CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

215809Orig1s000

PRODUCT QUALITY REVIEW(S)

QUALITY ASSESSMENT

Recommendation: Approval

NDA 215809
Review 1

Drug Name/Dosage Form	Trade Name (levothyroxine sodium) oral solution
Strength	150 mcg/100 mL (30 mcg/mL)
Route of Administration	Oral
Rx/OTC Dispensed	Rx
Applicant	Mylan Pharmaceuticals
US agent, if applicable	-

SUBMISSION(S) REVIEWED	DOCUMENT DATE	DISCIPLINE(S) AFFECTED
Original submission, and amendments	Original submission: 6/30/2021 Amendments: 8/13/2021,10/12/2021, 10/14/2021, 12/22/21, and 2/22/2022	Quality modules 3, 1.14, and 1.11

Quality Review Team

Discipline	Reviewer/Secondary	Branch/division
Drug Substance	Daniel Jansen/ Suong Tran	Branch III/Division of New Drug API/Office of New Drug Products (ONDP)
Drug Product	Rao Kambhampati / Muthukumar Ramaswamy	Branch V/Division of New Drug Products III/ONDP
Process/ Facility Microbiology	Shannon Heine/ Bethanie Lee	Division of Microbiology Assessment/ Office of Pharmaceutical Manufacturing Assessment (OPMA)
Regulatory Business Process Manager	Nowrin Kakon / Hamet Toure	Branch I/Regulatory Business Process Management I
Application Technical Lead	Muthukumar Ramaswamy	Branch V/Division of New Drug Products III/ONDP
Environmental Analysis (EA)	Rao Kambhampati / Muthukumar Ramaswamy	Branch V/Division of New Drug Products III /ONDP

Quality Review Data Sheet

1. RELATED/SUPPORTING DOCUMENTS

A. DMFs:

DMF #	Type	Holder	Item Referenced	Status	Date Assessment Completed	Comments
(b) (4)	II		(b) (4)	Active	June 25, 2021	LOA dated January 21, 2021
	III			Active	*	LOA dated 2/02/2021
	III			Active	*	LOA dated January 26, 2021
	III			Active	*	LOA dated May 12, 2021

*Sufficient information provided in the NA

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

DOCUMENT	APPLICATION NUMBER	DESCRIPTION
IND	141382	Levothyroxine sodium solution

2. CONSULTS: None

DISCIPLINE	STATUS	RECOMMENDATION	DATE	REVIEWER
Pharm./Tox. – Limit for impurities	Completed	Acceptable	9/20/2021	Dr. Dongyu Guo

Executive Summary

I. Recommendations and Conclusion on Approvability

The recommendation from the Office of Pharmaceutical Quality (OPQ) for NDA 215809 is approval, which includes an acceptable recommendation for the facilities listed in the application.

II. Summary of Quality Assessments

A. Product Overview

The proposed 505(b)(2) application is for TRADENAME (levothyroxine sodium) oral solution, 150 mcg/5 mL. Each mL of the drug product contains 30 mcg of levothyroxine sodium. The proposed drug product is a clear, colorless solution provided in a multiple-dose amber glass bottle with child resistant closure. The dose will be measured and administered using a co-packaged oral dosing syringe. An oral solution offers flexibility with respect to ease of administration to people having swallowing difficulty and dose adjustment.

This NDA references Synthroid (levothyroxine sodium) tablets as the listed drug (NDA 021402). Synthroid was approved in 2002. The proposed product is for treatment of hypothyroidism and Pituitary TSH suppression (see below, proposed indication section).

The drug product should be stored at 20°C to 25°C (68°F to 77°F) in original bottle protected away from light. Excursions permitted between 15°C and 30°C (59°F and 86°F). The product needs to be used within 90 days of first opening.

Proposed Indication(s) including Intended Patient Population	Hypothyroidism and Pituitary TSH suppression
Duration of Treatment	See CDTL memo
Maximum Daily Dose	300 mcg
Alternative Methods of Administration	Not applicable

B. Quality Assessment Overview

Drug Substance

The drug substance is manufactured by (b) (4) The applicant provided reference to (b) (4) for all chemistry manufacturing and control (CMC) information related to the drug substance, levothyroxine sodium USP. The chemical name for the drug substance is monosodium L-thyroxine hydrate. The molecular formula and molecular weight of the drug substance is respectively $C_{15}H_{10}I_4NNaO_4 . xH_2O$ and

798.85 g/mol (anhydrous). The drug substance is a light yellow to buff colored powder, hygroscopic, and slightly soluble in water. Dr. Daniel Jansen reviewed the CMC drug substance information.

Dr. Jansen's review concluded that the CMC information provided in the NDA and DMF (b) (4) is adequate to support the NDA. There is no risk of (b) (4) impurities associated with the commercial drug substance manufacturing process. The drug substance will be stored at (b) (4) with a retest period of (b) (4) months. For additional details, please refer to Dr. Jansen's CMC reviews dated 10/19/2021 under NDA 215809 and under DMF (b) (4) (dated June 25, 2021) in Panorama.

Drug Product

the drug product is a clear, colorless to nearly colorless solution provided in 75 mL or 150 mL amber glass bottle sealed with a child resistant closure. Each mL contains 30 mcg levothyroxine sodium, (b) (4) glycerin, and (b) (4) edetate disodium, in purified water. (b) (4) The composition of the proposed commercial product is the same as the composition of the batch used in BE and stability studies. The excipients used in the drug product are compendial grade.

Dr. Kambhampati reviewed the drug product information including drug product composition, drug product specification including assay and limits proposed for impurities, excipient information, analytical methods, container closure system, dosing syringe information, compatibility information, stability data, and environmental assessment (EA). Excipients proposed for use in the product are present at or below the levels present in approved product. Dr. Kambhampati granted the exemption for environmental assessment per 21 CFR 25.31.

The drug product is tested for appearance, identity, pH, assay of active, impurities, deliverable volume, uniformity of dosage units, closure integrity, and microbiological contamination test. Dr. Kambhampati reviewed the chemistry testing aspects of the drug product specification and Dr. Shannon Heine reviewed the microbiological contamination controls part of the product specification. The microbiology and drug product reviewers concluded that the proposed drug product specification is adequate to support the NDA. For details, please refer to Dr. Kambhampati' s drug product review dated 3/14/2022 and Dr. Heine's review dated 10/25/2021 in Panorama.

The application contains 18 months of long-term stability data (25°C/60% RH), 90day in-use stability data, and 6 month accelerated stability data (40°C/65% RH) for 3 primary stability batches manufactured at commercial scale ((b) (4) kg). Based on available stability data, an expiration period of 24 months is granted for the product, when stored at 20°C to 25°C (68°F to 77°F) in commercial packaging. An in-use period of 90 days after first opening is granted for the product. Dr. Kambhampati also completed CMC labeling review for this NDA. Dr. Kambhampati' s overall recommendation for this NDA is adequate. Please refer to Dr. Kambhampati' s drug product and labeling reviews dated 2/22/2022 in panorama for additional information. Comments related to the carton and container label will be resolved during OND labeling review.

Manufacturing Process and Facility: Dr. Shannon Heine reviewed the manufacturing process controls, batch record, and facility compliance information . The drug product manufacturing process, and the packaging system used to manufacture the drug product used in stability and BE studies is the same as that proposed for commercial use. The manufacturing process involves the (b) (4)

(b) (4)

The overall manufacturing inspection recommendation (OMIR) from the Office of Process Manufacturing Assessment (OPMA) for this NDA is approve. The Panorama screen shot of the facility assessment recorded on 3/15/2022 is shown below. Dr. Heine's review concluded that the process and facility information in the NDA is adequate. For additional details, please refer to Dr. Heine's process/facility review in Panorama dated 11/10/2021.

(b) (4)

(b) (4)

OVERALL ASSESSMENT AND SIGNATURES:

At present, there are no outstanding deficiencies related to the drug substance, drug product, process/facility, and microbiology sections of the NDA. The OPQ overall recommendation for NDA *215809 is approval.*

Muthukumar Ramaswamy, Ph.D. 3/15/2022

Application Technical Lead Name and Date

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FDA U.S. FOOD & DRUG ADMINISTRATION

CHAPTER IV: LABELING
NDA 215809

1.0 PRESCRIBING INFORMATION

Assessment of Product Quality Related Aspects of the Prescribing Information:

Note: Labeling comments related to the Prescribing Information (PI) will be finalized during the OND labeling review. The comments listed in this review are preliminary.

Some changes are recommended to the following subsections and, the deficiencies are listed in the "Items for Additional Assessment" section of this review near the end:

Highlights of Prescribing Information (DOSAGE FORMS and STRENGTHS);

Section 3 (DOSAGE FORMS AND STRENGTHS);

Section 16 (HOW SUPPLIED/STORAGE AND HANDLING); and

Name and location of business of the manufacturer, distributor, and/or packer.

1.1 HIGHLIGHTS OF PRESCRIBING INFORMATION

Item	Items in Proposed in Prescribing Information (PI) Labeling (choose "Adequate", "Inadequate", or "N/A")	Assessor's Comments on PI labeling (If an item is Inadequate, provide more details on the issues, as appropriate)
Product Title in Highlights		
Established name(s)[1]	Adequate	Tradename™ (levothyroxine sodium) oral solution.
Route(s) of administration	Adequate	Oral
Dosage Forms and Strengths Heading in Highlights		
Summary of the dosage form(s) and strength(s) in metric system	Adequate	Oral Solution: 150 mcg per 5 mL (30 mcg per mL) in 90 mL or 180 mL bottles.

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

Assess if the tablet is scored. If product meets guidelines and criteria for a scored tablet, state "functionally scored".	N/A	
For injectable drug products for parental administration, use appropriate package type term (e.g., single-dose, multiple-dose, single-patient-use). Other package terms include pharmacy bulk package and imaging bulk package.	N/A	
If the drug product contains an active ingredient that is a salt, clearly state whether the strength is based on the active moiety (e.g., Tablets: 10 mg of drug-x) or active ingredient (e.g., Tablets: 10 mg of drug-x hydrochloride).	Inadequate	Change the current statement to the following: Oral Solution: 150 mcg levothyroxine sodium per 5 mL (30 mcg levothyroxine sodium per mL) in 90 mL or 180 mL Note: The reason for not including the "levothyroxine sodium" in the Dosage Forms and Strengths probably because the strength in the USP monographs for tablets and injection dosage forms and in approved FDA drug products (including oral solution formulation, Thyquidity™) is based on the sodium salt.

1.2 FULL PRESCRIBING INFORMATION

1.2.1 Section 2 (DOSAGE AND ADMINISTRATION)

Item	Items in Proposed Labeling (choose "Adequate", "Inadequate", or "N/A")	Assessor's Comments (If an item is Inadequate, provide more details on the issues, as appropriate)
DOSAGE AND ADMINISTRATION section		
Special instructions for product preparation (e.g., reconstitution and resulting concentration, dilution, compatible diluents, storage conditions needed to maintain the stability of	N/A	

the reconstituted or diluted product)		
Important administration instructions supported by product quality information (e.g., do not crush or chew extended-release tablets, instructions for mixing with food)	N/A	
For parenteral products: include statement: *"Parenteral drug products must be inspected visually for particulate matter and discoloration prior to administration, whenever solution and container permit"*	N/A	
If there is a USP monograph for the drug product and it contains a labeling requirement, ensure the labeling requirement is fulfilled. Note the labeling requirement may be applicable to another section of the PI (e.g., Section 11).	N/A	
For radioactive products, include radiation dosimetry for the patient and healthcare practitioner(s) who administer the drug	N/A	
For hazardous products, include the statement *"DRUG X is a hazardous drug. Follow applicable special handling and disposal procedures.[x]"* with x numerical citation to "OSHA Hazardous Drugs".	N/A	

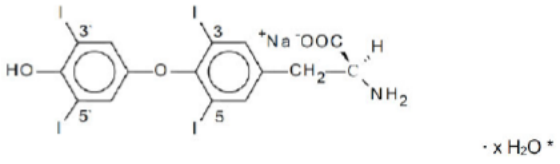
1.2.2 Section 3 (DOSAGE FORMS AND STRENGTHS)

Item	Items in Proposed Labeling (choose "Adequate", "Inadequate", or "N/A")	Assessor's Comments (If an item is Inadequate, provide more details on the issues, as appropriate)
DOSAGE FORMS AND STRENGTHS section		
Available dosage form(s)	Adequate	Oral solution
Strength(s) in metric system	Adequate	150 mcg/5 mL (30 mcg/mL)
If the active ingredient is a salt, apply the USP Salt Policy per FDA Guidance. Clearly state whether the strength is based on the active moiety (e.g., Tablets: 10 mg of drug-x) or active ingredient (Tablets: 10 mg of drug-x hydrochloride).	Inadequate	Change the current statement to the following: Oral Solution: 150 mcg levothyroxine sodium per 5 mL (30 mcg levothyroxine sodium per mL) in 90 mL or 180 mL amber glass bottle with child-resistant closure. Note: The reason for not including the "levothyroxine sodium" in the Dosage Forms and Strengths section probably because the strength in the USP monographs for tablets and injection dosage forms and in the approved FDA drug products (including oral solution formulation, Thyquidity™) is based on the sodium salt.
A description of the identifying characteristics of the dosage forms, including shape, color, coating, scoring, imprinting, and color and clarity of the solution, when applicable	Adequate	Clear, colorless solution supplied in a 90 mL or 180 mL amber glass bottle with child-resistant closure.
Assess if the tablet is scored. If product meets guidelines and criteria for a scored tablet, state "functionally scored"	N/A	
For injectable drug products for parental administration, use appropriate package type term (e.g., single-dose, multiple-dose, single-patient-use). Other package type terms include pharmacy bulk package and imaging bulk package.	N/A	

Section 11 (DESCRIPTION)

Appears this way on original

Item	Items in Proposed Labeling (choose "Adequate", "Inadequate", or "N/A")	Assessor's Comments (If an item is Inadequate, provide more details on the issues, as appropriate)
DESCRIPTION section		
Proprietary and established name(s)	Adequate	Tradename™ (levothyroxine sodium) oral solution.
Dosage form(s) and route(s) of administration	Adequate	Oral solution
If the active ingredient is a salt, apply the USP Salt Policy and include the equivalency statement per Salt Guidance and MAPP. For example: "TRADENAME contains 100 mg of drug-x (equivalent to 123.7 mg of drug-x hydrochloride)"	Adequate	TRADENAME oral solution is supplied in the following strength: 150 mcg per 5 mL (30 mcg per mL). Note: No equivalency statement is included because USP monographs for tablets and injection dosage forms and approved FDA drug products (including oral solution formulation, Thyquidity™) are based on the sodium salt. However, it is advisable to include an equivalency statement.
List names of all inactive ingredients. Use USP/NF names in alphabetical order. Avoid brand names.	Adequate	TRADENAME oral solution contains the inactive ingredients: edetate disodium, glycerin and purified water.
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.	N/A	
If alcohol is present, must provide the amount of alcohol in terms of percent volume of absolute alcohol	N/A	
Sterility statement (if applicable)	N/A	
Pharmacological/Therapeutic class	Adequate	Synthetic L-3,3',5,5'-tetraiodothyronine sodium salt [levothyroxine (T4) sodium]

Chemical name, structural formula, molecular weight	Adequate	Levothyroxine (T4) sodium hydrate has an empirical formula of $C_{15}H_{10}I_4NNaO_4$ with x ≈ 5*, molecular weight of 798.85 (anhydrous), and structural formula as shown:  $\cdot x H_2O$ *
If radioactive, statement of important nuclear characteristics.	N/A	
Other important chemical or physical properties (such as pKa or pH)	Adequate	Very slightly soluble in water.

Section 11 (DESCRIPTION) Continued

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

1.2.4 Section 16 (HOW SUPPLIED/STORAGE AND HANDLING)

Appears this way on original

Item	Items in Proposed Labeling (choose "Adequate", "Inadequate", or "N/A")	Assessor's Comments (If an item is Inadequate, provide more details on the issues, as appropriate)
HOW SUPPLIED/STORAGE AND HANDLING section		
Available dosage form(s)	Adequate	Oral Solution
Strength(s) in metric system	Adequate	150 mcg per 5 mL (30 mcg per mL) is a clear, colorless solution supplied in a 90 mL or 180 mL amber glass bottle with a child-resistant closure.
Available units (e.g., bottles of 100 tablets)	Adequate	NDC 49502-378-75 75 mL oral solution in 90 mL amber glass bottles NDC 49502-378-15 150 mL oral solution in 180 mL amber glass bottles
Identification of dosage forms (e.g., shape, color, coating, scoring, imprinting, and color and clarity of the solution, when applicable); Include NDC(s)	Adequate	Clear, colorless solution. NDC 49502-378-75 75 mL oral solution in 90 mL amber glass bottles NDC 49502-378-15 150 mL oral solution in 180 mL amber glass bottles
Assess if the tablet is scored. If product meets guidelines and criteria for a scored tablet, state "functionally scored"	N/A	
For injectable drug products for parental administration, use appropriate package type term (e.g., single-dose, multiple-dose, single-patient-use). Other package terms include pharmacy bulk package and imaging bulk package.	N/A	

Special handling about the supplied product (e.g., protect from light, refrigerate). If there is a statement to "Dispense in original container," provide reason why (e.g., to protect from light or moisture, to maintain stability, etc.). For hazardous drugs, state "DRUG X is a hazardous drug. Follow applicable special handling and disposal procedures.[x]" with x numerical citation to "OSHA Hazardous Drugs."	Adequate	Protect from light. Use within 90 days of opening the bottle. Store and dispense in original bottle. Use within 90 days of opening the bottle.

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

Item	**Items in Proposed Labeling** (choose "Adequate", "Inadequate", or "N/A")	**Assessor's Comments** (If an item is Inadequate, provide more details on the issues, as appropriate)
Storage conditions. Where applicable, use USP storage range rather than storage at a single temperature.	Inadequate	Store at 20° to 25°C (68° to 77°F). [See USP Controlled Room Temperature.] Protect from light. It is recommended to modify the statement to the following including excursion: 20°C to 25°C (68°F to 77°F), excursions permitted between 15°C to 30°C (59°F to 86°F) [See USP Controlled Room Temperature]. Protect from light.
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	Adequate	Glass bottle with a child-resistant closure.

1.2.5 Other Sections of Labeling: Not applicable.

1.2.6 Manufacturing Information After Section 17 (for drug products)

Item	Items in Proposed Labeling (choose "Adequate", "Inadequate", or "N/A")	Assessor's Comments (If an item is Inadequate, provide more details on the issues, as appropriate)
Manufacturing Information After Section 17		
Name and location of business (street address, city, state, and zip code) of the manufacturer, distributor, and/or packer	Inadequate	Information was not included.

2.0 PATIENT LABELING:

Assessment of Patient Information Document:

Item	Items Proposed in Patient Information Document (choose "Adequate", "Inadequate", or "N/A")	Assessor's Comments on Proposed Patient Information Document (If an item is Inadequate, provide more details on the issues, as appropriate)
Established name[2]	Adequate	TRADENAME™ (levothyroxine) sodium) Oral Solution
Special preparation instructions (if applicable)	Adequate	
Storage and handling information (if applicable)	Inadequate	**How should I store TRADENAME?** • Store TRADENAME at room temperature between 20° to 25°C (68° to 77°F). • Protect from light. • Store TRADENAME in the original bottle. Use TRADENAME within 90 days of opening the bottle. **Keep TRADENAME and all medicines out of the reach of children.** Change storage statement to the following: Store TRADENAME at room temperature between 68°F to 77°F (20°C to 25°C).
If the product contains a desiccant, ensure the desiccant has a warning (e.g., "Do not eat.") and the size and shape of the desiccant differs from the dosage form.	N/A	
Active ingredient(s) (if applicable)	Adequate	Levothyroxine sodium
Alphabetical listing of inactive ingredients (if applicable)	Adequate	Edetate disodium, glycerin, and purified water.
Name and location of business (street address, city, state, and zip code) of manufacturer, distributor, and/or packer	Adequate	Manufactured for: Mylan Specialty, L.P., Morgantown, WV 26505 U.S.A.

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

3.0 CONTAINER AND CARTON LABELING

3.1 Container (bottle) Labels

In the NDA copies of the labels on the 75 mL and 150 mL drug product bottles were provided. A representative example of the 150 mL bottle label is provided below:

(b) (4)

3.2 Carton Labeling

In the NDA, copies of the carton labels were provided for the 75 mL and 150 mL drug product bottle presentations. A representative example of the carton label proposed for the 150 mL bottle is provided below:

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Item	Items Proposed for Container and Carton Labeling (choose "Adequate", "Inadequate", or "N/A")	Assessor's Comments on Container and Carton Labeling (If an item is Inadequate, provide more details on the issues, as appropriate)
Established name[3], (font size and prominence)	Adequate	Tradename™ (levothyroxine sodium) Oral Solution.
Strength(s) in metric system	Adequate	150 mcg/5mL (30 mcg/mL)
Route(s) of administration	Adequate	For Oral Administration Only
If the active ingredient is a salt, include the equivalency statement per Salt Guidance and MAPP.	Adequate	Each 5 mL contains: Levothyroxine sodium, USP 150 mcg. No equivalency statement is included because USP monographs for tablets and injection dosage forms and approved FDA drug products (including oral solution formulation, Thyquidity™) are based on the sodium salt. However, it is advisable to include an equivalency statement.
Net contents (e.g., tablet count, volume of liquid)	Adequate	150 mcg/5 mL (30 mcg/mL)
"Rx only" displayed on the principal display	Adequate	Rx Only
NDC	Adequate	NDC 49502-378-15
Lot number and expiration date	Adequate	Yes, space was included for lot number and expiration date.
Storage conditions. If applicable, include a space on the carton labeling for the user to write the new beyond-use-date (BUD).	Inadequate	Store at 20° to 25°C (68° to 77°F) [See USP Controlled Room Temperature.] It is recommended to modify the storage statement to the following by including excursion: Store at 20°C to 25°C (68°F to 77°F), excursions permitted between 15°C to 30°C (59°F to 86°F) [See USP Controlled Room Temperature].

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

For injectable drug products for parental administration, use appropriate package type term (e.g., single-dose, multiple-dose, single-patient-use). Other package terms include pharmacy bulk package and imaging bulk package, and these products require a “Not for direct infusion” statement.	N/A	
For parenteral injectable dosage forms, include the name and quantities of all active and inactive ingredients in alphabetical order. For ingredients added to adjust the pH or make isotonic, include the name and statement of effect.	N/A	
If alcohol is present, must provide the amount of alcohol in terms of percent volume of absolute alcohol	N/A	
Linear Bar code	Adequate	Included

Item	Items Proposed in Container and Carton Labeling (choose "Adequate", "Inadequate", or "N/A")	Assessor's Comments on Container and Carton Labeling (If an item is Inadequate, provide more details on the issues, as appropriate)
Name of manufacturer/distributor /packer	Adequate	Manufactured for: Mylan Specialty L.P. Morgantown, WV 26505 U.S.A. Manufactured by: DPT Laboratories, Ltd. San Antonio, TX 78215 U.S.A.
If there is a Medication Guide, must include a statement about dispensing a Medication Guide to each patient.	N/A	
No text on Ferrule and Cap overseal, unless a cautionary statement is required.	N/A	
If there is a USP monograph for the drug product and it contains a labeling requirement, ensure the labeling requirement is fulfilled.	N/A	There is no USP monograph for oral solution product.
When a drug product differs from the relevant USP standard of strength, quality, or purity, as determined by the application of the tests, procedures, and acceptance criteria set forth in the relevant compendium, its difference shall be plainly stated on its label.	N/A	
And others, if space is available.	N/A	

Assessment of Container and Carton Labeling: ***Adequate after the proposed changes (see Items for Additional Assessment section below) are made in the revised documents.***

ITEMS FOR ADDITIONAL ASSESSMENT

The following deficiencies were identified:

1. ***In the Highlights of Prescribing Information (DOSAGE FORMS AND STRENGTHS) Section of the PI, change the current statement to the following by including the name of the active ingredient as salt: "Oral Solution: 150 mcg levothyroxine sodium per 5 mL (30 mcg levothyroxine sodium per mL) in 90 mL or 180 mL".***

2. ***In the Section 3 (DOSAGE FORMS AND STRENGTHS) section of the PI, change the current statement to the following by including the name of the active ingredient as salt: "Oral Solution: 150 mcg levothyroxine sodium per 5 mL (30 mcg levothyroxine sodium per mL) in 90 mL or 180 mL amber glass bottle with child-resistant closure.***
3. ***In the Section 16 (HOW SUPPLIED/STORAGE AND HANDLING) of the PI and on the bottle and carton labels, change the current statement to the following by including excursion: " Store at 20°C to 25°C (68°F to 77°F), excursions permitted between 15°C to 30°C (59°F to 86°F) [See USP Controlled Room Temperature].***
4. ***In the Prescribing Information document include the following information: Name and location of business (street address, city, state, and zip code) of the manufacturer, distributor, and/or packer.***
5. ***In the Patient Information Document, change the storage statement to the following: "Store TRADENAME at room temperature between 68°F to 77°F (20°C to 25°C)."***

Overall Assessment and Recommendation:

Adequate after the proposed changes (see "Items for Additional Assessment" section above) are made in the revised labeling documents.

Primary Labeling Assessor Name and Date: Rao V. Kambhampati, Ph.D. 2/22/2022

Rao Kambhampati

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Muthukumar Ramaswamy

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CHAPTER VII: MICROBIOLOGY

IQA NDA Assessment Guide Reference

Product Information	
NDA Number	215809
Assessment Cycle Number	1
Drug Product Name/ Strength	Levothyroxine Sodium Oral Solution, 150 mcg/5 mL
Route of Administration	Oral
Applicant Name	Mylan Pharmaceuticals, Inc
Manufacturing Site	DPT Laboratories, Ltd. 307 E. Josephine Street San Antonio, TX 78215
Method of Sterilization	N/A (non-sterile product)

Assessment Recommendation: **Adequate**

Assessment Summary:

Document(s) Assessed	Date Received
Seq 0001 (1)	30 June 2021
Seq 0002 (2)	13 August 2021
Seq 0003 (3)	12 October 2021

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

Remarks: The subject drug product is a clear, colorless solution free from any suspended or foreign particles presented in either a 90 or 180 mL (b) (4) Amber Glass Bottle with a white child-resistant (b) (4) Cap and (b) (4) film. It is a combination product, co-packaged with 5 and 10 mL oral syringes and indicated as a replacement therapy in congenital or acquired hypothyroidism. A product quality microbiology Information Request was conveyed to the applicant, dated 13 September 2021.

The submission is recommended for approval from the standpoint of product quality microbiology.

Concise Description of Outstanding Issues: N/A

Supporting Documents: N/A

S DRUG SUBSTANCE

The manufacturing process for the drug substance is not reviewed because the drug product is non-sterile.

P.1 DESCRIPTION OF THE COMPOSITION OF THE DRUG PRODUCT

- **Description of drug product**
  (See Section 3.2.P.1 (Seq 0001), *Description and Composition of the Drug Product*)
  The subject drug product is a is a clear, colorless solution free from any suspended or foreign particles presented in either a 90 or 180 mL (b) (4) Amber Glass Bottle with a white child-resistant (b) (4) Cap and (b) (4) film.

- **Drug product composition**

Ingredient	mg per mL	Pharmaceutical Function
Levothyroxine Sodium*	0.03	Active
Glycerin	(b) (4)	
Edetate Disodium		
Purified Water		

*Nominal amount. Actual amount will be calculated based on purity

- **Description of container closure system**

Configuration	Component	Description	Manufacturer
90 mL	Bottle	90 mL, (b) (4) Amber Glass. 28mm	(b) (4)
	Closure	Cap, 28/20 CRC (Child Resistance Cap), White, Tamper Evident Closure w/ (b) (4)	(b) (4)
180 mL	Bottle	180 mL, (b) (4) Amber Glass, 28mm	(b) (4)
	Closure	Cap, 28/20 CRC (Child Resistance Cap), White, Tamper Evident Closure w/ (b) (4)	(b) (4)

Assessment: *Adequate*
The applicant provided an adequate description of the drug product composition and the container closure system.

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(b) (4)

R REGIONAL INFORMATION

Executed Batch Records
(See Section 3.2.R (Seq 0001), *Drug Product Executed Batch Records*)

Executed batch record #(s): PDS-C, PDT-C, and PDW-C

Assessment: *Adequate*
The executed batch records provide adequate support for the manufacturing of the drug product.

Comparability Protocols
No CP was included in the application.

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

2.A. Prescribing Information
(See Section 1.14.1.3 (Seq 0001), *Draft Labeling Text*)

Storage temperature: Store at 20° to 25°C (68° to 77°F). [See USP Controlled Room Temperature.] Protect from light.
Store and dispense in original bottle. Use within 90 days of opening the bottle
Route of administration: oral
Container: multi-dose
Post-dilution/constitution hold time- N/A

Assessment: *Adequate*
The applicant has met regulatory expectations regarding product quality microbiology information provided in the package insert.

MICROBIOLOGY LIST OF DEFICIENCIES

None.

Primary Microbiology Assessor Name and Date: Shannon Heine, PhD, 20 October 2021

Secondary Assessor Name and Date: Bethanie Lee, PhD, 20 October 2021
"I concur."

Shannon Heine

Digitally signed by Shannon Heine
Date: 10/26/2021 06:45:12AM
GUID: 5d3b22d0000f55e971f4d77300610879

Bethanie Lee

Digitally signed by Bethanie Lee
Date: 10/25/2021 02:51:02PM
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/s/

MUTHUKUMAR RAMASWAMY
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