CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

215870Orig1s000

OTHER REVIEW(S)

FOOD AND DRUG ADMINISTRATION
Center for Drug Evaluation and Research
Office of Prescription Drug Promotion

****Pre-decisional Agency Information****

Memorandum

Date: January 12, 2023

To: Joyce Chin, PharmD, Regulatory Project Manager, Division of Anesthesiology, Addiction Medicine, and Pain Medicine (DAAP)

Lee Anne Connell-Templin, MD, DAAP

Lisa Basham, MS, Associate Director for Labeling, DAAP

From: Phillip Williams, PharmD, RAC, Regulatory Review Officer
Office of Prescription Drug Promotion (OPDP)

CC: Sam Skariah, PharmD, RAC, Team Leader, OPDP

Subject: OPDP Labeling Comments for Fentanyl Citrate injection, for intravenous use, CII

NDA: 215870

Background:
In response to DAAP's consult request dated May 19, 2022, OPDP has reviewed the proposed Prescribing Information (PI) and carton and container labeling for the original NDA submission for Fentanyl Citrate injection, for intravenous use, CII.

PI:
OPDP's review of the proposed PI is based on the draft labeling emailed to OPDP on January 3, 2023, and our comments are provided below.

Carton and Container Labeling:
OPDP's review of the proposed carton and container labeling is based on the draft labeling submitted by the sponsor to the electronic document room on December 14, 2022, and our comments are provided below.

Thank you for your consult. If you have any questions, please contact Phillip Williams at (240) 402-3974 or Phillip.Williams@fda.hhs.gov.

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/s/

PHILLIP A WILLIAMS
01/12/2023 11:34:32 AM

M E M O R A N D U M

Department of Health and Human Services
Food and Drug Administration
Center for Drug Evaluation and Research

Date: January 10, 2023

To: Rigoberto Roca, M.D., Director
Division of Anesthesiology, Addiction Medicine, and Pain Medicine

Through: Dominic Chiapperino, Ph.D., Director
Joshua Lloyd, M.D., Medical Officer Team Leader
Controlled Substance Staff

From: Shalini Bansil, M.D., Medical Officer
Controlled Substance Staff

Subject: **NDA 215870**; **Fentanyl Citrate Injection, USP**
Strengths: 2.5 mg/50 mL and 5 mg/100 mL (50 mcg/mL)
Indications:

- 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

Applicant: Exela Pharma Sciences, LLC
PDUFA Goal Date: February 8, 2023

Materials Reviewed:

- Abuse-related data and labeling in Original NDA submission, dated April 8, 2022, and subsequent amendments
- NDA 215870 DARRTS; S Bansil, May 23, 2022, CSS filing checklist

1. Background

This memorandum responds to a consult request from the Division of Anesthesiology, Addiction Medicine, and Pain Medicine (DAAP) dated April 25, 2022, to the Controlled Substance Staff (CSS) for **NDA 215870**; **Fentanyl Citrate Injection, 2.5 mg/50 mL and 5 mg/100 mL (50 mcg/mL)** submitted by Exela Pharma Sciences, LLC (referred to as "the Applicant").

The application is a 505(b)(2) New Drug Application (NDA) that relies on FDA's findings of safety and effectiveness for the Listed Drug (LD), Fentanyl Citrate Injection, 50 mcg/mL, held by Hikma and approved under NDA 19101. The Applicant's proposed Drug Product contains Fentanyl Citrate at a concentration equivalent to 50 mcg fentanyl per mL and will be provided as two strengths – 2.5 mg/50 mL and 5 mg/100 mL in molded clear glass vials. The LD product, Fentanyl Citrate manufactured by Hikma Pharmaceuticals, is available as single dose, 2.5 mg/50 mL vials, as well as other strengths, including 100 mcg/2 mL, 250 mcg/5 mL and 1000 mcg/20 mL.

The Applicant's proposed product presents the same chemical entity as the currently approved LD and is provided at the same concentration (50 mcg mg/mL) as the currently approved product. One of the proposed strengths for the product is 2.5 mg/50 mL, which is the same as one of the approved strengths for Fentanyl Citrate Injection (NDA 019101). The Applicant also proposes a 5 mg/100 mL strength to address a clinical need for higher volumes of the medication, especially during open heart surgery or certain complicated neurological or orthopedic procedures that require moderate to high doses of fentanyl (50 – 150 mcg/kg). The 100 mL presentation may be useful in moderate to high dose situations by minimizing the number of vials to be dosed. No clinical studies were conducted in support of this application.

Fentanyl Citrate Injection contains fentanyl, a Schedule II controlled drug substance. Since the Applicant proposes a larger volume presentation for fentanyl, DAAP requests CSS's input on concerns with abuse/diversion of this product.

2. Conclusions

- Fentanyl is a potent opioid agonist and is a Schedule II controlled substance under the Controlled Substances Act (CSA). Fentanyl, like other opioid agonists, is a substance with a high potential for abuse and is associated with misuse, abuse, the development of physical dependence, overdose, and death.
- The application is a 505(b)(2) NDA that relies on FDA's findings of safety and effectiveness for the Listed Drug (LD), Fentanyl Citrate Injection, 50 mcg/mL (NDA 19101). The Applicant's proposed product presents the same chemical entity as the currently approved product and is provided at the same concentration (50 mcg mg/mL) as the currently approved product. One presentation of the proposed product, 2.5 mg/50 mL, is the same as one of the approved presentations for Fentanyl Citrate Injection. The Applicant also offers a 5 mg/100 mL presentation of the proposed product and notes that

the higher volume product of 5 mg/100 mL will provide convenience for dosing, especially during open heart surgery or certain complicated neurological or orthopedic procedures that require moderate to high doses of fentanyl (50 – 150 mcg/kg). The 100 mL presentation may be useful in moderate to high dose situations by minimizing the number of vials to be dosed.

- The Applicant states that they have supplied (b) (4) vials of the proposed drug product presentations as a 503B compounded drug since May 2020 to alleviate drug shortages and have not identified any significant risks related to their product. Additionally, the Applicant reached out to its largest consumer of the 100 mL vial presentation, (b) (4) to determine additional risks or issues associated with the 100 mL presentation. According to the Applicant, (b) (4) officials stated that their facility uses fentanyl as an adjunct to anesthesia and that they did not experience any increased risk of misuse, abuse, opioid use disorder, accidental exposure, or overdose with the use of the 100 mL presentation.
- Fentanyl is a substance that has a high potential for abuse and diversion. Although the concentration of fentanyl in the proposed formulation is the same as the LD, the Applicant is proposing a higher volume presentation than what is currently available for the LD (i.e., 5 mg/100 mL). The Applicant notes that they have not identified any novel risks or concerns through their postmarketing pharmacovigilance monitoring of their 503B compounded drug product manufactured since May 2020, which is identical to the product proposed under this NDA. This type of postmarketing safety monitoring generally relies on spontaneous reports and is particularly useful for identifying potential safety signals that require further investigation. Although important, this type of monitoring would have more limited utility in quantifying potential differences between the 5 mg/100 mL and the 2.5 mg/50 mL presentations on serious abuse- and diversion-related outcomes. 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 product will continue to be a prescription product accessible only to healthcare professionals and not to patients or other non-healthcare persons, including members of the patient's household.

3. Recommendations

- CSS has not identified any issues that would preclude approval of this NDA.
- Fentanyl is a Schedule II controlled substance under the CSA. The proposed product, if approved, would require section 9 labeling consistent with the LD under NDA 19101.

4. Discussion

According to the Applicant, the proposed product has the same formulation as the previously approved product (NDA 019101) with the exception of adding Sodium Chloride to make the product isotonic whereas the LD product is hypotonic. The Applicant states that isotonic injectable drug products help to prevent pain at the injection site and hemolysis associated with hypotonic solutions.

The Applicant states that the drug product is a prescription product accessible only to healthcare professionals and is not accessible to patients or other non-healthcare persons, such as members of the patient's household. It is administered in a weight dependent manner in an inpatient critical care/surgical setting for induction and maintenance of anesthesia. In addition, the patients are carefully observed and monitored during administration of fentanyl doses due to known life-threatening respiratory depressive effects of fentanyl. Thus, potentially mitigating some of the broader public health effects associated with Schedule II opioids, such as the risks of misuse, abuse, accidental exposure, and overdose.

In their initial submission, the Applicant noted that they had supplied (b) (4) vials of the proposed drug product presentations as a 503B compounded drug since May 2020 to alleviate drug shortages and have not identified any significant risks related to their product. However, the Applicant did not provide any reports or their analysis of the reports to support their assertion. In the 74-day filing letter, CSS asked the Applicant to provide a summary and analysis of marketing reports related to the abuse, misuse, and/or diversion of their product (NDA 215870 DARRTS; S Bansil May 23, 2022, CSS filing checklist). The Applicant states that the 100 mL presentation was manufactured in response to requests from health care systems (as a 503B compounded drug product) following a shortage of the drug. The Applicant stated that the assertion in their initial submission was based on not receiving any adverse event reports as part of their internal inventory monitoring system (pharmacovigilance monitoring). The Applicant states that they have complied with the bi-annual 503B reporting, where the amount manufactured is submitted via CDER DIRECT portal.

Additionally, the Applicant reached out to its largest consumer of the 100 mL vial presentation, Grady Memorial located in Atlanta, GA to determine additional risks or issues associated with the 100 mL presentation. They spoke with the (b) (4) (b) (4) on August 17, 2022, who stated that their facility uses fentanyl as an adjunct to anesthesia and that they did not experience any increased risk of misuse, abuse, opioid use disorder, accidental exposure, and overdose with the use of the 100 mL presentation.

The Applicant's proposed label incorporates language similar to the LD's label with respect to Abuse and Dependence.

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/s/

SHALINI M BANSIL
01/10/2023 01:56:42 PM

JOSHUA M LLOYD
01/10/2023 02:02:46 PM

DOMINIC CHIAPPERINO
01/10/2023 04:14:44 PM

MEMORANDUM

REVIEW OF REVISED LABEL AND LABELING

Division of Medication Error Prevention and Analysis 1 (DMEPA 1)

Office of Medication Error Prevention and Risk Management (OMEPRM)

Office of Surveillance and Epidemiology (OSE)

Center for Drug Evaluation and Research (CDER)

Date of This Memorandum:	December 9, 2022
Requesting Office or Division:	Division of Anesthesiology, Addiction Medicine, and Pain Medicine (DAAP)
Application Type and Number:	NDA 215870
Product Name and Strength:	Fentanyl citrate injection, 2,500 mcg/50 mL (50 mcg/mL), 5,000 mcg/100 mL (50 mcg/mL)
Applicant/Sponsor Name:	Exela Pharma Sciences, LLC. (Exela)
TTT ID #:	2022-2541-1
DMEPA 1 Safety Evaluator:	Damon Birkemeier, PharmD
DMEPA 1 Team Leader:	Valerie S. Vaughan, PharmD

1 PURPOSE OF MEMORANDUM

The Applicant submitted revised container labels and carton labeling received on December 9, 2022 for fentanyl citrate. The Division of Anesthesiology, Addiction Medicine, and Pain Medicine (DAAP) requested that we review the revised container labels and carton labeling for fentanyl citrate (Appendix A) to determine if they are acceptable from a medication error perspective. The revisions are in response to recommendations that we made during a previous label and labeling review.[a]

2 CONCLUSION

The Applicant clarified that the "MM" in their expiration date format consists of numeric characters. The Applicant implemented all of our recommendations and we have no additional recommendations at this time.

[a] Birkemeier D. Label and Labeling Review for fentanyl citrate (NDA 215870). Silver Spring (MD): FDA, CDER, OSE, DMEPA 1 (US); 2022 DEC 7. TTT ID No.: 2022-2541.

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/s/

DAMON A BIRKEMEIER
12/09/2022 04:49:44 PM

VALERIE S VAUGHAN
12/11/2022 09:13:52 PM

LABEL AND LABELING REVIEW

Division of Medication Error Prevention and Analysis 1 (DMEPA 1)

Office of Medication Error Prevention and Risk Management (OMEPRM)

Office of Surveillance and Epidemiology (OSE)

Center for Drug Evaluation and Research (CDER)

*** This document contains proprietary information that cannot be released to the public***

Date of This Review:	December 7, 2022
Requesting Office or Division:	Division of Anesthesiology, Addiction Medicine, and Pain Medicine (DAAP)
Application Type and Number:	NDA 215870
Product Name and Strength:	fentanyl citrate injection, 2,500 mcg/50 mL (50 mcg/mL), 5,000 mcg/100 mL (50 mcg/mL)
Product Type:	Single Ingredient Product
Rx or OTC:	Prescription (Rx)
Applicant/Sponsor Name:	Exela Pharma Sciences, LLC. (Exela)
FDA Received Date:	April 8, 2022; August 31, 2022; November 22, 2022
TTT #:	2022-2541
DMEPA 1 Safety Evaluator:	Damon Birkemeier, PharmD
DMEPA 1 Team Leader:	Valerie S. Vaughan, PharmD

1 REASON FOR REVIEW

As part of the approval process for fentanyl citrate injection, the Division of Anesthesiology, Addiction Medicine, and Pain Medicine (DAAP) requested that we review the proposed fentanyl citrate prescribing information (PI), container labels and carton labeling for areas of vulnerability that may lead to medication errors.

1.1 BACKGROUND

NDA 215870 is a 505(b)(2) NDA and the listed drug product is fentanyl citrate, NDA 019101.

2 MATERIALS REVIEWED

Table 1. Materials Considered for this Label and Labeling Review

Material Reviewed	Appendix Section (for Methods and Results)
Product Information/Prescribing Information	A
Previous DMEPA Reviews	B
ISMP Newsletters*	C – N/A
FDA Adverse Event Reporting System (FAERS)*	D – N/A
Other	E – N/A
Labels and Labeling	F

N/A=not applicable for this review
*We do not typically search FAERS or ISMP Newsletters for our label and labeling reviews unless we are aware of medication errors through our routine postmarket safety surveillance

3 DISCUSSION

We note that Exela is proposing 2,500 mcg/50 mL and 5,000 mcg/100 mL single-dose vial presentations and Exela initially proposed the following indications:

- (b) (4)
- Use as an analgesic (b) (4) supplement in general (b) (4) anesthesia
- Administration with a neuroleptic (b) (4) for the induction of anesthesia 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 procedures

We note that the dosing for some of these indications result in very small doses to be administered. For example, as a (b) (4) the recommended dose is (b) (4). Using the proposed single-dose vial presentations would result in (b) (4) mcg of waste. We reached out to our

clinical colleagues who shared our concern. In response to an information request (IR) issued by the clinical team, Exela modified their proposed indications to the following:

- Use as an opioid analgesic supplement in general anesthesia
- Administration with a neuroleptic for the inductions 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

Exela conducted a benefit-risk assessment for the 50 mL and 100 mL vial presentations.[a] Regarding the modification of the proposed indications (above) Exela states "*The larger volumes of the proposed presentations are suitable for intravenous administration of moderate to high doses by* (b) (4) *. Much smaller volumes are needed for intramuscular and bolus/short infusion intravenous administration for other indications. Since the product is preservative free and is intended as a single-dose vial, use of the product for* (b) (4) *would lead to unnecessary product wastage. Therefore, Exela revised the Dosage and Administration section to remove* (b) (4) *added the following statement to the Dosage Forms and Strengths section:* (b) (4) (b) (4) For the currently proposed indications, Exela indicates "*[they] believe that the proposed 50 mL and 100 mL presentations provide a convenient dose package for patients of higher than average weight or those requiring high doses to induce and maintain the anesthetic effects.*" For patients undergoing open heart surgery or certain complicated neurological or orthopedic procedures where doses range from 50 mcg/kg to 100 mcg/kg, Exela indicates "*[they] believe that the proposed 50 mL and 100 mL presentations are particularly suitable for this indication.*"

Exela further states "*fentanyl citrate injection has been on drug shortage since April 2, 2020. To alleviate this shortage Exela has supplied the market with fentanyl citrate injection vials as 503B compounded drug product. Exela has thus far distributed* (b) (4) *vials of the 50 mcg/mL product [50 mL and 100 mL vials] (May 4, 2020, through July 18, 2022). Exela has not received any complaints with regards to the usability of these vials.*" Regarding risk and risk management, Exela states "*The proposed product offers the same treatment options as the previously approved product (NDA 019101). Exela has not received any adverse event reports associated with the [compounded 503B] product.*"

Regarding benefits of the proposed products, Exela states (b) (4) *Isotonic injectable drug products help to prevent pain at the injection site and hemolysis associated with hypotonic*

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[a] Benefit-Risk Assessment for Fentanyl Citrate Injection (50 mcg/mL) in 50 mL and 100 mL Vial Presentations. Lenoir (NC): Exela Pharma Sciences, LLC; 2022 NOV 22. Available from: \\CDSESUB1\EVSPROD\nda215870\0010\m1\us\111-info-not-covered-under-m2-m5\multi-module-info-amend\mult-mod-benefit-risk-0010.pdf

solutions. The 100 mL presentation may be useful in moderate to high dose situations by minimizing the number of vials to be dosed."

Regarding broader public health effects, Exela states "*the proposed presentation poses minimal risk of broader public health effects.*" Exela argues that "*the drug product is a prescription product accessible only to healthcare professionals administered in a weight dependent manner in an inpatient critical care setting for induction and maintenance of anesthesia, [therefore] the approximate dosage required can be predetermined and the appropriate size dose container can be prescribed. In addition, patients are carefully observed and monitored during administration of fentanyl doses.*" Regarding the 100 mL vial, Exela states "*the 100 mL presentation was manufactured in response to requests from health care systems (503B customers) following a shortage of the drug.*" Exela additionally reached out to three consumers of the 100 mL presentation to illicit how the 100 mL presentation is used and whether they have experienced any issues with the use of the 100 mL presentation. These consumers provided various reasons for use such as "an adjunct to anesthesia", "increasing fentanyl requirements", "COVID patients seemed to have an increased metabolic rate requiring more fentanyl to keep them sedated", and "many of these sedated patients have additional organ failures going on that require the need to concentrate drips." None of the consumers reported issues with the 100 mL presentation.

After discussion with our clinical colleagues, we agree that the risk of excessive waste has been minimized and that the benefit outweighs the risk in this case.

4 CONCLUSION AND RECOMMENDATIONS

The proposed PI, container labels and carton labeling may be improved to promote the safe use of this product from a medication error perspective. We provide the identified medication error issues, our rationale for concern, and our proposed recommendations to minimize the risk for medication error in Section 5 for the Division and in Section 6 for Exela Pharma Sciences, LLC.

5 RECOMMEDATIONS FOR DIVISION OF ANESTHESIOLOGY, ADDICTION MEDICINE, AND PAIN MEDICINE (DAAP)

Table 2. Identified Issues and Recommendations for Division of Anesthesiology, Addiction Medicine, and Pain Medicine (DAAP)

	IDENTIFIED ISSUE	RATIONALE FOR CONCERN	RECOMMENDATION
Prescribing Information – General Issues			
1.	We note that the product strength is described in terms of mcg (b) (4) throughout the prescribing	Concurrent use of multiple units of measurement (e.g., mcg (b) (4)) increases the risk of confusion and could lead to medication dosing	We recommend describing the strength based on a single unit of measurement; in this case, mcg given fentanyl is typically dosed based on mcg. As such,

Table 2. Identified Issues and Recommendations for Division of Anesthesiology, Addiction Medicine, and Pain Medicine (DAAP)			
	IDENTIFIED ISSUE	RATIONALE FOR CONCERN	RECOMMENDATION
	information (e.g., 50 mcg (b) (4)	errors.[b] Additionally, our clinical colleagues confirmed that fentanyl is typically dosed in terms of "mcg" or "mcg/kg".	we recommend removing the use of (b) (4) to describe the strength throughout the prescribing information.
2.	We note dosages are described using multiple units of measurement. Non-weight based dosages are described based on mcg, mg, and mL and weight-based dosages are described based on mcg/kg, (b) (4) and (b) (4) throughout Section 2 *Dosage and Administration*.	Concurrent use of multiple units of measurement (i.e., mcg, mg, and mL; mcg/kg, (b) (4)) increases the risk for confusion and could lead to medication dosing errors.[b] Additionally, our clinical colleagues confirmed that fentanyl is typically dosed in "mcg" or "mcg/kg".	We recommend revising the *Dosage and Administration* sections of the Highlights and Full Prescribing Information to remove dosage described in terms of (b) (4) and retaining dosages described in terms of "mcg" and "mcg/kg".
Full Prescribing Information – Section 3 Dosage Forms and Strengths			
1.	As currently presented, the appropriate information to facilitate identification of the dosage form is not included.	Section 3 *Dosage Forms and Strengths* should contain information suitable for product identification in accordance with 21 CFR 201.57(c)(4)(ii).	We recommend including identifying information in Section 3 *Dosage Forms and Strengths* (e.g., add solution color and clarity information).
Full Prescribing Information – Section 16 How Supplied/Storage and Handling			
1.	As currently presented, the appropriate information to facilitate identification of the dosage form is not included.	Section 16 *How Supplied/Storage and Handling* should contain information suitable for product identification in accordance with 21 CFR 201.57(c)(17)(iii).	We recommend including identifying information in Section 16 *How Supplied/Storage and Handling* (e.g., add solution color and clarity information).

[b] Guidance for Industry: *Safety Considerations for Container Labels and Carton Labeling Design to Minimize Medication Errors.* 2022. Available from https://www.fda.gov/media/158522/download.

6 RECOMMENDATIONS FOR EXELA PHARMA SCIENCES, LLC.

Table 3. Identified Issues and Recommendations for Exela Pharma Sciences, LLC. (entire table to be conveyed to Applicant)			
	IDENTIFIED ISSUE	RATIONALE FOR CONCERN	RECOMMENDATION
Container Labels and Carton Labeling			
1.	Numbers greater than or equal to 1,000 are presented without the use of a comma on the labels and labeling.	Misinterpretation of thousands "1000" as hundreds "100" or ten-thousands "10000" may occur.	Present numbers greater than or equal to 1,000 with a comma.
2.	As currently presented, the format of the expiration date on the carton labeling and case labeling is denoted as, "EXP: MM/YYYY," and the format of the expiration date on the container label is denoted as, "YYYY MM". It is unclear if the month portion, "MM," of the expiration date format will use alphabetical or numerical characters.	The expiration date should be clearly defined to minimize confusion and risk for deteriorated drug errors. For example, confusion has occurred with use of the alphabetical abbreviation "JU," which can represent both "June" and "July" and the alphabetical abbreviation "MA," which can represent both "March" and "May."	Clarify if you intend to use only numerical characters to express each portion of the expiration date.
3.	The usual dosage statement is missing on the container label and carton labeling.	21 CFR 201.55 requires that labels for prescription drugs bear a statement of the recommended or usual dosage.	On the container label and carton labeling, revise the statement, (b) (4) to read as "Recommended Dosage: See Prescribing Information." Alternatively, you may choose to revise to "Dosage and Administration: See Prescribing Information" if you also seek to direct healthcare providers to the Prescribing Information for important administration instructions.

Table 3. Identified Issues and Recommendations for Exela Pharma Sciences, LLC. (entire table to be conveyed to Applicant)			
	IDENTIFIED ISSUE	RATIONALE FOR CONCERN	RECOMMENDATION
4.	We note your product is not intended for (b) (4) However, as currently presented, the principle display panel states, "(b) (4)	The word (b) (4) could be interpreted to mean that the product should be administered as a (b) (4)	Revise the statement (b) (4) to state "For Intravenous Use".

APPENDICES: METHODS & RESULTS FOR EACH MATERIAL REVIEWED

APPENDIX A. PRODUCT INFORMATION/PRESCRIBING INFORMATION

Table presents relevant product information for fentanyl citrate that Exela Pharma Sciences, LLC. submitted on August 31, 2022, and the listed drug (LD).

Table 4. Relevant Product Information for Listed Drug and Fentanyl citrate

Product Name	Listed Drug – Fentanyl citrate	Fentanyl citrate
Initial Approval Date	July 11, 1984	N/A
Active Ingredient	Fentanyl citrate	Fentanyl citrate
Indication	• 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	• Use as an opioid analgesic supplement in general anesthesia • Administration with a neuroleptic for the inductions 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
Route of Administration	Intravenous	
Dosage Form	Injection	
Strength	100 mcg/2 mL (50mcg/mL)	2,500 mcg/50 mL

<table>
<tr><td></td><td>250 mcg/5 mL (50 mcg/mL)
1,000 mcg/20 mL (50 mcg/mL)
2,500 mcg/50 mL (50 mcg/mL)</td><td>5,000 mcg/100 mL</td></tr>
<tr><td>Dose and Frequency</td><td><u>Premedication in Adults:</u>
50 to 100 mcg may be administered intravenously 30 to 60 minutes prior to surgery

<u>Adjunct to General Anesthesia:</u>
<table><tr><th>Total Dosage (expressed as fentanyl base)</th></tr><tr><td>Low Dose – 2 mcg/kg
For use in minor, but painful, surgical procedures
May also provide some pain relief in the immediate postoperative period</td></tr><tr><td>Moderate Dose – 2 mcg/kg to 20 mcg/kg
For use in more major surgical procedures, in addition to adequate analgesia, may abolish some of the stress response
Expect respiratory depression requiring artificial ventilation during anesthesia and careful observation of ventilation postoperatively is essential</td></tr><tr><td>High Dose – 20 mcg/kg to 50 mcg/kg
For open heart surgery and certain more complicated neurosurgical and orthopedic procedures where surgery is more prolonged, and the stress response to surgery would be detrimental to the well-being of the patient</td></tr></table></td><td><u>Adjunct to General Anesthesia:</u>
<table><tr><th>Total Dosage (expressed as fentanyl base)</th></tr><tr><td>Moderate Dose – 2 mcg/kg to 20 mcg/kg
For use in more major surgical procedures, in addition to adequate analgesia, may abolish some of the stress response
Expect respiratory depression requiring artificial ventilation during anesthesia and careful observation of ventilation postoperatively is essential</td></tr><tr><td>High Dose – 20 mcg/kg to 50 mg/kg
For open heart surgery and certain more complicated neurosurgical and orthopedic procedures where surgery is more prolonged, and the stress response to surgery would be detrimental to the well-being of the patient
In conjunction with nitrous oxide/oxygen has been shown to attenuate the stress response as defined by increased levels of circulating growth hormone, catecholamine, ADH and prolactin
Expect the need of postoperative ventilation and observation due to extended postoperative respiratory depression</td></tr><tr><td><u>Maintenance Dose (expressed as fentanyl base)</u></td></tr></table></td></tr>
</table>

	• In conjunction with nitrous oxide/oxygen has been shown to attenuate the stress response as defined by increased levels of circulating growth hormone, catecholamine, ADH and prolactin • Expect the need of postoperative ventilation and observation due to extended postoperative respiratory depression	Moderate Dose – 2 mcg/kg to 20 mcg/kg; 25 mcg to 100 mcg • Administer intravenously as needed when movement and/or changes in vital signs indicate surgical stress or lightening of analgesia
	Maintenance Dose (expressed as fentanyl base)	High Dose – 20 mcg/kg to 50 mcg/kg • Maintenance dosage [ranging from 25 mcg to one half the initial loading dose] as needed based on vital signs indicative of stress and lightening of analgesia Individualize the dosage especially if the anticipated remaining operative time is short
	Low Dose – 2 mcg/kg • Additional dosages infrequently needed in these minor procedures	
	Moderate Dose – 2 mcg/kg to 20 mcg/kg; 25 mcg to 100 mcg • Administer intravenously as needed when movement and/or changes in vital signs indicate surgical stress or lightening of analgesia	<u>As a General Anesthetic:</u> As a technique to attenuate the responses to surgical stress without the use of additional anesthetic agents, doses of 50 mcg/kg to 100 mcg/kg may be administered with oxygen and a muscle relaxant. In certain cases, doses up to 150 mcg/kg may be necessary to produce this anesthetic effect. It has been used for open heart surgery and certain other major surgical procedures in patients for whom protection of the myocardium from excess oxygen demand is particularly indicated, and for certain complicated neurological and orthopedic procedures
	High Dose – 20 mcg/kg to 50 mcg/kg • Maintenance dosage [ranging from 25 mcg to one half the initial loading dose] as needed based on vital signs indicative of stress and lightening of analgesia • Individualize the dosage especially if the anticipated remaining operative time is short	

	<u>Adjunct to Regional Anesthesia:</u> 50 to 100 mcg may be administered slowly intravenously, over one to two minutes, when additional analgesia is required <u>Postoperatively (recovery room):</u> 50 to 100 mcg may be administered intravenously for the control of pain, tachypnea and emergence delirium. The dose may be repeated in one to two hours as needed. <u>For Induction and Maintenance in Children 2 to 12 Years of Age:</u> Reduced dose as low as 2 to 3 mcg/kg is recommended <u>As a General Anesthetic:</u> As a technique to attenuate the responses to surgical stress without the use of additional anesthetic agents, doses of 50 mcg/kg to 100 mcg/kg may be administered with oxygen and a muscle relaxant. In certain cases, doses up to 150 mcg/kg may be necessary to produce this anesthetic effect. It has been used for open heart surgery and certain other major surgical procedures in patients for whom protection of the myocardium from excess oxygen demand is particularly indicated, and for certain complicated neurological and orthopedic procedures	
How Supplied	• 2 mL single-dose ampules packages in 10s • 2 mL single-dose vials packaged in 25s	• 50 mL single-dose vials packaged individually • 50 mL single dose vials packaged in 25s

	• 5 mL single-dose ampules packaged in 10s • 5 mL single-dose vials packaged in 25s • 20 mL single-dose ampules packaged in 5s • 20 mL single-dose vials packaged in 25s • 50 mL single-dose vials packaged individually	• 100 mL single dose vials packaged individually • 100 mL single dose vials packaged in 25s
Storage	Keep covered in carton until time of use. Store at 25°C to 25°C (68°F to 77°F), excursions permitted to 15°C to 30°C (59°F to 86°F) [see USP Controlled Room Temperature].	

APPENDIX B. PREVIOUS DMEPA REVIEWS

On April 21, 2022, we searched for previous DMEPA reviews relevant to this current review using the terms "fentanyl". Our search identified five relevant previous reviews[c,d,e,f,g] and we considered our previous recommendations to see if they are applicable for this current review.

APPENDIX F. LABELS AND LABELING

F.1 List of Labels and Labeling Reviewed

Using the principles of human factors and Failure Mode and Effects Analysis,[h] along with postmarket medication error data, we reviewed the following Fentanyl citrate labels and labeling submitted by Exela Pharma Sciences, LLC.

- Container labels received on April 8, 2022
- Carton labeling received on April 8, 2022
- Prescribing Information (Image not shown) received on April 8, 2022, available from \\CDSESUB1\evsprod\nda215870\0001\m1\us\114-labeling\listed-drug-label\annot-comparison\annot-comparison-pdf-0001.pdf;
  Received on August 31, 2022, available from \\CDSESUB1\EVSPROD\nda215870\0005\m1\us\114-labeling\draft-labeling\draft-label-text\draft-label-text-pi-track-change-0005.docx or \\CDSESUB1\EVSPROD\nda215870\0005\m1\us\114-labeling\draft-labeling\draft-label-text\draft-label-text-pi-clean-pdf-0005.pdf

[c] Birkemeier Damon. Label and Labeling Review Memo for Sublimaze (NDA 016619/S-052). Silver Spring (MD): FDA, CDER, OSE, DMEPA 1 (US); 2022 MAR 24. RCM No.: 2021-2184-1.

[d] Birkemeier Damon. Label and Labeling Review Memo for Sublimaze (NDA 016619-S-052). Silver Spring (MD): FDA, CDER, OSE, DMEPA 1 (US); 2022 JAN 11. RCM No.: 2021-2184-1.

[e] Johnson Cameron. Labeling Review Memo for Sublimaze (NDA 016619). Silver Spring (MD): FDA, CDER, OSE, DMEPA (US); 2021 JUL 7. RCM No.: 2021-1073.

[f] Farshneshani Zahra. Label and Labeling Review Memo for fentanyl citrate (NDA 019101/S-55). Silver Spring (MD): FDA, CDER, OSE, DMEPA (US); 2021 MAR 11. RCM No.: 2021-192-1.

[g] Farshneshani Zahra. Label and Labeling Review for fentanyl citrate (NDA 019101/S-55). Silver Spring (MD): FDA, CDER, OSE, DMEPA (US); 2021 MAR 8. RCM No.: 2021-192.

[h] Institute for Healthcare Improvement (IHI). Failure Modes and Effects Analysis. Boston. IHI:2004.

5 Page(s) of Draft Labeling have been Withheld in Full as b4 (CCI/TS) immediately following this page

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