CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

213330Orig1s000

PRODUCT QUALITY REVIEW(S)

MANUFACTURING INTEGRATED ASSESSMENT

Application ID	NDA 213330
Drug Product Name	Labetalol Hydrochloride in Dextrose Injection and Labetalol Hydrochloride in Sodium Chloride Injection
Strengths	1 mg/mL
Dosage Form	Sterile Injectable
Administration Route	Infusion
Indication	Labetalol HCl Injection, USP is indicated for control of blood pressure in severe hypertension.
Applicant Name	Hikma Pharmaceuticals International Limited

I. Manufacturing Summary

Facility Assessment Recommendation: Adequate

Process Assessment Recommendation: Adequate

Assessment Summary:

Labetalol Hydrochloride in Dextrose and in Sodium Chloride Injection are (b) (4) (b) (4) sterilized. The drug products are preservative-free and the packaging is (b) (4) bags which are controlled effectively with (b) (4) (b) (4) checks.

The (b) (4) operations are low risk because the facility has experience and appropriate in-process controls are in place. The drug substance facility was low risk due to an acceptable inspectional history.

List Submissions being assessed (Table):

Document Description (SD #)	Date Received
0001 (1) Original Submission	01/10/2020
0003 (3) IR Response	04/07/2020
0006 (6) IR Response	5/22/2020
0008 (8) IR Response	09/29/2020

Highlight Key Issues from Last Cycle and Their Resolution: None

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

1. Post-Approval Commitments and Lifecycle Management Considerations

Postmarketing commitments (PMC)?	No
Post-approval inspection?	No
Lifecycle considerations	No

2. Facilities Table

Facility name and address	FEI	Responsibilities and profile code(s)	Status
Hikma Farmaceutica (Portugal), S.A. Estrada do Rio da Mo 8/8A/8B, Terrugem , SNT (Sintra), Portugal, 2705-906	3002807173	Manufacturing Steps: Finished Product Manufacture/Labeling/Packaging/Testing: Drug Substance Release Testing (except as indicated by contract laboratory), Excipient Release Testing, Drug Product Release Testing, and Drug Product Stability Testing. Storage of Accelerated Stability Samples. || 356h Status: Active LVP PRF	Approve - Based on Previous History
(b) (4)			Approve - Based on Previous History
			Approve - Based on Previous History
			No Evaluation Necessary

II. Drug Product Manufacturing

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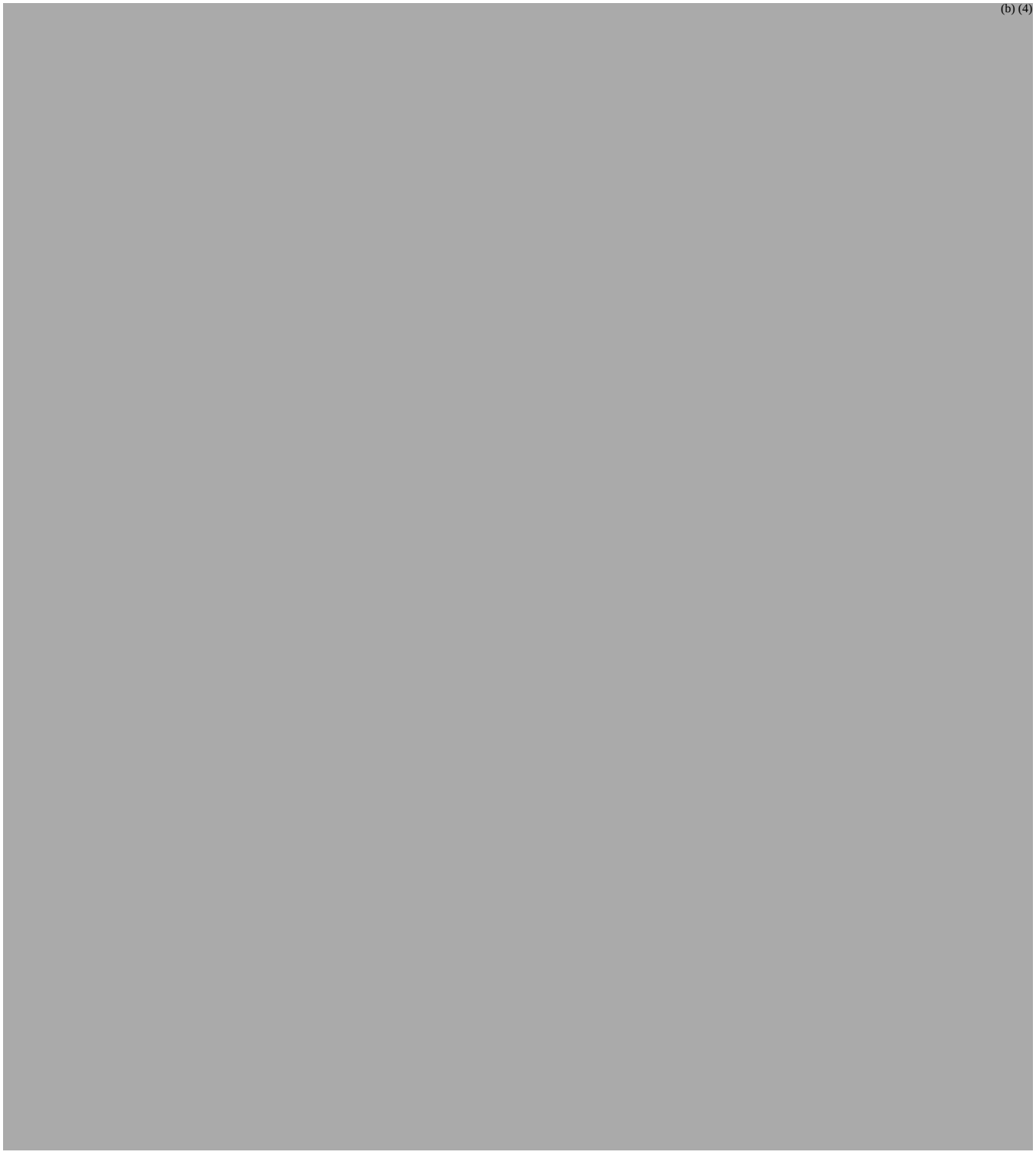
(b) (4)



V. List of Outstanding Information Request/Deficiencies:

Outstanding Deficiencies Collation Table

VI. Signature Block

Round#	Primary Name	Secondary & Other Names	Date of Completion	Assessment Outcome	Facility OMIR
1	Allison Aldridge	Kumar Janoria	9/30/2020	Adequate	Approve
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Choose an item.			Click to enter a date.	Choose an item.	Choose an item.

Allison Aldridge

Digitally signed by Allison Aldridge
Date: 9/30/2020 03:33:18PM
GUID: 508da7170002981da764ca33dfb39a19

Kumar Janoria

Digitally signed by Kumar Janoria
Date: 9/30/2020 03:14:04PM
GUID: 53160a1a0000844db16f58dfff6949ed

NDA 213330: Labetalol Hydrochloride in Sodium Chloride Injection and Labetalol Hydrochloride in Dextrose Injection

Integrated Quality Review

Recommendation: Approval

Drug Name/Dosage Form	Labetalol Hydrochloride in Sodium Chloride Injection and Labetalol Hydrochloride in Dextrose Injection
Strength	Labetalol HCl in Sodium Chloride Injection in a single-dose bag: • 100 mg/100 mL (1 mg/mL) • 200 mg/200 mL (1 mg/mL) • 300 mg/300 mL (1 mg/mL) Labetalol HCl in Dextrose Injection in a single-dose bag: • 200 mg/200 mL (1 mg/mL)
Dosage Form; Route of Administration	Parenteral (injection, for intravenous use)
Rx/OTC Dispensed	Rx
Applicant	Hikma Pharmaceuticals International Limited (HPIL)
Submissions (s) Reviewed	p-IND 137361; DMF (b) (4) (b) (4); NDA (b) (4)

Quality Review Team

DISCIPLINE	REVIEWER	BRANCH/DIVISION
Drug Substance	Daniel Jansen	OPQ/ONDP/DNDAPI/NDB3
Drug Product,	Rao Kambhampati	OPQ/ONDP/DNDPIII/NDPB5
Microbiology	Xia Xu	OPQ/OPMA/DMAI/MAB1
Process and Facility	Allison Aldridge	OPQ/OPMA/DPMAIII/PMB7
Biopharmaceutics	Min Sung Suh	OPQ/ONDP/DB/BB3
Application Technical Lead	Mohan Sapru	OPQ/ONDP/DNDPIII/NDPB5

RBPM: Grafton Adams (OPQ/OPRO/DRBPMI/RBPMB2)

Executive Summary

I. Recommendations

A. Recommendation and Conclusion on Approvability

From the chemistry, manufacturing, and controls (CMC)/quality perspective, NDA 213330 (Labetalol Hydrochloride in Sodium Chloride Injection and Labetalol Hydrochloride in Dextrose Injection) is recommended for approval. A shelf-life of 24 months is approved for the drug products when stored at 20°C to 25°C (68°F to 77°F) in the proposed commercial container closure system. Excursions are permitted between 15°C to 30° C (59°F to 86° F).

B. Recommendation on Post-Marketing Commitments (PMCs), Agreements, and/or Risk Management Steps, if Applicable

Not applicable.

II. Quality Assessment Summary

A. Background: The Applicant, Hikma Pharmaceuticals International Limited, submitted 505(b)(2) NDA for ready-to-use (RTU) Labetalol Hydrochloride in Sodium Chloride Injection, 100 mg/100 mL, 200 mg/200 mL and 300 mg/300 mL (1 mg/mL; preservative free) and Labetalol Hydrochloride in Dextrose Injection, 200 mg/200 mL (1 mg/mL; preservative-free), USP. The proposed drug products intended solely for slow continuous infusion at a rate of 2 mL/minute (2 mg/minute) are indicated for control of blood pressure in severe hypertension. The Applicant has listed TRANDATE® (labetalol hydrochloride) Injection as the as the Listed Drug (LD), which is a discontinued product; not discontinued or withdrawn for safety or efficacy reasons.

B. Drug Substance (Labetalol hydrochloride): The drug substance (Labetalol hydrochloride), a racemate, is an adrenergic receptor blocking agent that has both selective alpha1-adrenergic and nonselective beta-adrenergic receptor blocking actions. The applicant has cross-referenced CMC information about the drug substance to DMF (b) (4), which has been previously reviewed (Review #6, April 2020) and found adequate. The information provided in the NDA, about general properties of the drug substance, specification, and certificates of analysis for drug substance batches used to produce the drug product, is acceptable. The drug substance manufacturing details and control strategies are adequate. The identity, quality, and purity of each batch of the drug substance are assessed and confirmed as per the specification, which involves testing for the critical quality attributes (CQAs) for the drug substance. A retest period of (b) (4) months at (b) (4) is supported by stability data.

C. Drug Product (Labetalol Hydrochloride in Sodium Chloride Injection, USP and Labetalol Hydrochloride in Dextrose Injection, USP).

C.1. Product Design, Specification: Labetalol HCl in Sodium Chloride Injection and Labetalol HCl in Dextrose Injection are two preservative-free, ready-to-use aqueous, sterile, isotonic formulations of labetalol for intravenous injection. All the excipients proposed are compendial

grade and their proposed levels are lower than those present in the FDA-approved IV Injection formulations. Adequate formulation development studies have been conducted. All the product critical quality attributes such as identification, pH, volume in container, particulate matter, assay of dextrose or sodium chloride, levels of degradants and (b) (4) (b) (4) osmolality, leak testing, bacterial endotoxins, and sterility, and elemental impurities (per USP < 232>, ICH Q3D Option 2) are controlled by product release specification. The proposed specifications comply with the USP monograph for Labetalol Injection. The proposed impurity limits have been adequately justified. The method validation details provided for all non-compendial methods are adequate. From product quality perspective, the proposed control strategies are adequate to ensure consistent product quality with regard to identity, strength, purity, sterility, and stability.

C.2. Manufacturing: Labetalol Hydrochloride in Dextrose and in Sodium Chloride Injection are (b) (4). The drug products are preservative-free, and the packaging is (b) (4) bags, which are controlled effectively with (b) (4) (b) (4) checks. Based on the control strategy, including in-process controls, and environmental controls, the manufacturing process is adequately controlled.

C.3. Microbiological Aspects: The bulk drug product solution is (b) (4) (b) (4) filled into single port IV bags, closed with Twist-Off closures, and (b) (4) sterilized. The (b) (4) sterilization process for the finished drug products, and the proposed maximum hold times was adequately validated. Specifically, the production (b) (4) (b) (4) specification, (b) (4), methods and controls to monitor production cycles, requalification, reprocessing policy, and bulk/raw material bioburden limit are adequately described. Microbiological quality acceptance criteria for drug substance/excipients comply with those specified by USP <1111> for non-sterile substances for pharmaceutical use. Given that the proposed formulations are single-dose and do not contain a preservative, antimicrobial effectiveness testing is not required. The container closure integrity was been adequately validated. The product release specification includes testing for bacterial endotoxins and sterility per USP <85> and USP <71>, respectively. In conclusion, the microbiology information provided is adequate.

C.4. Biopharmaceutics Aspects: The Applicant provided comparative *in vitro* study results for demonstrating bridging with the LD, Sebela Ireland Ltd.'s Trandate®, 5 mg/mL vial dosage, NDA 019425, and the Reference Standard (RS), Hospira's Labetalol Hydrochloride Injection, 5 mg/mL vial dosage, ANDA 075239. The proposed single-dose, ready-to-administer drug products are equivalent to the post-diluted RLD or RS solution for intravenous infusion administration at a final concentration of 1 mg/mL of Labetalol Hydrochloride, except that the parabens (methyl- and propyl-) preservatives are present in the RLD or RS, but not in the proposed formulations. The intravenous infusion administration rate and dose remain the same between the RLD, RS and the proposed products. The Applicant has demonstrated that removing preservatives from the proposed formulations has no impact on CQAs such as the pH, assay, and degradation products. The route of administration of the proposed products is identical to that of the LD and RS, post-dilution; specifically, the slow infusion requirement listed in the approved drug products' package inserts. Given that intravenous solutions are 100% bioavailable, the active ingredient in Hikma's proposed products is 100% bioavailable in the same manner as the slow infusion preparations, as described in the LD or RS package inserts. To support formulation bridging, the Applicant has provided information regarding the comparative composition and

physicochemical (pH, osmolality) properties to demonstrate equivalency between the diluted LD/RS and proposed ready-to-use drug products. Additionally, the Applicant has included references to support that the removal of parabens from the formulation is unlikely to impact the PK properties of labetalol in the proposed drug products. Thus, a bridging information/data to demonstrate equivalence of the proposed product to the diluted LD/RS is acceptable, and formulation bridging under CFR 320.23 (b)(6) is deemed established.

C.5. Container Closure System: The proposed IV bag container closure system is commonly used in the packaging of ready-to-use formulations. The IV bag also contains an additional outer overwrap, (b) (4) . The extractable and leachable data are adequate. The product stability data indicate suitability of the proposed container closure system for the intended use. Evidence of adequate functionality of the container closure system is also provided by sterility testing during the stability program.

C.6. Expiration Date & Storage Conditions: The Applicant has provided justification for (b) (4) limit for (b) (4) impurity proposed in the drug product shelf-life specification: (b) (4) (b) (4) (b) (4) Therefore, there is no safety concern from the structural alert standpoint for this impurity. Per USP monograph for labetalol hydrochloride drug substance, the recommended limit for any individual impurity is 0.5%, and limit for total impurities is 1.0%; no USP specific limits have been recommended for the labetalol hydrochloride injection formulation. Per the BP monograph, the acceptance limit of 2%, for (b) (4) impurity in labetalol injection, is acceptable. According to the CDER MAPP 5310.7 Rev.1 (Acceptability of Standards from Alternative Compendia), BP/EP/JP monographs recommended acceptance limits for impurities can be used for evaluating impurity acceptance limits for a drug product. Viewed in the context of this CDER MAPP 5310.7 Rev.1, the Applicant's proposed (b) (4) limit for (b) (4) impurity per the shelf-life specification is acceptable. The non-clinical reviewer has also been consulted regarding this issue. Based on the real-time 18 months of long-term, 12-month intermediate and 6-month accelerated stability data, an expiration dating period of 24 months is acceptable when the proposed drug products are stored, protected from light, at controlled room temperature conditions of 20°C to 25°C (68°F to 77°F) in the proposed commercial container closure system. Excursions are permitted between 15°C to 30° C (59°F to 86° F).

C.7. Environmental Assessment: The Applicant's claimed categorical exclusion in accordance with 21 CFR§ 21 CFR 25.15(d) is acceptable.

III. Assessment of Manufacturing Facilities

Regarding the listed manufacturing and testing facilities, there are no outstanding cGMP issues and are deemed acceptable. Specifically, the drug product and drug substance facilities have been approved based on inspection history and manufacturing experience of the concerned facilities.

IV. Product Quality Labeling Recommendations

The USP salt policy is not applicable because the drug product monograph includes the name of the salt, and the strength of the drug product is expressed in terms of the salt form. All labeling recommendations from quality perspective are reflected in the most recent version of the product labeling.

V. Life Cycle Knowledge Information: Final Product Risk Assessment

NDA 213330: Labetalol Hydrochloride in Sodium Chloride Injection and Labetalol Hydrochloride in Dextrose Injection

From Initial Risk Identification			Review Assessment		
Attribute/ CQA	**Factors Affecting CQA**	**Initial Risk Ranking**	**Risk Mitigation**	**Final Risk Evaluation**	**Comments**
Sterility	Formulation Container Closure Process Parameters Scale/Equipment/ Site	**H (High)**	Drug product release specification includes sterility (USP <71>) testing. Container closure integrity studies indicate that the container closure system remains integral and therefore can maintain the sterility of the product. Microbiology information is adequate.	Acceptable	Given that the product sterility is the high-risk attribute, any proposed changes in manufacturing process or microbiological testing-related product specification may need to be carefully evaluated.
Endotoxin Pyrogen	Formulation Container Closure Process Parameters Scale/equipment/ Site	**M (Moderate)**	Tested on release per (USP <85>.	Acceptable	Any proposed changes concerning acceptance limits for endotoxin levels will need to be evaluated based on the maximum total daily dose.
Assay (API), Stability	Formulation Container Closure Raw Materials Process Parameters Scale/Equipment/ Site	L (Low)	Stability of the API and the drug product, and suitability of commercial container closure system have been well demonstrated. Manufacturing process is reasonably well-controlled.	Acceptable	
Uniformity of Dose – Fill/ deliverable Volume	Formulation Container Closure Process Parameters Scale/equipment/ site	L (Low))	Volume in container tested on release per USP <697>.	Acceptable	

Final Risk Assessment (continued)

From Initial Risk Identification			Review Assessment		
Attribute/ CQA	**Factors Affecting CQA**	**Initial Risk Ranking**	**Risk Mitigation**	**Final Risk Evaluation**	**Comments**
Osmolality	Formulation Raw materials Process parameters Scale/equipment/ site	L (Low)	Osmolality is monitored on release per USP <785>.	Acceptable	
pH (High)	Formulation Container Closure Raw materials Process parameters Scale/equipment/ site	L (Low)	The pH is monitored per USP <791> on release.	Acceptable	
Particulate Matter	Formulation Container Closure Process Parameters Scale/equipment/ site	**M (Moderate)**	Particulate matter is monitored on release per USP <788>.	Acceptable	
Leachable Extracts	Formulation Container Closure Raw materials Process parameters Scale/equipment/ site	L (Low)	The extractables and leachables studies indicate no product quality risk from container closure system used to package the drug product.	Acceptable	
Appearance	Formulation Raw materials Process Parameters Scale/equipment/ site	L (Low)	The product appearance is routinely monitored on release.	Acceptable	

OVERALL ASSESSMENT AND SIGNATURES: EXECUTIVE SUMMARY

Application Technical Lead (ATL) Assessment and Signature:

From the chemistry, manufacturing, and controls (CMC)/quality perspective, NDA 213330 (Labetalol Hydrochloride in Sodium Chloride Injection and Labetalol Hydrochloride in Dextrose Injection) is recommended for approval. A shelf-life of 24 months is approved for the proposed drug products when stored at 20°C to 25°C (68°F to 77°F) in the proposed commercial container closure system. Excursions are permitted between 15°C to 30° C (59°F to 86° F).

Mohan Sapru, M.S., Ph.D.
Application Technical Lead (ATL)
CMC Lead; Division of Cardiology and Nephrology
CDER/OPQ/ONDP/DNDPIII/NDPB5

Mohan K. Sapru -S
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DN: c=US, o=U.S. Government, ou=HHS, ou=FDA, ou=People, cn=Mohan K. Sapru -S, 0.9.2342.19200300.100.1.1=2000589315
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Rao Kambhampati

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David Claffey

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CHAPTER IV: LABELING
NDA 213330

Note: This NDA contains two drug products and they are as follows and this labeling review covers both the drug products:

1) Labetalol Hydrochloride in Sodium Chloride Injection, 100 mg/100 mL; 200 mg/200 mL; and 300 mg/300 mL (1 mg/mL)
2) Labetalol Hydrochloride in Dextrose Injection, 200 mg/200 mL (1 mg/mL) and

1.0 PRESCRIBING INFORMATION

Assessment of Product Quality Related Aspects of the Prescribing Information:

1.1 HIGHLIGHTS OF PRESCRIBING INFORMATION

Item	Information Provided in the NDA	Assessor's Comments
Product Title in Highlights		
Proprietary name	Not applicable	
Established name(s)	1) Labetalol hydrochloride in sodium chloride injection 2) Labetalol hydrochloride in dextrose injection	Adequate
Route(s) of administration	Intravenous use	Adequate
Dosage Forms and Strengths Heading in Highlights		
Summary of the dosage form(s) and strength(s) in metric system.	1) 100 mg/100 mL (1mg/1mL) 200 mg/200 mL (1 mg/mL) 300 mg/300 mL (1mg/mL) 2) 200 mg/200 mL (1mg/1mL)	Adequate
Assess if the tablet is scored. If product meets guidelines and criteria for a scored tablet, state "functionally scored"	Not applicable	

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.	Single-dose bags	Adequate

1.2 FULL PRESCRIBING INFORMATION

1.2.1 Section 2 (DOSAGE AND ADMINISTRATION)

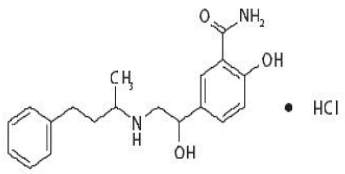
Item	Information Provided in the NDA	Assessor's Comments
DOSAGE AND ADMINISTRATION section		
Special instructions for product preparation (e.g., reconstitution and resulting concentration, dilution, compatible diluents, storage conditions needed to maintain the stability of the reconstituted or diluted product)	Not applicable	

1.2.2 Section 3 (DOSAGE FORMS AND STRENGTHS)

<table>
<tr><th>Item</th><th>Information Provided in the NDA</th><th>Assessor's Comments</th></tr>
<tr><td colspan="3">DOSAGE FORMS AND STRENGTHS section</td></tr>
<tr><td>Available dosage form(s)</td><td>1) In sodium chloride injection
2) In dextrose injection</td><td>Adequate</td></tr>
<tr><td>Strength(s) in metric system</td><td><table><tr><th>Diluent</th><th>Labetalol Dose</th><th>Volume</th></tr><tr><td>Sodium Chloride</td><td>100 mg</td><td>100 mL</td></tr><tr><td>Sodium Chloride</td><td>200 mg</td><td>200 mL</td></tr><tr><td>Sodium Chloride</td><td>300 mg</td><td>300 mL</td></tr><tr><td>Dextrose</td><td>100 mg</td><td>100 mL</td></tr></table></td><td>Adequate</td></tr>
<tr><td>If the active ingredient is a salt, apply the USP Salt Policy per FDA Guidance</td><td>USP salt policy is not applied because the strengths of several approved products of this API are based on the hydrochloride salt.</td><td>Adequate</td></tr>
<tr><td>A description of the identifying characteristics of the dosage forms, including shape, color, coating, scoring, and imprinting</td><td>Preservative-free, clear, colorless to light yellow solution.</td><td>Adequate</td></tr>
<tr><td>Assess if the tablet is scored. If product meets guidelines and criteria for a scored tablet, state "functionally scored"</td><td>Not applicable</td><td></td></tr>
</table>

For injectable drug products for parental administration, use appropriate labeling term (e.g., single-dose, multiple-dose, single-patient-use). Other package type terms include pharmacy bulk package and imaging bulk package.	Single-dose bag	Adequate

Item	Information Provided in the NDA	Assessor's Comments
DESCRIPTION section		
Proprietary and established name(s)	Proprietary name is not applicable. Labetalol HCl in Sodium Chloride Injection and Labetalol HCl in Dextrose Injection	Adequate
Dosage form(s) and route(s) of administration	In Sodium Chloride Injection and in dextrose Injection. Intravenous	Adequate
If the active ingredient is a salt, apply the USP Salt Policy and include the equivalency statement per FDA Guidance.	USP salt policy is not applied because the strengths of several approved products of this API are based on the hydrochloride salt.	Adequate
List names of all inactive ingredients. Use USP/NF names. Avoid Brand names.	1) Sodium chloride, anhydrous dextrose, edetate disodium; and citric acid monohydrate and sodium hydroxide, as necessary. 2) Anhydrous dextrose, edetate disodium; and citric acid monohydrate and sodium hydroxide, as necessary.	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.	1) Each 1 mL contains 7.2 mg sodium chloride, 9 mg of dextrose (anhydrous), 0.02 mg of edetate disodium; and citric acid monohydrate and sodium hydroxide, as necessary, to bring the solution into the pH range of 3.5 to 4.5. 2) Each 1 mL contains 9 mg of dextrose (anhydrous), (b) (4) 0.02 mg of edetate disodium; and citric acid monohydrate and sodium hydroxide, as necessary, to bring the solution into the pH range of 3.5 to 4.5.	Adequate

If alcohol is present, must provide the amount of alcohol in terms of percent volume of absolute alcohol	Not applicable	
Statement of being sterile (if applicable)	Sterile	Adequate
Pharmacological/ therapeutic class	Adrenergic receptor blocking agent	Adequate
Chemical name, structural formula, molecular weight	Labetalol hydrochloride (HCl) is a racemate chemically designated as 5-[1-Hydroxy-2-[(1-methyl-3-phenylpropyl)amino]ethyl]-salicylamide monohydrochloride and it has the following structural formula:  Labetalol HCl has the molecular formula $C_{19}H_{24}N_2O_3$•HCl and a molecular weight of 364.87. It has two asymmetric centers and therefore exists as a molecular complex of two diastereoisomeric pairs.	Adequate
If radioactive, statement of important nuclear characteristics.	Not applicable	
Other important chemical or physical properties (such as pKa or pH)	pH 3.5 to 4.5	Adequate

1.2.3 Section 11 (DESCRIPTION)

Section 11 (DESCRIPTION) Continued

Item	Information Provided in the NDA	Assessor's Comments
For oral prescription drug products, include gluten statement if applicable	Not applicable	
Remove statements that may be misleading or promotional (e.g., "synthesized and developed by Drug Company X," "structurally unique molecular entity"	Not applicable	

Item	Information Provided in the NDA	Assessor's Comments
HOW SUPPLIED/STORAGE AND HANDLING section		
Available dosage form(s)	1) In sodium chloride injection 2) In dextrose injection	Adequate
Strength(s) in metric system	mg/mL	Adequate
Available units (e.g., bottles of 100 tablets)	1) Labetalol HCl in Sodium Chloride Injection: 100 mg/100 mL (1 mg/mL), 200 mg/200 mL (1 mg/mL), and 300 mg/300 mL (1 mg/mL) 2) Labetalol HCl in Dextrose Injection: 200 mg/200 mL (1 mg/mL)	Adequate
Identification of dosage forms, e.g., shape, color, coating, scoring, imprinting, NDC number	Preservative-free, clear, colorless to light yellow sterile solution that is available in a single-dose single-port bag with an aluminum overwrap.	Adequate
Assess if the tablet is scored. If product meets guidelines and criteria for a scored tablet, state "functionally scored"	Not applicable	
For injectable drug products for parental administration,	Single-dose bag, Box of 10 bags	Adequate

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.		

1.2.4 Section 16 (HOW SUPPLIED/STORAGE AND HANDLING)

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

Item	Information Provided in the NDA	Assessor's Comments
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.)	Do not freeze. Protect from light. Do not remove from overwrap until ready to use.	Adequate
If the product contains a desiccant, ensure the size and shape differ from the dosage form and desiccant has a warning such as "Do not eat."	Not applicable	
Storage conditions. Where applicable, use USP storage range rather than storage at a single temperature.	Store at 20° to 25°C (68° to 77°F) with excursions permitted between 15° to 30°C (59° to 86°F) [see USP Controlled Room Termperature]	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."	Not applicable	

Include information about child-resistant packaging	Not applicable	

1.2.5 Other Sections of Labeling

Please include your comments about other sections of labeling if they contain product quality information: None

1.2.6 Manufacturing Information After Section 17 (for drug products)

Item	Information Provided in the NDA	Assessor's Comments
Manufacturing Information After Section 17		
Name and location of business (street address, city, state and zip code) of the manufacturer, distributor, and/or packer	Manufactured by: Hikma Farmaceutica (Portugal), S.A. Estrada do Rio da Mó, 8, 8A e 8B – Fervença – 2705-906 Terrugem SNT, Portugal. Distributed by: Hikma Pharmaceuticls USA Inc. Eatontown, NJ 07724	Adequate

2.0 PATIENT LABELING: Not applicable

3.0 CARTON AND CONTAINER LABELING

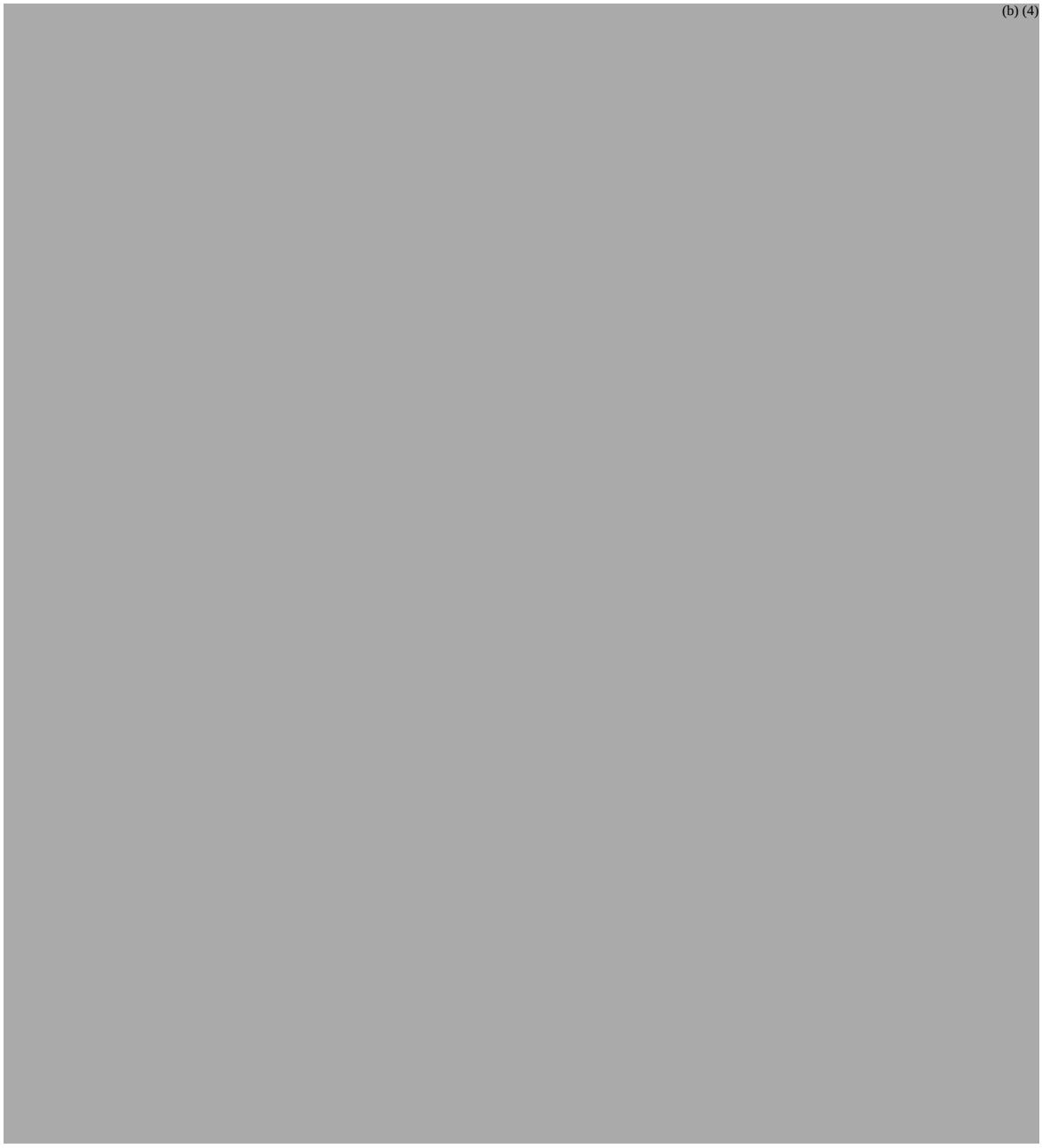
3.1 Container Label

Note: Labetalol hydrochloride in sodium chloride injection is manufactured in three strengths: 100 mg/100 mL; 200 mg/200 mL; and 300 mg/300 mL (1 mg/mL). A representative example is provided below for the inner Bag label of 100 mg/100 mL (1 mg/mL) strength:

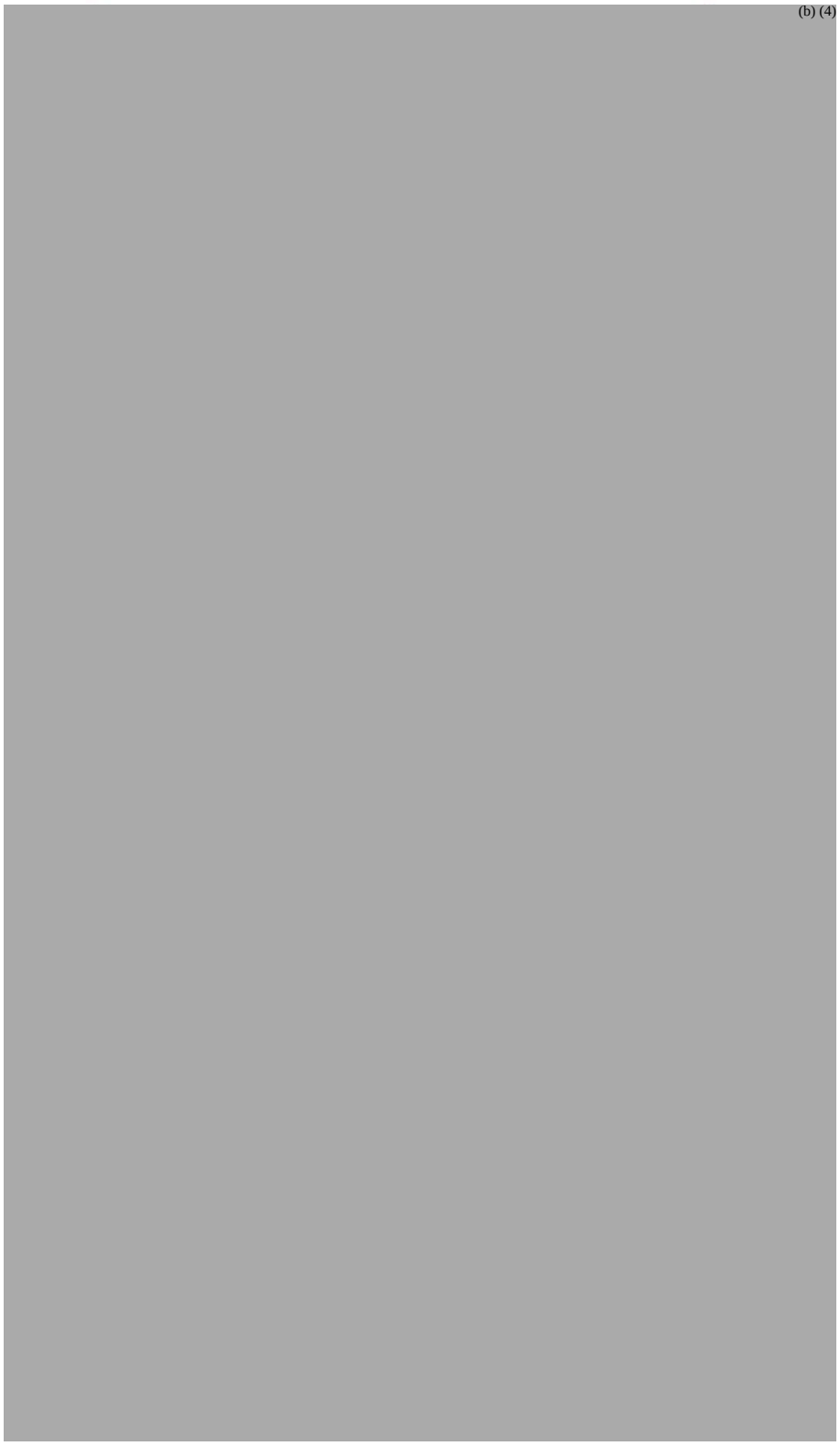
A representative example is provided below for the overwrap label of 100 mg/100 mL (1 mg/mL) strength:


(b) (4)

Inner Bag Label of Labetalol Hydrochloride in Dextrose Injection, 200 mg/200 mL (1mg/mL):



Overwrap Label of Labetalol Hydrochloride in Dextrose Injection, 200 mg/200 mL (1mg/mL):



Carton Labeling: Not applicable

Item	Information Provided in the NDA	Assessor's Comments about Carton Labeling
Proprietary name, established name, and dosage form (font size and prominence	Proprietary name is not applicable. Labetalol HCl in Sodium Chloride Injection and Labetalol HCl in Dextrose Injection	Adequate
Dosage strength	Included	Adequate
Route of administration	Intravenous use	Adequate
If the active ingredient is a salt, include the equivalency statement per FDA Guidance	USP salt policy is not applied because the strengths of several approved products of this API are based on the hydrochloride salt.	Adequate
Net contents (e.g. tablet count)	Included	Adequate
"Rx only" displayed on the principal display	Rx only	Adequate
NDC number	Included	Adequate
Lot number and expiration date	Included	Adequate
Storage conditions. If applicable, include a space on the carton labeling for the user to write the new BUD.	Included	Adequate
For injectable drug products for parental administration, use appropriate package type term (e.g., single-dose, multiple-dose, single-patient-use)	Single-dose bag	Adequate
Other package terms include pharmacy bulk package and imaging bulk package which require "Not	Not applicable	

for direct infusion" statement.		
If alcohol is present, must provide the amount of alcohol in terms of percent volume of absolute alcohol	Not applicable	
Bar code		

Item	Information Provided in the NDA	Assessor's Comments about Carton Labeling
Name of manufacturer/distributor	Included	Adequate
Medication Guide (if applicable)	Not applicable	
No text on Ferrule and Cap overseal	Not applicable	
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.	Not applicable	
And others, if space is available	Not applicable	

Assessment of Carton and Container Labeling: *Adequate*
The bag inner labels and overwrap label contained all the required information so that the health care professionals can easily identify and administer the drug appropriately.

ITEMS FOR ADDITIONAL ASSESSMENT: None

Overall Assessment and Recommendation:

The package insert and container labels contained all the required information, therefore, from the labeling review stand point the NDA is recommended for approval.

Primary Labeling Assessor Name and Date: Rao V. Kambhampati, Ph.D. 9/10/2020.

Rao Kambhampati

Digitally signed by Rao Kambhampati
Date: 9/10/2020 07:22:50PM
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David Claffey

Digitally signed by David Claffey
Date: 9/10/2020 09:43:24PM
GUID: 508da71e00029e20b201195abff380c2

MANUFACTURING INTEGRATED ASSESSMENT

Application ID	NDA 213330
Drug Product Name	Labetalol Hydrochloride in Dextrose Injection and Labetalol Hydrochloride in Sodium Chloride Injection
Strengths	1 mg/mL
Dosage Form	Sterile Injectable
Administration Route	Infusion
Indication	Labetalol HCl Injection, USP is indicated for control of blood pressure in severe hypertension.
Applicant Name	Hikma Pharmaceuticals International Limited

I. Manufacturing Summary

Facility Assessment Recommendation: Adequate

Process Assessment Recommendation: Adequate

Assessment Summary:

Labetalol Hydrochloride in Dextrose and in Sodium Chloride Injection are (b) (4) (b) (4) sterilized. The drug products are preservative-free and the packaging is (b) (4) bags which are controlled effectively with (b) (4) (b) (4) checks.

The (b) (4) operations are low risk because the facility has experience and appropriate in-process controls are in place. The drug substance facility was low risk due to an acceptable inspectional history.

List Submissions being assessed (Table):

Document Description (SD #)	Date Received
0001 (1) Original Submission	01/10/2020
0003 (3) IR Response	04/07/2020
0006 (6) IR Response	5/22/2020

Highlight Key Issues from Last Cycle and Their Resolution: None

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

1. Post-Approval Commitments and Lifecycle Management Considerations

Postmarketing commitments (PMC)?	No
Post-approval inspection?	No
Lifecycle considerations	No

2. Facilities Table

Facility name and address	FEI	Responsibilities and profile code(s)	Status
Hikma Farmaceutica (Portugal), S.A. Estrada do Rio da Mo 8/8A/8B, Terrugem , SNT (Sintra), Portugal, 2705-906	3002807173	Manufacturing Steps: Finished Product Manufacture/Labeling/Packaging/Testing: Drug Substance Release Testing (except as indicated by contract laboratory), Excipient Release Testing, Drug Product Release Testing, and Drug Product Stability Testing. Storage of Accelerated Stability Samples. || 356h Status: Active LVP	Approve - Based on Previous History
(b) (4)			Approve - Based on Previous History
			Approve - Based on Previous History
			No Evaluation Necessary

II. Drug Product Manufacturing

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Allison Aldridge

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Date: 7/08/2020 09:29:20AM
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Kumar Janoria

Digitally signed by Kumar Janoria
Date: 7/08/2020 10:29:45AM
GUID: 53160a1a0000844db16f58dfff6949ed

BIOPHARMACEUTICS

IQA Review Guide Reference

Product Background:

NDA: 213330

Drug Product Name / Strength:
Labetalol Hydrochloride in Dextrose Injection Bags, 200 mg/200 mL (1 mg/mL) (preservative-free)
Labetalol Hydrochloride in Sodium Chloride Injection Bags, 100 mg/mL, 200 mg/200 mL, and 300 mg/300 mL (1 mg/mL) (preservative-free)

Route of Administration: Injection, intravenous infusion

Applicant Name: Hikma Pharmaceuticals USA Inc.

Review Recommendation:
This NDA 213330 is recommended for approval from a biopharmaceutics perspective.

Review Summary:
The Applicant, Hikma Pharmaceuticals USA Inc, submitted this NDA 213330 in accordance with Section 505 (b)(2) of the Fedral Food, Drug and Cosmetic Act and part 314.50 and 314.94 (a)(3) of Title 21 of the Code of Federal Regulations to seek an approval for Labetalol Hydrochloride in Dextrose Injection Bags, 200 mg/200 mL (1 mg/mL) (preservative-free), and Labetalol Hydrochloride in Sodium Chloride Injection Bags, 100 mg/mL, 200 mg/200 mL, and 300 mg/300 mL (1 mg/mL) (preservative-free). The Applicant provided comparative in vitro study results for a bridge with the Listed Drug (LD), Sebela Ireland Ltd's Trandate®, 5 mg/mL vial dosage, NDA 019425, and the Reference Standard (RS), Hospira's Labetalol Hydrochloride Injection, 5 mg/mL vial dosage, ANDA 075239. The LD product is discontinued, and Orange Book and drugs@fda states "Federal Register determination that product was not discontinued or withdrawn for safety or efficacy reasons".
This Biopharmaceutics review evaluated the overall data submitted in support of bridging to the LD and RS, as detailed below:

1) Biowaiver request:
The Applicant requested a waiver of an *in vivo* bioavailability/bioequivalence (BA/BE) study for the drug product that is the subject of this application (Labetalol Hydrochloride in Dextrose Injection) in accordance with 21 CFR 320.22 (b)(1). However, the proposed drug product is not equivalent to the LD in terms of concentration (5 mg/ml vs. 1 mg/ml) and composition. Formulation bridging under 21 CFR 320.24 (b)(6) is appropriate to

demonstrate bioequivalence in lieu of biowaiver. In addition, the Applicant was suggested to provide comparative physicochemical characteristics (pH, osmolality) for the bridge during IND.
For bridging, the Applicant provided following supportive data/information in this NDA:

- Composition comparison of diluted LD, RS, and proposed drug product (Ready-to-use)
- Comparative Physicochemical properties RS after dilution to 1 mg/mL vs. the proposed drug products for both types of IV infusion bags (dextrose and NaCl injection).
- Justification of effect of removing preservatives

2) Bridging assessment:
The Applicant provided the comparative composition and physicochemical (pH, osmolality) properties to demonstrate equivalency between the diluted LD/RS and proposed drug product (Ready-to-use). The pH, assay, and impurity results of the proposed drug product with/without preservatives after sterilization process showed no impact on its physicochemical properties. The Applicant also provided justification that removing preservatives do not impact the bioavailability of the proposed drug product. The PK/PD profiles of Parabens in humans are unlikely to impact the pharmacokinetic properties of labetalol hydrochloride. Thus, a bridging information/data to demonstrate equivalence of the proposed product to the diluted LD/RS is acceptable.

List Submissions being reviewed (table):

Module	Contents
M 1.12.15	Request for waiver of in vivo bioavailability studies
M 2.3.S	Quality overall summary (Drug substance)
M 2.3.P	Quality overall summary (Drug product)
M 3.2.P	Drug product (Labetalol in dextrose and sodium chloride)
M 3.3	Literature references

Highlight Key Outstanding Issues from Last Cycle:
No issue for a briding of the proposed product to the LD has been found.

Concise Description Outstanding Issues Remaining:
No issue for a briding of the proposed product to the LD has been found.

List Number of Comparability Protocols (ANDA only): Not applicable

Bridging of Formulations

Reviewer's Assessment: ***{Adequate}***

The Applicant's justification for bioequivalence study waiver request

- The Route of Administration is identical to that of the LD and RS, post-dilution; specifically, the slow infusion requirement listed in the approved drug products' package inserts.
- Intravenous solutions are 100% bioavailable. The LD, RS and the proposed Hikma products are true solutions at the point of administration. As such, the active ingredient in Hikma's proposed product, Labetalol Hydrochloride, USP, is 100% bioavailable in the same manner as the slow infusion preparations as described in the LD or RS package inserts.
- The proposed Hikma drug products are quantitatively and qualitatively equivalent to the LD and RS (when diluted to 1 mg/mL, in accordance with the approved package insert) with regards to the following ingredients:
  - Labetalol Hydrochloride;
  - Dextrose;
  - Edetate Disodium;
- Composition comparison between the LD and RS is shown in the table below.

Table 3: Comparison of RLD (Trandate®) and Hospira's RS for Labetalol Hydrochloride Injection (5 mg/mL)

Component	Amount per mL	
	RLD (Trandate®) (NDA 019425)	Hospira's RS (ANDA 075240)
Labetalol Hydrochloride	5 mg	5 mg
Dextrose Anhydrous	45 mg	45 mg
Edetate Disodium Dihydrate	0.1 mg	0.1 mg
Methylparaben	0.8 mg	0.8 mg
Propylparaben	0.1 mg	0.1 mg
Citric Acid Monohydrate		As needed to adjust pH
Citric Acid Anhydrous	As needed to adjust pH	
Sodium Hydroxide	As needed to adjust pH	As needed to adjust pH
pH Range	3 to 4	3.0 to 4.5
Water for Injection	q.s. to 1 mL	q.s to 1 mL
Packaging	Vial/Stopper/Flip-Off Seal	Vial/Stopper/Flip-Off Seal

Assessment #1: Bridging of formulations

1) Labetalol hydrochloride in dextrose injection, 200 mg/200 mL (1 mg/mL)

Composition comparison between the diluted LD/RS and the proposed product in dextrose, 200 mg/200 mL is shown in the table below.

Table 5: Composition Comparison of Diluted RLD (Trandate) and Hospira's RS (1 mg/ mL) to Hikma's Labetalol Hydrochloride in Dextrose Injection (1 mg/mL)

Component	Amount per 200 mL		
	RLD (Trandate®) (NDA 019425)	Hospira's RS (ANDA 075240)	Hikma's Proposed Drug Product
Labetalol Hydrochloride	200 mg	200 mg	200 mg
Dextrose Anhydrous	(b) (4)		
Edetate Disodium Dihydrate			
Citric Acid Monohydrate			
Methylparaben			
Propylparaben			
Citric Acid Monohydrate		As needed to adjust pH	As needed to adjust pH
Citric Acid Anhydrous	As needed to adjust pH		
Dextrose Monohydrate	(b) (4)		
Sodium Hydroxide	As needed to adjust pH	As needed to adjust pH	As needed to adjust pH
Final Volume	q.s. to 200 mL with 5% Dextrose Solution, USP	q.s. to 200 mL with 5% Dextrose Solution, USP	q.s. to 200 mL

The physicochemical properties comparison between the diluted RS (two Lots) and the proposed product (three batches), Labetalol hydrochloride in dextrose injection, 200 mg/200 mL are shown in the table below.

Table 1: Physicochemical Properties Comparison of Hospira's RS After Dilution to 1 mg/mL in Dextrose Injection vs. Hikma's Proposed Drug Product, Labetalol Hydrochloride in Dextrose Injection

Property	Method	Lot 74350DD, exp. 01- Feb-2019 (NDC 0409-2267-20, 100 mg / 20 mL) Final Concentration 1 mg/mL		Lot 74330DD, exp. 01-Feb-2019 (NDC 0409-2267-54, 200 mg / 40 mL) Final Concentration 1 mg/mL		Hikma Submission Batches 1707069.1, 1707070.1, 1707074.1 (200 mg/200 mL)
		Initial	Expiry	Initial	Expiry	Long-Term (25 ± 2°C / 40 ± 5% RH) 0, 3, 6, 9 and 12 months
Description	QCC839	Clear, colorless to pale yellow solution essentially free from visible signs of contamination.	Clear, colorless to pale yellow solution essentially free from visible signs of contamination.	Clear, colorless to pale yellow solution essentially free from visible signs of contamination.	Clear, colorless to pale yellow solution essentially free from visible signs of contamination.	All Batches: Clear, colorless to pale yellow solution essentially free from visible signs of contamination
pH	QCC839	(b) (4)				1707069.1: All results range (b) (4)
						1707070.1: All results range (b) (4)
						1707074.1: All results range (b) (4)
Assay of Labetalol HCl	QCC840					1707069.1: All results range (b) (4)
						1707070.1: All results range (b) (4)
						1707074.1: All results range (b) (4)
Osmolality	QCC839					1707069.1: All results range (b) (4)
						1707070.1: All results range (b) (4)
						1707074.1: All results range (b) (4)

The proposed product, Labetalol hydrochloride in dextrose injection (1 mg/mL), 200 mg/200 mL is not quantitatively and qualitatively equivalent to the LD and RS due to removal of the preservatives in the proposed product. However, the physicochemical properties of the diluted RS (1 mg/mL) in dextrose and the proposed product are similar and thus, bridging for equivalence between the proposed product and the diluted LD/RS (1 mg/mL in dextrose) is adequate on the basis of the similarity of the comparison, which has no significant impact on the in vivo performance of Labetalol hydrochloride in dextrose (1 mg/mL).

2) Labetalol hydrochloride in sodium chloride injection, 100 mg/100 mL, 200 mg/200 mL, 300 mg/300 mL (1 mg/mL)

Composition comparison between the diluted LD/RS and the proposed product in sodium chloride, 200 mg/200 mL is shown in the table below.

Table 5: Composition Comparison of Diluted RLD (Trandate) and Hospira's RS (1 mg/ mL) to Hikma's Labetalol Hydrochloride in Sodium Chloride Injection (1 mg/mL)

Component	Amount per 200 mL		
	RLD (Trandate®) (NDA 019425)	Hospira's RS (ANDA 075240)	Hikma's Proposed Drug Product
Labetalol Hydrochloride	200 mg	200 mg	200 mg
Dextrose Anhydrous	[redacted] (b) (4)		
Sodium Chloride			
Edetate Disodium Dihydrate			
Citric Acid Monohydrate			
Methylparaben			
Propylparaben			
Citric Acid Monohydrate		As needed to adjust pH	As needed to adjust pH
Citric Acid Anhydrous	As needed to adjust pH		
Sodium Hydroxide	As needed to adjust pH	As needed to adjust pH	As needed to adjust pH
Water for Injection	q.s. to 200 mL	q.s to 200 mL	q.s. to 200 mL

The physicochemical properties comparison between the diluted RS (two Lots) and the proposed product (multiple batches), Labetalol hydrochloride in sodium chloride injection, 100 mg/100 mL, 200 mg/200 mL, 300 mg/300 mL are shown in the tables below.

Table 2: Physicochemical Properties Comparison of Hospira's RS after dilution to 1 mg/mL in 0.9% Sodium Chloride Injection vs. Hikma's Proposed Drug Product, Labetalol Hydrochloride in Sodium Chloride Injection

Property	Method	Lot 74350DD, exp. 01- Feb-2019 (NDC 0409-2267-20, 100 mg / 20 mL)		Lot 74330DD, exp. 01-Feb-2019 (NDC 0409-2267-54, 200 mg / 40 mL)		Hikma Submission Batches on Long Term (25 ± 2°C / 40 ± 5% RH) 0, 3, 6, 9 and 12 months		
						100 mg/100 mL	200 mg/200 mL	300 mg/300 mL
		Initial	Expiry	Initial	Expiry	1707066.1 1707067.1 1707075.1	1707068.1	1707071.1 1707072.1 1707073.1
Description	QCC839	Clear, colorless to pale yellow solution essentially free from visible signs of contamination.	Clear, colorless to pale yellow solution essentially free from visible signs of contamination.	Clear, colorless to pale yellow solution essentially free from visible signs of contamination.	Clear, colorless to pale yellow solution essentially free from visible signs of contamination.	Clear, colorless to pale yellow solution essentially free from visible signs of contamination	Clear, colorless to pale yellow solution essentially free from visible signs of contamination	Clear, colorless to pale yellow solution essentially free from visible signs of contamination
pH	QCC839	[redacted] (b) (4)				1707066.1: Range (b) (4) 1707067.1: Range (b) (4) 1707075.1: Range (b) (4)	Range (b) (4)	1707071.1: Range (b) (4) 1707072.1: Range (b) (4) 1707073.1: Range (b) (4)
Assay of Labetalol HCl	QCC840					1707066.1: Range (b) (4) 1707067.1: Range (b) (4) 1707075.1: Range (b) (4)	Range: (b) (4)	1707071.1: Range (b) (4) 1707072.1: Range (b) (4) 1707073.1: Range (b) (4)

Table 3: Physicochemical Properties Comparison of Hospira's RS after dilution to 1 mg/mL in 0.9% Sodium Chloride Injection vs. Hikma's Proposed Drug Product, Labetalol Hydrochloride in Sodium Chloride Injection (continued)									
Osmolality	QCC839	(b) (4)				1707066.1: Range (b) (4) 1707067.1: Range (b) (4) 1707075.1: Range (b) (4)	Range: (b) (4) mOsm/kg	1707071.1: Range (b) (4) 1707072.1: Range (b) (4) 1707073.1: Range (b) (4)	

Similarly, the phycochemical properties of the diluted RS in sodium chloride (1 mg/mL) are comparable to the ones of the proposed product, Labetalol hydrochloride in sodium chloride injection, 100 mg/100 mL, 200 mg/200 mL, 300 mg/300 mL, which supports an adequate bridge for formulations between the diluted LD/RS and the proposed product in sodium chloride is established.

The Applicant's justification for effect of removing preservatives from the formulations

- The proposed product is a single use, presertive-free dosage form terminally sterilized. The current marketed RS vial product contains methylparaben and propylparaben as preservatives while the proposed products remove the preservatives. The impact of removing preservatives from the formulation was evaluated using 1 mg/mL Labetalol with/without preservatives. The pH, assay, and degradation products results confirmed that removing the preservatives had no impact on physicochemical properties, and bioavailabilty of the product.

Assessment #2: Effect of removing preservatives

The Applicant conducted a study to evaluate the impact of removing preservatives from the formulation on pH, assay, and degradation products, and the results are shown in the tables below.

Table 14: pH, Assay, and Impurity Results for Labetalol Hydrochloride in Dextrose Injection, 1 mg/mL, Preserved and Preservative-Free					
Sample	Presentation	pH	% Assay	% Impurity	
				Highest Impurity	Total
Labetalol Hydrochloride in Dextrose Injection, 1 mg/mL	Preserved	(b) (4)			
Labetalol Hydrochloride in Dextrose Injection, 1 mg/mL	Preservative-Free				

Table 14: pH, Assay, and Impurity Results for Labetalol Hydrochloride in Sodium Chloride Injection, 1 mg/mL, Preserved and Preservative-Free					
Sample	Presentation	pH	% Assay	% Impurity	
				Highest Impurity	Total
Labetalol Hydrochloride in Sodium Chloride Injection, 1 mg/mL	Preserved	(b) (4)			
Labetalol Hydrochloride in Sodium Chloride Injection, 1 mg/mL	Preservative-Free				

The results show that removing the preservatives had no impact on physicochemical properties of the diluted formulation. Additionally, the Applicant included references to support that the removal of parabens from the formulation is unlikely to impact the PK properties of Labetalol in the proposed drug products. Thus, the Applicant's justification

addressing that removal of preservatives from the IV bag formulation should have no impact on in vivo performance of the proposed drug product, is adequate.

Biowaiver Request

Reviewer's Assessment:
Fomulation bridging under CFR 320.23 (b)(6) is appropriate to demonstrate bioequivalence in lieu of biowaver since the proposed product is not a Q1/Q2 equivalent formulation to the LD. The bridge is established based on the provided comparative data for the proposed drug product versus LD/RS.

R Regional Information

Comparability Protocols

Reviewer's Assessment: ***{Adequate/Inadequate}***

None

Post-Approval Commitments (For NDA only)

Reviewer's Assessment: ***{Adequate/Inadequate}***

None

Lifecycle Management Considerations

None

Primary Biopharmaceutics Reviewer: *Min Sung Suh, Ph.D., 08/28/2020*

Secondary Reviewer: *Poonam Delvadia, Ph.D., 08/28/2020*

Min Sung Suh

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Poonam Delvadia

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CHAPTER VII: MICROBIOLOGY

IQA NDA Assessment Guide Reference

Product Information	Labetalol Hydrochloride (HCl) in Sodium Chloride Injection and Labetalol HCl in Dextrose Injection are indicated for control of blood pressure in severe hypertension.
NDA Number	213330
Assessment Cycle Number	01
Drug Product Name/ Strength	Labetalol Hydrochloride in Sodium Chloride Injection and Labetalol Hydrochloride in Dextrose Injection, 1 mg/mL
Route of Administration	Intravenous
Applicant Name	Hikma Pharmaceuticals International Limited US Agent: Hikma Pharmaceuticals USA Inc.
Therapeutic Classification/ OND Division	Alpha-/Beta-adrenergic blocking agent/Cardiovascular agent
Manufacturing Site	Hikma Farmacêutica (Portugal), S.A. Estrada do Rio da Mó 8, 8A, 8B 2705-906 Terrugem SNT Portugal FEI 3002807173 DUNS 452742943
Method of Sterilization	(b) (4)

(b) (4)

(b) (4)

Twist-Off closures, and (b) (4) sterilized. The process validation meets the product quality microbiology review criteria.

List Submissions being assessed (table):

Document(s) Assessed	Date Received
Supporting Document # 1 (SEQ-0001)	01/10/2020
Supporting Document # 3 (SEQ-0003)	04/07/2020
Supporting Document # 4 (SEQ-0004)	04/14/2020
Supporting Document # 6 (SEQ-0006)	05/22/2020

Highlight Key Issues from Last Cycle and Their Resolution: None

Remarks: This is a 505(b)(2) application. The Reference Listed Drug (RLD), Trandate® (labetalol hydrochloride) Injection (NDA 019425 registered by

Sebela Ireland Ltd) is discontinued, not due to safety or efficacy reasons. The RLD is packaged in multiple dose vials, 20 mL (100 mg/vial) and 40 mL (200 mg/vial) (5 mg/mL).

The RLD may be administered through repeated IV (bolus) injection or slow continuous infusion. For the continuous IV infusion of Trandate® Injection, one example method to prepare the infusion solution is to add 40 mL of Trandate® Injection to 160 mL of a commonly used IV fluid to prepare a 1 mg/mL Labetalol Hydrochloride solution and the diluted solution is administered at a rate of 2 mL/min to deliver 2 mg/min. Another example method is to prepare an approximately 2 mg/3 mL solution for IV infusion administration at a rate of 3 mL/min to deliver approximately 2 mg/min.

Trandate® Injection was found to be compatible at final concentrations of 1.25 mg/mL to 3.75 mg/mL with and stable (for 24 hours refrigerated or at room temperature) in mixtures with 5% dextrose, USP, 0.9% sodium chloride injection, USP, and 8 other commonly used IV fluids (such as ringer's injection (and or with lactate or with dextrose, or both), and dextrose/sodium chloride injection).

The Reference Standard (RS, ANDA 075240), Labetalol Hydrochloride Injection, USP, 5 mg/mL from Hospira, Inc. are also supplied in 20 mL and 40 mL multiple dose vials, same as the approved ANDA 075303 product from the applicant (Hikma).

The subject NDA product is a single-dose, ready-to-administer drug product, equivalent to the post-diluted RLD or RS solution for intravenous infusion administration at a final concentration of 1 mg/mL of Labetalol Hydrochloride, except that the parabens (methyl- and propyl-) preservatives are present in the RLD or RS, but not in subject NDA product. The intravenous infusion administration rate and dose remain the same. The subject NDA product is administered as a slow continuous infusion at a rate of 2 mL/min to deliver 2 mg/min.

Concise Description of Outstanding Issues: None.

Supporting Documents: N/A

S DRUG SUBSTANCE

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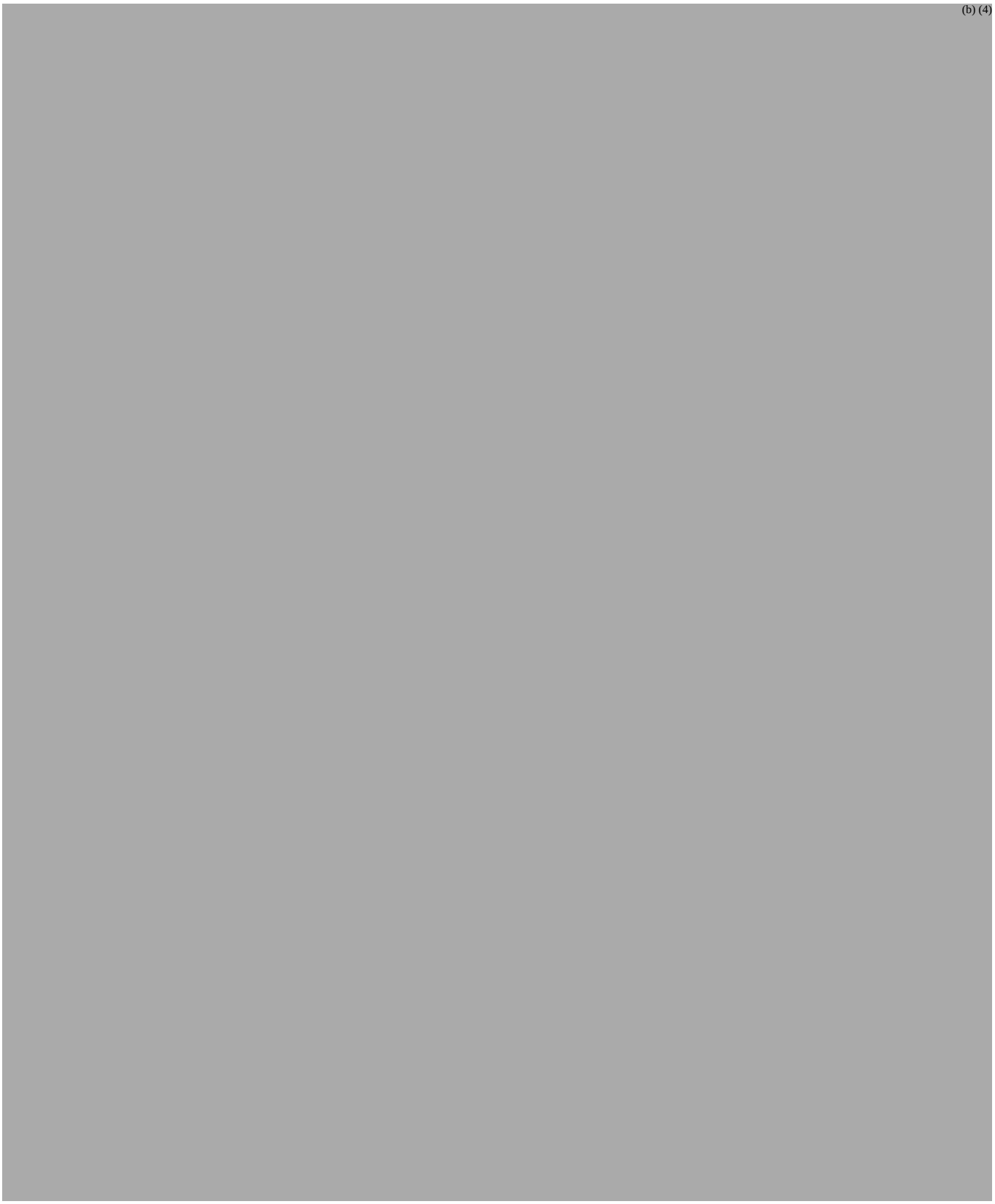
(b) (4)



R REGIONAL INFORMATION
Executed Batch Records

The exhibit batch records for Labetalol Hydrochloride in Sodium Chloride Injection (100 mg/100 mL, 200 mg/200 mL, and 300 mg/300 mL, total 7 batches) and for Labetalol Hydrochloride in Dextrose Injection 200 mg/200 mL (3 batches) are provided in 3.2.R. See P.5.1 or P.8.3 for batch numbers. The batch records confirm that production (b) (4) (b) (4) the manufacture of the exhibit batches. The primary container and closure used in exhibit batches are identical to those to be used for commercial production.

Assessment: ***{Adequate}***

Comparability Protocols – N/A.

2. ASSESSMENT OF COMMON TECHNICAL DOCUMENT – QUALITY (CTD-Q) MODULE 1

2.A. Prescribing Information

Storage temperature: 20-25ºC (68-77ºF), excursions permitted to 15-30ºC (59-86ºF)

Route of administration: Intravenous infusion

Container: Single dose

Labetalol Hydrochloride in Sodium Chloride Injection and Labetalol Hydrochloride in Dextrose injection are ready-to-use solutions and should not be further diluted. Once intravenous infusion has started, the infusion of the remaining content in the bag should be completed within 24 hours. Any unused portion is to be discarded.

Assessment: ***{Adequate}***

Post-Approval Commitments **– See P.8.2**

MICROBIOLOGY LIST OF DEFICIENCIES

None.

Primary Microbiology Assessor Name and Date: Xia Xu, Ph.D. 07/14/2020

Secondary Assessor Name and Date (and Secondary Summary, as needed): Neal Sweeney, Ph.D. 07/14/2020

Xia Xu

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Neal Sweeney

Digitally signed by Neal Sweeney
Date: 7/14/2020 10:49:06PM
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MOHAN K SAPRU
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