# CENTER FOR DRUG EVALUATION AND RESEARCH

***APPLICATION NUMBER:***

# 215870Orig1s000

# SUMMARY REVIEW

**Food and Drug Administration**
**CENTER FOR DRUG EVALUATION AND RESEARCH**
**Division of Anesthesiology, Addiction Medicine, and Pain Medicine**
10903 New Hampshire Ave.
Silver Spring, MD 20993-0002

# Cross-Discipline Team Leader and Division Director Summary Review

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|---|---|
| **Date** | February 8, 2023 |
| **From** | Lee Anne Connell-Templin, MD; Renee Petit-Scott, MD; Alla Bazini, MD; Rigoberto Roca, MD |
| **NDA#** | 215870 |
| **Applicant** | Exela Pharma Sciences, LLC |
| **Date of Original Submission** | April 8, 2022 |
| **PDUFA Goal Date** | February 8, 2023 |
| **Established or Proper Name** | Fentanyl Citrate Injection, USP |
| **Dosage Form** | Intravenous injection; 50 mcg/mL, 50 mL; 50 mcg/mL, 100 mL vials |
| **Applicant Proposed Indication** | Opioid Agonist indicated for:<br>• use as an opioid analgesic supplement in general anesthesia.<br>• administration with a neuroleptic for the induction of anesthesia and as an adjunct in the maintenance of general anesthesia.<br>• 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. |
| **Applicant Proposed Dosing Regimen** | In Adults:<br>As an Adjunct to General Anesthesia-Total Dosage<br>Moderate Dose: 2 to 20 mcg/kg (0.002 to 0.02 mg/kg) (0.04 to 0.4 mL/kg)<br>High Dose: 20 to 50 mcg/kg (0.02 to 0.05 mg/kg) (0.4 to 1 mL/kg)<br><br>As an Adjunct to General Anesthesia- Maintenance Dose<br>Moderate Dose: 2 to 20 mcg/kg (0.002 to 0.02 mg/kg) (0.04 to 0.4 mL/kg)<br>High Dose: 20 to 50 mcg/kg (0.02 to 0.05 mg/kg) (0.4 to 1 mL/kg)<br><br>As a General Anesthetic<br>50 to 100 mcg/kg (0.05 to 0.1 mg/kg) (1 to 2 mL/kg), up to 150 mcg/kg (0.15 mg/kg) (3 mL/kg) may be necessary<br><br>In Pediatrics:<br>For Induction and Maintenance in Children 2 to 12 Years of Age<br>A reduced dose as low as 2 to 3 mcg/kg is recommended. |
| **Regulatory Action** | Approval |

| **OND Action Package included reviews by the following:** | | |
|---|---|---|
| Clinical Reviewer<br>Clinical Team Leader | Lee Anne Connell-Templin MD<br>Renee Petit-Scott MD | CDER/OND/DAAP<br>CDER/OND/ON/DAAP |
| Clinical Pharmacology Reviewer<br>Clinical Pharmacology Team Leader | Hongwu Shen PhD<br>Yun Xu PhD | CDER/OTS/OCP/DNP<br>CDER/OTS/OCP/DNP |
| Non-Clinical Reviewer<br>Non-Clinical Team Leader | Elizabeth Bolan PhD<br>Newton Woo PhD | CDER/OND/ON/DPT<br>CDER/OND/ON/DPT |
| OSE Regulatory Project Manager | Ruth Maduro | CDER/OSE/PMS |
| Division of Medication Error Prevention and Analysis 1 (DMEPA 1)<br>DMEPA 1 Safety Evaluator<br>DMEPA 1 Team Leader | <br>Damon Birkemeier PharmD<br>Valerie S. Vaughan PharmD | <br>CDER/OSE/OMEPRM/DMEPAI<br>CDER/OSE/OMEPRM/DMEPAI |
| Office of Product Quality Review Team<br>Drug Substance | <br>Zhixing Shan PhD | <br>CDER/OPQ/ONDP/DNDAPI/NDB2 |

| | | |
|---|---|---|
| Drug Product | Gaetan Ladouceur PhD | CDER/OPQ/ONDP/DNDAPI/NDB2 |
| | Mari Chelliah PhD | CDER/OPQ/ONDP/DNDPII/NDPB3 |
| | Valerie Amspacher PhD | CDER/OPQ/ONDP/DNDPII/NDPB3 |
| Manufacturing | Helen Ngai PhD | CDER/OPQ/OPMA/DMAI/MAB1 |
| | Paul Dexter MS | CDER/OPQ/OPMA/DMAI/MAB1 |
| Biopharmaceutics | Assad Noory PhD | CDER/OPQ/ONDP/DB/BB2 |
| | Ta-Chen Wu PhD | CDER/OPQ/ONDP/DB/BB2 |
| Microbiology | Helen Ngai PhD | CDER/OPQ/OPMA/DMAI/MAB1 |
| | Paul Dexter MS | CDER/OPQ/OPMA/DMAI/MAB1 |
| Application Technical Lead | Valerie Amspacher PharmD | CDER/OPQ/ONDP/DNDPII/NDPB3 |
| RBPM | Anika Lalmansingh PhD | CDER/OPQ/OPRO/DRBPMI/RBPMB2 |
| Controlled Substance Staff Reviewer | Shalini Bansil MD | CDER/OCD/CS |
| Controlled Substance Staff Team Leader | Dominic Chiapperino PhD | CDER/OCD/CS |
| Regulatory Project Manager | Joyce Chin PharmD | CDER/OND/ORO/DRON |

# 1. Benefit-Risk Assessment

The proposed presentations of preservative-free Fentanyl Citrate Injection, 50 mcg/mL (2.5 mg/50 mL and 5 mg/100 mL) in clear glass vials, are for intravenous (IV) administration only by persons specifically trained in the use of IV anesthetics and management of the respiratory effects of potent opioid analgesics. This 505(b)(2) NDA for Fentanyl Citrate Injection relies on FDA's previous findings of efficacy and safety for the Listed Drug (LD), Fentanyl Citrate Injection, USP 50 mcg/mL, NDA 019101, held by Hikma Pharmaceuticals, for approval.

The Applicant, Exela Pharma Sciences, LLC (Exela), has developed two large volume presentations to provide clinicians with potentially more suitable options when moderate and high fentanyl dosing is indicated, and to decrease the number of lower volume fentanyl vials or ampules needed. While there is no approved 100 mL presentation of fentanyl, the Division acknowledges the increased use of compounded large volume fentanyl presentations for continuous infusion in the critical care setting, an unapproved indication.

During the review cycle, the Division discussed potential safety issues associated with the use of a large volume presentations of fentanyl for an indication that generally only require a fraction of the amount of drug available in the proposed presentations. Specifically, the Division had concerns regarding increase in the possibility of dosing errors and overdose, misuse, abuse, and diversion. Based on these considerations, the Division determined that the 100 mL, single-dose vial would not be appropriate (b) (4) The Division agreed that the large volume presentation (b) (4)

The Applicant's proposed benefits of the 50 mL and 100 mL vial presentations of Fentanyl Citrate Injection include the following:

- Convenient dose package for patients of higher-than-average weight or those requiring high doses to induce and maintain the anesthetic effects
- Proposed indications are a subset of currently approved indications, that appropriately correlate to the proposed presentation strength
- May help to alleviate current Fentanyl Citrate drug shortages

- Exela has manufactured the proposed drug product presentations as a 503B compounded drug since May of 2020 to alleviate drug shortages, and has not received any adverse event reports associated with use of the product
- Suitable for IV administration by (b) (4)
- Same concentration (50 mcg/mL) as the currently approved product
- Previously approved container closure system
- The 2.5 mg/50 mL presentation is an approved strength of the LD
- Provides convenience, and may decrease the number of vials accessed, especially during high fentanyl use procedures
- Proposed product formulation differs from the LD by the addition of Sodium Chloride, USP (0.9%), resulting in an isotonic product, helping to prevent pain at the injection site and the hemolysis associated with hypotonic solutions.

The Applicant acknowledges the following risks of the 50 mL and 100 mL vial presentations of Fentanyl Citrate Injection:

- Misuse
- Abuse
- Opioid use disorder
- Accidental exposures
- Overdose

Based on review of the information included in the NDA submission, specifically the Benefit: Risk Analysis Report, and clinical expertise, the Division concludes that the benefits of Fentanyl Citrate Injection, USP, 50 mcg/mL (2.5 mg/50 mL and 5 mg/100 mL) in clear glass vials, outweigh the risks for three main reasons.

First, the Division agrees with the Applicant that approval and availability of these vial presentations may reduce the risk of drug shortages. During the coronavirus global pandemic of 2019 (COVID-19), the U.S. was faced with drug shortages of nearly all sedative medications, as well as some opioid analgesics, including fentanyl. Two additional fentanyl presentations, with approved labeling, available for clinical use may help off-set this risk.

Second, the moderate and high dose adjunct to anesthesia indications and when administered as a general anesthetic, support the use of the proposed presentations. For example, a 70 kg patient who requires a high dose (i.e., 20 to 50 mcg/kg) Fentanyl Citrate Injection, would require a total dose of 1,400 to 3,500 mcg (28 to 70 mL) of the proposed product. When administered as a general anesthetic, the same 70 kg patient may require 3,500 mcg to 10,500 mcg (50 to 150 mcg/kg; 70 to 210 mL) of the drug product. Therefore, the proposed presentations may decrease the number of vials accessed for the indications the require administration of large doses.

And third, while misuse, abuse, opioid use disorder, accidental exposures, and overdose are risks associated with opioid analgesics, they do not appear to be increased with use of the proposed presentations. Specifically, these presentations will be administered only by healthcare professionals, and must adhere to the same controlled substance regulations as the

LD. In addition, the Applicant has been manufacturing the 100 mL presentation via the 503B compounding pathway (due to a fentanyl drug shortage) since May 2020, and distribution data indicate (b) (4) - 100 mL vials have been sold. The Applicant has provided information from several consumers of the compounded product, which suggests that there has not been an increased risk of misuse, abuse, or opioid use disorder with the 100 mL presentation.

In sum, the Division concludes that the benefits of the proposed Fentanyl Citrate Injection 2.5 mg/50 mL and 5 mg/100 mL in clear glass vials outweigh the risks, particularly in the settings of moderate and high fentanyl dosing, and when used as a general anesthetic for adults. Therefore, the Division recommends approval of this NDA.

# 2. Background

This document will serve as the Cross-Discipline Team Leader and the Division Director Summary Review of NDA 215870 for the proposed product, Fentanyl Citrate Injection, USP 50 mcg/mL, 2.5 mg/50 mL and 5 mg/100 mL by Exela.

Fentanyl, a Schedule II controlled substance, binds to G-protein-coupled opioid receptors, especially the mu opioid receptor. Activation of these receptors causes guanosine triphosphate (GTP) to be exchanged for guanosine diphosphate (GDP) on G-proteins, which in turn down regulates adenylate cyclase, reducing concentrations of cyclic adenosine monophosphate (cAMP). Additionally, these complexes interact with a number of ion channels, producing activation of potassium conductance and an inhibition of calcium conductance. The net effect of these changes is a reduced intracellular cAMP, a hyperpolarization of the cell in question and, for neuronal cells, reduced neurotransmitter release.[1]

The principal therapeutic actions of fentanyl are analgesia and sedation. The most common serious adverse reactions reported to occur with fentanyl are respiratory depression, apnea, rigidity, and bradycardia, as stated in the most recently approved USPI for the LD. If untreated, these adverse reactions can result in respiratory arrest, circulatory depression, and/or cardiac arrest. Other adverse reactions that have been reported are hypertension, hypotension, dizziness, blurred vision, nausea, emesis, laryngospasm, diaphoresis, serotonin syndrome, adrenal insufficiency, and anaphylaxis.

Given intravenously, the onset of action is almost immediate; however, the maximal analgesic effect may not be noted for several minutes. The usual duration of action of the analgesic effect is 30 to 60 minutes after a single intravenous dose of up to 100 mcg. A dose of 100 mcg (0.1 mg, 2 mL) of Fentanyl Citrate Injection is approximately equivalent in analgesic activity to 10 mg of morphine or 75 mg of meperidine. The minimum effective analgesic dose of fentanyl varies among individual patients, especially among patients who have been previously treated with opioid analgesics. Additionally, the minimum effective analgesic dose for an individual patient may increase over time due to an increase in pain, or the development of analgesic tolerance, or both.

[1] Pathan H, Williams J. Basic opioid pharmacology: an update. Br J Pain. 2012 Feb;6(1):11-6.

The following discussion will include a brief overview of the regulatory history of this application.

On April 8, 2022, the Applicant submitted NDA 215870, Fentanyl Citrate Injection, USP 50 mcg per mL, 2.5 mg/50 mL and 5 mg/100 mL, in glass vials under the provisions of Section 505(b)(2) of the United States Food, Drug, and Cosmetic Act (FD & C Act), relying on the Agency's previous findings of safety and effectiveness for the LD, Fentanyl Citrate Injection, USP 50 mcg/mL, NDA 019101.

On June 22, 2022, the Division provided the 74-day correspondence containing three potential clinical, and two potential nonclinical, review issues. The clinical review issues involved the large volume presentation and the proposed route of administration (IV only) for all indications included in the LD label (refer to Section 12 of this summary review for additional information regarding the labeling comments included in the 74-day letter). The nonclinical review issues included drug product degradants, and nonclinical support for the proposed (b) (4) route of administration. One additional Controlled Substance Staff (CSS) comment regarding analysis of marketing reports was included.

On July 5, 2022, a Response to Filing Communication was received, in which the Applicant acknowledged the Divisions clinical, nonclinical, and CSS comments. Regarding the IV-only route of administration, (b) (4)

On August 22, 2022, the Applicant provided the 120-day safety update.

A response to the August 4, 2022, IR was received on August 31, 2022, in which the Applicant provided updated draft labeling to include (b) (4) . In addition, the Applicant removed (b) (4) for each proposed indication.

A response to an IR sent on November 16, 2022, regarding distribution and consumer use information, was received on November 22, 2022. The Applicant provided additional distribution data and consumer use information regarding misuse, overdose, and diversion based on the sale of the 100 mL compounded product.

## 3. Product Quality

The Office of Product Quality (OPQ) recommends approval of this NDA based on the reviews completed by the drug substance, drug product, process and facilities, biopharmaceutics, and microbiology teams.

The following assessment was reproduced from the Integrated Quality Assessment, dated December 21, 2022 (verbatim):

> *Drug Substance: Adequate*
> The Applicant has provided adequate general information on the drug substance, Fentanyl Citrate.
>
> The Applicant's specification for Fentanyl Citrate drug substance is established based on the manufacturer's specification, USP current monograph for Fentanyl Citrate, and USP General Chapters. From the active pharmaceutical ingredient (API) perspective, the Applicant's specification for the drug substance is compliant with the USP monograph for Fentanyl Citrate drug substance, ICH Q6A, and the referenced Drug Master File (DMF) (b) (4). The Applicant has provided the satisfactory justifications for all the testing parameters and their acceptance criteria. The Applicant's specification for the Fentanyl Citrate drug substance is adequate. For bacterial endotoxins, microbiology reviewer team will assess the acceptance criteria and justifications.
>
> *Drug Product: Adequate*
> Fentanyl Citrate Injection, USP 50 mcg/mL, is supplied as a clear, colorless sterile, non-pyrogenic, preservative-free solution in two strengths, 2.5 mg/50 mL and 5 mg/100 mL. It contains sodium chloride (b) (4) hydrochloric acid and sodium hydroxide as pH adjusting agents. All the excipients are compendial and their respective maximum daily exposures are considered qualified.
>
> The drug product is packaged in 50/100 mL molded clear glass vial and closed with grey rubber stopper. The Applicant conducted risk assessment, which shows that the vials have low risk for delamination. The extractable study was conducted at reflux condition using aqueous solvents that bracketed the product pH. The leachable study was conducted on the six primary batches at T = 6 months (long term and accelerated storage) and T = 12 months (long-term). The data show that the primary container closure components have adequate extractable and leachable profile. The components also meet the appropriate USP chapters and are suitable for packaging this parenteral product. The available stability data show that the primary container closure systems are expected to provide adequate protection to the drug product through the proposed shelf-life.
>
> The proposed specification is adequate to assure the product quality through the proposed shelf-life. The impurities are controlled per ICH Q3B and M7 Guidelines. The specification does not include control for elemental impurities. The Applicant has provided risk assessment per ICH Q3D, which supports the omission of this test. The Applicant has provided batch data for three batches per strength, which demonstrate that the Applicant could manufacture the drug product in consistent quality. All the batches showed low levels of impurities. The Applicant has adequately validated the non-compendial method used for the assay and impurity quantitation.

The Applicant has provided up to 18 months of long-term (25°C/60%RH) and 6 months of accelerated (40°C/75%RH) stability data for three batch per strength. None of the attributes showed any trending. Based on the available stability data, the proposed shelf-life of 24 months may be granted, when stored at 20°C–25°C (68°F– 77°F).

*Quality Labeling: Adequate*
Overall Assessment and Recommendation: Adequate
Note that there is a disconnect between the established name in the product title and how the strength is expressed, a detailed justification follows:

1. Listed Drug (NDA 019101): Fentanyl Citrate Injection, for intravenous or intramuscular use. Fentanyl Citrate Injection, equivalent to 50 mcg (0.05 mg) fentanyl base per mL, is a preservative-free solution, available in 2 mL, 5 mL, 20 mL single use glass ampuls and 2 mL, 5 mL, 20 mL, 50 mL single use glass vials.
2. Proposed Product (NDA 215870): Fentanyl Citrate Injection, for intravenous Use. Injection: 50 mcg fentanyl base per mL, available in 50 mL and 100 mL single dose glass vials.

Although the established name for the listed product is "fentanyl citrate," the strength is expressed in terms of "fentanyl base," which does not meet the USP salt policy. While the FDA Guidance, *Naming of Drug Products Containing Salt Drug Substances*[2], provides exception from the USP salt policy for historical drug products, the exception does not cover this particular case, i.e., where the established name is a "salt", but the strength is in terms of "active moiety." The exception seems to apply only for drug products where the established name is a "salt", and the strength is also expressed in "salt."

The Division also notes that the following historical fentanyl citrate injection/injectable products use similar labeling convention (i.e., "Fentanyl Citrate" is the established name, but the strength is expressed in terms of "fentanyl base"):

- NDA 019115: Fentanyl Citrate Injection, for intravenous or intramuscular use
- NDA 016619: Fentanyl Citrate Injection, for intravenous or intramuscular use

Therefore, if the Division expresses the strength of the proposed product in terms of "fentanyl citrate" or changes the established name to "fentanyl," it can potentially confuse healthcare providers, as it will differ from the labeling convention used for the listed drug and its generic equivalents. However, the Division was equally concerned that if the product strength is labeled in terms of "fentanyl base," it could potentially be considered as misbranded. Therefore, the Division sought the subject matter expert guidance from Dr. David Claffey of the Office of Pharmaceutical Quality (OPQ) and Jibril Abdus-Samad of the Office of Policy for Pharmaceutical Quality (OPPQ). Per both offices, because there is a USP monograph for this product, the proposed product

[2] https://www.fda.gov/files/drugs/published/Naming-of-Drug-Products-Containing-Salt-Drug-Substances.pdf

is required to use that name i.e., Fentanyl Citrate injection. OPPQ further emphasized that the Division cannot delete "citrate" from the product title, as the name "Fentanyl" will not match the name "Fentanyl Citrate" in the USP monograph, which will be considered misbranding.

Both OPQ and OPPQ stated that to minimize the risk of medication error, the Division should continue to label the strength of the proposed product in terms of "fentanyl base" and that the salt policy has exceptions based on historical condition such as this and other products (see: NORVASC (amlodipine besylate) tablets and LIPITOR (atorvastatin calcium) tablets). OPQ and OPPQ also recommended the following format for the salt equivalency statement: Each mL contains 50 mcg fentanyl base (equivalent to 79 mcg fentanyl citrate).

*Manufacturing: Adequate*
Facilities: The facilities proposed for commercial production are in a state of compliance.

Manufacturing: The overall manufacturing process includes a (b) (4) batch size,

(b) (4)

*Biopharmaceutics: Adequate*
The Biopharmaceutics Review focused on the evaluation of the Applicant's biowaiver request and supporting justification. The Applicant requested a biowaiver citing 21 CFR §320.22(b), considering the same route of administration, same dosage form, and same indication as the LD. FDA determined that the Applicant's biowaiver request per 21 CFR §320.22(b) is not feasible because the formulation of the proposed to-be-marketed parenteral drug product is not qualitatively and quantitatively (Q1/Q2) the same as that of LD. Note that the proposed parenteral drug product, though with similar formulation composition, contains sodium chloride in the formulation for isotonicity, whereas LD product does not contain sodium chloride being a hypotonic solution. In the November 22, 2022, response to the FDA Information Request dated November 15, 2022, the Applicant provided a scientific justification, including literature, to support that the presence of sodium chloride in the proposed parental product does not significantly affect the fluid balance, electrolyte homeostasis, and the safety or efficacy compared to LD. The Applicant has provided sufficient justification to establish the scientific bridge between the proposed product and the LD, permitting reliance on FDA's findings for that LD, in accordance with 21 CFR §320.24(b)(6).

*Microbiology: Adequate*
The submission is recommended for approval on the basis of sterility assurance.

For additional information refer to the Integrated Quality Review completed by the Chemistry, Manufacturing and Controls (CMC) team, dated December 21, 2022. OPQ has recommended approval with no postmarketing commitments or requirements. The Division agrees with the recommendations by the OPQ review team.

# 4. Nonclinical Pharmacology/Toxicology

Based on review of the information submitted, the pharmacology/toxicology review team recommends approval of the NDA. The following assessment was reproduced from the pharmacology/toxicology review, by Dr. Elizabeth Bolan, PhD, dated January 26, 2023, in DARRTS.

> 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.

The Division agrees with the recommendations of the pharmacology/toxicology review team. Refer to the review completed by the pharmacology/toxicology review team, dated January 26, 2023, for additional information.

# 5. Clinical Pharmacology

The Applicant did not conduct any clinical or clinical pharmacology studies to support the safety and efficacy of the proposed product and submitted a Request for Waiver of in Vivo Bioavailability Studies (biowaiver request). Refer to Section 3 of this summary review, and the review completed by the OPQ team for additional information regarding the biowaiver request.

The Applicant is relying on the clinical pharmacology information in the LD label to support the NDA submission. The clinical pharmacology review team did not identify any issues that would preclude approval. The Division concurs with the recommendations of the clinical pharmacology review team.

# 6. Clinical Microbiology

Fentanyl Citrate Injection, USP 50 mcg/mL, 50 mL and 100 mL, is not a therapeutic antimicrobial. Therefore, clinical microbial data were neither required nor submitted.

# 7. Clinical/Statistical- Efficacy

This application relies upon the Agency's previous findings of effectiveness for the LD, Fentanyl Citrate Injection, USP 50 mcg/mL (NDA 019101). The Applicant did not conduct any clinical efficacy studies; therefore, Section 7 of this summary review is not relevant to this 505(b)(2) application.

# 8. Safety

The Applicant did not conduct any clinical studies in support of the safety of this marketing application, and is relying upon the Agency's previous findings of safety for the LD.

A safety update was included in the NDA submission, and a 120-Day safety update was received on August 22, 2022. Both documents were reviewed by Dr. Lee Anne Connell-Templin, who determined that there were no new safety findings that would adversely impact an approval decision or that needed to be included in labeling.

Regarding submitted adverse event (AE) information:

- In the safety update submitted with the initial NDA, the Applicant searched the FDA Adverse Events Reporting System (FAERS) for the terms "Fentanyl" and "Fentanyl Citrate" beginning October 1, 2019 (based on the most recently approved label for the LD), through March 25, 2022. This search identified 6,863 deaths, 19,498 serious AEs (SAEs), and 22,287 total AEs.
- The 120-Day Safety Update Report included "…information on clinical trials and published clinical safety studies that were identified during the safety update period of March 26, 2022, through August 8, 2022. This safety update report also provides data from the FDA Adverse Events Reporting System for the year 2022." This search identified 2,419 deaths, 4,347 SAEs and 4,697 total AEs.

While there were large numbers of deaths, SAEs, and AEs reported in the FAERS database searches, a large proportion of these cases were due to drug abuse, drug dependence, toxicity to various agents, overdose, and completed suicide, not due adverse outcomes associated with clinical use of the drug based on current labeling recommendations.

Based on a thorough benefit: risk assessment of these large volume Fentanyl Citrate presentations, including review of information in the NDA submission and clinical expertise, there does not appear to be increased risk associated with use of these presentations compared to use of the lower volume presentations.

# 9. Advisory Committee Meeting

An advisory committee meeting was not convened for this application, as there were no issues that required presentation or discussion at an advisory committee meeting.

# 10. Pediatrics

Safety and effectiveness of Fentanyl Citrate have been established in pediatric age groups, two years and above. Because the proposed presentations do not represent new routes of administration, new indications, new dosage forms, or new dosing regimens, and do not contain new active ingredients, pediatric studies under the Pediatric Research Equity Act (PREA) are not required.

In the Response to Filing Communication received August 31, 2022, the Applicant had removed pediatric dosing from the proposed label based on the likely limited need for the large volume presentation in the pediatric population, and on the potential for a large amount of fentanyl waste. Subsequent to review of the Applicant's response, there were multiple internal discussions regarding the appropriateness of a pediatric indication and dosing for the large volume presentation of fentanyl. Because the Division's concern was not based on the safety or effectiveness of the drug in the pediatric population, the Division determined that pediatric dosing information should be included in the label. Pediatric dosing information was added back into the label during labeling negotiations with the Applicant. Refer to Section 12 of this summary review for additional labeling information.

# 11. Other Relevant Regulatory Issues

The consult memorandum provided by the Controlled Substance Staff (CSS) dated January 10, 2023, focused on the proposed 5 mg/100 mL presentation, and included the following information (verbatim):

> The proposed 5 mg/100 mL presentation is intended to offer a more convenient formulation for settings where higher doses of fentanyl are required that would have otherwise been achieved with more vials of the lower volume but similarly concentrated solution. Therefore, it is reasonable to anticipate that the abuse- and diversion-related risk profile for the proposed fentanyl product will be comparable to that of the LD. Regardless, continued postmarketing pharmacovigilance will be important to monitor for any emerging safety concerns that may arise with the higher volume presentation.

The review completed by CSS also stated that no issues were identified that would preclude approval of this NDA, and that fentanyl is a Schedule II controlled substance under the CSA, and if approved, would require Section 9 labeling consistent with the LD.

The Division agrees with the recommendations of the CSS review team. Refer to the review completed by CSS for additional information.

# 12. Labeling

The approved labeling for the LD Fentanyl Citrate Injection, NDA 019101, includes the following indications:

- analgesic action of short duration during the anesthetic periods, premedication, induction and maintenance, and in the immediate postoperative period (recovery room) as the need arises.
- use as an opioid analgesic supplement in general or regional anesthesia.
- administration with a neuroleptic as an anesthetic premedication, for the induction of anesthesia and as an adjunct in the maintenance of general and regional 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 Applicant's draft label (b) (4)

Based on internal discussion, two comments regarding the proposed indications (summarized below) were sent to the Applicant in the 74-Day Letter.

- The Division did not agree that the Applicant's proposed large volume presentation (b) (4)
- Regarding the Applicant's proposed route of administration, the Division had the following two concerns:
  - The proposed route of administration, (b) (4) is not an approved route of administration of the LD.
  - (b) (4)

In the July 5, 2022, Response to Filing Communication, the Applicant confirmed that they did not intend to pursue an indication for (b) (4) noting it was included in error, and agreed to remove all language regarding (b) (4) from the draft label. Regarding (b) (4)

(b) (4)


for pediatrics. Refer to Section 10 above regarding pediatric dosing.

The agreed-upon labeling includes the following indications for adults and pediatrics above two years of age, via the IV route only:

- use as an opioid analgesic supplement in general anesthesia.
- administration with a neuroleptic for the induction of anesthesia and as an adjunct in the maintenance of general 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 review team in the Division of Medication Error Prevention and Analysis (DMEPA 1) reviewed the container labels, carton labeling and the proposed prescribing information (PI), and concluded that the PI, syringe label, and blister and carton labeling may be improved to promote the safe use of this product from a medication error perspective. The Applicant has incorporated the recommendations made by DMEPA into the label. The Division has no outstanding concerns regarding labeling.

The Division agrees with the recommendations from the DMEPA team. Refer to the review completed by DMEPA 1 for additional information.

# 13. Decision/Action/Benefit:Risk Assessment

Regulatory Action
Approval

Benefit:Risk Assessment
The Benefit:Risk Assessment for the proposed presentations Fentanyl Citrate Injection 2.5 mg/50 mL and 5 mg/100 mL in clear glass vials, outweigh the risks, particularly in the settings of moderate and high dose administration as adjuncts to general anesthesia, and as a general anesthetic for adults. In addition, the Applicant has provided adequate justification that the marketed compounded 100 mL presentation has not resulted in increased risk of misuse,

overdose, and diversion. Finally, the Division notes the potential benefit of two additional fentanyl presentations available to clinicians to help alleviate drug shortages.

Post Marketing Requirements
There are no post marketing requirements or commitments for this application. As noted in Section 10, PREA is not triggered, and pediatric studies are not required.

# 14. Comments to the Applicant

There are no comments to the Applicant.

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**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.**

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/s/

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LEE ANNE A CONNELL-TEMPLIN
02/08/2023 10:16:10 AM

RENEE L PETIT-SCOTT
02/08/2023 10:22:04 AM

ALLA T BAZINI
02/08/2023 10:29:06 AM

ALLA T BAZINI on behalf of RIGOBERTO A ROCA
02/08/2023 01:08:37 PM