit (b) (4) ng/stopper), semi-volatile organic compounds by GC-FID/MS (reporting limit (b) (4) ng/stopper), non-volatile organic compounds by LC-DAD/MS (reporting limit (b) (4) ng/stopper), and inorganic elements by ICP-MS (reporting limit (b) (4) % of the PDE of ICH Q3D Elements). All compounds detected above reporting limits were quantified. There is no gap in identification and quantification of potential leachable compounds extracted from the stopper because the respective reporting limits for each analytical technique are less than the 50% uncertainty AET (i.e., (b) (4) ng/stopper) described above.

Analytical Evaluation Threshold (AET)
The AET was calculated based on a safety concern threshold (SCT) of (b) (4) mcg/day, which is appropriate for an acute indication, and a maximum daily dose (MDD) and maximum daily volume (MDV) of 24 mg/day and 12 mL/day or 0.6 vials/day (e.g., 12 mL/day of 20 mL/vial), respectively, following the calculation below. An additional uncertainty factor (UF) of 50% was also employed.

$$^{*}\text{AET} = \frac{\text{Safety Concern Threshold (SCT)}}{\text{Maximum Daily Volume (MDV)}}$$

$$^{**}\ \text{AET considering 50\% Uncertainty factor} = \frac{\text{Safety Concern Threshold (SCT)}}{\text{Maximum Daily Volume (MDV)}} \text{ x } 0.5$$

AET = (b) (4) mcg/day ÷ 12 mL/day = (b) (4) ng/mL or
AET = (b) (4) mcg/day ÷ 0.6 vials/day = (b) (4) ng/vial
AET (with 50% UF) = (b) (4) ng/mL or (b) (4) ng/vial

Table 6: Primary Container Closure Components Extraction Surface Area to Volume Ratios	
Description	**Extraction**
SA/V ratio of extraction study	(b) (4)
Total surface area	
SA/V ratio of drug product	
Product contact surface area	
Product contact SA/V ratio of drug product	

Sponsor's table

Extractable Results

The ICP-MS analysis for inorganic extractables for the glass vials is summarized in the table below:

Table 4: ICP-MS Analysis of Extractables from Glass Vial			
Detected Compounds	**Amount detected (µg/mL)**	**MDI[C] (µg/day)**	**PDE (µg/day)**
(b) (4)			

Table 4: ICP-MS Analysis of Extractables from Glass Vial			
Detected Compounds	Amount detected (µg/mL)	MDI[C] (µg/day)	PDE (µg/day)
(b) (4)			

[C] The maximum daily intake, MDI is (b) (4) stoppers (or (b) (4) vials) of Hydromorphone Hydrochloride Injection, (b) (4) 40 mg/20 mL (2 mg/mL) multi-dose vial per day. Based on this information, the MDI of each of the detected extractable was calculated using the following equation,
MDI(µg/day) = Extractable amount (µg/mL) *20mL/vial * (b) (4) vials/day

(b) (4)

Sponsor's table

All the extracted element concentrations were found to be lower than 30% of the PDEs listed in ICH Q3D for all 24 elementals.

HS-GC/MS analysis results for volatile extractables of the stopper are summarized in the table below:

Table 8: Headspace GC/MS Analysis of Volatile Extractables from (b) (4) Stopper				
Detected Compounds	CAS	Amount detected in (b) (4) mm stopper ng/stopper	Amount calculated for (b) (4) mm stopper ng/stopper[H]	Maximum Daily Intake (MDI)[I] (µg/day)
(b) (4)				

Table 8: Headspace GC/MS Analysis of Volatile Extractables from (b) (4) Stopper				
Detected Compounds	CAS	Amount detected in (b) (4) mm stopper ng/stopper	Amount calculated for (b) (4) mm stopper ng/stopper[H]	Maximum Daily Intake (MDI)[I] (µg/day)
(b) (4)				

(b) (4)

[I] The maximum daily intake, MDI is (b) (4) stoppers (or (b) (4) vials) of Hydromorphone Hydrochloride Injection, (b) (4) 40 mg/20 mL (2 mg/mL) multi-dose vial per day. Based on this information, the MDI of each of the detected extractable was calculated using the following equation,
MDI(µg/day) = Extractable amount (ng/stopper) * (b) (4) vials/day* (b) (4) µg/ (b) (4) ng

Sponsor's table

GC-FID/MS analysis results for semi-volatile extractables of the stopper are summarized in the table below:

Table 9: Direct Injection GC-FID/MS Analysis of Semi-volatile Extractables from (b) (4) Grey Stopper						
Detected Compounds	CAS	Amount detected (b) (4) mm stopper (ng/stopper)			Amount calculated (b) (4) mm stopper (ng/stopper) [J]	MDI[K] µg/day
		50% IPA	pH 2	pH 10		
(b) (4)						

(b) (4)

[K] The maximum daily intake, MDI is (b) (4) stoppers (or (b) (4) vials) of Hydromorphone Hydrochloride Injection, (b) (4) 40 mg/20 mL (2 mg/mL) multi-dose vial per day. Based on this information, the MDI of each of the detected extractable was calculated using the following equation,

MDI(µg/day) = Extractable amount (ng/stopper) * (b) (4) vials/day * (b) (4) µg/ (b) (4) ng

Sponsor's table

LC-DAD/MS analysis results for non-volatile extractables of the stopper are summarized in the table below:

Table 10: LC-DAD/MS Analysis of Non-Volatile Extractables from (b) (4) Stopper

(b) (4)

Table 10: LC-DAD/MS Analysis of Non-Volatile Extractables from (b) (4) Stopper									
Detected Compounds	CAS	Amount detected (b) (4) mm stopper (ng/stopper)						Amount calculated (b) (4) mm stopper (ng/ stopper) [L]	MDI[M] (µg/day)
		50% IPA		pH 2		pH 10			
		ESI (+Ve)	ESI (-Ve)	ESI (+Ve)	ESI (-Ve)	ESI (+Ve)	ESI (-Ve)		
(b) (4)									

(b) (4)

[M] The maximum daily intake, MDI is (b) (4) stoppers (or (b) (4) vials) of Hydromorphone Hydrochloride Injection, (b) (4) 40 mg/20 mL (2 mg/mL) multi-dose vial per day. Based on this information, the MDI of each of the detected extractable was calculated using the following equation,

MDI(µg/day) = Extractable amount (ng/stopper) * (b) (4) vials/day* (b) (4) µg/ (b) (4) ng

Sponsor's table

ICP-MS analysis results for elemental impurities of the stopper are summarized in the table below:

Table 11: ICP-MS Analysis of Extractables from (b) (4) Stopper

Detected Compounds	Amount Detected in (b) (4) nm stopper ng/stopper			Amount calculated (b) (4) nm stopper (ng/stopper) [N]	MDI [O] (µg/day)	PDE (µg/day)
	pH 2	50% IPA	pH 10			
(b) (4)						

Sponsor's table

All the extracted element concentrations were found to be much lower than the 30% of the PDEs listed in ICH Q3D for all 24 elementals. Most of the detected elements are classified as (b) (4) for which PDEs have not been established due to their low inherent toxicity and/or differences in regional regulations are not addressed in ICH Q3D. There is no risk of elemental impurities leachables from the stopper when in contact with the drug product.

Leachable Results

Based on the extraction results for the glass vial, the Applicant selected 24 ICH Q3D and non-ICH Q3D elementals (b) (4) as targets for elemental leachable screening.

Based on the extraction results for the rubber stopper, all the extractables higher than AET with 50% uncertainty ((b) (4) ng/stopper) and some extractable components at below (b) (4) mcg/day safety concern threshold (SCT) were selected as targets for the leachable study. From the general toxicology perspective, the Applicant's SCT at (b) (4) mcg/day (i.e., an SCT of (b) (4) mcg/day with a 50% uncertainty factor) is appropriate.

The selected leachable targets are presented in the table below. (b) (4) were also selected as surrogates for all leachables that can elute from (b) (4).

Table 12: Leachable Targets for Hydromorphone Hydrochloride Injection, (b) (4) 40 mg/20 mL (2 mg/mL) Multi-Dose Vial		
Detected Extractables	Extractable Maximum Daily Intake (µg/day)	Targets for Leachable Screen
(b) (4)		

Table 12: Leachable Targets for Hydromorphone Hydrochloride Injection, (b) (4) 40 mg/20 mL (2 mg/mL) Multi-Dose Vial		
Detected Extractables	Extractable Maximum Daily Intake (µg/day)	Targets for Leachable Screen
(b) (4)		

Sponsor's table

Screening Methods

The leachable screening methods were validated for Method Precision (Repeatability and Intermediate Precision), Linearity, Limit of Quantitation, Limit of Detection, Accuracy and Specificity using target leachables. The LOQ and spike recoveries of various target molecules were at (b) (4) ng/mL, which is less than AET considering a 50% Uncertainty

Factor ((b) (4) ng/mL) for volatile leachable screening method. The LOQ and spike recoveries of various target molecules were at (b) (4) ng/mL, which is less than AET considering a 50% Uncertainty Factor ((b) (4) ng/mL) for semi volatile and nonvolatile leachable screening method except for fatty acids. For fatty acids LOQ was established at AET (b) (4) ng/mL which is less than AET considering a 50% uncertainty factor ((b) (4) ng/mL). The Reporting limit of various elementals were at less than 24% of the PDEs of all elementals. Refer to the CMC review for additional details regarding methodology and its validation.

Methods

Leachable testing was performed on 3 lots of stability batches stored at long term and accelerated condition for 3 M and 6 M and at long term condition for 15M and 18M following USP<1664> guidelines. The leachable methods used are summarized in the table below.

Table 13: Leachable Method Validation Summary

Leachable Methods	Volatile by Headspace GC/MS	Semi volatile by DI/GC/MS	Non volatile by LC-UV/MS	Elemental by ICP/MS
Validation Report Number	BED-PN1314-VEN-2022-0491 Reference a.6	BED-PN1314-VEN-2022-0491 Reference a.6	BED-PN1314-VEN-2022-0491 (Reference a.6) and BED-PN1314-VEN-2022-0492 (Reference a.7)	BED-PN1314-VEN-2022-0491 Reference a.6
Parameters Validated	Linearity	Linearity	Linearity	Linearity
	Limit of Quantitation	Limit of Quantitation	Limit of Quantitation	Limit of Quantitation
	Limit of Detection	Limit of Detection	Limit of Detection	Limit of Detection
	Method Precision	Method Precision	Method Precision	Method Precision
	Accuracy	Accuracy	Accuracy	Accuracy
	Specificity	Specificity	Specificity	Specificity
Conclusion	The method was shown to be suitable for the purpose of quantitative analysis of leachable	The method was shown to be suitable for the purpose of quantitative analysis of leachable	The method was shown to be suitable for the purpose of quantitative analysis of leachable	The method was shown to be suitable for the purpose of quantitative analysis of leachable

Sponsor's table

Testing was performed on 3 lots of stability batches stored at long term and accelerated condition for 3 M and 6 M and at long term condition for 15M and 18M following USP<1664> guidelines. Batch information is summarized in the table below.

Table 14: Sample Summary for Hydromorphone Hydrochloride Injection, (b) (4) 40 mg/20 mL (2 mg/mL) Multi-Dose Vial			
Stability Time Points		**Batch Number**	**Stability Condition**
Leachable Timepoints Tested	3 M Long Term Samples	P110123Z	25°C/60% RH, 3 Months, Inverted
		P110125Z	
		P110127Z	
	3 M Accelerated Samples	P110123Z	40°C/75% RH, 3 Months, Inverted
		P110125Z	
		P110127Z	
	6M Long Term Samples	P110123Z	25°C/60% RH, 6 Months, Inverted
		P110125Z	
		P110127Z	
	6M Accelerated Samples	P110123Z	40°C/75% RH, 6 Months, Inverted
		P110125Z	
		P110127Z	
	15M Long Term Samples	P110123Z	25°C/60% RH, 12 Months, Inverted
		P110125Z	
		P110127Z	
	18M Long Term Samples	P110123Z	25°C/60% RH, 18 Months, Inverted
		P110125Z	
		P110127Z	

Sponsor's table

Results

No non-volatile, volatile, and semi-volatile organic compounds were detected in any of the 3M, 6M, 15M and 18M inverted stability samples above the AET.

None of the elementals were detected in any of the 3M, 6M, 15M and 18M inverted stability samples above the PDE.

Results of the leachable analyses are summarized in the table below.

Table 15: Leachable Testing Results

Analytical Instrument	Leachable detected (ng/mL)
Volatiles by HS-GC/MS	No volatile leachables was detected above the Reporting limit of 62.5ng/mL (AET = (b) (4) ng/mL)
Semi Volatiles by DI-GC/MS	No semi-volatile leachables was detected above the Reporting limit of 62.5ng/mL (AET = (b) (4) ng/mL)
Non-Volatiles by LC/UV/MS, ESI, +Ve and -Ve mode	No non-volatile leachables was detected above the Reporting limit of 62.5ng/mL (AET = (b) (4) ng/mL)
Elemental Impurities by ICP-MS	No Elemental leachable was detected above the (b) (4)% PDE

DP - Drug product; RL - Reporting limit; LOQ-Limit of Quantification
MDI, µg/day = maximum daily intake =Highest amount of leachable detected (ng/mL) * Max. daily volume ((b) (4) mL/day) * (b) µg/ (b) (4) ng
PDE = Permitted Daily Exposure. For elemental impurities, the PDEs were from ICHQ3D or derived from Oral minimal risk level mg/kg/day.
ND = Not detected or below the detection limit

Sponsor's table

From discussions with the CMC reviewer, it is noted that (b) (4) was observed at a level of (b) (4) ng/mL in one batch (b) (4) We note that (b) (4) is used as an excipient in FDA-approved products and is listed in the IID at up to (b) (4) mcg/day for the IV route and in the mg/day range for other routes. Taken together, the detected level does not pose a safety concern.

Risk Assessment of Process Contact Materials

Note that summary information is provided in this review. See the CMC review for full details and adequacy of the studies conducted.

Potential materials the bulk solution may contact during the manufacturing process:

- (b) (4)
- (b) (4)
- (b) (4)

The process risk assessment for leachables from these surfaces was performed according to USP <665>/<1665>, which uses a 3-step risk assessment to establish values for each risk dimension based on duration of contact, temperature of contact, chemical composition of the pross stream, and chemical composition of the component, which is then linked with a level of characterization and corresponding required testing. Up to two mitigating factors are also considered for the characterization level.

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/s/

JESSICA F HOFFMAN
11/03/2023 11:47:25 AM

MISOL AHN
11/03/2023 11:50:26 AM

JAY H CHANG
11/03/2023 11:58:10 AM