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APPLICATION NUMBER:

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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:	215870
Supporting document/s:	SDN 1, SDN 2, SDN 3
Applicant's letter date:	April 8, 2022, June 28, 2022, July 5, 2002
CDER stamp date:	April 8, 2022, June 28, 2022, July 5, 2002
Product:	Fentanyl Citrate Injection, USP (50 mcg/mL fentanyl as base)
Indication:	(b) (4)
Applicant:	Exela Pharma Sciences, LLC
Clinical Review Division:	Division of Anesthesiology, Addiction Medicine and Pain Medicine Products (DAAP)
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Any information or data necessary for approval of 215870 that Exela does not own or have a written right to reference constitutes one of the following: (1) published literature, or (2) a prior FDA finding of safety or effectiveness for a listed drug, as reflected in the drug's approved labeling. Any data or information described or referenced below from reviews or publicly available summaries of a previously approved application is for descriptive purposes only and is not relied upon for approval of Exela.

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1 Executive Summary

1.1 Introduction

Exela Pharma Sciences, LLC submitted NDA 215870 for Fentanyl Citrate Injection, USP, an injectable fentanyl formulation in glass vials. The Fentanyl Citrate Injection, USP will be available as 2.5 mg/50 mL and 5 mg/100 mL vials.

This NDA is a 505(b)(2) application and is relying on the Agency's findings of safety and efficacy of Fentanyl Citrate Injection (NDA 01901). No new pharmacology, general toxicology, genetic toxicology, reproductive and developmental toxicology, or carcinogenicity studies were conducted for this application. All impurities in the drug substance and degradants in the drug product are controlled at acceptable levels. The formulation does not contain any novel excipients. The Applicant conducted extractable and leachable assessments in order to characterize the new container closure for this product.

The Applicant submitted a toxicological risk assessment for thirteen leachables detected in the leachable study above the (b) (4) mcg/day threshold. The levels of all leachable compounds detected in the leachables study above the (b) (4) mcg/day threshold were below the calculated permissible daily exposure levels. The levels of all detected leachable compounds are considered acceptable.

From a Pharmacology Toxicology perspective, the proposed product is recommended for approval.

1.2 Brief Discussion of Nonclinical Findings

All impurities in the drug substance and degradants in the drug product are controlled at acceptable levels. The formulation does not contain any novel excipients.

The Applicant conducted extractable and leachable assessments on the new container closure system including six batches on stability for six and 12-months. The Applicant calculated an Analytical Evaluation Threshold (AET) in their extractable and leachables assessment of (b) (4) mcg/L, which is considered acceptable. The methods for the extractable and leachable assessment are acceptable per the review by the Chemist, Dr Mariappan Chelliah.

Thirteen leachables were identified that exceeded the (b) (4) mcg/day threshold. The Applicant submitted a toxicological risk assessment for each leachable. The calculated permissible daily exposure levels for each leachable were higher than the total daily intake of each leachable and it is concluded that the potential levels of the leachables in the drug product do not represent a unique toxicologic concern.

From a pharmacology toxicology perspective, NDA 215870 is recommended for approval.

1.3 Recommendations

1.3.1 Approvability

The recommendation from pharmacology/toxicology is that NDA 215870 may be approved.

1.3.2 Additional Nonclinical Recommendations

None.

1.3.3 Labeling

No changes to the proposed labeling are recommended from pharmacology toxicology.

2 Drug Information

2.1 Drug

CAS Registry Number: 990-73-8

Generic Name: Fentanyl Citrate

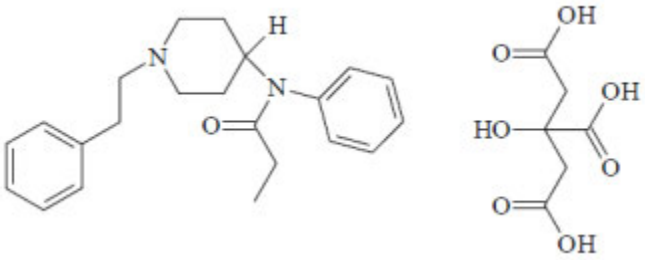
Code Names: Fentanyl

Chemical Name: N-phenyl-N-[1-(2-phenylethyl)-4-piperidinyl] propenamide citric acid salt

Molecular Formula/Molecular Weight: $C_{28}H_{26}N_2O_8$; MW=528.6 g/mol

Structure:

Figure 1. Structure of Fentanyl Citrate



Pharmacologic Class: Opioid Agonist (EPC)

2.2 Relevant INDs, NDAs, BLAs and DMFs

NDA#	Drug Name	Div	Route	Marketing Status	AP Date	Company
19101	Fentanyl Citrate Injection	DAAAP	IV	Approved	7/11/1984	Hikma

DMF#	Subject of DMF	Holder	Reviewer's Comment
(b) (4)	Fentanyl Citrate	(b) (4)	Adequate
	Molded clear glass vials		Adequate
	Grey, (b) (4) (b) (4)		Adequate

2.3 Drug Formulation

The Fentanyl Citrate Injection, USP formulation will be available as 2.5 mg/50 mL and 5 mg/100 mL vials. The concentration of the 50 and 100 mL vials is 50 mcg/mL. The (b) (4) dosing regimen for this product is the same as the referenced product. The maximum daily dose (MDD) of this product, as determined by the clinical team, is (b) (4) mg/day. The composition of the drug product formulation is depicted in the table below.

Table 1. Composition of Fentanyl Citrate Injection, USP

Ingredients	Function	IID Intravenous Solution Levels[1] % w/v	Concentration (% w/v) in the proposed product
Sodium Chloride, USP	(b) (4)	0.9% w/v	0.9% w/v
Hydrochloric Acid NF	pH Adjuster	(b) (4)	NA
Sodium Hydroxide, NF	pH Adjuster		NA
Water for Injection, USP	(b) (4)	N/A	q.s to 100%

[1]http://www.accessdata.fda.gov/scripts/cder/iig/getiigWEB.cfm

2.4 Comments on Novel Excipients

This product does not contain any novel excipients.

2.5 Comments on Impurities/Degradants of Concern

Drug Substance Impurities

The qualification threshold according to the ICH Q3A(R2) guideline for impurities in the drug substance for a maximum daily dose (MDD) of drug substance < 2 g/day is 0.15%. For this product, the clinical team determined that the MDD of fentanyl is (b) (4) mg. The

Applicant is obtaining the fentanyl drug substance for the marketed drug product from [redacted]. Three impurities in the drug substance have impurity specifications set at [redacted]%, which meets the threshold for qualification per ICH Q3A(R2). Two impurities contain [redacted] moieties which is a structural alert for mutagenicity. Per ICH M7, potentially genotoxic impurities should be controlled at a level <1.5 mcg/day. For a MDD of [redacted] mg of fentanyl, the specification of [redacted]% would yield [redacted] mcg. Therefore, the specification for these three impurities is considered acceptable. The impurities are presented in the table below. All drug substance impurity specifications in the Fentanyl Citrate Injection, USP product are considered acceptable.

Table 2. Fentanyl Citrate Drug Substance Impurity Specifications

Fentanyl Citrate Drug Substance Impurity Specifications			
Impurity	***Chemical Name***	***Specification***	***Acceptable***
[redacted]	[redacted]	NMT [redacted]	Yes
		NMT	Yes
		NMT	Yes
		NMT	Yes
		NMT	Yes

*structural alert for mutagenicity

Drug Product Degradants

The qualification threshold according to the ICH Q3B(R2) guidance for impurities/degradants in the drug product for a MDD of a drug substance 10 mg–100 mg is 0.5 % or 200 mcg TDI, whichever is lower. For this product, DAAAP has determined that the MDD of fentanyl to be [redacted] mg. Seven degradants in the drug product have impurity specifications set at [redacted] or [redacted]%, which meet the threshold for qualification of 0.5% per ICH Q3B(R2). Three impurities, [redacted] and [redacted] contain [redacted] moieties which is a structural alert for mutagenicity. Per ICH M7, potentially genotoxic impurities should be controlled at a level <1.5 mcg/day. For a MDD of [redacted] mg of fentanyl, the specification of [redacted]% would yield [redacted] mcg of the compound and is deemed acceptable. All drug product degradant specifications in the Fentanyl Citrate Injection, USP product are considered acceptable.

Table 3. Fentanyl Citrate Injection, USP Drug Product Degradant Specifications

Fentanyl Citrate Injection, USP Drug Product Degradant Specifications			
Impurity	***Chemical Name***	***Specification***	***Acceptable***
(b) (4)		(b) (4) NMT	Yes
		NMT	Yes
		NMT	Yes
		NMT	Yes
		NMT	Yes
		NMT	Yes
		NMT	Yes
		NMT	Yes
		NMT	Yes

*structural alert for mutagenicity

Residual Solvents
Isopropyl alcohol is used in the manufacturing of the drug substance and the Applicant has set a specification of (b) (4)%. Isopropyl alcohol is a Class 3 solvent per ICH Q3C and therefore a specification of (b) (4)% is acceptable.

Elemental Impurities
The Applicant analyzed the Fentanyl Citrate Injection, USP drug product for elemental impurities as per ICH Q3D. CMC has concurred with the analysis submitted by the Applicant. No elemental impurities exceed the permitted daily exposures for a parenteral drug product. Refer to the review by the Chemist Dr. Mariappan Chelliah for details.

(b) (4) *Risk Assessment*
The Applicant performed a risk assessment for potential (b) (4) on the Fentanyl Citrate Injection, USP drug product and determined that there is low risk for (b) (4) originating in the formula, manufacturing components or process,

container closure system and stability testing. For details on the acceptability of the risk assessment, refer to the review by Dr. Mariappan Chelliah.

Container Closure

The container closure for Fentanyl Citrate Injection, USP 2.5 mg/50 mL and 5 mg/100 mL consists of 50 and 100 mL molded clear glass vials [redacted] stoppered with [redacted] Grey, [redacted] and topped with top-blue overseals. The [redacted] clear glass vials and [redacted] Grey, [redacted] are used in many products with similar aqueous formulations indicated for intravenous injection.

Extraction studies were conducted on the primary container-closure components and selected manufacturing components (details provided in the table below) for the presence of elemental, volatile, semi-volatile, and non-volatile compounds.

Table 4. Materials Evaluated for Extractable Analysis

Exela Part #	Component Name	Supplier
[redacted]	[redacted]	[redacted]
	50 mL Molded Clear Vial	
	100 mL Molded Clear Vial	
[redacted]	Gray	[redacted]

The extractable studies exposed the materials to extreme conditions (reflux in buffered solutions over a pH range of about 2 to 12). Analytical Evaluation Thresholds (AETs) (derived from a Safety Concern Threshold of [redacted] mcg/day and the maximum labeled daily dose of fentanyl for this product) were employed to evaluate extractable and leachable compounds. For details and acceptability of the methods, refer to the chemistry review by Dr Mariappan Chelliah.

Compounds in the extraction study were targeted for evaluation in six stability lots of Fentanyl Citrate Injection, USP (Batches MBR-000824 and MBR-000825).

Extractables/Leachables Evaluation

To justify the safety of leachables arising from the container closure systems or from upstream manufacturing processes that are in direct contact with the drug product, the Applicant performed extractables and leachables studies.

Extraction studies were conducted on primary container-closure components and selected manufacturing components which are outlined in the table above. The components were subjected to extraction conditions and evaluated for the presence of elemental, volatile, semi- volatile, and non-volatile compounds. The extraction studies were conducted by taking the individual components and reducing them down to smaller pieces to expose significantly more surface area to the extraction solvent. The samples were then refluxed in 25 mM NaH_2PO_4, pH 1.8, 2, 6 and 12 for a minimum of eight hours.

The following excerpt is from Dr Mariappan Chelliah's review regarding the acceptability of the methods:

> The choice of solvents used in the extractable study are appropriate and their pH values bracket the formulation pH. The pulverized samples and the reflux extraction conditions are considered harsh. The analytical methods used for the detection of volatile, semi-volatile, non-volatile, and elemental impurities are suitable for their detection as demonstrated by the LOQs of representative reference compounds.

The Analytical Evaluation Threshold (AET) of (b) (4) ppb (equivalent to (b) (4) mcg/day) and (b) (4) ppb (equivalent to (b) (4) mcg/day) were established by the Applicant based on a Safety Concern Threshold of (b) (4) mcg/day and Qualification Threshold of (b) (4) mcg/day and a maximum daily dose of Fentanyl Citrate Injection, USP of (b) (4) mg (see Table below).

Table 5. Calculations for the SCT, AET, and QT Values Provided by the Applicant

Max Daily Dose Fentanyl Citrate =	(b) (4)	µg/day					
[Fentanyl Citrate]-DP =	50	µg/mL					
Max Daily Dose Volume =	(b) (4)	mL/day					
Duration of Treatment =	≤ 1	month					
Safety Concern Threshold (SCT) =	(b) (4)	µg/day	Qualification Threshold (QT)	(b) (4)	µg/day	(b) (4)	µg/day
Analytical Evaluation Threshold (AET) =		ppb	Analytical Evaluation Threshold (AET)		ppb		ppb

Note: ppb for the AET is expressed in units of w/v with respect to maximum daily dose volume of the drug product.
† - ICH M7[13] limit for dosage durations of less than 30 days for a single or multiple mutagenic compounds

Leachables testing was conducted at six and 12-months on six batches (Batches B0000012, B0000013, and B0000014B0000015, B0000016, and B0000017). Volatile leachables were evaluated using a headspace gas chromatographic method. Semi-volatile leachables were evaluated using a direct injection gas chromatographic method.

Non-volatile leachables were evaluated using an ultra-high performance liquid chromatographic method. Elemental leachables were evaluated using an inductively coupled plasma mass spectrometric method. All methods were validated. Refer to the review of Dr. Mariappan Chelliah for details on the methods.

Allowable elemental concentration (AEC) limits were calculated using the maximum daily dose volume for the product and the PDEs as specified in USP <232>. The values are presented in the tables below. All observed elemental leachables were below their respective AEC limits and are considered acceptable.

Table 6. Elemental Leachable Results for Fentanyl Citrate Injection, USP for Batches B0000012, B0000013, and B0000014

Compound	PDE (µg/day)	AEC (ppb) (w/v)	QL (ppb)	B0000012			B0000013			B0000014		
				6M		12M	6M		12M	6M		12M
				25/60	40/75	25/60	25/60	40/75	25/60	25/60	40/75	25/60
(b) (4)												

Where: QL = Quantitation limit; PDE = Permitted Daily Exposure, AEC = Allowable Elemental Concentration

Table 7. Elemental Leachable Results for Fentanyl Citrate Injection, USP for Batches B0000015, B0000016, and B0000017

Compound	PDE (µg/day)	AEC (ppb) (w/v)	QL (ppb)	B0000015			B0000016			B0000017		
				6M		12M	6M		12M	6M		12M
				25/60	40/75	25/60	25/60	40/75	25/60	25/60	40/75	25/60
(b) (4)												

Where: QL = Quantitation limit; PDE = Permitted Daily Exposure, AEC = Allowable Elemental Concentration

Table 8. PDE and AEC Values of Elemental Impurities in the Leachable Study

Element	Parenteral PDE (µg/day)	AEC (ppb)
	(b) (4)	

The five volatile, zero semi-volatile and nine non-volatile leachables that were detected at levels above the SCT (b) (4) ppb) and below the QT ((b) (4) ppb) are presented in the table below. Two of the volatile compounds (RRT (b) (4) and RRT (b) (4)) and four of the non-volatile compounds (RRT (b) (4) RRT (b) (4) RRT (b) (4) and RRT (b) (4) were identified as leachables but structures were not determined. The potential for mutagenicity of these compounds is unknown. The duration of treatment with the Fentanyl Citrate Injection, USP drug product is less than 1 month. As per ICH M7, for potentially mutagenic compounds with treatment duration ≤ 1 month, a limit of 120 mcg/day (AET= (b) (4) ppb) is set. The level of the individual leachable or the sum of the six unidentified leachables ((b) (4) ppb) are below the threshold of (b) (4) ppb. The levels of the six unidentified compounds are considered acceptable and do not require further identification or qualification.

Table 9. Acceptability of Leachables Observed at Levels >SCT of (b) (4) ppb ((b) (4) mcg/day) and <QT of (b) (4) ppb (b) (4) mcg/day): ppb and mcg/day

Compound	***CAS #***	***Maximum concentration observed in leachable studies***		***Acceptable***
		ppb	***mcg/day***	

(b) (4)		
		Yes
		Yes
		Yes
		Yes
		Yes
		Yes
		Yes
		Yes
		Yes
		Yes
		Yes
		Yes

The identified leachables that were > (b) (4) ppb (equivalent to (b) (4) mcg/day) were evaluated in silico for mutagenic potential using the EPA T.E.S.T. QSAR analysis. All compounds were predicted to be negative for mutagenicity with the exception of (b) (4) (b) (4) which is discussed below. The negative results in the QSAR are considered adequate to show that the leachables do not have mutagenic potential. Therefore, the levels of the leachables presented in the table above are considered acceptable.

Seven volatile, three semi-volatile and three non-volatile leachables were (b) (4) ppb. Any leachable that was (b) (4) ppb was identified and evaluated for its general toxicity potential. The Applicant provided risk assessments for each leachable observed at > (b) (4) ppb and provided Permissible Daily Exposures (PDE) calculations. The calculations and acceptability of PDEs are shown below.

Table 10. Acceptability of Leachables Observed at Levels >QT of (b) (4) ppb (b) (4) mcg/day): ppb and mcg/day

Compound	***CAS #***	***Maximum concentration in leachable studies***		***Acceptable?***
		ppb	***mcg/day***	
(b) (4)				
				Yes
				Yes
				Yes
				Yes

(b) (4)		Yes
		Yes
		Yes
		Yes
		Yes
		Yes
		Yes
		Yes
		Yes

Toxicologic Risk Assessments

In the Applicant's toxicological risk assessment, an in silico mutagenicity assessment was submitted for all the leachable compounds at levels (b) (4) ppb/day and all were reported to be negative for mutagenic potential, with the exception of (b) (4) (b) (4) which is discussed below. In addition, a Permitted Daily Exposure (PDE) was calculated for all leachables included in the toxicological risk assessment. This Reviewer established a PDE for each leachable in the toxicological risk

(b) (4)

(b) (4)

The following is a toxicological risk assessment for each leachable above (b) (4) mcg/day.

(b) (4)

(b) (4)

(b) (4) was measured at (b) (4) ppb ((b) (4) mcg/day) as a volatile compound in the leachable study (b) (4)

level of this leachable is considered acceptable.

(b) (4)

(b) (4)

(b) (4) was measured at (b) (4) ppb ((b) (4) mcg/day) as a volatile compound in the leachable study. (b) (4)

(b) (4)

The level of this leachable is considered acceptable.

(b) (4)

(b) (4)

(b) (4) was measured at (b) (4) ppb ((b) (4) mcg/day) as a volatile compound in the leachable study. (b) (4)

The level of this leachable is considered acceptable.

(b) (4)

(b) (4)

(b) (4) was measured at (b) (4) ppb ((b) (4) mcg/day) as a volatile compound in the leachable study. This Reviewer located an Integrated Risk Information System (IRIS) Chemical Assessment Summary for (b) (4) by the EPA (found at

(b) (4)

(b) (4)

(b) (4)

(b) (4)

The PDEs calculated by this Reviewer were (b) (4) mcg/day and (b) (4) mcg/day. However, the MDI of (b) (4) as a leachable (b) (4) mcg/day) does not exceed either Reviewer's calculated PDEs. The resulting margin 5.6 fold. This Reviewer also notes that this compound is below the limit of (b) (4) mcg/day that is a less than lifetime acceptable intake of a potentially carcinogenic compound as calculated by the TD_{50} value outlined in ICH M7. The level of this leachable is considered acceptable.

(b) (4)

(b) (4)

(b) (4) was measured at (b) (4) ppb ((b) (4) mcg/day) as a volatile compound in the leachable study. (b) (4) is a (b) (4) substituted with a single (b) (4) group. It was predicted to be negative for mutagenicity in a study submitted by the Applicant using QSAR US EPA T.E.S.T. software (Study SUP-001942).
No carcinogenicity data have been located for (b) (4)

(b) (4)

(b) (4)

(b) (4)

The PDE of (b) (4) mg is (b) (4) fold higher than the measured levels of (b) (4) mcg of (b) (4) The level of this leachable is considered acceptable.

(b) (4)

(b) (4)

(b) (4) was measured at (b) (4) ppb (b) (4) mcg/day) as a volatile compound in the leachable study. It was predicted to be negative for mutagenicity in a study submitted by the Applicant using QSAR US EPA T.E.S.T. software (Study SUP-001942).

(b) (4)

(b) (4)

(b) (4)

The PDE of (b) (4) mg is (b) (4) fold higher than the measured levels of (b) (4) mcg of (b) (4) (b) (4) The level of this leachable is considered acceptable

(b) (4)

(b) (4)

(b) (4) was measured at (b) (4) ppb ((b) (4) mcg/day) as a volatile compound in the leachable study. It was predicted to be negative for mutagenicity in a study submitted by the Applicant using QSAR US EPA T.E.S.T. software (Study SUP-001942).
No carcinogenicity data have been located for (b) (4) A subacute inhalation (b) (4)

(b) (4)

The PDE of (b) (4) mg is (b) (4) fold higher than the measured levels of (b) (4) mcg of (b) (4) (b) (4) The level of this leachable is considered acceptable.

(b) (4)

(b) (4)

(b) (4)

(b) (4)

The semi-volatile leachable (b) (4) was measured at (b) (4) ppb (b) (4) in the leachable study. It was evaluated in silico for its mutagenicity potential using the EPA T.E.S.T. QSAR analysis. The analysis predicted the compound was positive for mutagenic potential. However, internally (b) (4) was evaluated by the CDER Computational Toxicology Consulting Service and a negative result for mutagenic potential was predicted. Since the internal service uses a more current database, the compound will be considered negative for mutagenic potential.

(b) (4)

(b) (4)

(b) (4)

(b) (4)

(b) (4)

(b) (4) was measured at (b) (4) ppb ((b) (4) mcg/day) as a semi-volatile compound in the leachable study. It was predicted to be negative for mutagenicity in a study submitted by the Applicant using QSAR US EPA T.E.S.T. software (Study SUP-001942).

(b) (4)

(b) (4)

(b) (4)

Additionally, when used as a (b) (4) JECFA established an ADI of (b) (4) mg/kg body weight for (b) (4) which equals (b) (4) mg/day based on a 60 kg body weight. The ADI of (b) (4) mg is (b) (4) fold higher than the maximum daily intake of (b) (4) mcg of (b) (4) The level of this leachable is considered acceptable.

(b) (4)

(b) (4)

(b) (4) was measured at (b) (4) ppb ((b) (4) mcg/day) as a semi-volatile compound in the leachable study. (b) (4) is a (b) (4) that consists of a (b) (4) with one (b) (4) substituent. It was predicted to be negative for mutagenicity in a study submitted by the Applicant using QSAR US EPA T.E.S.T. software (Study SUP-001942). There are no carcinogenicity data available for (b) (4)

(b) (4)

(b) (4)

The PDE of (b) (4) mg is (b) (4) fold higher than the measured levels of (b) (4) mcg of (b) (4) The level of this leachable is considered acceptable.

(b) (4)

(b) (4)

(b) (4)

(b) (4) was measured at (b) (4) ppb (b) (4) mcg/day) as a non-volatile compound in the leachable study. It was predicted to be negative for mutagenicity in a study submitted by the Applicant using QSAR US EPA T.E.S.T. software (Study SUP-001942).

(b) (4)

(b) (4)

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(b) (4)

The PDEs calculated by this Reviewer of (b) (4) mg/day for (b) (4) and (b) (4) mg/day for (b) (4). The (b) (4) as a leachable (b) (4) mcg/day) does not exceed either calculated PDEs. The resulting safety margin 198x and 15.9x. The level of this leachable is considered acceptable.

(b) (4)

(b) (4)

(b) (4)

(b) (4)

(b) (4)

(b) (4)

(b) (4) was measured at (b) (4) ppb ((b) (4) mcg/day) as a non-volatile compound in the leachable study. It was predicted to be negative for mutagenicity in a study submitted by the Applicant using QSAR US EPA T.E.S.T. software (Study SUP-001942).

No general toxicology or carcinogenicity data with (b) (4) were identified. The structurally related compound (b) (4) was used as a surrogate. The structures are presented above. In the (b) (4)

(b) (4)

(b) (4)

(b) (4)

The PDE of (b) (4) mg is (b) (4) fold higher than the measured levels of (b) (4) mcg of (b) (4) (b) (4) The level of this leachable is considered acceptable.

(b) (4)

(b) (4)

(b) (4) was measured at (b) (4) ppb ((b) (4) mcg/day) as a non-volatile compound in the leachable study. (b) (4) is a primary (b) (4) resulting from the formal condensation of the (b) (4) group of (b) (4) with (b) (4) It was predicted to be negative for mutagenicity in a study submitted by the Applicant using QSAR US EPA T.E.S.T. software (Study SUP-001942). No data on the carcinogenic potential of

(b) (4)

The PDE of (b) (4) mg is (b) (4) fold higher than the measured levels of (b) (4) mcg of (b) (4) The level of this leachable is considered acceptable.

All leachables that were detected above the QT of (b) (4) ppb were below their PDEs and do not pose any concern for toxicity as leachables in the drug product.

2.6 Proposed Clinical Population and Dosing Regimen

The indication for Fentanyl Citrate Injection, USP is:

- (b) (4)
- Use as (b) (4) analgesic supplement in general (b) (4) anesthesia. (b) (4) and as an adjunct in the maintenance of general (b) (4) anesthesia.
- use as an anesthetic agent with oxygen in selected high-risk patients, such as those undergoing open heart surgery or certain complicated neurological or orthopedic procedures.

The dosing of the product differs for each indication and is outlined in detail in the product label.

2.7 Regulatory Background

The Applicant is submitting NDA 215870 via the 505(b)(2) regulatory pathway and is relying on the Agency's previous findings of safety and efficacy for Fentanyl Citrate Injection (NDA 19101, Hikma). The Applicant does not have an IND for this program.

Two nonclinical filing issues for this NDA were identified (#4 and 5) and are presented below. The Applicant responded to both issues and their responses are acceptable.

4. Several of the drug product degradants contain structural alerts for mutagenicity.
Therefore, the specification for these impurities should be reduced to conform to ICH M7 limits. Otherwise, provide adequate safety qualification for your proposed specifications for degradants that contain structural alerts for mutagenicity.

Exela's Response:
The mutagenicity of each potential degradant of Fentanyl Citrate Injection, USP was evaluated using QSAR using the EPA T.E.S.T software; (b) (4) and (b) (4) were found to be mutagenic positive.
Per ICH M7, the acceptable intake of a potentially mutagenic impurity in drug products with a treatment duration of ≤ 1 month is 120 µg/day. This limit applies to Fentanyl Citrate Injection, USP as the treatment duration for this drug product is much less than 1 month. Based on the maximum daily dose of (b) (4) mg for fentanyl citrate and the acceptable intake limit of 120 µg/day, the maximum acceptable limit of any individual impurity is (b) (4) ppb ((b) (4) µg/mL). The specification for both (b) (4) and (b) (4) is (b) (4)%, which is equivalent to (b) (4) ppb (b) (4) µg/mL) and significantly lower than the limit of (b) (4) ppb (b) (4) µg/mL). Therefore, the specification of (b) (4) and (b) (4) conform to ICH M7 limits. Please see the equation below for reference:

Maximum mutagenic impurity limit	(b) (4) ppb = (b) (4) µg/L = (b) (4) µg/mL
Fentanyl Citrate Injection drug product concentration (DP concentration)	50 µg/mL
Specification for (b) (4) and (b) (4)	(b) (4) (See 3.2.P.5.1 specification, Sequence 0001)
Specification for (b) (4) and (b) (4) based on DP concentration	(b) (4) % x 50 µg/mL = (b) (4) µg/mL

5. If the dosing regimen differs from the referenced product (i.e., (b) (4) (b) (4), you may address the safety of the new dosing regimen via a nonclinical GLP local toxicity study of adequate duration. The design of this study should mimic the proposed clinical dosing regimen as closely as possible, taking into consideration the drug substance concentration, volume to be administered, infusion rate and duration, and evaluation of relevant endpoints e.g., local tissue reactions in life and histopathology of local tissues including injection site and surrounding tissue for peripheral catheters and may also include cardiac and lung tissues to monitor for embolism.

Exela's Response:
Exela's proposed dosing regimen for Fentanyl Citrate Injection, USP (intravenous administration) is the same as that for the RLD. While Exela believes a nonclinical GLP local toxicity study is not applicable to our drug product, as we are not proposing a new dosing regimen that differs from the RLD, Exela will contact purchasers of our drug product and inquire how they administer our drug product. Exela intends to submit the feedback as well as a complete response to this issue by August 31, 2022.

3 Studies Submitted

3.1 Studies Reviewed

The studies in the table below are located in the EDR in eCTD format.

Study Title	***Study #***
Leachable Impurities in Fentanyl Citrate Injection, USP	SMRY-001817
Elemental Impurities Risk Assessment for Fentanyl Citrate Injection, USP	SMRY-001696
QSAR Analysis- T.E.S.T. Results	SUP-001942

3.2 Studies Not Reviewed

All studies submitted to the NDA were reviewed.

3.3 Previous Reviews Referenced

No previous reviews have been referenced.

4 Pharmacology

Fentanyl is a synthetic phenylpiperidine opioid analgesic which acts as an agonist on the mu opioid receptor. The analgesic properties of fentanyl are similar to that of morphine and other mu opioids. Fentanyl is more lipid soluble than morphine and is roughly 100 times more potent as an analgesic than morphine. Time to peak analgesia of fentanyl is rapid and the duration of action is short (Gutstein HB and Akil H, 2006). The safety concerns of fentanyl are similar to those of other potent opioids with the major concerns being respiratory depression and the potential for abuse.
No new pharmacology studies were submitted by the Applicant. The Applicant is relying on the information in the label of the referenced product Fentanyl Citrate Injection (NDA 19101, Hikma).

5 Pharmacokinetics/ADME/Toxicokinetics

Mechanism of action: Fentanyl is an opioid agonist which exerts its analgesic effects primarily through the mu opioid receptor.

Drug activity related to proposed indication: Fentanyl is a potent opioid that is lipophilic and rapidly crosses the blood brain barrier resulting in a rapid onset of action.

No new PK, TK, or ADME studies were submitted by the Applicant. The Applicant is relying on the information in the label of the referenced product Fentanyl Citrate Injection (NDA 19101, Hikma).

6 General Toxicology

No new general toxicology studies or data were submitted by the Applicant.

8 Carcinogenicity

No new studies were submitted by the Applicant. The Applicant is relying on the information in the label of the referenced product Fentanyl Citrate Injection (NDA 19101, Hikma).

9 Reproductive and Developmental Toxicology

No new studies were submitted by the Applicant. The Applicant is relying on the information in the label of the referenced product Fentanyl Citrate Injection (NDA 19101, Hikma).

10 Special Toxicology Studies

No special toxicology studies were conducted.

11 Integrated Summary and Safety Evaluation

Fentanyl is a well-characterized mu opioid. No pharmacology or toxicology data with fentanyl were required for this NDA and no data with fentanyl were submitted. The excipients used in the Fentanyl Citrate Injection, USP formulation are all found at higher levels in drugs previously approved by FDA for IV use and do not pose any unique toxicologic concerns. The impurities/degradants in the drug substance and drug product are controlled at acceptable levels. There are no concerns with extractables or leachables from the container closure for this product. There are no outstanding concerns with this NDA that would preclude approval. The recommendation from Pharmacology/Toxicology is that NDA 215870 be approved with no post-marketing requirements.

This is a representation of an electronic record that was signed electronically. Following this are manifestations of any and all electronic signatures for this electronic record.

/s/

ELIZABETH BOLAN
01/26/2023 08:18:53 AM

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