

**CENTER FOR DRUG EVALUATION AND
RESEARCH**

APPLICATION NUMBER:

215870Orig1s000

PRODUCT QUALITY REVIEW(S)

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Title:	NDA Executive Summary		
Document ID:	OPQ-ALL-TEM-0013		
Effective Date:	20 Oct 2022	Revision:	00
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Template Revision: 03

NDA Executive Summary

1. Application/Product Information

NDA Number.	215870		
Applicant Name	Exela Pharma Sciences, LLC		
Drug Product Name	Fentanyl Citrate Injection		
Dosage Form.	Injection		
Proposed Strength(s)	50 mcg / mL; available as 2.5 mg/50 mL and 5 mg/100 mL		
Route of Administration	Intravenous		
Maximum Daily Dose	(b) (4) mg		
Rx/OTC Dispensed	Rx		
Proposed Indication	Use as an opioid analgesic supplement in general anesthesia.		
Drug Product Description	clear, colorless sterile, non-pyrogenic, preservative-free solution intended for intravenous use		
Co-packaged product information	N/A		
Device information:	N/A		
Storage Temperature/ Conditions	20°C–25°C (68°F– 77°F)		
Review Team	Discipline	Primary	Secondary
	<i>Drug Substance</i>	Zhixing Shan PhD	Gaetan Ladouceur PhD
	<i>Drug Product/ Labeling</i>	Mari Chelliah PhD	Valerie Amspacher PharmD
	<i>Manufacturing</i>	Helen Ngai PhD	Paul Dexter MS
	<i>Biopharmaceutics</i>	Assad Noory PhD	Ta-Chen Wu PhD



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	<i>Microbiology</i>	Helen Ngai PhD	Paul Dexter MS
	<i>Other (specify):</i>		
	<i>RBPM</i>	Anika Lalmansingh PharmD	
	<i>ATL</i>	Valerie Amspacher PharmD	
Consults			

2. Final Overall Recommendation - Approval

3. Action Letter Information

a. Expiration Dating: The proposed shelf-life of 24 months may be granted, when stored at 20°C–25°C (68°F– 77°F).

b. Additional Comments for Action

4. Basis for Recommendation:

a. Summary of Rationale for Recommendation:

CMC recommends approval for this drug product based on reviews by drug substance, drug product, process and facilities, biopharmaceutics and microbiology.

b. Is the overall recommendation in agreement with the individual discipline recommendations? Yes

Recommendation by Subdiscipline:

- Drug Substance - Adequate**
- Drug Product - Adequate**
- Quality Labeling - Adequate**
- Manufacturing - Adequate**
- Biopharmaceutics - Adequate**
- Microbiology - Adequate**



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Environmental Assessment: Categorical Exclusion - Adequate
QPA for EA(s): No

5. Life-Cycle Considerations

Established Conditions per ICH Q12: No
Comments:

Comparability Protocols (PACMP): No
Comments:

Additional Lifecycle Comments:



Valerie
Ampacher

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CHAPTER IV: LABELING

1.0 PRESCRIBING INFORMATION

Assessment of Product Quality Related Aspects of the Prescribing Information: Adequate

1.1 HIGHLIGHTS OF PRESCRIBING INFORMATION

Item	Items in Proposed Labeling (choose "Adequate", "Inadequate", or "N/A")	Assessor's Comments (If an item is Inadequate, provide more details on the issues, as appropriate)
Product Title in Highlights		
Established name(s) ¹	Adequate	
Route(s) of administration	Adequate	
Dosage Forms and Strengths Heading in Highlights		
Summary of the dosage form(s) and strength(s) in metric system	Adequate	
Assess if the tablet is scored. If product meets guidelines and criteria for a scored tablet, state "functionally scored".	N/A	
For injectable drug products for parental administration, use appropriate package type term (e.g., single-dose, multiple-dose, single-patient-use). Other package terms include pharmacy bulk package and imaging bulk package.	Adequate	
If the drug product contains an active ingredient that is a salt, clearly state whether the strength is based on the active moiety (e.g., Tablets: 10 mg of drug-x) or active ingredient (e.g., Tablets: 10 mg of drug-x hydrochloride).	Adequate	

¹ Established name = [Drug] [Route of Administration] [Dosage Form]

1.2 FULL PRESCRIBING INFORMATION

1.2.1 Section 2 (DOSAGE AND ADMINISTRATION)

Item	Items in Proposed Labeling (choose "Adequate", "Inadequate", or "N/A")	Assessor's Comments (If an item is Inadequate, provide more details on the issues, as appropriate)
DOSAGE AND ADMINISTRATION section		
Special instructions for product preparation (e.g., reconstitution and resulting concentration, dilution, compatible diluents, storage conditions needed to maintain the stability of the reconstituted or diluted product)	N/A	
Important administration instructions supported by product quality information (e.g., do not crush or chew extended-release tablets, instructions for mixing with food)	N/A	
For parenteral products: include statement: <i>"Parenteral drug products must be inspected visually for particulate matter and discoloration prior to administration, whenever solution and container permit"</i>	Adequate	
If there is a USP monograph for the drug product and it contains a labeling requirement, ensure the labeling requirement is fulfilled. Note the labeling requirement may be applicable to another section of the PI (e.g., Section 11).	N/A	

For radioactive products, include radiation dosimetry for the patient and healthcare practitioner(s) who administer the drug	N/A	
For hazardous products, include the statement <i>“DRUG X is a hazardous drug. Follow applicable special handling and disposal procedures.x”</i> with x numerical citation to <i>“OSHA Hazardous Drugs”</i>.	N/A	

1.2.2 Section 3 (DOSAGE FORMS AND STRENGTHS)

Item	Items in Proposed Labeling (choose "Adequate", "Inadequate", or "N/A")	Assessor's Comments (If an item is Inadequate, provide more details on the issues, as appropriate)
DOSAGE FORMS AND STRENGTHS section		
Available dosage form(s)	Adequate	
Strength(s) in metric system	Adequate	
If the active ingredient is a salt, apply the USP Salt Policy per FDA Guidance. Clearly state whether the strength is based on the active moiety (e.g., Tablets: 10 mg of drug-x) or active ingredient (Tablets: 10 mg of drug-x hydrochloride).	Adequate	
A description of the identifying characteristics of the dosage forms, including shape, color, coating, scoring, imprinting, and color and clarity of the solution, when applicable	Adequate	
Assess if the tablet is scored. If product meets guidelines and criteria for a scored tablet, state "functionally scored"	N/A	
For injectable drug products for parental administration, use appropriate package type term (e.g., single-dose, multiple-dose, single-patient-use). Other package type terms include pharmacy bulk package and imaging bulk package.	Adequate	

Section 11 (DESCRIPTION)

Item	Items in Proposed Labeling (choose "Adequate", "Inadequate", or "N/A")	Assessor's Comments (If an item is Inadequate, provide more details on the issues, as appropriate)
DESCRIPTION section		
Proprietary and established name(s)	Adequate	
Dosage form(s) and route(s) of administration	Adequate	
If the active ingredient is a salt, apply the USP Salt Policy and include the equivalency statement per Salt Guidance and MAPP . For example: "TRADENAME contains 100 mg of drug-x (equivalent to 123.7 mg of drug-x hydrochloride)"	Adequate	
List names of all inactive ingredients. Use USP/NF names in alphabetical order. Avoid brand names.	Adequate	
For parenteral injectable dosage forms, include the name and quantities of all inactive ingredients. For ingredients added to adjust the pH or make isotonic, include the name and statement of effect.	Adequate	
If alcohol is present, must provide the amount of alcohol in terms of percent volume of absolute alcohol	Adequate	
Sterility statement (if applicable)	Adequate	
Pharmacological/Therapeutic class	Adequate	
Chemical name, structural formula, molecular weight	Adequate	
If radioactive, statement of important nuclear characteristics.	N/A	
Other important chemical or physical properties (such as pKa or pH)	Adequate	

Section 11 (DESCRIPTION) Continued

Item	Items in Proposed Labeling (choose "Adequate", "Inadequate", or "N/A")	Assessor's Comments (If an item is Inadequate, provide more details on the issues, as appropriate)
For oral prescription drug products, include gluten statement (if applicable)	N/A	
Remove statements that may be misleading or promotional (e.g., "synthesized and developed by Drug Company X," "structurally unique molecular entity")	N/A	
If there is a USP monograph for the drug product and it contains a labeling requirement, ensure the labeling requirement is fulfilled. Note the labeling requirement may be applicable to another section of the PI (e.g., Section 2).	N/A	

1.2.4 Section 16 (HOW SUPPLIED/STORAGE AND HANDLING)

Item	Items in Proposed Labeling (choose "Adequate", "Inadequate", or "N/A")	Assessor's Comments (If an item is Inadequate, provide more details on the issues, as appropriate)
HOW SUPPLIED/STORAGE AND HANDLING section		
Available dosage form(s)	Adequate	
Strength(s) in metric system	Adequate	
Available units (e.g., bottles of 100 tablets)	Adequate	
Identification of dosage forms (e.g., shape, color, coating, scoring, imprinting, and color and clarity of the solution, when applicable); Include NDC(s)	Adequate	
Assess if the tablet is scored. If product meets guidelines and criteria for a scored tablet, state "functionally scored"	N/A	
For injectable drug products for parental administration, use appropriate package type term (e.g., single-dose, multiple-dose, single-patient-use). Other package terms include pharmacy bulk package and imaging bulk package.	Adequate	
Special handling about the supplied product (e.g., protect from light, refrigerate). If there is a statement to "Dispense in original container," provide reason why (e.g., to protect from light or moisture, to maintain stability, etc.). For hazardous drugs, state "DRUG X is a hazardous drug. Follow applicable special handling and disposal procedures. ^x " with x numerical citation to "OSHA Hazardous Drugs."	Adequate	

Section 16 (HOW SUPPLIED/STORAGE AND HANDLING) (Continued)

Item	Items in Proposed Labeling (choose "Adequate", "Inadequate", or "N/A")	Assessor's Comments (If an item is Inadequate, provide more details on the issues, as appropriate)
Storage conditions. Where applicable, use USP storage range rather than storage at a single temperature.	Adequate	
Latex: If product does not contain latex and manufacturing of product and container did not include use of natural rubber latex or synthetic derivatives of natural rubber latex, state: <i>"Not made with natural rubber latex. Avoid statements such as "latex-free."</i>	Adequate	
Include information about child-resistant packaging	N/A	

1.2.5 Other Sections of Labeling

There may be other sections of labeling that contain product-quality related information. For example, there are specific required/recommended warnings for certain inactive ingredients [e.g., aspartame, aluminum in large and small volume parenterals, sulfites, FD&C Yellow Number 5 (tartrazine), and benzyl alcohol]. Please notify the prescription drug review division if the product contains any of these inactive ingredients.

Please include your comments about other sections of labeling if they contain product quality information.

1.2.6 Manufacturing Information After Section 17 (for drug products)

Item	Items in Proposed Labeling (choose "Adequate", "Inadequate", or "N/A")	Assessor's Comments (If an item is Inadequate, provide more details on the issues, as appropriate)
Manufacturing Information After Section 17		
Name and location of business (street address, city, state, and zip code) of the manufacturer, distributor, and/or packer	Adequate	

2.0 PATIENT LABELING

Assessment of Product Quality Related Aspects of Patient Labeling (e.g., Medication Guides, Instructions for Use, Patient Information):

Item	Items in Proposed Labeling (choose "Adequate", "Inadequate", or "N/A")	Assessor's Comments about Carton Labeling (If an item is Inadequate, provide more details on the issues, as appropriate)
Established name ²	N/A	
Special preparation instructions (if applicable)	N/A	
Storage and handling information (if applicable)	N/A	
If the product contains a desiccant, ensure the desiccant has a warning (e.g., "Do not eat.") and the size and shape of the desiccant differs from the dosage form.	N/A	
Active ingredient(s) (if applicable)	N/A	
Alphabetical listing of inactive ingredients (if applicable)	N/A	
Name and location of business (street address, city, state, and zip code) of manufacturer, distributor, and/or packer	N/A	

Any deficiencies should be listed at the end in the "ITEMS FOR ADDITIONAL ASSESSMENT."

3.0 CONTAINER AND CARTON LABELING

3.1 Container Labels



² Established name = [Drug] [Route of Administration] [Dosage Form]

Item	Items in Proposed Labeling (choose “Adequate”, “Inadequate”, or “N/A”)	Assessor’s Comments about Carton Labeling (If an item is Inadequate, provide more details on the issues, as appropriate)
Established name ³ , (font size and prominence)	Adequate	
Strength(s) in metric system	Adequate	
Route(s) of administration	Adequate	
If the active ingredient is a salt, include the equivalency statement per Salt Guidance and MAPP .	Inadequate	We will ask the Applicant to include the appropriate salt equivalency statement.
Net contents (e.g., tablet count, volume of liquid)	Adequate	
“Rx only” displayed on the principal display	Adequate	
NDC	Adequate	
Lot number and expiration date	Adequate	
Storage conditions. If applicable, include a space on the carton labeling for the user to write the new beyond-use-date (BUD).	Adequate	
For injectable drug products for parental administration, use appropriate package type term (e.g., single-dose, multiple-dose, single-patient-use). Other package terms include pharmacy bulk package and imaging bulk package, and these products require a “Not for direct infusion” statement.	Adequate	
For parenteral injectable dosage forms, include the name and quantities of all active and inactive ingredients in alphabetical order. For ingredients added to adjust the pH or make isotonic, include the name and statement of effect.	Adequate	
If alcohol is present, must provide the amount of alcohol in terms of percent volume of absolute alcohol	N/A	
Linear Bar code	Adequate	

³ Established name = [Drug] [Route of Administration] [Dosage Form]

Item	Items in Proposed Labeling (choose "Adequate", "Inadequate", or "N/A")	Assessor's Comments about Carton Labeling (If an item is Inadequate, provide more details on the issues, as appropriate)
Name of manufacturer/distributor /packer	Adequate	
If there is a Medication Guide, must include a statement about dispensing a Medication Guide to each patient.	N/A	
No text on Ferrule and Cap overseal, unless a cautionary statement is required.	N/A	
If there is a USP monograph for the drug product and it contains a labeling requirement, ensure the labeling requirement is fulfilled.	N/A	
When a drug product differs from the relevant USP standard of strength, quality, or purity, as determined by the application of the tests, procedures, and acceptance criteria set forth in the relevant compendium, its difference shall be plainly stated on its label.	N/A	
And others, if space is available.	N/A	

Assessment of Carton and Container Labeling: Adequate

ITEMS FOR ADDITIONAL ASSESSMENT

Assess consistency of product-quality information in prescription drug labeling (PI, c/c labeling, and FDA-approved patient labeling). See [Carton/Container Labeling Specific Resources](#) for a presentation about inappropriate inconsistencies of product quality information between labeling. If there are inappropriate inconsistencies between the labeling (e.g., established name, strength(s), package type term, discard statement, identifying characteristics, storage, reconstitution/dilution instructions), please list these as deficiencies in this section.

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](#), 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.”

We also note 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 we express the strength of the proposed product in terms of “fentanyl citrate” or change the established name to “fentanyl”, it can potentially confuse the healthcare providers, as it will differ from the labeling convention used for the listed drug and its generic equivalents. However, we were equally concerned whether, if we label the strength in terms of “fentanyl base”, it could potentially be considered as misbranded. Therefore, we sought the subject matter expert guidance from Dr. David Claffey of OPQ and Jibril Abdus-Samad of OPPQ. Per David and Jibril, because there is a USP monograph for this product, the proposed product is required to use that name i.e. fentanyl citrate injection. Jibril further emphasized that we 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 David and Jibril stated that to minimize the risk of medication error, we 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](#)).

They also recommended the following format for the salt equivalency statement: *Each mL contains 50 mcg fentanyl base (equivalent to 79 mcg fentanyl citrate).*

Primary Labeling Assessor: Mariappan V. Chelliah

Secondary Assessor: Julia Pinto



Mariappan
Chelliah

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CHAPTER VI: BIOPHARMACEUTICS

NDA Number	NDA 215870-ORIG-1
Assessment Cycle Number	1
Drug Product Name/ Strength	Fentanyl Citrate Injection, 2.5 mg/50 mL, 5 mg/100 mL
Route of Administration	Intravenous Injection
Applicant Name	Exela Pharma Sciences, LLC
Therapeutic Classification/ OND Division	Opioid Agonist / DAAAP
LD/RS Number	NDA 019101
Proposed Indication	Fentanyl Citrate Injection is an opioid agonist indicated for 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.
Primary Reviewer	Assadollah Noory, Ph.D.
Secondary Reviewer	Ta-Chen Wu, Ph.D.

Assessment Recommendation: Adequate

Assessment Summary:

The proposed preservative-free Fentanyl Citrate Injection, for intravenous use, 50 mcg/mL (2.5 mg/50 mL and 5 mg/100 mL) in clear glass vials is for intravenous (IV) administration only by persons specifically trained in the use of intravenous anesthetics and management of the respiratory effects of potent opioids. This 505(b)(2) NDA for Fentanyl Citrate Injection (50 mcg/mL) vials relies for approval, in part, on FDA's findings of efficacy and safety for the Listed Drug (LD), Fentanyl Citrate Injection, USP 50 mcg/mL [NDA 019101 held by Hikma]. The proposed parental drug product contains the same concentration and IV route of administration as that of LD.

The Biopharmaceutics Review focused on the evaluation of the Applicant's biowaiver request and supporting justification. The Applicant requested 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 (b) (4), whereas LD

product does not contain sodium chloride being a hypotonic solution. In the 11/22/2022 response to the FDA Information Request dated 11/15/2022, 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).

Recommendation and Conclusion:

From a Biopharmaceutics perspective, NDA 215870 for Fentanyl Citrate Injection, 2.5 mg/50 mL and 5 mg/100 mL, is adequate and recommended for approval.

Document(s) Assessed	Date Received
Seq-0001: Original Submission	04/08/2022
Seq-0011: Response To Information Request	11/22/2022

Highlighted Key Issues from Last Cycle and Their Resolution: N/A

Concise Description of Outstanding Issues (list bullet points with key information and update as needed): N/A

B. 13 BIOWAIVER REQUEST

Reviewer's Assessment: *BIOWAIVER REQUEST WAS NOT GRANTED; SCIENTIFIC BRIDGE WAS ESTABLISHED PURSUANT TO 21 CFR 320.24(B)(6).*

1. Comparison of Formulation Composition

Fentanyl is soluble more than 100 mcg/mL over the pH range of 4.0 to 7.5, which is higher than the proposed strength over the proposed pH range of the finished drug product. the proposed parental drug product is in 2.5 mg/50 mL and 5 mg/100 mL vials and contains the same concentration as that available for the Listed Drug (LD), 50 mcg/mL or 0.05 mg/mL single-dose vial. Per the FDA's recommends "Each mL contains: 50 mcg fentanyl base (equivalent to 79 mcg fentanyl citrate) and 9.0 mg sodium chloride in water for injection; may contain hydrochloric acid and/or sodium hydroxide as needed to adjust pH to 4.0-7.5" for container/carton labels (Seq-0013). The formulation of the proposed to-be-marketed parenteral drug product is not qualitatively and quantitatively (Q1/Q2) the same as that of LD. However, the proposed drug product has the same active ingredient (fentanyl citrate), same dosage form (parental IV

injectable solution), same route of administration (IV) with respect to indications as the LD.

(b) (4)
Intravenous

administration is the only route of administration indicated for (b) (4) proposed indications. These changes during the review cycle also addressed the concerns when relying on scientific bridge pursuant to 21 CFR 320.24(b)(6).

Unlike the LD, the proposed drug product contains Sodium Chloride, USP (9 mg/mL) for (b) (4) Hydrochloric Acid, NF, and Sodium Hydroxide, NF, are used as pH adjusters, which is the same as LD. The table below shows formulation comparison of the proposed product and the LD. See Table 1 for comparison of formulation of the proposed product and the LD.

2. Comparative Physicochemical Properties

The Applicant reported no significant differences in physicochemical properties between the proposed parental drug product and the LD. Composition comparison between proposed product and LD is provided in Table 1.

Table 1: Formulation for Proposed Product and the LD

Composition per mL	RLD product ¹ Fentanyl Citrate Injection, USP 50 mcg/mL	Proposed product Fentanyl Citrate Injection, USP 50 mcg/mL
Fentanyl Citrate equivalent to Fentanyl	50 mcg/mL	50 mcg/mL
Sodium Chloride	Nil	9 mg/mL
Hydrochloric acid	4.0 – 7.5	4.0 – 7.5
Sodium hydroxide	4.0 – 7.5	4.0 – 7.5
Water for Injection	q.s. to 1 mL	q.s. to 1 mL
How supplied	20/50 mL vials	50/100 mL vials
Fentanyl/unit	1 mg/2.5 mg	2.5 mg/5 mg
Indications and use	As per the RLD product label	Same as the RLD product

¹ Information regarding RLD product was obtained from the DailyMed website.

<https://dailymed.nlm.nih.gov/dailymed/drugInfo.cfm?setid=ce5db1c2-feb1-4ad2-847a-d02e865bd47e>

The Applicant manufactured six stability exhibit batches for comparison with the LD. Both assessed products were shown to be clear, colorless solutions. As reported, the measured pH ranges of the proposed parental product (4.2 - 4.6) and the LD (4.5 – 5.5) are considered similar, within the proposed specification range of (b) (4). The proposed drug product contains sodium chloride (9 mg/mL) (b) (4) with osmolality being isotonic 270-310 mOsm/kg, whereas LD product doesn't contain sodium chloride, being a hypotonic solution (0 mOsm/kg). Additionally, the Proposed Product and RLD

Because of the difference in osmolality of the proposed product and the LD an Information Request dated 11/15/2022 (see *Appendix I*) was sent to the Applicant requesting documentation to support that the difference in osmolality would not significant alter the drug disposition of the proposed product, compared to that of the LD. In the 11/22/2022 response to the FDA Information Request, the Applicant provided a

scientific justification, including literature, to support that the presence of sodium chloride in the proposed drug product does not significantly affect the fluid balance, electrolyte homeostasis, and the safety or efficacy compared to LD, as summarized below.

- The Applicant believes that their proposed intravenous solutions with increased or different osmolality is likely to have significant impact on factors like urine output, fluid balance, and electrolyte homeostasis between the LD and the proposed drug product, given the low volume (105 mL) of Fentanyl that is to be administered intravenously. [REDACTED] (b) (4)

[REDACTED] *Regenmortel, NV, et.al.* reported differences in these parameters between isotonic and hypotonic maintenance fluid therapy at 25 mL/kg body weight/day with total volume of approximately 1750 mL.¹

- Fentanyl was reported to be highly bound to plasma proteins (86-89%).² Additionally, Fentanyl was reported to have high volume of distribution of 4 L/kg with extensive tissue distribution into skeletal muscle and fat with slow release back to the systemic circulation.³ Significant changes in urine output, fluid balance, and electrolyte homeostasis resulting from differences in osmolality given the injection volume are unlikely to have a significant impact on the distribution of Fentanyl.
- The proposed parental drug product is iso-osmolar which is considered a potentially safer product, unlike the LD with low osmolality (0 mOsm/L) which needs to be administered with care and has a potential for adverse effects. Administration of hypo-osmolar solutions, such as sterile water, is associated with adverse effects such as pain at the injection site and hemolysis.⁴

Assessment and Conclusion:

The Applicant's biowaiver requested citing 21 CFR §320.22(b) is not feasible because the proposed parental drug product does not meet the criteria that in vivo bioavailability or bioequivalence of the drug product may be self-evident.

This Reviewer agrees that the isotonic injectable drug product would be preferred from a safety standpoint. Of note, as a general anesthetic, higher doses or total injection volume may be administered for with oxygen and a muscle relaxant. However, significant alteration of PK drug disposition as a result of osmolality difference would not be anticipated based on the availability information. Communication with Clinical and Clinical Pharmacology review teams during the review cycle reveals no safety concerns or known effects on PK drug disposition.

This Reviewer concludes that the Applicant's responses to the FDA's Information Request has provided sufficient justification to establish a 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)

Literature information as provided:

1. Regenmortel, NV, et.al., *Effect of isotonic versus hypotonic maintenance fluid therapy on urine output, fluid balance, and electrolyte homeostasis: a crossover study in fasting adult volunteers*, *British Journal of Anaesthesia*, 118 (6): 892-900, 2017.
2. Bista, SR, *Protein binding of fentanyl and its metabolite nor-fentanyl in human plasma, albumin and a-1 acid glycoprotein*, *Xenobiotica*, 45 (3): 207-212, 2015.
3. *Fentanyl Citrate Injection Package Insert, Hikma*
(<https://dailymed.nlm.nih.gov/dailymed/drugInfo.cfm?setid=ce5db1c2-feb1-4ad2-847a-d02e865bd47e>)
4. Erstad, BL and Huckleberry, YC, *Extremely hypo-osmolar intravenous solutions to treat hypernatremia: The time has come to stop*, *Am J Health-Syst Pharm*, 79: 1122-1125, 2022.

BIOPHARMACEUTICS LIST OF DEFICIENCIES

None.

APPENDIX 1

Biopharmaceutics Information Request (dated 11/15/2022):

We acknowledge that you are requesting biowaiver based on 21 CFR §320.22(b) “bioequivalence of the drug product being self-evident”. Your proposed product has the same API, route of administration, same inactive ingredients except sodium chloride, and (b) (4). However, your proposed product differs from LD with respect to physiochemical properties, namely osmolality. Please provide documentation to support that the difference in osmolality will not influence the disposition of your proposed product to that of the listed drug (LD).

Applicant’s Responses (dated 11/22/2022):

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CHAPTER VII: MICROBIOLOGY

For more details about the items in this template, please see [Chapter VII \(Microbiology\) of the NDA IQA Guide](#)

Product Information	505(b)(2)
NDA Number	215870
Assessment Cycle Number	1
Drug Product Name/ Strength	Fentanyl Citrate Injection, USP
Route of Administration	Intravenous
Applicant Name	Excela Pharma Sciences, LLC
Therapeutic Classification/ OND Division	CDER/OND/ON/DAAP
Manufacturing Site*	(b) (4)
Method of Sterilization	(b) (4)

Assessment Recommendation: Adequate

Assessment Summary: The submission is **recommended** for approval on the basis of sterility assurance.

List Submissions Being Assessed :

Document(s) Assessed	Date Received
Orig -1 / Multiple categories (SD 1)	4/8/2022
Orig – 1 / Quality, response to IR (SD 6)	9/19/2022

Highlight Key Issues from Last Cycle and Their Resolution: n/a

Remarks:

1. The internal goal dates are: OPQ mid cycle meeting: 8/18/2022, OND mid cycle meeting: 9/1/2022, OPQ wrap up meeting 11/3/2022, PDUFA goal date: 2/8/2023.
2. The application references the Reference Listed Drug (RLD), Fentanyl citrate injection, USP 50 mcg/mL, held by Hikma for NDA # 019101. NDA 019101 is

Fentanyl Citrate Injection, equivalent to 50 mcg (0.05 mg) fentanyl base per mL, preservative free solution, available in 2 mL, 5 mL, 20 mL single use glass ampules and 1 mL, 2 mL, 5 mL, 20 mL, 50 mL single use glass vials.

3. The NDA 215870 applicant proposes to manufacture a 50 mL and 100 mL fill presentation.

Concise Description of Outstanding Issues: none

Supporting Documents:

Type III DMF (b) (4) from (b) (4) is referenced for the (b) (4) LOA dated 3/18/2021. Relevant endotoxin reduction validation runs were reviewed in D (b) (4) M41R01.docx (adequate) dated 3/8/2022.

DMA review A (b) (4) MR01 (1).pdf (adequate) dated 12/18/2018 is referenced for the same manufacturing building (b) (4) similar (b) (4)

The subject drug product is (b) (4) Sterilization processes other than the (b) (4) and (b) (4) are not reviewed.

S Drug substance

S.2. Manufacture

S.2.1 Manufacturers – (b) (4)

S.4 Control of drug substance

S.4.1 Specification – Bacterial endotoxin: NMT (b) (4) Bioburden not provided.

Assessment: **Adequate**. Non-sterile drug substance.

P.1 Description of the composition of the drug product

- Description of drug product – Fentanyl citrate injection, USP 50 mcg/mL is supplied as a clear, colorless, sterile, non-pyrogenic, preservative free solution intended for intravenous use. The proposed drug product is available in **two presentations; 2.5 mg/ 50 mL fill volume and 5 mg/ 100 mL fill volume.**
- Drug product composition –

Ingredient	Content per mL	Function
Fentanyl Citrate (Fentanyl base), USP	(b) (4) (0.05 base) mg	Active
Sodium chloride, USP	9.0 mg	Excipient
Hydrochloric acid, NF	pH to 4.0 to 7.5	pH adjust
Sodium hydroxide, NF	pH to 4.0 to 7.5	pH adjust
WFI, USP	q.s. to 1.0 mL	(b) (4)

Maximum registration batch size: 50 mL fill volume, (b) (4) 100 mL fill volume (b) (4)

Maximum commercial batch size: 50 mL fill volume, (b) (4) 100 mL fill volume, (b) (4)

- Description of container closure systems –

Configuration	Component	Description	Manufacturer
2.5 mg / 50 mL fill	Vial	50 ml molded clear glass (b) (4)	(b) (4)
	Stopper	(b) (4) Gray, (b) (4)	
	seal	Aluminum seal (matte top blue)	
5 mg / 100 mL fill	Vial	100 ml molded clear glass (b) (4)	
	Stopper	(b) (4) Gray, (b) (4)	
	Seal	Aluminum seal (matte top blue)	

Assessment: Adequate

P.2 Pharmaceutical Development

(b) (4)



Valerie
Amspacher

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