CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

210632Orig1s000

PRODUCT QUALITY REVIEW(S)

Recommendation: Approval

NDA 210632
Review 1

Drug Name/Dosage Form	Levothyroxine sodium
Strength	100 mcg, 200 mcg, and 500 mcg per 5 mL vial
Route of Administration	Intravenous
Rx/OTC Dispensed	Rx
Applicant	Fresenius Kabi
US agent, if applicable	

SUBMISSION(S) REVIEWED	DOCUMENT DATE	DISCIPLINE(S) AFFECTED
Original and amendments	Original submission (6/15/2018) and amendments (10/15/18, 11/16/18, 11/30/18, 12/07/18, 12/14/18, 12/28/18, 2/4/19, 2/12/19, and 2/21/19).	Quality module 3, 1.14 and 1.11

Quality Review Team

DISCIPLINE	REVIEWER	BRANCH/DIVISION
Drug Substance	Joseph Leginus	Branch II/New Drug API
Drug Product	Muthukumar Ramaswamy	Branch VI/New Drug Products II
Process	Ge Bai/Vidya Pai	Branch IV/Process Assessment II
Microbiology	Ash Bekele	Microbiology Assessment
Facility	Vidya Pai	Branch III/ Inspectional Assessment
Biopharmaceutics	Sarah Ibrahim	Branch II/Biopharmaceutics
Regulatory Business Process Manager	Anika Lalmansingh	Branch I/Regulatory Business Process Management I
Application Technical Lead	Muthukumar Ramaswamy	Branch VI/New Drug Products II
Environmental Analysis (EA)	Muthukumar Ramaswamy	Branch VI/New Drug Products II

Quality Review Data Sheet

1. RELATED/SUPPORTING DOCUMENTS

A. DMFs:

DMF #	Type	Holder	Item Referenced	Status	Date Review Completed	Comments
(b) (4)	Type II		(b) (4)	Adequate	9/5/2018 (Drug substance reviewer)	LOA 4/25/2018
	Type III			Adequate information in the NDA		LOA 2/9/2018
	Type III					LOA 2/12/ 2018
	Type III			Adequate	2/03/2017 (microbiology review)	LOA 2/9/2018
	Type V			Adequate	1/15/2015 & 2/08/2017 (microbiology review)	LOA 01/23/2017

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

DOCUMENT	APPLICATION NUMBER	DESCRIPTION
Not applicable		

2. CONSULTS

DISCIPLINE	STATUS	RECOMMENDATION	DATE	REVIEWER
Pharmacology/Toxicology	Complete	Acceptable. (Impurities and Leachables)	2/8/19	Dr. Thilagar/ Dr. Elmore

Executive Summary

I. Recommendations and Conclusion on Approvability

The recommendation from the Office of Pharmaceutical Quality for NDA 210632 is approval.

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) and marketed by Fresenius Kabi. Levothyroxine sodium for injection is a lyophilized powder and requires reconstitution before use.

The proposed levothyroxine sodium injection is a ready to use sterile, clear, colorless solution provided in single dose vials for intravenous injection. Each single dose vial contains 100 µg or 200µg or 500µg of active dissolved in 5mL of the product. The proposed product strengths (100 µg, 200µg and 500µg/vial) are the same as currently marketed levothyroxine sodium for injection product.

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 USP is manufactured by (b) (4). The applicant referenced (b) (4) Type II DMF (b) (4) for CMC information pertaining to drug substance. DMF (b) (4) was reviewed by Dr. J. Leginus. His review concluded that DMF (b) (4) contains adequate CMC information to support the NDA. It should be noted the same DMF was used previously to support the approval of Fresenius Kabi's levothyroxine sodium for injection product (NDA (b) (4)). Please refer to Dr. Leginus' s drug substance review dated 10/10/2018 for additional details.

Drug Product

Drug Product Formulation: The proposed drug product, levothyroxine sodium injection is a clear, colorless, sterile, isotonic solution packaged in a single dose vial.

Each vial contains 5mL of the proposed product containing either 100 or 200 or 500 mcg of levothyroxine sodium, 50mg of tromethamine USP, 0.7mg sodium iodide USP, and 32.4 mg sodium chloride USP in water for injection. pH of the formulation is adjusted (b) (4) using sodium hydroxide or hydrochloric acid. Drug substance solubility in the proposed pH is adequate to keep the excipients and active substance in solution during storage.

All excipients associated with the product are water soluble and present in approved products. Sodium iodide is provided (b) (4). Sodium chloride is provided (b) (4). The pH and osmolality of the proposed of the proposed product closely mimic the marketed levothyroxine sodium for injection after reconstitution with 0.9% sodium chloride.

The proposed drug product is filled in 10 mL (b) (4) glass vials, and sealed with (b) (4) stopper and aluminum seal. The product is light and oxygen sensitive. The vial contains (b) (4). Drug product filled in vial is packaged in carton. Storage in carton is recommended to prevent exposure to light during shelf-life. In-use study data support short-term exposure to indoor light (NMT 24 hours).

The compatibility of active ingredient with excipients and container closure components is supported by drug product stability data. The applicant provided extractable and leachable data to support the safety of the closure components proposed for use. Due to high pH of the proposed formulation (pH (b) (4)), the applicant evaluated the potential for glass delamination during real-time stability studies. Based on available data, the applicant concluded that the risk of glass delamination is low in the product (i.e., appearance of flake like particles) when stored at RT for up to 21-month time point. Please refer to M. Ramasamy's drug product review dated 2/19/19 for additional information.

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

The applicant is using the following in-process control tests to control quality of the product: (b) (4)

The proposed commercial manufacturing process and the process used for manufacturing stability batches are similar. The applicant submitted data from 3 exhibit batches for each of the three strengths manufactured at (b) (4) to (b) (4) scale.

Medium and high strength products (200 mcg and 500mcg per vial) were manufactured at (b) (4) scale. Low strength product batches (100mcg/vial) were manufactured at (b) (4) scale. The proposed commercial batch size for the low strength is (b) (4) times the size of exhibit batch. For the remaining two strengths, the proposed commercial batch size and exhibit batch size are comparable.

(b) (4)

(b) (4)

For detailed information on the manufacturing process and process control, refer to Dr. Vidya Pai's review in Panorama dated 2/19/19. Process review was initially performed Dr. Ge Bai till 11/5/2018. Final process review was completed Dr. Pai. Her process review concluded that the proposed drug product manufacturing process controls are adequate to support the NDA.

Microbiological control information: Microbiology reviewer, Dr. Ash Bekele reviewed the microbiological controls used in drug product manufacturing process. His review covered information on (b) (4) . Dr. Bekele also reviewed component sterilization and validation information provided in Type V DMF (b) (4). His review concluded that the proposed microbiological controls are adequate to support the NDA. Refer to CMC (Microbiology) review by Dr. Bekele dated 2/04/19 in Panorama under NDA 210632.

Control Strategy: The critical quality attributes of the product are controlled through batch records instructions, process design, component specifications, in-process controls (b) (4) , and adequate finished product specification.

The drug product is tested for visual clarity, color, appearance, identity, particulate matter, pH, osmolality, assay, impurities, closure integrity, endotoxin content, and sterility. drug product conforms to USP <1> injection, USP <788> particulate matter, US<71> sterility, and USP <85> bacterial endotoxin.

The proposed control strategy is adequate to assure the quality of the product. All impurities associated with the product are known or part of drug substance structure. Limits proposed for individual impurities were discussed with Pharm. Tox. reviewer. No safety concerns were identified. Please refer to M. Ramasamy's drug product review dated 2/19/19 for additional information.

Risk Assessment: CMC Reviewer's risk assessment for critical attributes is shown at the end of the review. In conclusion, the final risk is low for the proposed product. No further mitigation necessary (Attachment 1).

Facility compliance information: Facility compliance information for drug product and drug substance facilities was reviewed by Dr. Vidya Pai. Her facility compliance information review concluded that proposed facilities are acceptable to support the approval of NDA 210632. Please refer to her review in Panorama dated 2/12/2019.

Environmental assessment: The applicant sought exemption from environmental impact analysis per 21CFR 25.31(a) as the action on this NDA does not increase the use of levothyroxine sodium. Dr. M. Ramaswamy reviewed the request and granted categorical exclusion from submitting environment assessment. Please refer to drug product review dated 2/19/19 for additional information.

Biopharm Waiver:
Originally, the applicant requested a biowaiver for in-vivo bioavailability/ bioequivalence requirements in accordance with 21 CFR § 320.22(b). Since the inactive ingredients associated with the listed drug and the proposed ready to use levothyroxine sodium injection are not the same, it was determined that a biowaiver cannot be granted under 21 CFR 320.22(b)(1). However, the biopharm reviewer indicated she would consider the biowaiver request under 21 CFR 320.24(b)(6), if adequate justification was available to support the notion 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 formulation change will not affect the pharmacokinetic performance or clinical safety and efficacy outcomes of the proposed drug product when compared to the reference product.

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. Ibrahim's review dated 10/16/2018 in Panorama.

Expiration Date & Storage Conditions: The application contains 6 month accelerated stability (40°C/75% RH), 12 moths of intermediate storage stability data (30°C/65% RH) and 18 months of long-term stability data (25°C/60% RH) for 9 exhibit batches (3 batches per strength x three strengths). Stability update corresponding to the 18-month time point was provided during the end of review cycle. Stability information was reviewed by drug product reviewer and concluded that the product is stable. *An expiration period of 18 months is granted when stored at 20-25°C in commercial packaging. Product is sensitive to light. Product label requires storage of the*

product in carton at 20-25°C (68° to 77° F) to prevent degradation. Please refer to Dr. M. Ramaswamy's drug product review dated 2/15/19 in Panorama for additional information.

Container and Carton Label Review: Drug product reviewer completed review of container and carton label. *Dosage form, strength, established name, NDC #, Lot #/expiry, and storage conditions are adequately described in the carton and container label. Label information meets relevant regulatory requirements for labeling. Refer to Attachment II for copies of the container and carton label.*

OVERALL ASSESSMENT AND SIGNATURES:

At present, there are no outstanding deficiencies related to the drug substance, drug product, process/facilities, microbiology, biopharmaceutics environmental analysis, and container/ carton label sections of the NDA. *OPQ overall CMC recommendation for NDA 210632 is approval.*

The following CMC recommendation for shelf-life needs to be communicated to the applicant in the approval letter.

A shelf-life of 18 months is granted when stored in carton at 25°C/60% RH. Unopened vial may be stored exposed indoor lighting for up to 24hours outside of the carton.

Muthukumar Ramaswamy, Ph.D. 3/3/2019

Application Technical Lead Name and Date:

ATTACHMENT I: Final Risk Assessment

From Initial Risk Identification			*Review Assessment*		
Attribute/ CQA	***Factors that can impact the CQA***	***Initial Risk Ranking***	***Risk Mitigation Approach***	***Final Risk Ranking***	***Lifecycle Considerations/ Comments***
Drug content/ Assay	Solubility, Formulation, Process, Container closure	H	(b) (4)	L	none
Impurities/ degradants	Formulation, Process, Container closure & packaging	H		L	*Drug substance is sensitive to light, and oxygen. Mitigated through product label and process. Store in carton.* (b) (4) .
Appearance	Formulation, Process, Container closure	H		L	*none*
Sterility	Container closure Process (b) (4))	H		L	*none*
Endotoxins	Container closure Process	H		L	
Particulate matter	Formulation	H		L	*none*
pH	Formulation	H		L	*pH range (9.5-10.8)* (b) (4)
Leachable/ extractables	Formulation, Process, Container closure	M		L	*Potential for glass delamination exist, if stored beyond expiry. Future changes to container and closure system require leachables assessment.*

Muthukumar Ramaswamy, Ph.D., 3/3/2019

Application Technical Lead Name and Date:

Attachment II - LABELING

R Regional Information

1.14 Labeling

Immediate Container Label

(b) (4)

Reviewer's Assessment: *Adequate*
Dosage form, strength, established name, NDC #, Lot #/expiry, and storage conditions are adequately described in the carton and container label.

Carton Labeling

(b) (4)

Reviewer's Assessment: *Adequate*
Dosage form, strength, established name, NDC #, Lot #/expiry, and storage conditions are adequately described in the carton and container label, which meets relevant regulatory requirements under 21CFR 201.10(g)(2), 21 CFR.35(b)(3)(i), 21CFR 201.17 and 21CFR.201.25.

List of Deficiencies: None

Overall Assessment: Adequate

Muthukumar Ramaswamy, Ph.D., 3/3/2019

Primary Labeling Reviewer Name and Date:

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MICROBIOLOGY

Product Background:

NDA: 210632

Drug Product Name: Levothyroxine Sodium Injection
Strength: 100 mcg/5 mL, 200 mcg/5 mL and 500 mcg/5 mL

Route of Administration: IV Injection

Applicant Name: Fresenius Kabi USA, LLC

Manufacturing Site: Fresenius Kabi USA, LLC, 2020 North Ruby Street, Melrose Park, IL, US 60160. FEI: 1450022, DUNS: (b) (4)

Method of Sterilization: (b) (4)

Review Recommendation: **Adequate**

Theme (ANDA only): **N/A**

Justification (ANDA only): N/A

Review Summary:

List Submissions Being Reviewed:06/15/2018, 10/5/2018

Highlight Key Outstanding Issues from Last Cycle: N/A

Remarks: All the sterilization and validation information is referenced to a Type V DMF (b) (4). It was noted that the NDA applicant is also the holder of the DMF. The DMF (b) (4) has been repeatedly reviewed from the stand point of sterility assurance. The recent requalification information relevant to the sterility assurance of the subject NDA 210632 was reviewed in (b) (4), dated 11/09/2018 and deemed adequate.

Concise Description Outstanding Issues Remaining: None

Supporting Documents:
Microbiology reviews of the Type V DMF (b) (4) for the overall manufacturing processes, environmental controls and validation of the (b) (4) processes ((b) (4), dated 02/08/2017; (b) (4), dated 4/26/2018 and (b) (4), dated 11/09/2018, and deemed adequate)

Microbiology review of the (b) (4) of the rubber stoppers in DMF (b) (4)

((b) (4), 2/03/2017 and deemed adequate).

List Number of Comparability Protocols (ANDA only):N/A

P.1 Description of the Composition of the Drug Product

(Reference is made to 3.2.P.1. Description and Composition of the Drug Product)

- **Description of drug product** — The drug product, Levothyroxine Sodium Injection, is a sterile solution for intravenous injection. The drug product is presented in three strengths (100 mcg/5 mL, 200 mcg/5 mL, 500 mcg /5 mL 5 mL), 5 mL fill in 10 mL vial.
- **Drug product composition** —The drug product is compounded with the API (Levothyroxine Sodium, USP) and other USP/NF grade ingredients are listed in the applicant table below.

Composition of the drug product (100 mcg / 5 mL)

Ingredient	Content per mL	Content per 5 mL (unit)	Function	Quality of Ingredient
Levothyroxine Sodium	20 mcg	100 mcg	Active Ingredient	USP
Tromethamine	10 mg	50 mg	(b) (4)	USP
Sodium Iodide	0.14 mg	0.7 mg		USP
Sodium Chloride	6.48 mg	32.4 mg		USP
(b) (4)				
Hydrochloric Acid, (b) (4)/ Sodium Hydroxide, NF	As required	As required	pH Adjuster	NF

- **Description of container closure system** – (Reference is made to 3.2.P.7 Container Closure System (Levothyroxine Sodium Injection, 100µg/5mL, 200µg/5mL, 500µg/5mL, Injection, Solution). The DP is (b) (4) . The vials are purchased from (b) (4) and the (b) (4) stoppers are from (b) (4)

Reviewer's Assessment: (Adequate)
The applicant provided an adequate description of the drug product, its composition and the primary container closure system designed to maintain product sterility.

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BIOPHARMACEUTICS

Product Background: This New Drug Application is submitted by Fresenius Kabi USA, LLC (FK USA) in accordance with Section 505(b)(2) of the Federal Food, Drug and Cosmetic Act (21 U.S.C. 355) to seek marketing clearance for Levothyroxine Sodium Injection. Levothyroxine sodium injection is indicated for the treatment myxedema coma.

NDA: 210632

Drug Product Name / Strength: Levothyroxine Sodium Injection / 100 mcg/ 5mL (0.1 mg/vial); 200 mcg/ 5mL (0.2mg/vial); 500 mcg/ 5mL (0.5 mg/vial)

Route of Administration: Intravenous

Applicant Name: Fresenius Kabi USA, LLC

Review Summary:

The Applicant requested a biowaiver for Levothyroxine sodium injection per 21 CFR 320.24 (b)(6) since their proposed product contains the same active ingredient in the same concentration as the approved reference product, Levothyroxine Sodium For Injection, (By Fresenius Kabi USA LLC: Approved NDA 202231). However, the inactive ingredients of the proposed and reference products are not qualitatively and quantitatively (Q1/Q2) the same.

The Applicant provided adequate justification for the differences in the inactive ingredients, and in the physiochemical properties between the proposed and listed drug products. Consistent with 21 CFR 320.24 (b)(6), FDA deemed the information supporting the relative bioavailability of Fresenius Kabi USA's proposed drug product to the listed drug 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.

From the Biopharmaceutics perspective, NDA 210632 for Levothyroxine Sodium for Injection, 100 mcg/ 5mL (0.1 mg/vial); 200 mcg/ 5mL (0.2mg/vial); 500 mcg/ 5mL (0.5 mg/vial) is recommended for **approval.**

List Submissions being reviewed:

Submission Date	Purpose of Submission
June 15, 2018	Original
October 5, 2018	Amendment – Information Request

Highlight Key Outstanding Issues from Last Cycle: N/A

Concise Description Outstanding Issues Remaining: N/A

BCS Designation

Reviewer's Assessment: N/A for intravenous product

Solubility:

Permeability:

Dissolution:

Biowaiver Request

Reviewer's Assessment:

- The proposed Levothyroxine sodium injection for Injection product contains the same active ingredient in the same concentration as the approved reference product Levothyroxine Sodium For Injection, (By Fresenius Kabi USA LLC: Approved NDA 202231). However, the inactive ingredients of the proposed and reference products are not qualitatively and quantitatively (Q1/Q2) the same.
- The following tables compare the proposed product and the reference product:

Excipient	Strength		Functionality
	Levothyroxine Sodium For Injection, (By Fresenius Kabi USA LLC: Approved NDA 202231) (Lyophilized powder)	Fresenius Kabi USA LLC's Levothyroxine Sodium Injection (Liquid ready to use Injection)	
Sodium Chloride, USP	-	6.48 mg/mL	(b) (4)
Sodium Hydroxide, NF	(b) (4)	As needed	pH adjuster
Hydrochloric Acid, USP	-	As needed	pH adjuster
			(b) (4)
			(b) (4)

- The proposed product is meant to be ready for use formulation and has the same active ingredient as current lyophilized Reference Listed Drug (Levothyroxine Sodium for Injection) product.
- The difference between the formulations is in the inactive ingredients. The proposed product has tromethamine, sodium iodide and sodium chloride in place of mannitol, dibasic sodium phosphate heptahydrate and (b) (4).
- Tromethamine and sodium chloride are used as a (b) (4) and to (b) (4) of the proposed product, respectively.
- The pH, calculated ionic strength as well as measured osmolarity of the proposed drug product is identical to that of the reference listed drug

Property	The Proposed Drug Product (Fresenius Kabi USA's Levothyroxine Sodium Injection)	RLD (Fresenius Kabi USA's Levothyroxine Sodium for Injection)
Appearance	Clear colorless liquid free from visible particulates	Lyophilized product to be reconstituted with 0.9% sodium chloride injection. Reconstituted solution is a clear colorless liquid free from visible particulates
Calculated Ionic Strength (mOsm/L)	(b) (4)	(b) (4)
Measured Osmolality (mOsm/kg)	Average results of ICH batches Product code 100µg/5mL: 295 Product code 200µg/5mL: 294 Product code 500µg/5mL: 294	Reconstituted Solution of commercial batches: Product code 100µg/vial (lot # 6114622): 295 Product code 200µg/vial (lot # 6112864): 296 Product code 500µg/vial (lot # 6111345): 299
pH	FP specification: (b) (4)	FP specification: (b) (4)
	Average per code for ICH batches Product code 100µg/5mL: 10.3 Product code 200µg/5mL: 10.3 Product code 500µg/5mL: 10.3	Reconstituted Solution of commercial batches: Product code 100µg/5mL (Lot# 6113415): 10.5 Product code 200µg/5mL (Lot # 6112864): 10.6 Product code 500µg/5mL (Lot # 6113348): 10.6
Density (g/mL)	Average per code from Development samples: Product code 100µg/5mL: 0.999 Product code 200µg/5mL: 0.998 Product code 500µg/5mL: 0.998	Reconstituted solution of commercial batches: Product code 100µg/5mL (lot # 6114622): 0.953 Product code 200µg/5mL (lot # 6112864): 0.981 Product code 500µg/5mL (lot # 6111345): 0.958
Viscosity (cP)	Average per code from Development samples: Product code 100µg/5mL: 1.2 Product code 200µg/5mL: 1.0 Product code 500µg/5mL: 1.1	Reconstituted solution of commercial batches: Product code 100µg/5mL (lot # 6114622): 1.1 Product code 200µg/5mL (lot # 6112864): 1.0 Product code 500µg/5mL (lot # 6111345): 1.0

- The Applicant requests a waiver of the requirement for in vivo bioavailability testing of the proposed drug product per 21 CFR 20.24 (b)(6) – *Any other approach deemed adequate by FDA to measure bioavailability or establish bioequivalenc*e, and in response information request included in the 74 day letter and submitted data to justify the differences in the inactive ingredients between the proposed product and the reference product.

Reviewer's Note:

The following comments were conveyed to the Applicant in the 74-day letter dated 28 August 2018:

Since your product does not contain the same inactive ingredients as the reference drug, a biowaiver cannot be granted as per 21 CFR 320.22(b)(1). However, if you can provide justification that the proposed changes in formulation will not affect the PK of the listed drug and that the pH and osmolality of the proposed drug product are similar compared to those of the listed drug, based on 21 CFR 320.24(b)(6), the bridge (bioavailability/bioequivalence) between the listed and the proposed drug product may be established.

In addition, we recommend you to submit the following supporting data/information:
a. A table of side-by side comparison of the active and inactive ingredients between the listed drug and your proposed dug product.
b. Comparison of the physiochemical characteristics (i.e. pH and osmolality) between your proposed drug product and the listed drug products;
c. Your justification for any differences between the two formulations and to demonstrate that the difference for each active and/or inactive ingredient would not affect the pharmacokinetic performance towards any difference in clinical safety and/or efficacy outcome particularly the use of 0.14 mg/mL of sodium iodide.

A summary of the firm's 28 August 2018 response is as follows:

Comparative physicochemical data showing similarity between the proposed product and referenced product when reconstituted and diluted in 0.9% NaCl solution (as per the package insert). The following tests have been performed in order to demonstrate the sameness with Levothyroxine Sodium for Injection: pH, osmolality, surface tension, viscosity, and specific gravity and are Adequate.

The evaluated physicochemical parameters of the injectable solution (pH, viscosity and osmolality) are similar between test and reference product. Therefore, there are no differences that could affect the pharmacokinetic performance and/or the clinical safety and efficacy outcome of proposed drug product when compared with those of the reference product.

The minor differences noted in terms of ionic strength, osmolality, density and viscosity are considered to have very limited clinical relevance. From a biowaiver perspective alone, the minor differences of the injectable solution are not expected to influence the pharmacokinetic performance of the product, as long as the bioavailability of Levothyroxine Sodiumafter IV administration is always 100%.

In conclusion, from a clinical perspective, there is no expected inactive formulation affect on the pharmacokinetic performance and/or the clinical safety and efficacy outcome of proposed drug product compared with those of the reference product.

The applicant submitted reference and literature to support that the free iodide released from the conversion of T4 to T3 in peripheral tissues enters the general circulation where it may be re-used or eliminated. In conditions of excess of iodine supply, less than 10% of iodine is taken up by thyroid and approximately 90% is excreted in urine. It has also been reported in the literature that iodide does not affect the protein-binding and metabolism of exogenously administered levothyroxine.

In reference to the above information, sodium iodide is not likely to have an impact on the pharmacokinetics of the proposed product as the low iodine content will not have an effect on the body's homeostasis. Any excess iodide will be either excreted by the kidneys or re-used for thyroid hormone synthesis to maintain the equilibrium between the intra-thyroidal and extra-thyroidal levels of iodine.

Reviewer's comments:

- The reviewer agrees that the differences in pH, osmolality and viscosity of the final proposed and reference drug products (i.e. reconstituted and diluted to a final concentration of 1 mg/mL with 0.9% sodium chloride) are minor, and therefore the differences will not possibly affect the pharmacokinetic performance or clinical safety and efficacy outcomes of the proposed drug product when compared to the reference product. The following table highlights that these physiochemical properties are similar:

	The Proposed Drug Product (Fresenius Kabi USA's Levothyroxine Sodium Injection)	**Fresenius Kabi USA's Levothyroxine Sodium for Injection)**
pH	(b) (4) Product code 100µg/5mL: 10.3 Product code 200µg/5mL: 10.3 Product code 500µg/5mL: 10.3	(b) (4) Product code 100µg/5mL (Lot# 6113415): 10.5 Product code 200µg/5mL (Lot # 6112864): 10.6 Product code 500µg/5mL (Lot # 6113348): 10.6
Osmolality (mOsm/kg)	Product code 100µg/5mL: 295 Product code 200µg/5mL: 294	Reconstituted Solution of commercial batches: Product code 100µg/vial (lot # 6114622): 295

	Product code 500µg/5mL: 294	Product code 200µg/vial (lot # 6112864): 296 Product code 500µg/vial (lot # 6111345): 299
Viscosity (mm^2/s)	Product code 100µg/5mL: 1.2 Product code 200µg/5mL: 1.0 Product code 500µg/5mL: 1.1	Reconstituted solution of commercial batches: Product code 100µg/5mL (lot # 6114622): 1.1 Product code 200µg/5mL (lot # 6112864): 1.0 Product code 500µg/5mL (lot # 6111345): 1.0

- Based on the information provided, as it is consistent with 21 CFR 320.24. (b)(6), FDA deemed the information supporting the relative bioavailability of Fresenius Kabi USA's proposed drug product to the listed drug 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. The Drug Product and Pharmacology/Toxicology review addresses quality and safety of the proposed drug product formulation. The application is acceptable from Biopharmaceutics perspective.

List of Deficiencies: N/A

Primary Biopharmaceutics Reviewer Name and Date:

Sarah Ibrahim, Ph.D., October 16, 2018

Secondary Reviewer Name and Date:

Haritha Mandula, Ph.D. October 31, 2018

Acting Biopharmaceutics Lead

DB/ONDP/OPQ

Sarah Ibrahim

Digitally signed by Sarah Ibrahim
Date: 2/08/2019 02:04:27PM
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Haritha Mandula

Digitally signed by Haritha Mandula
Date: 2/08/2019 02:28:49PM
GUID: 508da6fb000282df41459408f32a1ce0

Muthukumar Ramaswamy

Digitally signed by Muthukumar Ramaswamy
Date: 3/05/2019 12:17:41PM
GUID: 508da7210002a0c0870017f6c83398f4