CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

217812Orig1s000

PRODUCT QUALITY REVIEW(S)

Table of Contents

NDA Executive Summary

1. Application/Product Information

NDA Number.	217812		
Applicant Name	Hikma Pharmaceuticals USA, Inc.		
Drug Product Name	Hydromorphone Hydrochloride Injection		
Dosage Form.	Injection		
Proposed Strength(s)	40 mg/ 20 mL (2 mg/mL)		
Route of Administration	Intravenous		
Maximum Daily Dose	24 mg		
Rx/OTC Dispensed	Rx		
Proposed Indication	for the management of pain severe enough to require an opioid analgesic and for which alternate treatments are inadequate		
Drug Product Description	Hydromorphone Hydrochloride Injection, 40 mg/20 mL (2 mg/mL) multiple-dose vial is a sterile aqueous solution in a multi-dose vial containing 40 mg of Hydromorphone Hydrochloride in 20 mL vial for subcutaneous, intramuscular and slow intravenous administration supplied as 1 vial per carton. The container closure is a glass vial with a rubber stopper		
Co-packaged product information	N/A		
Device information:	N/A		
Storage Temperature/ Conditions	20-25 ^{o}C		
Review Team	**Discipline**	**Primary**	**Secondary**
	Drug Substance	Katie Duncan	Gaetan Ladouceur
	Drug Product/ Labeling	Mari Chelliah	Valerie Amspacher

	Manufacturing	Khalid Khan	Cassie Abellard
	Biopharmaceutics	Bryan Ericksen	Hansong Chen
	Microbiology	Gouri Chattopadhyay	Paul Dexter
	Other (specify):	N/A	N/A
	RBPM	Anika Lalmansingh/Teicher Agosto	
	ATL	Valerie Amspacher	
Consults	N/A		

2. Final Overall Recommendation - Approval

3. Action Letter Information

a. Expiration Dating: The proposed expiry of 24 months is acceptable when stored at controlled room temperature (20°C to 25°C).

b. Additional Comments for Action

4. Basis for Recommendation:

a. Summary of Rationale for Recommendation:

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

The proposed expiry of 24 months is acceptable when stored at controlled room temperature (20°C to 25°C).

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**

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: N/A

Submission(s) Assessed	Document Date	Discipline(s) Affected
Supporting document 1; eCTD 0001	16 Feb 2023	All; original submission
Supporting document 6; eCTD 0006	14 Jul 2023	Process
Supporting document 7; eCTD 0007	26 Jul 2023	Microbiology
Supporting document 8; eCTD 0008	1 Aug 2023	Drug product
Supporting document 10; eCTD 0010	10 Oct 2023	Process
Supporting document 12; eCTD 0012	30 Oct 2023	Drug product

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CHAPTER IV: LABELING

For more details about the items in this template, please see Chapter IV (Labeling) of the NDA IQA Guide

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	Adequate	

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

ingredient (e.g., Tablets: 10 mg of drug-x hydrochloride).		

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)	Adequate	
Important administration instructions supported by product quality information (e.g., do not crush or chew extended-release tablets, instructions for mixing with food)	Adequate	
For parenteral products: include statement: *"Parenteral drug products must be inspected visually for particulate matter and discoloration prior to administration, whenever solution and container permit"*	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	N/A	

section of the PI (e.g., Section 11).		
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 *"DRUG X is a hazardous drug. Follow applicable special handling and disposal procedures.[x]"* with x numerical citation to "OSHA Hazardous Drugs".	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	N/A	
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: *"Not made with natural rubber latex. Avoid statements such as "latex-free."*	N/A	
Include information about child-resistant packaging	N/A	

1.2.5 Other Sections of Labeling

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):

Patient labeling is not applicable for this product.

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]	Adequate	
Special preparation instructions (if applicable)	Choose an item.	
Storage and handling information (if applicable)	Choose an item.	
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.	Choose an item.	
Active ingredient(s) (if applicable)	Choose an item.	
Alphabetical listing of inactive ingredients (if applicable)	Choose an item.	
Name and location of business (street address, city, state, and zip code) of manufacturer, distributor, and/or packer	Choose an item.	

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

3.0 CONTAINER AND CARTON LABELING

(b) (4)

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[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	Will send an IR asking to include the 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.	Inadequate	Will send an IR asking the list the ingredients alphabetically.
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*

We will send IR comments asking the Applicant to edit the carton label to address the requirements noted above.

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

Primary Labeling Assessor: Mariappan V. Chelliah

Secondary Assessor: Julia Pinto

Mariappan Chelliah

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Julia Pinto

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CHAPTER VI: BIOPHARMACEUTICS

NDA Number	NDA-217812-ORIG-1
Assessment Cycle Number	1
Drug Product Name/ Strength	Hydromorphone Hydrochloride Injection, (b) (4) / 40 mg/20 mL (2 mg/mL)
Route of Administration	Subcutaneous, intramuscular, and slow intravenous injection
Applicant Name	Hikma Pharmaceuticals
Therapeutic Classification/ OND Division	CDER/OND/ON/DAAP
LD/RS Number	NDA 019034
Proposed Indication	As an opioid agonist indicated for the management of pain severe enough to require an opioid analgesic and for which alternate treatments are inadequate
Primary Reviewer	Bryan Ericksen, Ph.D.
Secondary Reviewer	Hansong Chen, PharmD, Ph.D.

Assessment Recommendation: **Adequate**

Assessment Summary:

The Applicant proposes Hydromorphone Hydrochloride Injection, (b) (4) / 40 mg/20 mL (2 mg/mL). With the current submission, the Applicant seeks approval through 505(b)(2) regulatory pathway relying on the Agency's findings of efficacy and safety of the Listed Drug (LD), Dilaudid. The indication for the proposed drug is for the management of pain severe enough to require an opioid analgesic and for which alternate treatments are inadequate.

The Applicant submitted a biowaiver request. The Applicant has provided an adequate scientific justification to establish a scientific bridge between the proposed drug product and LD, permitting reliance on the Agency's findings of efficacy and safety of the LD, in accordance with 320.24(b)(6) given the following consideration:

1) The proposed product is a clear liquid solution for intravenous, intramuscular, and subcutaneous administration and contains the same active pharmaceutical ingredient in the same concentration and dosage form as Dilaudid 2 mg/mL Injection.
2) The proposed drug product contains different excipients from those presented in the LD. The differences in formulations are not expected to affect the disposition of hydromorphone.
3) The proposed drug product and LD have comparable osmolarities and pHs. Comparative physicochemical data are provided including pH, osmolality, viscosity, and density. Although a 2-fold decrease in osmolality was observed in the proposed product compared to Dilaudid, this difference is insignificant considering plasma osmolality is

approximately 300 mOsm/L. The Applicant noted that their other drug products with lower osmolality have been approved.

4) There is no drug-drug interaction between EDTA, parabens, and hydromorphone.

Recommendation and conclusion:
From a Biopharmaceutics perspective, NDA-217812-ORIG-1 for Hydromorphone Hydrochloride Injection, (b) (4), 40 mg/20 mL (2 mg/mL) is **adequate.**

Document(s) Assessed	Date Received
Sequence 0001/Original submission	02/16/2023

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

In accordance with 21 CFR 320.24(b)(6), the Applicant provided a side-by-side comparison of formulation composition between the proposed product and the listed drug, Dilaudid, as shown in Table 1.

Table 1: Side-by-side comparison of the proposed formulation compared to Dilaudid

Ingredients	Function	Concentration in Proposed Hikma Product (mg/mL)	Concentration in Dilaudid® (mg/mL)
Hydromorphone Hydrochloride, USP	Active Ingredient	2.0	2.0
Sodium Citrate, USP	Buffer	n/a	2.0
Citric Acid, USP	Buffer	n/a	2.0
Edetate Disodium Dihydrate, USP	(b) (4)	0.5	n/a
Methylparaben, NF		1.8	n/a
Propylparaben, NF		0.2	n/a
Sodium Hydroxide, NF	pH adjustment	pH adjustment (3.5 – 5.5)	n/a
Hydrochloric Acid, NF	pH adjustment	pH adjustment (3.5 – 5.5)	n/a
Water for Injection, USP	Aqueous Vehicle	q.s. ad 1 mL	q.s. ad 1 mL

The proposed product differs from Dilaudid in the use of (b) (4) pH adjustors, buffer, and (b) (4). The Applicant noted that there is no literature evidence that these differences in excipients will result in changes in the distribution, metabolism, or excretion of hydromorphone. In addition, bioequivalence has been established between the (b) (4) mg Dilaudid

oral suspension containing parabens and 8 mg Dilaudid tablets without parabens. In that case, parabens did not influence the rate or extent of absorption of hydromorphone or the elimination of hydromorphone.

Comparative physicochemical data are provided including pH, osmolality, viscosity, and density, as shown in Table 2.

Table 2: Comparative physicochemical properties between the proposed product and Dilaudid

Properties	Proposed Hikma Specification	Hikma MDV Submission Batches (Lots P110123, P110125, P110127)	Dilaudid Lot #6024409 Expiration Date 07/2023	Dilaudid Lot #6021709 Expiration Date 05/2024	Dilaudid Lot #6021709 Expiration Date 05/2024
pH	(b) (4) Shelf life: 3.5 to 5.5	(b) (4)	4.20	4.21	4.23
Osmolality	(b) (4)	23 mOsm/kg	50 mOsm/kg	50 mOsm/kg	53 mOsm/kg
Viscosity	Information Only	0.95 Cp at 25°C	1.000 Cp at 25°C	1.000 Cp at 25°C	1.000 Cp at 25°C
Density	Information Only	0.99809 g/mL at 25.0°C	0.99988 g/mL at 25.0°C	0.99995 g/mL at 25.0°C	1.00025 g/mL at 25.0°C

Reviewer's comment:
This Reviewer agrees that there is no evidence that the differences in excipients could alter hydromorphone pharmacokinetics because they are (b) (4)*, pH adjustors, or* (b) (4) .
The proposed drug and LD have similar pH. Although a 2-fold decrease in osmolality was observed in the proposed product compared to Dilaudid, both of them are hypotonic. It is expected that it will not bring additional safety issue compared to the LD. The Applicant noted that their other drug products with lower osmolality have been approved and are being safely used in patients. Therefore, the supporting data are sufficient to support to establish a scientific bridge between the LD and proposed drug.

BIOPHARMACEUTICS LIST OF DEFICIENCIES

None.

Hansong Chen

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Bryan Ericksen

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CHAPTER VII: MICROBIOLOGY

IQA NDA Assessment Guide Reference

Product Information	The drug product is used as an opioid agonist indicated for the management of pain severe enough to require an opioid analgesic and for which alternate treatments are inadequate.
NDA Number	**217812**
Assessment Cycle Number	01
Drug Product Name/ Strength	Hydromorphone Hydrochloride Injection, (b) (4) 40 mg/20 mL (2 mg/mL)
Route of Administration	Intramuscular, Subcutaneous, Slow Intravenous Injection
Applicant Name	Hikma Pharmaceuticals USA, Inc.
Therapeutic Classification/ OND Division	Type 5/New Formulation or New Manufacturer CDER/OND/ON/DAAP
Manufacturing Site	Hikma Pharmaceuticals USA Inc. (b) (4)
Method of Sterilization	(b) (4)

Assessment Recommendation: Adequate

List Submissions being assessed (table):

Document(s) Assessed	Date Received
• Original NDA Submission (SEQ 0001) • Response to Information Request Microbiology)	• 02/16/2023 • 07/26/2023

Assessment Summary: The finished drug product is a sterile solution supplied in a multi-dose 20 mL vial as 1 vial/carton. The drug product is (b) (4) (b) (4) (b) (4) **RS stoppers are purchased from** (b) (4) (b) (4) (b) (4) **The response to the Microbiology IRs are reviewed below.**

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

Remarks: None

Concise Description of Outstanding Issues (List bullet points with key information and update as needed): None

Supporting Documents:

- Environmental monitoring for the same facility was reviewed and found adequate in (b) (4) dated 5/26/2021.
- (b) (4) was reviewed and found adequate in (b) (4) dated 8/6/2020, (b) (4) dated 4/2/2020 and (b) (4) dated 2/17/2021. (b) (4) studies were reviewed and found adequate in (b) (4) dated 4/2/2020.
- The equivalency report 50039 for (b) (4) were reviewed and found adequate in (b) (4) dated 4/28/2009.
- (b) (4) was previously reviewed and found adequate in (b) (4) dated 8/6/2020 and (b) (4) dated 2/17/2021.
- DMF (b) (4) was reviewed and found adequate in (b) (4) dated 5/31/2016 and (b) (4), dated 7/11/2016, (b) (4), dated 3/29/2019, (b) (4) dated 1/19/2021, (b) (4) dated 5/4/2022, (b) (4) dated 6/27/2022, in (b) (4) dated 4/6/2023, (b) (4) dated 5/1/2023, in (b) (4) dated 6/27/2023.

S DRUG SUBSTANCE

No review was conducted on the drug substance as the drug substance is non-sterile.

P.1 DESCRIPTION OF THE COMPOSITION OF THE DRUG PRODUCT
(3.2.P.1/*description-and-composition.pdf*)

- **Description of drug product-** The finished drug product is a sterile aqueous solution, supplied in a multi-dose vial, as 1 vial per carton, containing 40 mg of Hydromorphone Hydrochloride in 20 mL for subcutaneous, intramuscular, and slow intravenous administration. The drug product is indicated for the management of pain severe enough to require an opioid analgesic and for which alternative treatments are inadequate.
- **Drug product composition-**

(b) (4)

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

(b) (4)

- **Description of container closure system-**

Component	Hikma Part #	Hikma Lot#	Hikma Specification #	Description	DMF #
Glass Vial	(b) (4)	2005239	(b) (4)	20 mL Vial, (b) (4) (b) (4	(b) (4)
Stopper		2005161, 2005162			
Seal		1904072, 1912032			N/A

Reviewer's Assessment: Adequate

The applicant has provided an adequate description of the drug product composition and the container closure system.

P.2 PHARMACEUTICAL DEVELOPMENT

(b) (4)

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Gouri Chattopadhyay

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Elizabeth Bearr

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Valerie Amspacher

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VALERIE R AMSPACHER
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