CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

214253Orig1s000

PRODUCT QUALITY REVIEW(S)

QUALITY ASSESSMENT

Recommendation: Approval

NDA 214253
Review 1

Drug Name/Dosage Form	Levothyroxine sodium injection
Strength	100 mcg/mL
Route of Administration	Intravenous injection
Rx/OTC Dispensed	Rx
Applicant	Custopharm, Inc.
US agent, if applicable	-

SUBMISSION(S) REVIEWED	DOCUMENT DATE	DISCIPLINE(S) AFFECTED
Pre-submission, Original submission, and amendments	Original submission: 7/17/2020 Amendments: 12/16/2020, 12/17/2020, 1/4/2021 (Manufacturing), 1/5/21 (drug product), 1/8/2021 (drug product and manufacture), 1/9/2021 (manufacturing), 3/09/2021 (label), 3/10/2021 (drug product)	Quality modules 3, 1.14, and 1.11

Quality Review Team

Discipline	Reviewer/Secondary	Branch/division
Drug Substance	Joseph Leginus/ Suong Tran	Branch III/Division of New Drug Active pharmaceutical
Drug Product	Dhanalakshmi Kasi / David J Claffey	Branch V/New Drug Products III
Process/ Facility	Laurie Nelson/Vidya Pai	Branch II/ Office of Pharmaceutical Manufacturing Assessment (OPMA)
Microbiology	Maritere Carattini/ Erika Pfeiler	OPMA
Regulatory Business Process Manager	Leeza Rahimi/ Hamet Toure	Branch I/Regulatory Business Process Management I
Application Technical Lead	Muthukumar Ramaswamy	Branch V/New Drug Products III
Environmental Analysis (EA)	Dhanalakshmi Kasi / David J Claffey	Branch V/New Drug Products III of New Drug Products

Quality Review Data Sheet

1. RELATED/SUPPORTING DOCUMENTS

A. DMFs:

DMF #	Type	Holder	Item Referenced	Status	Date Assessment Completed	Comments
(b) (4)	V	(b) (4)	(b) (4)	Adequate	3/2/2020	LOA dated 6/12/2020
	III			Active	*	LOA dated 04/02/2020
	II			Adequate	9/18/2020	LOA dated 5/20/2020
	V			Adequate	2/3/2017	LOA dated 3/18/2020
	III			Active	*	LOA dated 3/18/2020

*Sufficient information provided in the NDA

B. Other Documents: *IND, RLD, or sister applications*

DOCUMENT	APPLICATION NUMBER	DESCRIPTION
PIND	141631	Levothyroxine sodium injection

2. CONSULTS: None

DISCIPLINE	STATUS	RECOMMENDATION	DATE	REVIEWER
Pharm. Tox. (SBECD, impurities, and leachables)	Complete	Adequate (See Unireview)	3/29/2021	Pedrao L. Del Valle

Executive Summary

I. Recommendations and Conclusion on Approvability

The recommendation from the Office of Pharmaceutical Quality (OPQ) for NDA 214253 is approval. This recommendation includes acceptable recommendation for all the facilities listed in the application. At present, there are no outstanding deficiencies associated with drug substance, drug product, environmental assessment, biopharmaceutics, process, and microbiology sections of this application.

II. Summary of Quality Assessments

A. Product Overview

This NDA is a 505(b)(2) application for levothyroxine sodium injection with no non-clinical and clinical data. This NDA application references levothyroxine sodium for injection approved under NDA (b) (4), as the listed drug. The listed drug is a lyophilized powder available as 100 µg, 200µg and 500µg/vial and requires reconstitution with 5mL of 0.9% sodium chloride injection before use.

The proposed product, levothyroxine sodium injection, 100 mcg/mL is a sterile, clear, colorless to yellow solution provided in a 1mL single dose vial for intravenous injection. Each mL of the product contains 100 µg of levothyroxine sodium dissolved in water for injection along with 80 mg betdex sulfobutyl ether sodium (also known as sulfobutyl ether beta-cyclodextrin sodium, SBECD), 50 mcg arginine, 50 mcg disodium edetate dihydrate (EDTA), and (b) (4) mg sodium chloride. The final pH of the formulation is adjusted with hydrochloric acid or sodium hydroxide to (b) (4).

Although the concentration of the proposed product, 100 µg/mL is the same as the listed drug, levothyroxine sodium for injection, 500µg/vial after reconstitution with 5mL of 0.9% saline. The listed product strength contains 500 mcg levothyroxine sodium in the total quantity per unit (500µg/5mL). However, Custopharm's product contains 100 mcg in the total quantity per vial (100µg per 1 mL).

Since the proposed product contains the same active ingredient in the same concentration as the listed drug, the applicant requested a biowaiver for Levothyroxine sodium injection per 21 CFR 320.24(b)(6). Since the excipients present in the proposed product differ quantitatively and qualitatively (Q1/Q2) from the listed drug, the applicant provided additional information to bridge the proposed product to the listed drug via 21 CFR 320.24(b)(6) and requested a waiver of the in vivo bioavailability studies. This waiver request was granted by the biopharmaceutics reviewer (See Quality Assessment Overview section for additional details).

Proposed Indication(s) including Intended Patient Population	*Myxedema* coma
Duration of Treatment	*Refer to CTDL memo*
Maximum Daily Dose	*500µg*
Alternative Methods of Administration	*Not applicable*

B. Quality Assessment Overview

Drug Substance

The drug substance, levothyroxine sodium, is manufactured (b) (4) (b) (4) The molecular weight of Levothyroxine sodium is 798.9g/mol on an anhydrous basis. The molecular formula of levothyroxine sodium hydrate is $C_{15}H_{10}I_4NaO_4$. X H_2O.

The applicant referenced Type II DMF (b) (4) for all chemistry, manufacturing and control information for the drug substance. The CMC information provided in the DMF (b) (4) was recently reviewed by Dr. Leginus. His review indicates that the proposed drug substance specifications meet all requirements of the current USP monograph for levothyroxine sodium with the addition of appearance, residual solvents, bioburden and endotoxin. The limits for organic impurities/related substances conform to the limits listed in USP monograph The proposed drug substance specification acceptance criteria are acceptable.

Based on available stability data, a retest date of (b) (4) months is granted for levothyroxine sodium drug substance when stored at (b) (4) (b) (4).

Dr. Leginus's review concluded that the drug substance CMC information in the DMF is adequate to support the NDA. For additional details, please refer to CMC reviews for drug substance available under NDA 214253 (dated 12/09/2020) and DMF (b) (4) (dated 9/18/2020) in Panorama.

Drug Product

Drug Product Formulation: The proposed drug product, levothyroxine sodium injection, 100 mcg/mL is a clear, colorless to slightly yellow, sterile, aqueous solution packaged in a 2 mL (b) (4) clear glass vial and sealed with a 13mm (b) (4) (b) (4) stopper and a flip-off seal. The finished product is packaged in cartons.

Each vial contains 1 mL of the drug product. Each mL of the drug product solution contains 100 mcg of levothyroxine sodium, 80 mg of SBECD, 50 mcg arginine, 50 mcg EDTA, (b) (4) mg sodium chloride, and water for injection. The final pH of the formulation is adjusted with hydrochloric acid or sodium hydroxide to (b) (4).

The proposed excipients have previously been used in approved parenteral products and their levels in the drug product are well below the levels listed in FDA's inactive ingredient database. The choice of each excipient proposed for use in the product and their level are based on development work. SBECD is included in the proposed product for (b) (4) Sodium chloride is provided for tonicity adjustment. Arginine (b) (4) EDTA is provided for (b) (4)

The product is light sensitive. The storage of the product in carton is recommended to prevent exposure to light during shelf-life. The container closure components proposed for use in the product are known for use in approved products and the applicant provided leachable study assessment to assure the safety of the proposed container closure system.

Dr. Dhanalakshmi Kasi reviewed the drug product information including drug product composition, drug product specification, excipient information, analytical methods, container closure system, compatibility information including glass delamination study data, photostability and stability data. The compatibility of the active ingredient with excipients and the container closure components is supported by drug product stability data.

The drug product is tested for visual appearance, identity, particulate matter, pH, osmolality, assay, purity and impurities, extractable volume, uniformity of dosage units, closure integrity, EDTA content, endotoxin content, and sterility. Dr. Kasi's review concluded that the proposed specification is adequate to support the quality of the proposed product. Please refer to the drug product review dated 3/18/2021 for additional information.

Non-clinical reviewer, Dr. Pedro Del Valle was consulted regarding the safety of SBECD, impurities and potential leachable compounds associated with the product. No safety concerns were identified. Please refer to Dr. Del Valle's review under non-clinical section of the Unireview.

Manufacturing Process and Controls: The manufacturing process involves (b) (4)
(b) (4)

The applicant is using (b) (4)
to control quality of the product: (b) (4)

(b) (4)

The composition of the drug product, the drug product manufacturing process, batch size, and the packaging system used in registration stability studies are the same as that proposed for commercial use.

(b) (4)

For detailed information on the manufacturing process and process controls, refer to process review dated 3/15/2021 in Panorama. The process reviewer concluded that the proposed drug product manufacturing process controls are adequate to support the NDA.

Microbiological control information: Microbiology reviewer, Dr. Carattini reviewed the microbiological controls used in the drug product manufacturing process including (b) (4) (b) (4) Dr. Carattini also reviewed the depyrogenation and sterilization and validation information provided in Type V DMFs (b) (4) and (b) (4) (b) (4) Her review concluded that the proposed microbiological controls are adequate to support the NDA. Refer to Dr. Carattini dated 1/4/2021 in Panorama for details.

Control Strategy: The critical quality attributes of the product are controlled through (b) (4)

The proposed control strategy is adequate to assure the quality of the product. For additional information, please refer to the following CMC reviews in Panorama: Dr. Leginus's drug substance review dated 7/16/2020, Dr. Carattini 's microbiology review dated 1/4/2021, Dr. Kasi's drug product review dated 3/18/2021 and Nelson's process reviews dated 3/15/2021.

Facility compliance information: Facility compliance information for the drug product and drug substance manufacturing and testing facilities was reviewed by OPMA reviewer, Laurie Nelson. Her review concluded that the facilities associated with the application are adequate to support the application. Thus, the overall manufacturing inspection recommendation (OMIR) from the Office of Process Manufacturing Assessment (OPMA) for this NDA is approve. Panorama screen shot of the submission

facility status is shown below. For additional details, please refer to OPMA process/facility review in Panorama dated 3/15/2021.

(b) (4)

[redacted]

Environmental assessment: The applicant sought exemption from environmental impact analysis per 21CFR 25.31(a) as the action on this NDA may not significantly affect the quality of the human environment. Levothyroxine sodium is previously approved. A new dosage form that substitutes directly for an approved product is not considered to result in increased use of an active moiety already approved by the agency. Dr. Kasi granted categorical exclusion from submitting environmental assessment. Please refer to drug product review dated 3/18/2021 for additional information.

Expiration Date & Storage Conditions: The application contains up to 12 months of long-term stability data (25°C/60% RH), and 6 month accelerated stability (40°C/65% RH), for 3 stability batches manufactured at (b) (4) L scale. Dr. Kasi reviewed the stability information. In-use study stability data support short-term exposure of product to indoor light (NMT (b) (4) days). *Based on available stability data, an expiration period of 24 months is granted when stored at 25°C (77°F) in the commercial packaging protected away from light. The drug product is a preservative free product packaged in single dose vial. Discard any unused portion.* Please refer to the drug product review dated 3/18/21 in Panorama for additional information.

Container and Carton Label Review: The drug product reviewer completed review of the container and carton label. Comments related to prescribing information will be resolved during OND labeling review. Refer to the Dr. Kasi's labeling review dated 3/26/2021 for additional information.

Biopharm Waiver: The proposed product, levothyroxine sodium injection is a solution dosage form and is quantitatively and qualitatively (Q1/Q2) different from the listed drug, a lyophilized powder that requires reconstitution before use. The proposed product formulation uses SBECD for (b) (4) sodium chloride for tonicity adjustment, arginine for (b) (4) and EDTA for (b) (4) (b) (4) The pH of the proposed product is approximately (b) (4) pH units (b) (4) than the listed drug (pH (b) (4)). To bridge the proposed product to the LD product, the applicant requested a biowaiver of the *in vivo* bioavailability studies under 21 CFR 320.24(b)(6) on the basis that changes to the listed drug formulation will not affect the pharmacokinetic profile of levothyroxine sodium injection.

Accordingly, the applicant provided additional information including physicochemical properties comparison between the proposed drug product and the listed drug product after reconstitution in 0.9% sodium chloride solution. The applicant's response included rationale, why change in formulation and pH will not affect the pharmacokinetic performance or clinical safety and efficacy outcomes of the proposed drug product when compared to the reference product. Biowaiver request was reviewed by Dr. Rajesh Savkur. Biopharm reviewer deemed the applicant's justification as adequate to support the request for biowaiver and concluded that additional in vivo bioequivalence (BE) bridging study is not needed. Please refer to Dr. Savkur's review dated 3/19/2021 in Panorama for additional details.

OVERALL ASSESSMENT AND SIGNATURES:

At present, there are no outstanding deficiencies related to the drug substance, drug product, process, facility, microbiology, biopharmaceutics, and environmental analysis sections of this NDA. The OPQ overall recommendation for NDA *214253 is approval.*

Muthukumar Ramaswamy, Ph.D. 4/1/2021

Application Technical Lead Name and Date:

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CHAPTER IV: LABELING

IQA NDA Assessment Guide Reference

1.0 PRESCRIBING INFORMATION

Assessment of Product Quality Related Aspects of the Prescribing Information: Adequate with revisions provided below.

1.1 HIGHLIGHTS OF PRESCRIBING INFORMATION

Item	Information Provided in the NDA	Assessor's Comments
Product Title in Highlights		
Proprietary name	LEVOTHYROXINE SODIUM injection, for intravenous use	Adequate
Established name(s)		
Route(s) of administration		
Dosage Forms and Strengths Heading in Highlights		
Summary of the dosage form(s) and strength(s) in metric system.	(b) (4)	Injection: 100 mcg/mL in a single-dose vial. Ready-to-use solution. (3)
Assess if the tablet is scored. If product meets guidelines and criteria for a scored tablet, state "functionally scored"	NA	
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.		

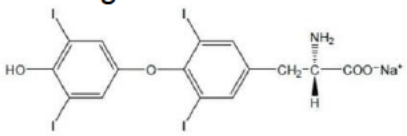
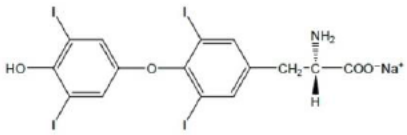
1.2 FULL PRESCRIBING INFORMATION

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)		

1.2.2 Section 3 (DOSAGE FORMS AND STRENGTHS)

Item	Information Provided in the NDA	Assessor's Comments
DOSAGE FORMS AND STRENGTHS section		
Available dosage form(s)	(b) (4)	• Levothyroxine sodium injection 100 mcg/mL is a clear, colorless to slightly yellow solution supplied as 1 mL per vial.
Strength(s) in metric system		
If the active ingredient is a salt, apply the USP Salt Policy per FDA Guidance		
A description of the identifying characteristics of the dosage forms, including shape, color, coating, scoring, and imprinting		
Assess if the tablet is scored. If product meets guidelines and criteria for a scored tablet, state "functionally scored"		
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.		

Item		Assessor's Comments
DESCRIPTION:		
Proprietary and established name(s)	Levothyroxine Sodium Injection contains synthetic (b) (4) levothyroxine (L-thyroxine) sodium salt. Levothyroxine sodium has an empirical formula of $C_{15}H_{10}I_4NNaO_4$, a molecular weight of 798.85 g/mol (anhydrous), and the following structural formula:  Levothyroxine Sodium Injection is a sterile, preservative-free, clear, colorless to slightly yellow, solution for intravenous administration available as (b) (4) Each mL of Levothyroxine Sodium Injection also contains 0.05 mg arginine, USP; 80 mg betadex sulfobutyl ether sodium, USP; 0.05 mg edetate disodium, USP; and water for injection, USP. Sodium chloride, USP was added to adjust tonicity. Hydrochloric acid, NF and/or sodium hydroxide, NF may have been added for pH adjustment. (b) (4) (b) (4)	Levothyroxine sodium injection contains synthetic levothyroxine (L-thyroxine) sodium salt. Levothyroxine sodium has an empirical formula of $C_{15}H_{10}I_4NNaO_4$, a molecular weight of 798.85 g/mol (anhydrous), and the following structural formula:  Levothyroxine sodium injection is a sterile, preservative-free, clear, colorless to slightly yellow solution for intravenous administration available as 100 mcg/mL in a single-dose clear glass vial. Each mL of levothyroxine sodium injection also contains 0.05 mg arginine, USP; 80 mg betadex sulfobutyl ether sodium, USP; 0.05 mg edetate disodium, USP; and water for injection, USP. Sodium chloride, USP was added to adjust tonicity. Hydrochloric acid, NF and/or sodium hydroxide, NF may have been added for pH adjustment.
If the active ingredient is a salt, apply the USP Salt Policy and include the equivalency statement per FDA Guidance.		
List names of all inactive ingredients. Use USP/NF names. Avoid Brand names.		
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.		
If alcohol is present, must provide the amount of alcohol in terms of percent volume of absolute alcohol		
Statement of being sterile (if applicable)		
Pharmacological/ therapeutic class		
Chemical name, structural formula, molecular weight		
If radioactive, statement of important nuclear characteristics.		
Other important chemical or physical properties (such as pKa or pH)		

Section 11 (DESCRIPTION) Continued

Item	Information Provided in the NDA	Assessor's Comments
For oral prescription drug products, include gluten statement if applicable	None.	
Remove statements that may be misleading or promotional (e.g., "synthesized and developed by Drug Company X," "structurally unique molecular entity"	None.	

Section 16 (HOW SUPPLIED/STORAGE AND HANDLING)

Item	Information Provided in the NDA	Assessor's Comments
HOW SUPPLIED/STORAGE AND HANDLING section		
Available dosage form(s) Strength(s) in metric system Available units (e.g., bottles of 100 tablets)	(b) (4)	Levothyroxine Sodium Injection 100 mcg/mL is a clear, colorless to slightly yellow solution, supplied as1 mL per vial. Package of 1 single-dose vial: NDC 24201-002-01
Identification of dosage forms, e.g., shape, color, coating, scoring, imprinting, NDC number	Protect from light and store product at 20° to 25°C (68° to 77°F) [see USP Controlled Room Temperature]. Drug product is preservative free. Discard any unused portion.	Protect from light and store product at 20° to 25°C (68° to 77°F) [see USP Controlled Room Temperature]. Drug product is preservative free. Discard any unused portion.
Assess if the tablet is scored. If product meets guidelines and criteria for a scored tablet, state "functionally scored"	(b) (4)	
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.		

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.)	See above	
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."	N/A	
Storage conditions. Where applicable, use USP storage range rather than storage at a single temperature.	See above.	
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	No Information included.	

1.2.3 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 for: Leucadia Pharmaceuticals Carlsbad, CA 92011 USA www.leucadiapharma.com	Comment was added to the Applicant in the PI to clarify the role of Leucadia Pharmaceuticals with respect to the applicant.

2.0 PATIENT LABELING

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

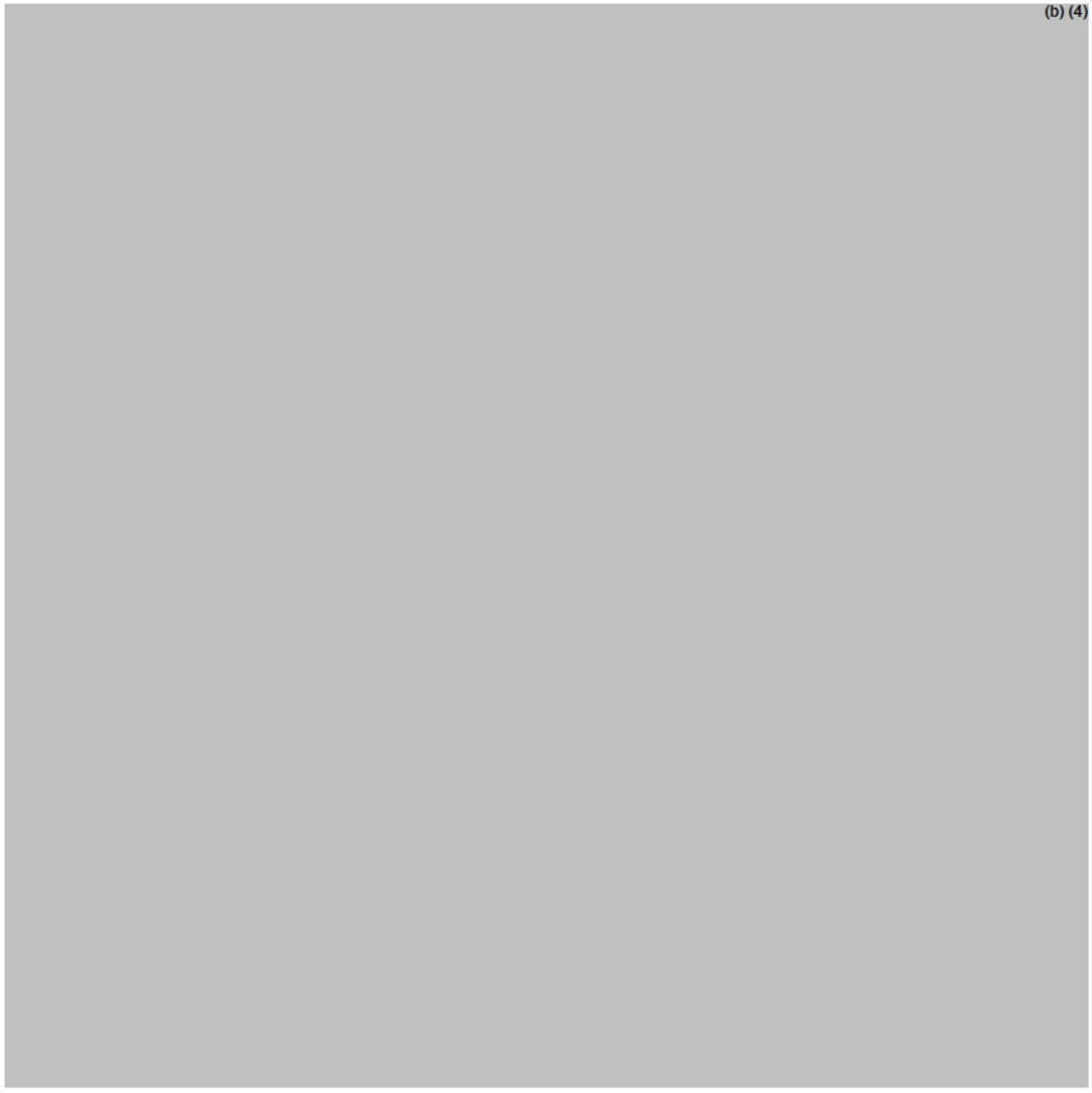
No Information included.

3.0 CARTON AND CONTAINER LABELING

3.1 Container Label

(b) (4)

3.2 Carton Labeling



Assessment of Carton and Container Labeling: *Adequate*

The following IR was sent to the applicant on 03/16/21:

1. Revise the strength format of the drug product in your carton and container labels to "100 mcg/mL" instead of "(b) (4)"

Overall Assessment and Recommendation:

The labeling/labels will be adequate from a quality perspective after the recommended changes have been made.

Dhanalakshmi Kasi

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David Claffey

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CHAPTER VII: MICROBIOLOGY

Product Information	
NDA Number	214253
Assessment Cycle Number	1
Drug Product Name/ Strength	Levothyroxine Sodium Injection 100 mcg/1 mL
Route of Administration	Intravenous injection
Applicant Name	Custopharm Inc.
Therapeutic Classification/ OND Division	Division of Metabolism and Endocrinology Products
Manufacturing Site	(b) (4)
Method of Sterilization	

Assessment Recommendation: **Adequate**

Assessment Summary:

List Submissions being assessed (table):

Document(s) Assessed	Date Received
0002	7/17/2020
0007	12/16/2020

Highlight Key Issues from Last Cycle and Their Resolution: Not applicable

Remarks: The drug product is indicated for the treatment of myxedema coma.

Concise Description of Outstanding Issues: None

Supporting Documents:

- Type V, DMF (b) (4) and the associated microbiology review D11648M33R01 for information on the stopper (b) (4)
- Type V, DMF (b) (4) and associated microbiology reviews D25912M01R01 and D25912M02R01.

S DRUG SUBSTANCE

The drug product is subjected to [redacted] (b) (4) Therefore, the drug substance will not be reviewed for sterility assurance.

P.1 DESCRIPTION OF THE COMPOSITION OF THE DRUG PRODUCT

(Section 3.2.P.1, "Description and Composition of the Drug Product," p. 2)

- **Description of drug product –** Levothyroxine Sodium Injection, 100 mcg/mL is a sterile clear solution filled as 1 mL single-dose per vial.

- **Drug product composition –**

Component	Function	Concentration (mg/mL)	Amount (mg) per Unit Container
Levothyroxine sodium, USP	Active ingredient	0.100	0.100
L-arginine, USP	[redacted] (b) (4)	0.05	0.05
Disodium edetate dihydrate, USP		0.05	0.05
Sulfobutyl ether beta-cyclodextrin sodium, NF (SBECD)		80.0	80.0
Sodium chloride, USP	Tonicity adjuster	[redacted] (b) (4)	
Sodium hydroxide, NF	pH adjuster	q.s. to pH [redacted] (b) (4)	
Hydrochloric acid [redacted] (b) (4) %, NF			
Water for Injection, USP	Diluent	q.s. to volume	q.s. to [redacted] (b) (4) mL

- **Description of the container closure system –**

Component	Description	Supplier
Vial	[redacted]	(b) (4)
Stopper		
Seal		

Assessment: *Adequate*

The information provided by the applicant regarding the drug product, ingredients, and container closure system meets regulatory expectations.

P.2 PHARMACEUTICAL DEVELOPMENT
P.2.5 MICROBIOLOGICAL ATTRIBUTES

Container/Closure and Package Integrity

(Section 3.2.P.7, "Container Closure Integrity Report VAL-1104-SUM")

[redacted] (b) (4)

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Assessment: *Adequate*

The applicant has met regulatory expectations with regard to the test method, acceptance criteria and verification of the suitability of use of the sterility test that will be performed on the drug product prior to its release.

P.7 CONTAINER CLOSURE- See Section P.1

P.8 STABILITY

P.8.1 STABILITY SUMMARY AND CONCLUSION

The proposed expiry is 24 months at 20 - 25 ºC. The drug product exhibit batches will be subject to sterility and bacterial endotoxins testing on samples stored upright and inverted position at long-term conditions (25 ± 2°C/60 ± 5% RH), at accelerated conditions (40 ± 2°C/75 ± 5% RH), and at intermediate conditions (30 ± 2°C/65 ± 5% RH). The stability specifications are the same as the drug product release criteria.

The stability of three exhibit batches are being evaluated (Batch # (B-19-024, B-19-025, and B-19-026). Bacterial endotoxins and sterility testing will be performed at 6 months for samples stored at accelerated conditions; at 12, 24, and 36 months for samples stored at long-term conditions; and at 12 months for samples stored at intermediate conditions.

P.8.2 POST-APPROVAL STABILITY PROTOCOL AND STABILITY COMMITMENT

The applicant commits to continue the stability studies on the three batches currently stored in long-term conditions. In addition, commits to add yearly thereafter at least one production batch to the stability program. Bacterial endotoxins and sterility testing will be performed at 12, 24, and 36 months for samples stored at long-term conditions.

P.8.3 STABILITY DATA

The applicant provided bacterial endotoxins and sterility data up to 6 months for samples stored at accelerated conditions, and up to 12 months at long-term conditions. The microbiological tests met the applicant's acceptance criteria.

Assessment: *Adequate*

The applicant has met regulatory expectations with regard to the design of the stability testing program to support the drug product's microbiological quality throughout its shelf life. In addition, the stability data submitted to date support the microbiological quality of the subject drug product.

R REGIONAL INFORMATION

Executed Batch Records

The following executed batch records are included in the subject submission: batch numbers B-19-024, B-19-025, and B-19-026, with a batch size of (b) (4) L.

The batch records confirm that validated sterilization process and component sterilization/depyrogenation processes were used for the manufacture of the exhibit batches.

Assessment: *Adequate*

The batch records generally confirm that validated sterilization and aseptic manufacturing processes were used for the manufacture of the exhibit batches.

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

Prescribing Information

- *Storage temperature*: Store at 20 -25 °C
- *Route of administration*: Intravenous injection
- *Container*: Single-dose vials. Discard unused portion.

Assessment: *Adequate*

The applicant has met regulatory expectations with regard to the information related to issues of product quality microbiology that is provided in the product labeling.

MICROBIOLOGY LIST OF DEFICIENCIES: N/A

Primary Microbiology Assessor Name and Date: Maritere Carattini, MS, 21 December 2020

Secondary Assessor Name and Date: Erika Pfeiler, PhD, 04 January 2021

Maritere Carattini

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Erika Pfeiler

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BIOPHARMACEUTICS

Product Background:
NDA/ANDA: NDA-214253-ORIG-1

Drug Product Name / Strength: Levothyroxine sodium injection, 100 µg/mL

Route of Administration: Intravenous injection

Applicant Name: Custopharm Inc.

Executive Summary:
The Applicant proposed a new formulation of the 100 µg/mL strength of Levothyroxine sodium for the treatment of myxedema coma (b) (4) The proposed drug is based on the Listed Drug (LD) product — Levothyroxine sodium that was developed by Fresenius Kabi USA LLC available as lyophilized powder for injection in single-dose vials of 100 µg, 200 µg and 500 µg. The LD product was approved under NDA 202231 on 6/24/2011. Being lyophilized powder, the LD product requires reconstitution prior to its administration as an intravenous (IV) injection. The proposed product offers a ready-to-use liquid formulation for IV injection. The dosing regimen of the proposed Levothyroxine sodium injection is the same as that of the LD product. This NDA (NDA-214253-ORIG-1) was submitted to the Division of General Endocrinology on 7/17/2020 under section 505 (b)(2).

Since the excipients in the proposed product quantitatively and qualitatively (Q1/Q2) differ from the LD product, the Applicant has intended to bridge the proposed product to the LD product via 21 CFR 320.24(b)(6) and has requested a waiver of the *in vivo* bioavailability studies. The Biopharmaceutics assessment focuses on the information submitted to bridge the two products. As part of the bridging strategy, the Applicant submitted comparative physicochemical data to demonstrate that the osmolality of the proposed product was similar to the LD. Although the pH of the LD and the proposed products are different, the difference in the pH between the LD and proposed product is not expected to be clinically meaningful since the product is to be administered intravenously as a bolus injection in a small volume (5 mL). The Applicant also submitted literature evidence wherein the metabolic pathways of excipients unique to the proposed product or the LD were shown not to compete with the metabolic pathway of Levothyroxine sodium. Hence, the presence of the excipients unique to the proposed product or the exclusion of the excipients from the LD product are not expected to alter the *in vivo* PK profile of Levothyroxine sodium when administered intravenously. The totality of the data supports the scientific bridge between the proposed Levothyroxine sodium injection and the LD product, which justified the reliance on the FDA's previous findings of safety and effectiveness of the LD product for the approval of the proposed drug product per 505 (b)(2) application pathway.

From a Biopharmaceutics perspective, this Reviewer concludes that NDA-214253-ORIG-1 for Levothyroxine sodium injection (100 µg/mL) is ADEQUATE and is RECOMMENDED for approval.

List Submissions being reviewed:	
07/17/2020	Original submission/Sequence 0002

Biopharmaceutics Assessment

Bridging:

The Listed Drug (LD) product is available as lyophilized powder in single-dose vials of 100 µg, 200 µg and 500 µg. The LD product is directed to be reconstituted with 5 mL of 0.9% sodium chloride prior to IV administration. The proposed product of 100 µg is developed as a ready-to-use injectable solution in a volume of 1 mL yielding a final concentration of 100 µg/mL.

The Applicant intends to bridge the proposed product to the LD via 21 CFR 320.24(b)(6) and has requested a waiver of the bioavailability studies. The Applicant has submitted information in support of the bridge between the LD and the proposed product. The details are presented in the Link to information to support bridging between proposed and LD products.

Reviewer's Assessment:

Formulation differences between the proposed and the LD product:

The proposed product – Levothyroxine sodium injection for the IV injection product contains the same active ingredient as the LD product. The composition of the LD and the proposed product are shown below in table 1.

Table 1: Composition of LD and proposed product

Ingredient	Function	LD Product[1]		Custopharm Proposed Product
		100 mcg/vial	500 mcg/vial	Amount per mL
Levothyroxine sodium	Active ingredient	100 mcg	500 mcg	100 mcg*
Sulfobutylether –β-cyclodextrin (SBECD)	(b) (4)			80 mg
Disodium edetate dihydrate				0.05 mg
L-arginine				0.05 mg
Hydrochloric acid, (b) (4)%				q.s. to adjust pH
Sodium hydroxide			(b) (4)	q.s. to adjust pH
Mannitol				
Dibasic sodium phosphate heptahydrate				
Sodium chloride				(b) (4)
0.9% Sodium chloride injection *(used for reconstitution)*		5 mL *(equivalent to 45 mg NaCl)*	5 mL *(equivalent to 45 mg NaCl)*	
Water for injection				q.s. to (b) (4) mL

* Batch quantity to be compensated based on the potency and water content

** Function is inferred based on Custopharm's understanding of the LD product

The LD product, when reconstituted with 5 mL of NaCl, yields final concentrations of 20 µg/mL, 40 µg/mL and 100 µg/mL for the 100 µg, 200 µg and 500 µg strengths, respectively. The proposed product of 100 µg is developed as a ready-to-use injectable solution in a volume of 1 mL yielding a final concentration of 100 µg/mL and is similar to the 500 µg strength of the LD product.

- The active ingredient, Levothyroxine sodium, in the proposed product is present in the same final concentration as the LD product(100 µg/mL).

- The inactive ingredients (highlighted in yellow) are not qualitatively/quantitatively (Q1/Q2) same.
- The LD contains mannitol as the (b) (4) dibasic sodium phosphate heptahydrate as the (b) (4) and sodium chloride (b) (4).
- The proposed product contains SBECD as the (b) (4) disodium EDTA as the (b) (4) (b) (4) HCl as the pH adjuster and sodium chloride as the tonicity adjuster.

The quantity of excipients in the LD and the proposed product administered at the maximum dose 500 µg of Levothyroxine is shown below in table 2:

Table 2: Quantity of excipients in the LD and proposed product at the maximum dose of 500 µg of Levothyroxine sodium

Ingredient	Qty. of excipient administered at max. levothyroxine dose of 500 mcg (b) (4) mL of proposed product) for 70 kg body weight	
	LD product	Custopharm's proposed product
Sulfobutylether –β-cyclodextrin (SBECD)		(b) (4)
Disodium edetate dihydrate		
L-arginine		
Mannitol	(b) (4)	
Dibasic sodium phosphate heptahydrate		
Sodium chloride		(b) (4)
Sodium hydroxide		q.s. to adjust pH
Hydrochloric acid, (b) (4)%		q.s. to adjust pH
Water for injection		NA

*Sodium chloride (0.9% Sodium chloride Injection is used for reconstitution)

The excipients in the LD product: Sodium phosphate heptahydrate and (b) (4) contribute towards (b) (4) Mannitol is an (b) (4) (b) (4)

The excipients in the proposed product: (b) (4) HCl contribute towards the pH. Sodium chloride, as the tonicity adjuster, (b) (4). Disodium EDTA is a (b) (4) (b) (4) SBECD functions as the (b) (4) (b) (4)

(b) (4)

(b) (4)

Comparison of physicochemical characteristics between the reconstituted LD and the proposed product:

A comparison of the physicochemical characteristics of reconstituted LD (one batch –batch# 6108767) and the proposed product (three batches – batch# B-19-024, B-19-025 and B-19-026) is shown below in table 3:

Table 3: Physicochemical characteristics of reconstituted LD and proposed product

Parameter	Proposed Product Specification	Results				
		LD batch 6108767, 500 mcg/vial (reconstituted to 100 mcg/mL*) Expiry: June 2016 Analysis date: 2016-03-02	LD batch 6119954, 500 mcg/vial Expiry: May 2020 Analysis date: 2020-02-25	Levothyroxine Sodium Injection, Exhibit Batch B-19-024[15] Mfg. date: 2019-04-30	Levothyroxine Sodium Injection, Exhibit Batch B-19-025[15] Mfg. date: 2019-04-30	Levothyroxine Sodium Injection, Exhibit Batch B-19-026[15] Mfg. date: 2019-05-01
Appearance	(b) (4)	Conforms		(b) (4)		
ID-A		Conforms		Meets specification	Meets specification	Meets specification
ID-B				Meets specification	Meets specification	Meets specification
Color of solution				(b) (4)		
pH of solution		(b) (4)				
Osmolality		304 mOsm/kg		302 mOsm/kg	303 mOsm/kg	303 mOsm/kg
Particulate matter – sub-visible particles by light obscuration particle count				(b) (4)		
Container content						

Based on the information submitted in table 3, the osmolality of the proposed product is similar to that of the reconstituted LD (304 mOsm/kg). The osmolality of the proposed product (303 mOsm/kg) and is controlled between (b) (4) mOsm/kg (the range is within (b) (4)% of the osmolality of the proposed product). This Reviewer finds this acceptable.

The pH of the proposed product is (b) (4) and is controlled (b) (4) whereas the pH of the reconstituted LD product is (b) (4) The pH of the proposed product is (b) (4) (b) (4) than the pH of the reconstituted LD solution. The Applicant has stated that both the proposed product and the LD reconstituted solution are labeled to be administered intravenously as a bolus injection without any further dilution with the highest volume of bolus injection to be only 5.0 mL. The Applicant has stated that the difference in pH between the products is not expected to influence availability of the drug *in vivo*. The Clinical Pharmacology Reviewer find's the Applicant's explanation acceptable.

Effect of excipients unique to the proposed product:

(i) L-arginine: L-arginine is a non-essential amino acid and is used as a (b) (4) (b) (4) The Applicant has stated that the normal physiological levels of L-arginine in plasma are 41 - 114 µmol/L which is equivalent to 36 - 99 mg for adult with 5 L of blood. The quantity of L-arginine administered at the maximum dose of 500 µg of the proposed product is 0.25 mg which results in a 0.25% to 0.69% increase in the levels of arginine *in vivo*. This increase in arginine

levels *in vivo* upon administration of proposed product is insignificant. The Applicant stated that the levels of L-arginine are self-regulated *in vivo*. Comparison of the metabolic pathways of Levothyroxine and arginine indicated that they do not compete with each other. Hence, the L-arginine administered with the proposed product does not influence *in vivo* pharmacokinetic profile of Levothyroxine sodium. This Reviewer finds the Applicant's explanation acceptable.

(ii) SBECD: SBECD is used as a [redacted] (b) (4) in the proposed product at a concentration of 80 mg/mL. The quantity of SBECD administered at maximum dose of Levothyroxine is 400 mg (5.71 mg/kg for an average body weight of 70 kg). To demonstrate that SEBCD does not alter the PK properties of the drug, the Applicant submitted literature evidence on two IV administered products that contain SBECD as the excipient (see below)

Product Name	Reported data on PK of the drug	Reference
Evomela (Melphalan) NDA 207155 **Highest drug dose per day:** 100 mg/m^2/day – 180 mg for 1.8m^2 **Qty. of SBECD administered at highest drug dose:** 9720 mg/day (i.e., 138.8mg/kg/day)	No significant differences in pharmacokinetic parameters or urinary excretion of melphalan were observed following single intravenous administration of melphalan in Captisol* or Captisol-free (Alkeran) formulations.	Pharmacology review (Page # 14/17) of Evomela for injection (NDA 207155) [21]
Baxdela (Delafloxacin) NDA 208611 **Highest drug dose per day:** 300 mg by intravenous infusion over 60 minutes, every 12 hours **Qty. of SBECD administered at highest drug dose:** 4800 mg/day (i.e., 68.5 mg/kg/day)	IV delafloxacin formulations (with or without SBECD). SBECD did not appear to alter delafloxacin PK.	Summary review (Page # 11/26) of Baxdela for injection (NDA 208611) [22]

*Captisol is a trade name for SBECD

The SBECD used in the formulation was not found to alter pharmacokinetics of the drug when compared to corresponding non SBECD formulation in normal subjects without renal impairment. This Reviewer notes that the quantity of SBECD administered at the highest dose in the proposed product is lower than the quantity of SBECD administered at the highest dose in the two drug products.

The Applicant has stated that there is no evidence of metabolism of SBECD in any animal species and that the excretion of SBECD is by renal elimination of unmetabolized. SEBCD was found to not undergo any metabolic changes after *in vivo* administration. There is no competing metabolic pathway of SBECD with that of levothyroxine sodium, hence the quantity of SBECD administered with proposed product does not influence *in vivo* levels of Levothyroxine sodium. Based on the submitted information, the Clinical Pharmacology Reviewer concludes that the SBECD in the formulation will not impact the PK of Levothyroxine in the proposed product.

(iii) Disodium EDTA dihydrate: Disodium edetate dihydrate is used as a [redacted] (b) (4) at a concentration of 0.05 mg/mL in the proposed product. At the highest dose of the proposed product (i.e., 500 µg of Levothyroxine), the total amount of disodium edetate dihydrate administered is only 0.25 mg/day (corresponds to 0.0036 mg/kg/day). The Applicant stated that EDTA is essentially not metabolized by the human body, and it is rapidly excreted in the urine. Comparison of metabolic pathways of Levothyroxine sodium and EDTA showed that they do not compete with each other and hence the pharmacokinetics of Levothyroxine sodium *in vivo* are not influenced by EDTA. Based on the Applicant's assessment, this Reviewer concludes that EDTA used in the proposed product is not expected to alter the *in vivo* PK parameters of Levothyroxine sodium.

(iv) Hydrochloric acid: HCl is used in the proposed product as a pH adjuster. [redacted] (b) (4) [redacted] (b) (4) The low quantities of H^+ ions do not cause any

significant change in physiological extracellular or intracellular acid-base balance, as these minute ionic changes are self-regulated in the body by elimination of H^+ or by acid-base buffering mechanisms and hence, are not expected to have any influence on the pharmacokinetics of Levothyroxine sodium. This Reviewer finds the Applicant's explanation acceptable.

Effect of excipients unique to the LD:

(i) Mannitol: Mannitol is a (b) (4) (b) (4) (b) (4) The Applicant stated that a comparison of metabolism of Levothyroxine sodium and mannitol showed that there is no competing metabolic pathway of mannitol with that of Levothyroxine sodium. Hence, the pharmacokinetics of Levothyroxine sodium *in vivo* was not expected to be influenced by mannitol. According to the Applicant, the dose of mannitol that did not cause any physiological effect has been reported as (b) (4) g (i.e. (b) (4) mg/kg). The quantity of mannitol administered with LD product at highest drug dose is only (b) (4) mg/kg and is (b) (4) times lower than the dose of mannitol ((b) (4) mg/kg) where no significant physiological effects are produced *in vivo*. Based on above assessment, the Applicant has stated that exclusion of mannitol from the LD product is not expected to influence *in vivo* levels of Levothyroxine sodium. This Reviewer finds the Applicant's explanation acceptable.

(ii) Dibasic sodium phosphate heptahydrate: Dibasic sodium phosphate heptahydrate is used as a (b) (4) in the LD product and at the highest drug dose (b) (4) mg (corresponding to (b) (4) mg/kg body weight) of (b) (4) is administered. The (b) (4) dissociates to phosphate and sodium ions. The Applicant stated that phosphate and sodium ions do not exhibit any competing metabolic pathway with that of Levothyroxine sodium, and hence are not expected to have any influence on pharmacokinetics of Levothyroxine sodium. This Reviewer finds the Applicant's explanation acceptable.

Effect of changes in the concentration of excipients in the proposed and LD products:

(i) Sodium hydroxide: Sodium hydroxide is used in proposed product and the reconstituted LD as a pH adjuster. (b) (4) The low quantities of OH^- ions do not cause any significant change in physiological extracellular or intracellular acid-base balance, as these minute ionic changes are self-regulated in the body by acid-base (b) (4) mechanisms are not expected to have any influence on the pharmacokinetics of Levothyroxine sodium. This Reviewer finds the Applicant's explanation acceptable.

(ii) Sodium chloride: Sodium chloride is used as tonicity adjusting aid in the proposed product (b) (4) The Applicant has stated that the quantity of NaCl administered at highest drug dose is (b) (4) (corresponds to (b) (4) body weight). Sodium chloride dissociates to Na^+ and Cl^- ions. Upon administration of proposed product, there is an insignificant increase (<0.2%) in the serum electrolytes concentration and such minor variations are self-regulated in the body fluids. Hence, sodium chloride is not expected to have any influence on the pharmacokinetics of Levothyroxine sodium *in vivo*. This Reviewer finds the Applicant's explanation acceptable.

Based on the above assessment, this Reviewer concludes that the presence of the excipients unique to the proposed product or the exclusion of the excipients from the LD are not expected to alter the *in vivo* PK profile of Levothyroxine sodium when administered intravenously. This Reviewer

concludes that the Applicant has submitted adequate information and justification in support of the bridge between the LD and the proposed product. Consistent with 21 CFR 320.24 (b)(6), this Reviewer has deemed the information supporting the relative bioavailability of the proposed drug product to the LD to be adequate, and a ***biobridge*** has been established to the Agency's finding of safety and effectiveness for the listed drug. Thus, an additional *in vivo* bioequivalence (BE) bridging study is not needed.

Rajesh Savkur

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