

**CENTER FOR DRUG EVALUATION AND
RESEARCH**

APPLICATION NUMBER:
202231Orig1s000

CHEMISTRY REVIEW(S)

NDA 202231

Levothyroxine Sodium for Injection

Summary of the Basis for the Recommended Action
from Chemistry, Manufacturing, and Controls

Applicant: APP Pharmaceuticals, LLC.
1501 E. Woodfield Rd.
Suite 300
E. Schaumburg, IL 60173

Indication: Levothyroxine sodium for injection is indicated to treat (b) (4) (b) (4) myxedema coma.

Presentation: Levothyroxine sodium for injection is packaged in single-use amber glass vials closed with a 20 mm gray (b) (4) rubber lyophilization stopper and capped with an aluminum crimped flip cap seal available in three dosage strengths: 100 mcg/vial, 200 mcg/vial and 500 mcg/vial.

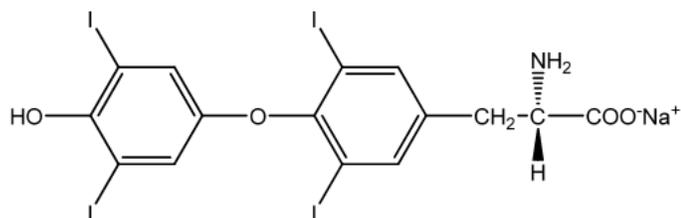
Establishments Evaluation Report (EER) Status: **Acceptable**

Consults:	EA -	Acceptable
	Statistics -	N/A
	Methods Validation -	Not requested
	Biopharm -	N/A
	Microbiology -	Acceptable
	Pharm Toxicology -	N/A

Original Submission: August 30, 2010
Re-submissions: N/A
Post-Approval CMC Agreements: None at this time.

Drug Substance

Levothyroxine sodium ($C_{15}H_{10}I_4NNaO_4$; MW = 798.85) is a light yellow to buff-colored, odorless, hygroscopic powder. It is stable in dry air but may assume a slight pink color upon exposure to light. It is very slightly soluble in water and slightly soluble in alcohol. Levothyroxine sodium is manufactured in the optically active L-form and has the following structure:



The drug substance specifications meet all requirements of the current USP monograph for levothyroxine sodium (updated Aug 1, 2008) with the addition of description, residual solvents, bioburden and bacterial endotoxins. All impurities and their limits are the same as listed in the USP monograph.

Information for the drug substance is provided in the (b) (4) DMF (b) (4) and is incorporated by reference herein. A copy of the letter of authorization to reference DMF (b) (4) has been provided. The DMF was reviewed by J. Leginus on Feb 11, 2011 and found to be adequate. The retest period for the drug substance is set at (b) (4) (b) (4)

Drug substance is satisfactory

Drug product

The drug product, levothyroxine sodium for injection, is a sterile, lyophilized powder consisting of the active ingredient, synthetic levothyroxine sodium, and the excipients dibasic sodium phosphate, heptahydrate, USP; mannitol, USP; and sodium hydroxide, NF. Levothyroxine sodium for injection is packaged in single-use amber glass vials available in three dosage strengths: 100 mcg/vial, 200 mcg/vial and 500 mcg/vial. The manufacturing process for the drug product involves (b) (4)

The proposed release specifications include description, reconstitution time, visual inspection, pH, (b) (4) uniformity of dosage units, instrumental color, identity (HPLC), assay (HPLC), individual and total impurities (HPLC), (b) (4) container/closure integrity, particulate matter, sterility and bacterial endotoxin. All noncompendial regulatory methods have been validated.

(b) (4) Also, amber glass vials are used as the primary packaging material, which have been shown to adequately protect the lyophilized drug product from degradation due to light.

The applicant has provided only 6 months of real time (25°C/60% RH) and accelerated (40°C/75% RH) stability data for the three strengths of the drug product in stoppered and sealed vials. Results from stability studies show that the drug product remains

stable through 6 months under both conditions. In-use results show that drug product reconstituted with the recommended reconstitution diluent (0.9% sodium chloride injection, USP) remains stable for up to 4 hours at room temperature following dissolution, which supports the drug product label statement of “Use immediately after reconstitution”. Based on these data, and following the recommendations outlined in ICH Q1E Evaluation of Stability Data, a shelf-life of 12 months is granted for levothyroxine sodium for injection when stored at controlled room temperature (20°C – 25°C).

Drug product is satisfactory

Overall Conclusion:

The NDA is recommended for Approval from the standpoint of chemistry, manufacturing and controls.

Ali Al-Hakim, Ph.D.
Branch Chief, Division III
ONDQA/CDRR/FDA

(b) (4)

This is a representation of an electronic record that was signed electronically and this page is the manifestation of the electronic signature.

/s/

ALI H AL HAKIM
04/29/2011

NDA 202231

**Levothyroxine Sodium
for Injection**

APP Pharmaceuticals, LLC

**Joseph Leginus, PhD
Division of Pre-Marketing Assessment III, Branch VII, ONDQA**

**For the Division of
Metabolism and Endocrinology Products**

CHEMISTRY REVIEW #2

Table of Contents

Table of Contents	2
Chemistry Review Data Sheet.....	3
The Executive Summary	7
I. Recommendations.....	7
A. Recommendation and Conclusion on Approvability.....	7
B. Recommendation on Phase 4 (Post-Marketing) Commitments, Agreements, and/or Risk Management Steps, if Approvable.....	7
II. Summary of Chemistry Assessments.....	7
A. Description of the Drug Product(s) and Drug Substance(s)	7
B. Description of How the Drug Product is Intended to be Used.....	9
C. Basis for Approvability or Not-Approval Recommendation.....	9
III. Administrative.....	10
A. Reviewer’s Signature: in DARRTS	10
B. Endorsement Block: in DARRTS	10
C. CC Block: in DARRTS.....	10
Chemistry Assessment	11

Chemistry Review Data Sheet

1. NDA 202231
2. REVIEW #: 2
3. REVIEW DATE: 29-Apr-2011
4. REVIEWER: Joseph Leginus, PhD
5. PREVIOUS DOCUMENTS:

Previous Documents

Original NDA

Document Date

30-Aug-2010

6. SUBMISSION(S) BEING REVIEWED:

Submission(s) Reviewed

NDA Amendment

Document Date

18-Feb-2100

7. NAME & ADDRESS OF APPLICANT:

Name: APP Pharmaceuticals, LLC

Address: 1501 E. Woodfield Rd. Suite 300 E, Schaumburg, IL 60173

Representative: Brent Yurschak, Regulatory Scientist

Telephone: 847-330-3896

8. DRUG PRODUCT NAME/CODE/TYPE:

a) Proprietary Name: N/A

b) Non-Proprietary Name (USAN): Levothyroxine Sodium for Injection

c) Code Name/# (ONDC only): CAS No.: 55-03-8

d) Chem. Type/Submission Priority (ONDC only):

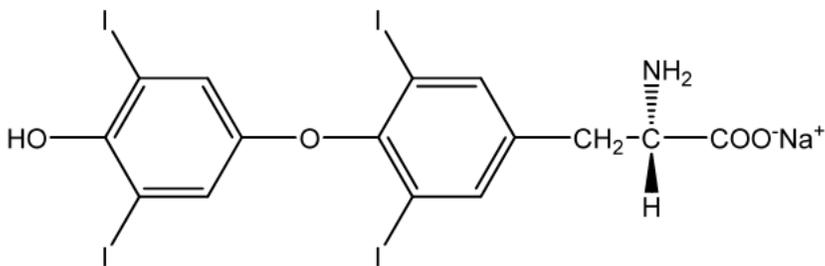
- Chem. Type: 3 (New Dosage Form)
- Submission Priority: Standard

Chemistry Review Data Sheet

9. LEGAL BASIS FOR SUBMISSION: This NDA is submitted as a 505(b)(2) application.
10. PHARMACOL. CATEGORY:
Replacement therapy for reduced or absent thyroid function of any etiology.
11. DOSAGE FORM: Lyophilized Powder for Injection
12. STRENGTH/POTENCY: 100, 200 and 500 mcg/vial
13. ROUTE OF ADMINISTRATION: Intravenous (IV) (b) (4)
14. Rx/OTC DISPENSED: Rx OTC
15. [SPOTS \(SPECIAL PRODUCTS ON-LINE TRACKING SYSTEM\)](#):
 SPOTS product – Form Completed
 Not a SPOTS product
16. CHEMICAL NAME, STRUCTURAL FORMULA, MOLECULAR FORMULA, MOLECULAR WEIGHT:

Chemical Name: L-Tyrosine, O-(4-hydroxy-3,5-diiodophenyl)-3,5-diiodo-, monosodium salt

Structural Formula:



Molecular Formula: $C_{15}H_{10}I_4NNaO_4$

Molecular Weight: 798.85 (sodium salt)

Chemistry Review Data Sheet

17. RELATED/SUPPORTING DOCUMENTS:

A. DMFs:

DMF #	Type	Holder	Item Referenced	Code ¹	Status ²	Date Review Completed	Comments
(b) (4)	II	(b) (4)	Levothyroxine Sodium Drug Substance	1	Adequate	11-Feb-2011	Reviewed by J. Leginus
	III	(b) (4)	(b) (4)	1	Adequate	15-Dec-2005	Reviewed by J. Boal
	III	(b) (4)	(b) (4)	1	Adequate	24-Feb-2009	Reviewed by C. Evans
	III	(b) (4)	(b) (4)	1	Adequate	19-Mar-2010	Reviewed by S. Zimmerman
	V	(b) (4)	(b) (4)	1	Adequate	12-Aug-2010	Reviewed by S. Donald

¹ Action codes for DMF Table:

1 – DMF Reviewed.

Other codes indicate why the DMF was not reviewed, as follows:

2 – Type 1 DMF

3 – Reviewed previously and no revision since last review

4 – Sufficient information in application

5 – Authority to reference not granted

6 – DMF not available

7 – Other (explain under "Comments")

² Adequate, Inadequate, or N/A (There is enough data in the application, therefore the DMF did not need to be reviewed)

B. Other Documents:

DOCUMENT	APPLICATION NUMBER	DESCRIPTION
Pre-IND	101,385	Levothyroxine Sodium for Injection

18. STATUS:

ONDC:

CONSULTS/ CMC RELATED REVIEWS	RECOMMENDATION	DATE	REVIEWER
EES	Acceptable. An Overall Compliance recommendation of Acceptable has been provided.	25-Jan-2011	N/A

Chemistry Review Data Sheet

Pharm/Tox	Not applicable. Impurity and degradant limits are below ICH qualification thresholds and/or comply with compendial limits.		
Biopharm	Not applicable (per A. Dorantes at filing meeting)		
Methods Validation	Validation may be requested of FDA labs after test methods are finalized.		
EA	Adequate	14-Jan-2011	Joseph Leginus
Microbiology	The application is recommended for approval from microbiology product quality standpoint.	26-Apr-2011	Robert Mello
QbD	N/A		

19. ORDER OF REVIEW: N/A

The Chemistry Review for NDA 202231

The Executive Summary

I. Recommendations

A. Recommendation and Conclusion on Approvability

NDA 202231 is recommended for Approval from the standpoint of chemistry, manufacturing and controls.

B. Recommendation on Phase 4 (Post-Marketing) Commitments, Agreements, and/or Risk Management Steps, if Approvable

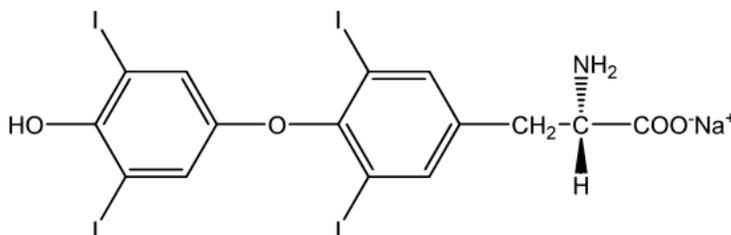
Not applicable.

II. Summary of Chemistry Assessments

A. Description of the Drug Product(s) and Drug Substance(s)

DRUG SUBSTANCE

Levothyroxine sodium ($C_{15}H_{10}I_4NNaO_4$; MW = 798.85) is a light yellow to buff-colored, odorless, hygroscopic powder. It is stable in dry air but may assume a slight pink color upon exposure to light. It is very slightly soluble in water and slightly soluble in alcohol. Levothyroxine sodium is manufactured in the optically active L-form and has the following structure:



The drug substance specifications meet all requirements of the current USP monograph for levothyroxine sodium (updated Aug 1, 2008) with the addition of description, residual solvents, bioburden and bacterial endotoxins. All impurities and their limits are the same as listed in the USP monograph.

Information for the drug substance is provided in the (b) (4) DMF (b) (4) and is incorporated by reference herein. A copy of the letter of authorization to reference DMF (b) (4) has been provided. The DMF was reviewed by J. Leginus on Feb 11, 2011 and found to be adequate. The retest period for the drug substance is set at (b) (4) (b) (4)

Executive Summary Section

DRUG PRODUCT

The drug product, levothyroxine sodium for injection, is a sterile, lyophilized powder consisting of the active ingredient, synthetic levothyroxine sodium, and the excipients dibasic sodium phosphate, heptahydrate, USP; mannitol, USP; and sodium hydroxide, NF. Levothyroxine sodium for injection is packaged in single-use amber glass vials available in three dosage strengths: 100 mcg/vial, 200 mcg/vial and 500 mcg/vial.

The manufacturing process for the drug product involves (b) (4)

The manufacture and lyophilization are conducted at APP Pharmaceuticals, Melrose Park, IL.

The proposed release specifications include description, reconstitution time, visual inspection, pH, (b) (4) uniformity of dosage units, instrumental color, identity (HPLC), assay (HPLC), individual and total impurities (HPLC), (b) (4) container/closure integrity, particulate matter, sterility and bacterial endotoxin. All non-compendial regulatory methods have been validated.

(b) (4) Also, amber glass vials are used as the primary packaging material, which have been shown to adequately protect the lyophilized drug product from degradation due to light.

The drug product is packaged in a 20 mm neck, USP Type I amber glass vial closed with a 20 mm gray (b) (4) rubber lyophilization stopper and capped with an aluminum crimped flipcap seal. The size of the glass vial will vary depending on the dose. A 6.5 mL vial is used for the 100 mcg dose and 10 mL vials are used for both the 200 mcg and 500 mcg doses. The storage condition for the drug product is controlled room temperature (20° - 25°C).

The applicant has provided only 6 months of real time (25°C/60% RH) and accelerated (40°C/75% RH) stability data for the three strengths of the drug product in stoppered and sealed vials. Results from stability studies show that the drug product remains stable through 6 months under both conditions. In-use results show that drug product reconstituted with the recommended reconstitution diluent (0.9% sodium chloride injection, USP)¹ remains stable for up to 4 hours at room temperature following dissolution, which supports the drug product label statement of "Use immediately after reconstitution". Based on these data, and following the recommendations outlined in ICH Q1E Evaluation of Stability Data, a shelf-life of 12 months is granted for levothyroxine sodium for injection when stored at controlled room temperature (20°C - 25°C). (b) (4)

Executive Summary Section

[REDACTED] (b) (4)
[REDACTED] a 12 month expiry is granted for the drug product at this time.

B. Description of How the Drug Product is Intended to be Used

Levothyroxine sodium for injection is indicated to treat [REDACTED] (b) (4) myxedema coma. Myxedema coma represents the extreme expression of severe hypothyroidism and is a life-threatening emergency characterized by poor circulation and hypometabolism. It may result in unpredictable absorption of levothyroxine sodium from the gastrointestinal tract, therefore, oral thyroid hormone drug products, such as the approved Synthroid® (NDA 21-402; Abbott), are not recommended to treat this condition. Thyroid hormone products formulated for intravenous administration should be administered.

The applicant states that pharmacokinetic and clinical data support an initial loading dose of levothyroxine between 300 mcg to 500 mcg followed by daily maintenance doses between 50 mcg and 100 mcg until the patient can tolerate oral therapy. As a result, 3 dosage strengths of levothyroxine sodium for injection have been manufactured: 100 mcg/vial, 200 mcg/vial and 500 mcg/vial. Each dosage strength requires reconstitution using 5 mL of 0.9% sodium chloride injection, USP (not provided) immediately prior to intravenous administration.

C. Basis for Approvability or Not-Approval Recommendation

All items in the List of Deficiencies from Chemistry Review #1 have been satisfactorily addressed in the 18-Feb-2011 amendment to the original NDA. See Chemistry Assessment section below for details.

Acceptable cGMP recommendations have been received from the Office of Compliance for all manufacturing and testing facilities. An Overall Compliance recommendation of Acceptable was provided on 25-Jan-2011.

A recommendation for approval was received from the microbiology product quality standpoint.

The applicant filed the NDA as a 505(b)(2) application for a new dosage form of levothyroxine sodium. The applicant's product has been marketed in the U.S. as an unapproved drug. The FDA recently categorized Levothyroxine Sodium for Injection a "Marketed Unapproved Drug," thus requiring submission of an NDA and FDA approval in order to keep the product on the market. This was communicated to the applicant in a Warning Letter issued by the FDA Chicago District on December 18, 2006. A pre-IND meeting was held with the Agency on March 18, 2008.

Executive Summary Section

The drug substance (levothyroxine sodium) will be manufactured for commercial use by (b) (4) with most of the CMC parameters provided in the (b) (4) DMF No. (b) (4). A copy of the letter of authorization to reference DMF (b) (4) has been provided. The drug substance specifications meet all requirements of the current USP monograph for levothyroxine sodium.

The drug product, levothyroxine sodium for injection, is manufactured by APP Pharmaceuticals, Melrose Park, IL, as a sterile, lyophilized powder comprised of levothyroxine sodium, and the compendial excipients dibasic sodium phosphate, heptahydrate, mannitol and sodium hydroxide.

Levothyroxine sodium for injection was found to be photosensitive, therefore, the primary container closure is an amber glass vial, which provides adequate protection from light. A label statement indicates to protect the drug product from light.

No additional impurities have been imparted to the drug product during its manufacture or found during stability testing.

Based on the limited stability data (6 months), a shelf life of 12 months at controlled room temperature (20°C – 25°C) is granted for levothyroxine sodium for injection.

III. Administrative

- A. Reviewer's Signature: in DARRTS
- B. Endorsement Block: in DARRTS
- C. CC Block: in DARRTS

5 Page(s) have been Withheld in Full as b4 (CCI/TS)
immediately following this page

This is a representation of an electronic record that was signed electronically and this page is the manifestation of the electronic signature.

/s/

JOSEPH M LEGINUS
04/29/2011

ALI H AL HAKIM
04/29/2011

NDA 202231

**Levothyroxine Sodium
for Injection**

APP Pharmaceuticals, LLC

**Joseph Leginus, PhD
Division of Pre-Marketing Assessment III, Branch VII, ONDQA**

**For the Division of
Metabolism and Endocrinology Products**

CHEMISTRY REVIEW #1

Table of Contents

Table of Contents	2
Chemistry Review Data Sheet.....	3
The Executive Summary	7
I. Recommendations.....	7
A. Recommendation and Conclusion on Approvability.....	7
B. Recommendation on Phase 4 (Post-Marketing) Commitments, Agreements, and/or Risk Management Steps, if Approvable.....	7
II. Summary of Chemistry Assessments.....	7
A. Description of the Drug Product(s) and Drug Substance(s)	7
B. Description of How the Drug Product is Intended to be Used.....	9
C. Basis for Approvability or Not-Approval Recommendation.....	9
III. Administrative.....	10
A. Reviewer’s Signature: in DFS.....	10
B. Endorsement Block: in DFS	10
C. CC Block: in DFS.....	10
Chemistry Assessment	11
I. Review of Common Technical Document-Quality (Ctd-Q) Module 3.2: Body of Data	11
S DRUG SUBSTANCE.....	11
P DRUG PRODUCT	21
A APPENDICES	54
R REGIONAL INFORMATION	54
II. Review of Common Technical Document-Quality (Ctd-Q) Module 1	55
A. Labeling & Package Insert.....	55
B. Environmental Assessment or Claim of Categorical Exclusion	62
List of Deficiencies To Be Communicated	63

Chemistry Review Data Sheet

1. NDA 202231
2. REVIEW #: 1
3. REVIEW DATE: 24-Jan-2011
4. REVIEWER: Joseph Leginus, PhD
5. PREVIOUS DOCUMENTS:

Previous Documents

N/A

Document Date

6. SUBMISSION(S) BEING REVIEWED:

Submission(s) Reviewed

Original NDA

Document Date

30-Aug-2010

7. NAME & ADDRESS OF APPLICANT:

Name: APP Pharmaceuticals, LLC

Address: 1501 E. Woodfield Rd. Suite 300 E, Schaumburg, IL 60173

Representative: Brent Yurschak, Regulatory Scientist

Telephone: 847-330-3896

8. DRUG PRODUCT NAME/CODE/TYPE:

a) Proprietary Name: N/A

b) Non-Proprietary Name (USAN): Levothyroxine Sodium for Injection

c) Code Name/# (ONDC only): CAS No.: 55-03-8

d) Chem. Type/Submission Priority (ONDC only):

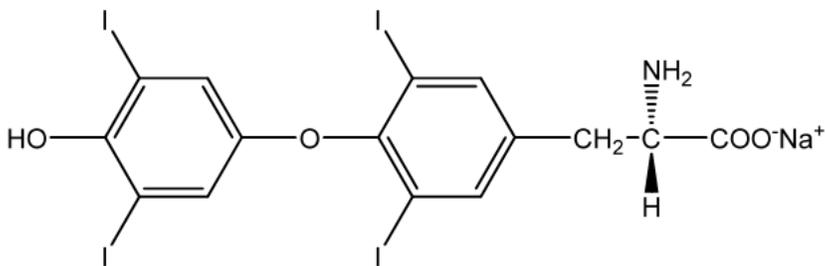
- Chem. Type: 7 (Drug Already Marketed but Without an Approved NDA)
- Submission Priority: Standard

Chemistry Review Data Sheet

9. LEGAL BASIS FOR SUBMISSION: This NDA is submitted as a 505(b)(2) application.
10. PHARMACOL. CATEGORY:
Replacement therapy for reduced or absent thyroid function of any etiology.
11. DOSAGE FORM: Lyophilized Powder for Injection
12. STRENGTH/POTENCY: 100, 200 and 500 mcg/vial
13. ROUTE OF ADMINISTRATION: Intravenous (IV)
14. Rx/OTC DISPENSED: X Rx OTC
15. [SPOTS \(SPECIAL PRODUCTS ON-LINE TRACKING SYSTEM\)](#):
 SPOTS product – Form Completed
 X Not a SPOTS product
16. CHEMICAL NAME, STRUCTURAL FORMULA, MOLECULAR FORMULA, MOLECULAR WEIGHT:

Chemical Name: L-Tyrosine, O-(4-hydroxy-3,5-diiodophenyl)-3,5-diiodo-, monosodium salt

Structural Formula:



Molecular Formula: C₁₅H₁₀I₄NNaO₄

Molecular Weight: 798.85 (sodium salt)

Chemistry Review Data Sheet

17. RELATED/SUPPORTING DOCUMENTS:

A. DMFs:

DMF #	Type	Holder	Item Referenced	Code ¹	Status ²	Date Review Completed	Comments
(b) (4)	II	(b) (4)	Levothyroxine Sodium Drug Substance	1	Deficient	05-Oct-2010	Reviewed by D. Klein
	III		(b) (4)	1	Adequate	15-Dec-2005	Reviewed by J. Boal
	III			1	Adequate	24-Feb-2009	Reviewed by C. Evans
	III			1	Adequate	19-Mar-2010	Reviewed by S. Zimmerman
	V			1	Adequate	12-Aug-2010	Reviewed by S. Donald

¹ Action codes for DMF Table:

1 – DMF Reviewed.

Other codes indicate why the DMF was not reviewed, as follows:

2 – Type 1 DMF

3 – Reviewed previously and no revision since last review

4 – Sufficient information in application

5 – Authority to reference not granted

6 – DMF not available

7 – Other (explain under "Comments")

² Adequate, Inadequate, or N/A (There is enough data in the application, therefore the DMF did not need to be reviewed)

B. Other Documents:

DOCUMENT	APPLICATION NUMBER	DESCRIPTION
Pre-IND	101,385	Levothyroxine Sodium for Injection

18. STATUS:

ONDC:

CONSULTS/ CMC RELATED REVIEWS	RECOMMENDATION	DATE	REVIEWER
EES	Pending		N/A
Pharm/Tox	Not applicable. Impurity and degradant limits are below ICH qualification thresholds		

Chemistry Review Data Sheet

	and/or comply with compendial limits.		
Biopharm	Not applicable (per A. Dorantes at filing meeting)		
Methods Validation	Validation may be requested of FDA labs after test methods are finalized.	N/A	N/A
EA	Adequate	14-Jan-2011	Joseph Leginus
Microbiology	Pending		Robert Mello
QbD	N/A		

19. ORDER OF REVIEW: N/A

The Chemistry Review for NDA 22-382

The Executive Summary

I. Recommendations

A. Recommendation and Conclusion on Approvability

The application is approvable from the standpoint of chemistry, manufacturing and controls pending a) satisfactory responses to the deficiencies delineated in the List of Deficiencies and Information Request (in the CMC Review #1 for NDA 202231), and b) an adequate response to the Master File Deficiency detailed in S. Khushboo's letter (10/12/2010) to the drug substance manufacturer, (b) (4)

B. Recommendation on Phase 4 (Post-Marketing) Commitments, Agreements, and/or Risk Management Steps, if Approvable

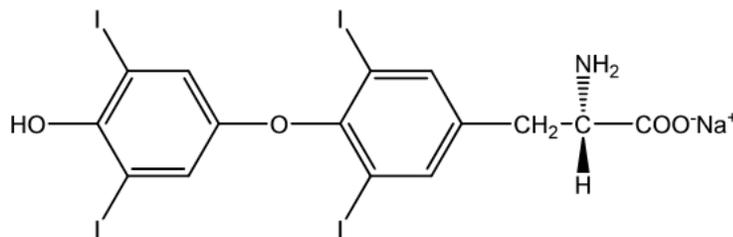
Not applicable.

II. Summary of Chemistry Assessments

A. Description of the Drug Product(s) and Drug Substance(s)

DRUG SUBSTANCE

Levothyroxine sodium ($C_{15}H_{10}I_4NNaO_4$; MW = 798.85) is a light yellow to buff-colored, odorless, hygroscopic powder. It is stable in dry air but may assume a slight pink color upon exposure to light. It is very slightly soluble in water and slightly soluble in alcohol. Levothyroxine sodium is manufactured in the optically active L-form and has the following structure:



The drug substance specifications meet all requirements of the current USP monograph for levothyroxine sodium (updated Aug 1, 2008) with the addition of description, residual solvents, bioburden and bacterial endotoxins. All impurities and their limits are the same as listed in the USP monograph.

Information for the drug substance is provided in the (b) (4) and is incorporated by reference herein. A copy of the letter of authorization to reference

Executive Summary Section

(b) (4) has been provided. The DMF was reviewed by K. Furnkranz on Apr 29, 2008 and found to be adequate, however, a Master File Deficiency letter was sent (10/12/2010) to the drug substance manufacturer, (b) (4) indicating that their 3/3/2010 Amendment, 3/4/2009 Annual Report and 3/24/2010 Annual Report did not have the required CMC data for the most recently manufactured drug substance batches. No response from manufacturer to this letter has been received at this time. The retest period for the drug substance (b) (4)

DRUG PRODUCT

The drug product, levothyroxine sodium for injection, is a sterile, lyophilized powder consisting of the active ingredient, synthetic levothyroxine sodium, and the excipients dibasic sodium phosphate, heptahydrate, USP; mannitol, USP; and sodium hydroxide, NF. Levothyroxine sodium for injection is packaged in single-use amber glass vials available in three dosage strengths: 100 mcg/vial, 200 mcg/vial and 500 mcg/vial.

The manufacturing process for the drug product involves (b) (4)

The manufacture and lyophilization are conducted at APP Pharmaceuticals, Melrose Park, IL.

The proposed release specifications include description, reconstitution time, visual inspection, pH, (b) (4) uniformity of dosage units, instrumental color, identity (HPLC), assay (HPLC), individual and total impurities (HPLC), (b) (4) container/closure integrity, particulate matter, sterility and bacterial endotoxin. All non-compensatory regulatory methods have been validated.

(b) (4) Also, amber glass vials are used as the primary packaging material, which have been shown to adequately protect the lyophilized drug product from degradation due to light.

The drug product is packaged in a 20 mm neck, USP Type I amber glass vial closed with a 20 mm gray (b) (4) rubber lyophilization stopper and capped with an aluminum crimped flipcap seal. The size of the glass vial will vary depending on the dose. A 6.5 mL vial is used for the 100 mcg dose and 10 mL vials are used for both the 200 mcg and 500 mcg doses. The storage condition for the drug product is controlled room temperature (20° - 25°C).

The applicant has provided only 6 months of real time (25°C/60% RH) and accelerated (40°C/75% RH) stability data for the three strengths of the drug product in stoppered and sealed vials. Results from stability studies show that the drug product remains stable

Executive Summary Section

through 6 months under both conditions. In-use results show that drug product reconstituted with either of the two recommended reconstitution diluents remains stable for up to 4 hours at room temperature following dissolution, which supports the drug product label statement of "Use immediately after reconstitution". Based on these data, and following the recommendations outlined in ICH QE1 Evaluation of Stability Data, a shelf-life of 12 months is granted for levothyroxine sodium for injection when stored at controlled room temperature (20°C – 25°C). (b) (4)

a 12 month expiry is granted for the drug product at this time.

B. Description of How the Drug Product is Intended to be Used

Levothyroxine sodium for injection is indicated to treat (b) (4) myxedema coma. Myxedema coma represents the extreme expression of severe hypothyroidism and is a life-threatening emergency characterized by poor circulation and hypometabolism. It may result in unpredictable absorption of levothyroxine sodium from the gastrointestinal tract, therefore, oral thyroid hormone drug products, such as the approved Synthroid® (NDA 21-402; Abbott), are not recommended to treat this condition. Thyroid hormone products formulated for intravenous administration should be administered.

The applicants states that pharmacokinetic and clinical data support an initial loading dose of levothyroxine between 300 µg to 500 µg followed by daily maintenance doses between 50 µg and 100 µg until the patient can tolerate oral therapy. As a result, 3 dosage strengths of levothyroxine sodium for injection have been manufactured: 100 mcg/vial, 200 mcg/vial and 500 mcg/vial. Each dosage strength requires reconstitution using 5 mL of either 0.9% sodium chloride injection, USP (b) (4) immediately prior to intravenous administration.

C. Basis for Approvability or Not-Approval Recommendation

The application is approvable from a CMC perspective pending a) satisfactory responses to the deficiencies identified in this review, and b) an adequate response to the Master File Deficiency detailed in S. Khushboo's letter (10/12/2010) to the drug substance manufacturer, (b) (4). Acceptable cGMP recommendations have been received from the Office of Compliance for three of the four manufacturing and testing facilities. An inspection has been scheduled for the drug substance manufacturer.

The applicant filed the NDA as a 505(b)(2) application for a new dosage form of levothyroxine sodium. The applicant's product has been marketed in the U.S. as an unapproved drug. The FDA recently categorized Levothyroxine Sodium for Injection a "Marketed Unapproved Drug," thus requiring submission of an NDA and FDA approval

Executive Summary Section

in order to keep the product on the market. This was communicated to the applicant in a Warning Letter issued by the FDA Chicago District on December 18, 2006. A pre-IND meeting was held with the Agency on March 18, 2008.

The drug substance (levothyroxine sodium) will be manufactured for commercial use by (b) (4) with most of the CMC parameters provided in the (b) (4) DMF No. (b) (4). A copy of the letter of authorization to reference DMF (b) (4) has been provided. No response has yet been received to the MF deficiency letter sent to the DMF holder on 10/12/2010. The drug substance specifications meet all requirements of the current USP monograph for levothyroxine sodium.

The drug product, levothyroxine sodium for injection, is manufactured by APP Pharmaceuticals, Melrose Park, IL, as a sterile, lyophilized powder comprised of levothyroxine sodium, and the compendial excipients dibasic sodium phosphate, heptahydrate, mannitol and sodium hydroxide.

Levothyroxine sodium for injection was found to be photosensitive, therefore, the primary container closure is an amber glass vial, which provides adequate protection from light. A label statement indicates to protect the drug product from light.

No additional impurities have been imparted to the drug product during its manufacture or found during stability testing.

Based on the limited stability data (6 months), a shelf life of 12 months at controlled room temperature (20°C – 25°C) is granted for levothyroxine sodium for injection.

III. Administrative

- A. Reviewer's Signature: in DARRTS
- B. Endorsement Block: in DARRTS
- C. CC Block: in DARRTS

53 Page(s) have been Withheld in Full as b4 (CCI/TS) immediately following this page

This is a representation of an electronic record that was signed electronically and this page is the manifestation of the electronic signature.

/s/

JOSEPH M LEGINUS
01/24/2011

ALI H AL HAKIM
01/24/2011

Initial Quality/CMC Assessment
ONDQA

Division of Metabolism and Endocrinology Products

NDA: 202231

Applicant: APP Pharmaceuticals LLC

Stamp Date: 30-AUG-2010

PDUFA Date: 30-JUN-2011

Proposed Proprietary Name: [none indicated]

Established Name: Levothyroxine sodium

Dosage form and strength: Powder for injection (to be reconstituted with saline (b) (4) not co-packaged)
100, 200 and 500 mcg

Route of Administration: (b) (4) IV injection

Indications: (b) (4)
(b) (4)

CMC Lead: Su (Suong) Tran, ONDQA

ONDQA Fileability: Yes

Initial Quality/CMC Assessment
ONDQA

CONSULTS/ CMC RELATED REVIEWS	COMMENT
CBER	<i>Not applicable</i>
CDRH	<i>Not applicable</i>
EA	The categorical exclusion claim will be assessed by Primary Reviewer.
Compliance (DMPQ)	EER was sent to Compliance by ONDQA PM on 08-SEP-2010.
Methods Validation	<i>Validation may be requested of FDA labs after test methods are finalized.</i>
Microbiology	Review of sterility assurance.
OBP	<i>Not applicable</i>
ONDQA Biopharm	<i>Not applicable (per A. Dorantes at the filing meeting)</i>
OSE	<i>Labeling consult request will be sent as part of DMEP's request.</i>
Pharm/Tox	<i>Not applicable. Impurity and degradant limits are below ICH qualification thresholds and/or comply with compendial limits.</i>
QbD	<i>Not applicable</i>

This is an electronic NDA, filed as a 505(b)(2) application, with no reference listed drugs (RLD) listed in Form 356h. Currently approved levothyroxine products are for oral administration.

Reference is made to the DMF (b) (4) for the CMC information on the drug substance.

The drug product is a lyophilized sterile powder to be reconstituted with normal saline (b) (4) (not co-packaged) for immediate administration.

The product will be packaged in single-use vials of 100, 200 and 500 mcg. The product is stored at room temperature.

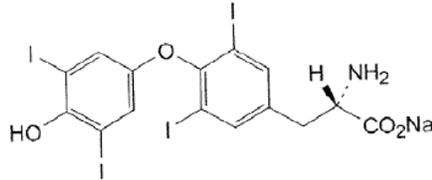
Initial Quality/CMC Assessment
ONDQA

Has all information requested during the IND phases, and at the pre-NDA meetings been included?
To be discussed in the itemized sections of this review.

Drug substance:

U. S. Adopted Name: Levothyroxine Sodium, USP

Molecular Structure:



Molecular Formula: $C_{15}H_{10}I_4NNaO_4$

Molecular Weight: 798.85

Table 1. Physicochemical Properties of the Drug Substance

Properties	Description of Properties
Appearance:	Light yellow to buff-colored powder. Is stable in dry air but may assume a slight pink color upon exposure to light.
Odor:	Odorless
pH:	8.35 to 9.35 (saturated water solution)
Melting/boiling range:	235-236° (decomposition)
Dissociation constant (pKa):	2.2, 6.7, 10.1
Specific rotation:	Between -5° and -6°
Solubility Profile:	15 mg/100 mL in water
Hygroscopicity:	Levothyroxine sodium has been reported to be slightly hygroscopic. Since the final drug product is compounded as a lyophilized drug product, this drug substance property is not critical
Polymorphs:	No polymorphous crystal forms have been reported
Chiral centers:	One chiral center; the L-form of thyroxine is the API

Reference is made to the DMF ^{(b) (4)} for all CMC information on the drug substance.

Review comments: The drug substance specification (copied on the next page) is the same as the current USP monograph for levothyroxine sodium, with the addition of Description, Residual Solvents, Bioburden, and Bacterial Endotoxins. All the impurities and their limits are the same as in the monograph. The referenced DMF has been reviewed 10 times in support of several other approved applications. The primary reviewer will evaluate any new information in the DMF submitted since the most recent review.

10 Page(s) has been Withheld in Full as b4 (CCI/TS)
immediately following this page

Initial Quality/CMC Assessment
ONDQA

PRODUCT QUALITY
FILING REVIEW FOR NDA (ONDQA)

NDA Number: 202231

Established/Proper Name:
Levothyroxine sodium

Applicant: APP
Pharmaceuticals LLC

Letter Date: 30-AUG-2010

Stamp Date: 30-AUG-2010

The following parameters are necessary in order to initiate a full review, i.e., complete enough to review but may have deficiencies. On **initial** overview of the NDA application for filing:

A. GENERAL				
	Parameter	Yes	No	Comment
1.	Is the CMC section organized adequately?	x		
2.	Is the CMC section indexed and paginated (including all PDF files) adequately?	x		
3.	Are all the pages in the CMC section legible?	x		
4.	Has all information requested during the IND phase, and at the pre-NDA meetings been included?	x		
B. facilities*				
	Parameter	Yes	No	Comment
5.	Is a single, comprehensive list of all involved facilities available in one location in the application?	x		
6.	For a naturally-derived API only, are the facilities responsible for critical intermediate or crude API manufacturing, or performing upstream steps, specified in the application? If not, has a justification been provided for this omission? This question is not applicable for synthesized API.			
7.	Are drug substance manufacturing sites identified on FDA Form 356h or associated continuation sheet? For each site, does the application list: <ul style="list-style-type: none"> • Name of facility, • Full address of facility including street, city, state, country • FEI number for facility (if previously registered with FDA) • Full name and title, telephone, fax number and email for on-site contact person. • Is the manufacturing responsibility and function identified for each facility?, and • DMF number (if applicable) 	x		

Initial Quality/CMC Assessment
ONDQA

8.	<p>Are drug product manufacturing sites are identified on FDA Form 356h or associated continuation sheet. For each site, does the application list:</p> <ul style="list-style-type: none"> • Name of facility, • Full address of facility including street, city, state, country • FEI number for facility (if previously registered with FDA) • Full name and title, telephone, fax number and email for on-site contact person. • Is the manufacturing responsibility and function identified for each facility?, and • DMF number (if applicable) 	x		
9.	<p>Are additional manufacturing, packaging and control/testing laboratory sites are identified on FDA Form 356h or associated continuation sheet. For each site, does the application list:</p> <ul style="list-style-type: none"> • Name of facility, • Full address of facility including street, city, state, country • FEI number for facility (if previously registered with FDA) • Full name and title, telephone, fax number and email for on-site contact person. • Is the manufacturing responsibility and function identified for each facility?, and • DMF number (if applicable) 	x		
10.	<p>Is a statement provided that all facilities are ready for GMP inspection at the time of submission?</p>	x		

* If any information regarding the facilities is omitted, this should be addressed ASAP with the applicant and can be a *potential* filing issue or a *potential* review issue.

C. ENVIRONMENTAL ASSESMENT

Initial Quality/CMC Assessment
ONDQA

	Parameter	Yes	No	Comment
11.	Has an environmental assessment report or categorical exclusion been provided?	x		
D. drug substance/active pharmaceutical ingredient (DS/api)				
	Parameter	Yes	No	Comment
12.	Does the section contain a description of the DS manufacturing process?			Reference is made to DMF (b) (4)
13.	Does the section contain identification and controls of critical steps and intermediates of the DS?			Reference is made to DMF.
14.	Does the section contain information regarding the characterization of the DS?			Reference is made to DMF.
15.	Does the section contain controls for the DS?			Reference is made to DMF.
16.	Has stability data and analysis been provided for the drug substance?			Reference is made to DMF.
17.	Does the application contain Quality by Design (QbD) information regarding the DS?		x	
18.	Does the application contain Process Analytical Technology (PAT) information regarding the DS?		x	
E. drug product (dp)				
	Parameter	Yes	No	Comment
19.	Is there a description of manufacturing process and methods for DP production through finishing, including formulation, filling, labeling and packaging?	x		
20.	Does the section contain identification and controls of critical steps and intermediates of the DP, including analytical procedures and method validation reports for assay and related substances if applicable?	x		
21.	Is there a batch production record and a proposed master batch record?	x		Deficiency sent to Applicant on 25-AUG-2010.
22.	Has an investigational formulations section been provided? Is there adequate linkage between the investigational product and the proposed marketed product?	x		
23.	Have any biowaivers been requested?		x	
24.	Does the section contain description of to-be-marketed container/closure system and presentations)?	x		
25.	Does the section contain controls of the final drug product?	x		
26.	Has stability data and analysis been provided to support the requested expiration date?	x		
27.	Does the application contain Quality by Design (QbD) information regarding the DP?		x	
28.	Does the application contain Process Analytical Technology (PAT) information regarding the DP?		x	

Initial Quality/CMC Assessment
ONDQA

F. METHODS VALIDATION (MV)				
	Parameter	Yes	No	Comment
29.	Is there a methods validation package?	x		See Comment at the end of this review.
G. microbiology				
	Parameter	Yes	No	Comment
30.	If appropriate, is a separate microbiological section included assuring sterility of the drug product?	x		
H. master files (DMF/MAF)				
	Parameter	Yes	No	Comment
31.	Is information for critical DMF references (i.e., for drug substance and important packaging components for non-solid-oral drug products) complete?	x		
I. Labeling				
	Parameter	Yes	No	Comment
32.	Has the draft package insert been provided?	x		
33.	Have the immediate container and carton labels been provided?	x		
J. filing conclusion				
	Parameter	Yes	No	Comment
34.	IS THE PRODUCT QUALITY SECTION OF THE APPLICATION FILEABLE?	x		
35.	If the NDA is not fileable from the product quality perspective, state the reasons and provide filing comments to be sent to the Applicant.			
36.	Are there any potential review issues to be forwarded to the Applicant for the 74-day letter?		x	

{See appended electronic signature page}

Su (Suong) Tran
CMC Lead
Office of New Drug Quality Assessment

Date *{see appended electronic signature page}*

{See appended electronic signature page}

Ali Al Hakim
Branch Chief
Office of New Drug Quality Assessment

Date *{see appended electronic signature page}*

This is a representation of an electronic record that was signed electronically and this page is the manifestation of the electronic signature.

/s/

SUONG T TRAN
10/14/2010

ALI H AL HAKIM
10/14/2010

**FDA CDER EES
ESTABLISHMENT EVALUATION REQUEST
DETAIL REPORT**

Application: NDA 202231/000

Action Goal:

Effective Date: 30-AUG-2010

District Goal: 30-DEC-2010

Regulatory: 30-JUN-2011

Applicant: APP PHARMS
1501 EAST WOODFIELD RD STE 300E
SCHAUMBURG, IL 60173

Brand Name: Levothyroxine sodium for Injection

Estab. Name:

Generic Name:

Priority: 7

Product Number; Dosage Form; Ingredient; Strengths

Org. Code: 510

001; POWDER, FOR INJECTION SOLUTION, LYOPHILIZED;
LEVOTHYROXINE SODIUM; 100MCG
002; POWDER, FOR INJECTION SOLUTION, LYOPHILIZED;
LEVOTHYROXINE SODIUM; 200MCG
003; POWDER, FOR INJECTION SOLUTION, LYOPHILIZED;
LEVOTHYROXINE SODIUM; 500MCG

Application Comment: PLEASE SEE ESTABLISHMENT COMMENTS (on 08-SEP-2010 by K. SHARMA ())

FDA Contacts: K. SHARMA

Project Manager

S. TRAN

Team Leader

301-796-1764

Overall Recommendation: ACCEPTABLE on 25-JAN-2011 by M. STOCK (HFD-320) 301-796-4753

**FDA CDER EES
ESTABLISHMENT EVALUATION REQUEST
DETAIL REPORT**

Establishment: CFN: 1450022 FEI: 1450022
APP PHARMACEUTICALS, LLC--A CO. OF THE FRESENIUS KABI GROUP
2020 N RUBY ST
MELROSE PARK, IL 601601112

DMF No: **AADA:**

Responsibilities: DRUG SUBSTANCE RELEASE TESTER
FINISHED DOSAGE MANUFACTURER
FINISHED DOSAGE RELEASE TESTER
FINISHED DOSAGE STABILITY TESTER

Estab. Comment:

Profile: SMALL VOLUME PARENTERAL, LYOPHILIZED **OAI Status:** NONE

<u>Milestone Name</u>	<u>Milestone Date</u>	<u>Request Type</u>	<u>Planned Completion</u>	<u>Decision</u>	<u>Creator</u>
<u>Comment</u>				<u>Reason</u>	
SUBMITTED TO OC	08-SEP-2010				SHARMAKH
SUBMITTED TO DO	09-SEP-2010	10-Day Letter			STOCKM
DO RECOMMENDATION INSPECTION CONDUCTED 1/12-2/12/10	17-SEP-2010			ACCEPTABLE BASED ON FILE REVIEW	LJARRELL
OC RECOMMENDATION	17-SEP-2010			ACCEPTABLE DISTRICT RECOMMENDATION	INYARDA

**FDA CDER EES
ESTABLISHMENT EVALUATION REQUEST
DETAIL REPORT**

Establishment: CFN: (b) (4) FEI: (b) (4)

(b) (4)

DMF No: AADA:

Responsibilities: (b) (4)

Estab. Comment: (b) (4) (on 08-SEP-2010 by K. SHARMA ())

Profile: (b) (4) OAI Status: NONE

<u>Milestone Name</u>	<u>Milestone Date</u>	<u>Request Type</u>	<u>Planned Completion</u>	<u>Decision</u>	<u>Creator</u>
<u>Comment</u>				<u>Reason</u>	
SUBMITTED TO OC	08-SEP-2010				SHARMAKH
SUBMITTED TO DO	09-SEP-2010	10-Day Letter			STOCKM
INSPECTION SCHEDULED	(b) (4)		(b) (4)		PHILPYE
DO RECOMMENDATION	25-JAN-2011			ACCEPTABLE BASED ON FILE REVIEW	PHILPYE
OC RECOMMENDATION	25-JAN-2011			ACCEPTABLE DISTRICT RECOMMENDATION	STOCKM

This is a representation of an electronic record that was signed electronically and this page is the manifestation of the electronic signature.

/s/

NIKOO N MANOCHEHRI-KALANTARI
07/07/2011