

CENTER FOR DRUG EVALUATION AND RESEARCH

APPROVAL PACKAGE FOR:

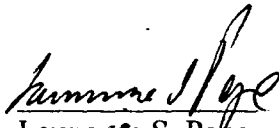
APPLICATION NUMBER

NDA 21-402

Administrative Documents

PATENT CERTIFICATION

Abbott Laboratories, Abbott Park, IL. certifies that there is no United States Patent that covers the compound levothyroxine sodium or the pharmaceutical composition of levothyroxine sodium which is the subject of this application and for which approval is sought.

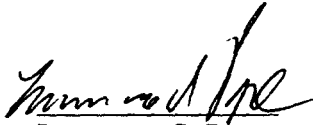

Lawrence S. Pope
Senior Counsel

7/18/01
Date


**APPEARS THIS WAY
ON ORIGINAL**

Patent Information

There is no known United States Patent that relates to levothyroxine that is relevant to this application under 21 USC 355(b).



Lawrence S. Pope
Senior Counsel



Date

APPEARS THIS WAY
ON ORIGINAL

EXCLUSIVITY SUMMARY for NDA # 21-462
21-401 SUPPL #

Trade Name: Synthroid; Generic Name: levothyroxine sodium tablets, USP

Applicant Name Abbott Laboratories HFD- 510

Approval Date

PART I: IS AN EXCLUSIVITY DETERMINATION NEEDED?

1. An exclusivity determination will be made for all original applications, but only for certain supplements. Complete Parts II and III of this Exclusivity Summary only if you answer "YES" to one or more of the following questions about the submission.

a) Is it an original NDA? YES/ X / NO / /

b) Is it an effectiveness supplement? YES / / NO / X /

If yes, what type (SE1, SE2, etc.)?

c) Did it require the review of clinical data other than to support a safety claim or change in labeling related to safety? (If it required review only of bioavailability or bioequivalence data, answer "NO.")

YES / / NO / X /

If your answer is "no" because you believe the study is a bioavailability study and, therefore, not eligible for exclusivity, EXPLAIN why it is a bioavailability study, including your reasons for disagreeing with any arguments made by the applicant that the study was not simply a bioavailability study.

Only bioavailability studies were required or
Submitted.

If it is a supplement requiring the review of clinical data but it is not an effectiveness supplement, describe the change or claim that is supported by the clinical data:

d) Did the applicant request exclusivity?

YES /___/ NO /_X_/

If the answer to (d) is "yes," how many years of exclusivity did the applicant request?

e) Has pediatric exclusivity been granted for this Active Moiety?

YES /___/ NO /_X_/

IF YOU HAVE ANSWERED "NO" TO ALL OF THE ABOVE QUESTIONS, GO DIRECTLY TO THE SIGNATURE BLOCKS ON Page 9.

2. Has a product with the same active ingredient(s), dosage form, strength, route of administration, and dosing schedule previously been approved by FDA for the same use? (Rx to OTC Switches should be answered No - Please indicate as such).

YES /_X_/ NO /___/

If yes, NDA # 21-301 Drug Name Levoxyl

IF THE ANSWER TO QUESTION 2 IS "YES," GO DIRECTLY TO THE SIGNATURE BLOCKS ON Page 9.

3. Is this drug product or indication a DESI upgrade?

YES /___/ NO /_X_/

IF THE ANSWER TO QUESTION 3 IS "YES," GO DIRECTLY TO THE SIGNATURE BLOCKS ON Page 9 (even if a study was required for the upgrade).

PART II: FIVE-YEAR EXCLUSIVITY FOR NEW CHEMICAL ENTITIES

(Answer either #1 or #2, as appropriate)

1. Single active ingredient product.

Has FDA previously approved under section 505 of the Act any drug product containing the same active moiety as the drug under consideration? Answer "yes" if the active moiety (including other esterified forms, salts, complexes, chelates or clathrates) has been previously approved, but this particular form of the active moiety, e.g., this particular ester or salt (including salts with hydrogen or coordination bonding) or other non-covalent derivative (such as a complex, chelate, or clathrate) has not been approved. Answer "no" if the compound requires metabolic conversion (other than deesterification of an esterified form of the drug) to produce an already approved active moiety.

YES /___/ NO /___/

If "yes," identify the approved drug product(s) containing the active moiety, and, if known, the NDA #(s).

NDA #

NDA #

NDA #

2. Combination product.

If the product contains more than one active moiety (as defined in Part II, #1), has FDA previously approved an application under section 505 containing any one of the active moieties in the drug product? If, for example, the combination contains one never-before-approved active moiety and one previously approved active moiety, answer "yes." (An active moiety that is marketed under an OTC monograph, but that was never approved under an NDA, is considered not previously approved.)

YES /___/ NO /___/

If "yes," identify the approved drug product(s) containing the active moiety, and, if known, the NDA #(s):

NDA #

NDA #

NDA #

IF THE ANSWER TO QUESTION 1 OR 2 UNDER PART II IS "NO," GO DIRECTLY TO THE SIGNATURE BLOCKS ON Page 9. IF "YES," GO TO PART III.

PART III: THREE-YEAR EXCLUSIVITY FOR NDA'S AND SUPPLEMENTS

To qualify for three years of exclusivity, an application or supplement must contain "reports of new clinical investigations (other than bioavailability studies) essential to the approval of the application and conducted or sponsored by the applicant." This section should be completed only if the answer to PART II, Question 1 or 2, was "yes."

1. Does the application contain reports of clinical investigations? (The Agency interprets "clinical investigations" to mean investigations conducted on humans other than bioavailability studies.) If the application contains clinical investigations only by virtue of a right of reference to clinical investigations in another application, answer "yes," then skip to question 3(a). If the answer to 3(a) is "yes" for any investigation referred to in another application, do not complete remainder of summary for that investigation.

YES /___/ NO /___/

IF "NO," GO DIRECTLY TO THE SIGNATURE BLOCKS ON Page 9.

2. A clinical investigation is "essential to the approval" if the Agency could not have approved the application or supplement without relying on that investigation. Thus, the investigation is not essential to the approval if 1) no clinical investigation is necessary to support the supplement or application in light of previously approved applications (i.e., information other than clinical trials, such as bioavailability data, would be sufficient to provide a basis

for approval as an ANDA or 505(b)(2) application because of what is already known about a previously approved product), or 2) there are published reports of studies (other than those conducted or sponsored by the applicant) or other publicly available data that independently would have been sufficient to support approval of the application, without reference to the clinical investigation submitted in the application.

For the purposes of this section, studies comparing two products with the same ingredient(s) are considered to be bioavailability studies.

- (a) In light of previously approved applications, is a clinical investigation (either conducted by the applicant or available from some other source, including the published literature) necessary to support approval of the application or supplement?

YES /___/ NO /___/

If "no," state the basis for your conclusion that a clinical trial is not necessary for approval **AND GO DIRECTLY TO SIGNATURE BLOCK ON Page 9:**

- (b) Did the applicant submit a list of published studies relevant to the safety and effectiveness of this drug product and a statement that the publicly available data would not independently support approval of the application?

YES /___/ NO /___/

- (1) If the answer to 2(b) is "yes," do you personally know of any reason to disagree with the applicant's conclusion? If not applicable, answer NO.

YES /___/ NO /___/

If yes, explain:

- (2) If the answer to 2(b) is "no," are you aware of published studies not conducted or sponsored by the applicant or other publicly available data that could independently demonstrate the safety and effectiveness of this drug product?

YES /___/ NO /___/

If yes, explain:

- (c) If the answers to (b) (1) and (b) (2) were both "no," identify the clinical investigations submitted in the application that are essential to the approval:

Investigation #1, Study #

Investigation #2, Study #

Investigation #3, Study #

3. In addition to being essential, investigations must be "new" to support exclusivity. The agency interprets "new clinical investigation" to mean an investigation that 1) has not been relied on by the agency to demonstrate the effectiveness of a previously approved drug for any indication and 2) does not duplicate the results of another investigation that was relied on by the agency to demonstrate the effectiveness of a previously approved drug product, i.e., does not redemonstrate something the agency considers to have been demonstrated in an already approved application.

- (a) For each investigation identified as "essential to the approval," has the investigation been relied on by the agency to demonstrate the effectiveness of a previously approved drug product? (If the investigation was relied on only to support the safety of a previously approved drug, answer "no.")

Investigation #1 YES /___/ NO /___/

Investigation #2 YES /___/ NO /___/

Investigation #3 YES /___/ NO /___/

If you have answered "yes" for one or more investigations, identify each such investigation and the NDA in which each was relied upon:

NDA # _____ Study # _____
NDA # _____ Study # _____
NDA # _____ Study # _____

- (b) For each investigation identified as "essential to the approval," does the investigation duplicate the results of another investigation that was relied on by the agency to support the effectiveness of a previously approved drug product?

Investigation #1 YES /___/ NO /___/

Investigation #2 YES /___/ NO /___/

Investigation #3 YES /___/ NO /___/

If you have answered "yes" for one or more investigations, identify the NDA in which a similar investigation was relied on:

NDA # _____ Study # _____

NDA # _____ Study # _____

NDA # _____ Study # _____

- (c) If the answers to 3(a) and 3(b) are no, identify each "new" investigation in the application or supplement that is essential to the approval (i.e., the investigations listed in #2(c), less any that are not "new"):

Investigation #__, Study # _____

Investigation #__, Study # _____ ;

Investigation #__, Study # _____

4. To be eligible for exclusivity, a new investigation that is essential to approval must also have been conducted or sponsored by the applicant. An investigation was "conducted or sponsored by" the applicant if, before or during the conduct of the investigation, 1) the applicant was the sponsor of the IND named in the form FDA 1571 filed with the Agency, or 2) the applicant (or its predecessor in interest) provided substantial support for the study. Ordinarily, substantial support will mean providing 50 percent or more of the cost of the study.

- (a) For each investigation identified in response to question 3(c): if the investigation was carried out under an IND, was the applicant identified on the FDA 1571 as the sponsor?

Investigation #1 !
!
IND # _____ YES /___/ ! NO /___/ Explain:
!
!
!
!

Investigation #2 !
!
IND # _____ YES /___/ ! NO /___/ Explain:
!
!
!
!

- (b) For each investigation not carried out under an IND or for which the applicant was not identified as the sponsor, did the applicant certify that it or the applicant's predecessor in interest provided substantial support for the study?

Investigation #1 !
!
YES /___/ Explain _____ ! NO /___/ Explain _____
!

!

!

Investigation #2 !
!
YES /___/ Explain _____ ! NO /___/ Explain _____
!

!

!

- (c) Notwithstanding an answer of "yes" to (a) or (b), are there other reasons to believe that the applicant should not be credited with having "conducted or sponsored" the study? (Purchased studies may not be used as the basis for exclusivity. However, if all rights to the drug are purchased (not just studies on the drug), the applicant may be considered to have sponsored or conducted the studies sponsored or conducted by its predecessor in interest.)

YES /___/ NO /___/

If yes, explain: _____

{See appended electronic signature}

Enid Galliers
Chief, Project Management Staff, DMEDP

Date

{See appended electronic signature}

David G. Orloff, M.D.
Director, DMEDP

Date

cc:
Arch. NDA 21-402
HFD- 510/RPM
HFD-093/Mary Ann Holovac
HFD-104/PEDS/T.Crescenzi

Form OGD-011347
Revised 8/7/95; edited 8/8/95; revised 8/25/98, edited 3/6/00

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

/s/

Mary Parks
7/22/02 09:55:28 AM
for Dr. Orloff

APPEARS THIS WAY
ON ORIGINAL

DEBARMENT STATEMENT

In compliance with the Generic Drug Enforcement Act of 1992, Section 306(k)(1) of the act (21 USC 335a(k)(1)), we, Abbott Laboratories, certify the following with respect to this New Drug Application for Synthroid® (levothyroxine sodium tablets, USP).

The applicant hereby certifies that it did not and will not use in any capacity the services of any person debarred under section 306 of the Federal Food, Drug, and Cosmetic Act, in connection with this application.

Ernesto J. Rivera

Ernesto J. Rivera, Pharm.D.
PPD Regulatory Affairs
Dept. 491, Bldg. AP6B-1,
(847) 937-7847
Abbott Laboratories
100 Abbott Park Road
Abbott Park, Illinois 60064-6108

Date

July 31, 2001

**FIELD COPY CERTIFICATION REQUIREMENT FOR ALL APPLICATIONS
REGARDING APPROVAL OF A NEW DRUG PRODUCT**

**New Drug Application-Synthroid (levothyroxine sodium tablets, USP)
NDA 21-402**

Pursuant to 21 CFR 314.50(d)(1)(v), for the Chemistry, Manufacturing, and Controls section it is noted that, "Except for a foreign applicant, the applicant shall include a statement certifying that the field copy of the application has been provided to the applicant's home FDA district office."

Abbott Laboratories hereby certifies that the field copy is a "true" copy of the technical chemistry, manufacturing, and controls section contained and submitted in the archival and review copies of the above referenced New Drug Application.

Ernesto J. Rivera

Ernesto J. Rivera, Pharm.D.
Regulatory Affairs
Department 491, Building AP6B-1SW
Abbott Laboratories
100 Abbott Park Road
Abbott Park, Illinois 60064-6108

July 31, 2001

Date

NDA 21-402

Synthroid

(levothyroxine sodium tablets, USP)

Financial disclosure addressed in

MOR (final 05.16.2002) on page 8.

**APPEARS THIS WAY
ON ORIGINAL**

MEMORANDUM

DEPARTMENT OF HEALTH AND HUMAN SERVICES
Public Health Service
Food and Drug Administration
Center For Drug Evaluation and Research

DATE: July 23, 2002

FROM: David G. Orloff, M.D.
Director, Division of Metabolic and Endocrine Drug Products

TO: NDA 21-402
Synthroid (levothyroxine sodium tablets, USP)
Abbott Laboratories

SUBJECT: NDA review issues and action

Background

This application was submitted July 31, 2001.

In the Federal Register of August 14, 1997, FDA announced that oral drug products containing levothyroxine sodium (T4) are considered new drugs and subject to the new drug requirements of the FFD&C Act. This declaration was based upon longstanding and repeated documentation of problems in product quality relating to lack of stability and variability in batch-to-batch potency. Such problems have occurred with many levothyroxine products across different manufacturers, including Synthroid. These deficiencies in drug quality have the potential to cause serious health consequences to patients requiring chronic levothyroxine therapy. In normals, thyroid hormone levels are extremely tightly regulated, and patients may suffer significant short and long-term problems if plasma thyroid hormone concentrations are either too high or too low.

As per the Federal Register of August 14, 1997, with revisions issued in the Federal Register of April 26, 2000, sponsors wishing to continue to market oral T4 products after August 14, 2001 were required to submit NDAs, including 505(b)(2) applications, containing literature references supporting the safety and effectiveness of LT4 for the proposed indications and acceptable data relating to chemistry, manufacturing, and controls. In addition, bioavailability and *in vitro* dissolution studies are required in order to establish that the product proposed for marketing is readily and consistently absorbed across the full dosage range proposed. In short, the approach to development of levothyroxine-containing new drug products relies on the fact that levothyroxine itself is the appropriate treatment for supplementation or replacement in patients with insufficient endogenous thyroid hormone and for suppression of TSH in patients with thyroid nodules or cancer. However, the approvability of an oral T4 drug product based on a judgment that the specific product is safe and effective depends upon demonstration by the sponsor of acceptable quality, quantity, and *in vitro* and *in vivo* performance. This is accomplished through submission and review of manufacturing information, data from stability studies, and the results of bioequivalence/bioavailability and dissolution studies.

NDA # 21-402

Drug: Synthroid (levothyroxine sodium tablets, USP)

Proposal: replacement of suppressive therapy

07/23/02

Of note, and relevant to the currently marketed Synthroid product, those sponsors of applications pending before the Agency as of August 14, 2001, have two years to obtain final approval, during which time they must reduce distribution of product according to a prescribed "ramp-down" process such that by August 14, 2003, absent approval, distribution of unapproved LT4 products will cease. To date, Abbott has complied with the ramp down requirement.

NDA 21-402 was submitted with the clinical section in accordance with the August 1997 FR notice, with the required sections addressing chemistry, manufacturing, and stability, and with additional content in accordance with Division guidance on the bioavailability/bioequivalence and dissolution studies required for approval of levothyroxine-containing products.

Abbott's application contains satisfactory information in support of approval of Synthroid.

Clinical rationale

This is a 505(b)(2) application and contains no clinical data. The sponsor has provided extensive literature references supporting the safety and effectiveness of LT4 for its proposed uses. Dr. Temeck has reviewed these references and has completed her independent review of the clinical literature addressing thyroid physiology, thyroid hormone action and metabolism, clinical states of thyroid hormone excess and deficiency, and on the clinical efficacy and safety of levothyroxine. In addition, she has summarized the available information on thyroxine dosage and administration in adults and children and on drug-drug and drug-disease interactions for thyroid hormone. Much of the aforementioned has been adequately incorporated or reflected in draft labeling for LT4 drug products that is appended to Dr. Temeck's review.

Levothyroxine is an iodinated derivative of tyrosine and is the major product of the mammalian (including man) thyroid gland. While T4 is the most abundant circulating thyroid hormone, activation of thyroid hormone receptors intracellularly requires enzymatic deiodination to T3 in the periphery. Thus, T3 is the major active thyroid hormone in the circulation. Thyroid hormones are essential for survival. Administration of T4 simply supplements or replaces endogenously synthesized T4. Levothyroxine is used to supplement patients with absent or diminished thyroid function due to a variety of causes. In addition, replacement doses of T4 will suppress the hypothalamic-pituitary-thyroid axis, resulting specifically in reduced circulating TSH, and is thus used in the therapy of goiter, thyroid nodules, and thyroid cancer, all potentially TSH dependent.

For the uses described above, T4 is safe and effective. Of critical clinical importance, though, is that dose must be titrated to optimum TSH and T4 blood levels in order to ensure effectiveness and to avoid consequences of over- or under-treatment. These include, among others, effects on growth and development, cardiovascular function, bone, reproductive function, cognitive and emotional state, and on glucose and lipid metabolism. Safe and effective titration requires availability of multiple dosage strengths that permit the full range of total daily dosages (e.g., 25-300 mcg) in increments of 12 or 12.5 mcg. This may be accomplished clinically by combined dosing using more than one dosage strength to render the total daily dose needed and may also involve splitting tablets (e.g., for 12.5 mcg increments, taking half a 25 mcg tablet one day and the other half the next).

NDA # 21-402

Drug: Synthroid (levothyroxine sodium tablets, USP)

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07/23/02

As above, no new clinical data have been submitted, pursuant to guidance from the Division.

Labeling

The product label proposed conforms to the template label developed by the division for LT4 products. Final labeling has been submitted and is acceptable. ODS has recommended changes to the blister labels for the hospital packs of Synthroid as well as to the professional samples. These recommendations are included in the action letter as suggested changes at a subsequent printing.

Biopharmaceutics

Dr. Johnson reviewed the reports of studies M01-324 and M01-323, relative bioavailability and dosage strength proportionality studies, respectively. The relative bioavailability of two Synthroid 300 mcg tablets was approximately 93% of a single 600 mg oral dose of levothyroxine. In study 323, the proportionality between 50, 100, and 300 mcg tablets was established based on Cmax and AUC. OCPB therefore finds the bioavailability and "dosage-form equivalence" data acceptable. Dissolution method and tolerance specifications have been set, are included in the review, and will be conveyed in the action letter.

Pharmacology/Toxicology

There are no preclinical toxicology issues with this product or with levothyroxine sodium generally.

Chemistry/ Microbiology

Dr. Lewis has reviewed the chemistry, manufacturing, and controls information in the application. The currently marketed product is manufactured using a _____, and targets greater than 100% of labeled claim at release. The registry lots for this NDA and the proposed product are manufactured using _____ ranging from _____ depending on the dosage strength, targeting 100% of labeled claim at release. This specification (100% of labeled claim at release) has been met by the current manufacturing method. Otherwise, the formulation for Synthroid has not changed from currently marketed product to NDA product. Stability information has been provided sufficient to support a 10-month expiry for all strengths packaged in 1000-count bottles and a 9-month expiry for all strengths packaged in 100-count bottles). The ONDC team recommends approval with 10- and 9-month expiration dating as in the preceding.

The establishment evaluations were all acceptable.

A categorical exclusion from the environmental assessment was claimed by the sponsor and accepted by the Agency.

DSI/Data Integrity

The analytical portions of the bioavailability studies were audited by DSI. Minor deficiencies were noted and a Form 483 was issued. The sponsor addressed the 483 item to the satisfaction of DSI. DSI recommends that the data are acceptable for review.

Financial disclosure

NDA # 21-402

Drug: Synthroid (levothyroxine sodium tablets, USP)

Proposal: replacement of suppressive therapy

07/23/02

The financial disclosure information is in order.

OPDRA/nomenclature

The proprietary name, Synthroid, has been found acceptable by ODS and is likewise acceptable to the Division.

Pediatric Rule

The sponsor has requested a waiver of requirements for pediatric studies based on the fact that adequate information exists in the published medical and scientific literature to support the safety and efficacy of LT4 (and thus Synthroid) in children.

A waiver has been granted.

Phase 4 commitments

The sponsor has made a commitment to develop an analytical method for the determination of impurities and degradation products in the drug substance and the drug product. The sponsor is reminded of this commitment in the letter.

Conclusions

The current application contains adequate information to support the clinical use of Synthroid for the proposed indications.

Recommendation

NDA 21-402 may be approved.

**APPEARS THIS WAY
ON ORIGINAL**

NDA # 21-402

Drug: Synthroid (levothyroxine sodium tablets, USP)

Proposal: replacement of suppressive therapy

07/23/02

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

/s/

David Orloff
7/23/02 05:41:03 PM
MEDICAL OFFICER

**APPEARS THIS WAY
ON ORIGINAL**

DEPARTMENT OF HEALTH AND HUMAN SERVICES
PUBLIC HEALTH SERVICE
FOOD AND DRUG ADMINISTRATION

Form Approved: OMB No. 0910-0297
Expiration Date: February 29, 2004.

USER FEE COVER SHEET

See Instructions on Reverse Side Before Completing This Form

A completed form must be signed and accompany each new drug or biologic product application and each new supplement. See exceptions on the reverse side. If payment is sent by U.S. mail or courier, please include a copy of this completed form with payment. Payment instructions and fee rates can be found on CDER's website: <http://www.fda.gov/cder/pdufa/default.htm>

1. APPLICANT'S NAME AND ADDRESS

Abbott Laboratories
100 Abbott Park Road
Abbott Park, IL 60064-6108

Attn: Peter W. Noblin
D-491/AP6B-1SW
Pharmaceutical Products Division
Regulatory Affairs

2. TELEPHONE NUMBER (Include Area Code)

(847) 937-5091

3. PRODUCT NAME

Synthroid (levothyrosine sodium tablets, USP)

4. BLA SUBMISSION TRACKING NUMBER (STN) / NDA NUMBER

21-402

5. DOES THIS APPLICATION REQUIRE CLINICAL DATA FOR APPROVAL?

☒ YES ☐ NO

IF YOUR RESPONSE IS "NO" AND THIS IS FOR A SUPPLEMENT, STOP HERE AND SIGN THIS FORM.

IF RESPONSE IS "YES", CHECK THE APPROPRIATE RESPONSE BELOW:

☒ THE REQUIRED CLINICAL DATA ARE CONTAINED IN THE APPLICATION.

☐ THE REQUIRED CLINICAL DATA ARE SUBMITTED BY
REFERENCE TO:

(APPLICATION NO. CONTAINING THE DATA.)

6. USER FEE I.D. NUMBER

7. IS THIS APPLICATION COVERED BY ANY OF THE FOLLOWING USER FEE EXCLUSIONS? IF SO, CHECK THE APPLICABLE EXCLUSION.

☐ A LARGE VOLUME PARENTERAL DRUG PRODUCT
APPROVED UNDER SECTION 505 OF THE FEDERAL
FOOD, DRUG, AND COSMETIC ACT BEFORE 9/1/92
(Self Explanatory)

☒ A 505(b)(2) APPLICATION THAT DOES NOT REQUIRE A FEE
(See item 7, reverse side before checking box.)

☐ THE APPLICATION QUALIFIES FOR THE ORPHAN
EXCEPTION UNDER SECTION 736(a)(1)(E) of the Federal Food,
Drug, and Cosmetic Act
(See item 7, reverse side before checking box.)

☐ THE APPLICATION IS A PEDIATRIC SUPPLEMENT THAT
QUALIFIES FOR THE EXCEPTION UNDER SECTION 736(a)(1)(F) of
the Federal Food, Drug, and Cosmetic Act
(See item 7, reverse side before checking box.)

☐ THE APPLICATION IS SUBMITTED BY A STATE OR FEDERAL
GOVERNMENT ENTITY FOR A DRUG THAT IS NOT DISTRIBUTED
COMMERCIALY
(Self Explanatory)

8. HAS A WAIVER OF AN APPLICATION FEE BEEN GRANTED FOR THIS APPLICATION?

☐ YES ☐ NO

(See Item 8, reverse side if answered YES)

Public reporting burden for this collection of information is estimated to average 30 minutes per response, including the time for reviewing instructions, searching existing data sources, gathering and maintaining the data needed, and completing and reviewing the collection of information. Send comments regarding this burden estimate or any other aspect of this collection of information, including suggestions for reducing this burden to:

Department of Health and Human Services
Food and Drug Administration
CDER, HFD-99
1401 Rockville Pike
Rockville, MD 20852-1448

Food and Drug Administration
CDER, HFD-94
and 12420 Parklawn Drive, Room 3046
Rockville, MD 20852

An agency may not conduct or sponsor, and a person is not
required to respond to, a collection of information unless it
displays a currently valid OMB control number.

SIGNATURE OF AUTHORIZED COMPANY REPRESENTATIVE



TITLE

Associate Director, Regulatory Affairs

DATE

July 31, 2001

NDA/EFFICACY SUPPLEMENT ACTION PACKAGE CHECKLIST

NDA	<u>21-402</u> / SE _____	
Drug	<u>SYNTHROID</u> (<u>levothyroxine sodium</u>) <u>tablets, USP</u>	Applicant <u>Abbott Laboratories</u>
RPM	<u>Enid Galliers</u>	Phone <u>301-827-6429</u>
<input type="checkbox"/> 505(b)(1)		
<input checked="" type="checkbox"/> 505(b)(2)	Reference listed drug <u>Unithroid NDA 21-210; Levoxyl NDA 21-301</u>	
<input type="checkbox"/> Fast Track	<input type="checkbox"/> Rolling Review	Review priority: <input checked="" type="checkbox"/> S <input type="checkbox"/> P
Pivotal IND(s)	_____	
Application classifications:		PDUFA Goal Dates:
Chem Class <u>5</u>		Primary <u>June 1, 2002</u>
Other (e.g., orphan, OTC) _____		Secondary <u>Aug 1, 2002</u>

Arrange package in the following order:

Indicate N/A (not applicable),
X (completed), or add a
comment.

GENERAL INFORMATION:

- ◆ User Fee Information: ☐ User Fee Paid
☐ User Fee Waiver (attach waiver notification letter)
☐ User Fee Exemption
- ◆ Action Letter..... ☒ AP ☐ AE ☐ NA
- ◆ Labeling & Labels

FDA revised labeling and reviews.....	<u>7/9/02 template PI</u>	<u>✓</u>
Original proposed labeling (package insert, patient package insert)		<u>✓</u>
Other labeling in class (most recent 3) or class labeling.....		<u>N/A</u>
Has DDMAC reviewed the labeling?	<input checked="" type="checkbox"/> Yes (include review) <input type="checkbox"/> No	
Immediate container and carton labels		<u>✓</u>
Nomenclature review	<u>8.21.01</u>	<u>✓</u>
- ◆ Application Integrity Policy (AIP) ☐ Applicant is on the AIP. This application ☐ is ☒ is not on the AIP.
 Exception for review (Center Director's memo).....
 OC Clearance for approval.....

- ◆ Status of advertising (if AP action) ☐ Reviewed (for Subpart H – attach review) ☒ Materials requested in AP letter
- ◆ Post-marketing Commitments
 Agency request for Phase 4 Commitments..... CMC dependent method ✓
 Copy of Applicant's commitments 7/23/02 ✓
- ◆ Was Press Office notified of action (for approval action only)?..... ☒ Yes ☐ No
 Copy of Press Release or Talk Paper.....
- ◆ Patent
 Information [505(b)(1)] ✓
 Patent Certification [505(b)(2)] ✓
 Copy of notification to patent holder [21 CFR 314.50 (i)(4)] NA
- ◆ Exclusivity Summary ✓
- ◆ Debarment Statement ✓
- ◆ Financial Disclosure
 No disclosable information NA
 Disclosable information – indicate where review is located 8/5/02 MGR ✓
- ◆ Correspondence/Memoranda/Faxes ✓
- ◆ Minutes of Meetings ✓
 Date of EOP2 Meeting NA
 Date of pre NDA Meeting 6.27.02
 Date of pre-AP Safety Conference NA
- ◆ Advisory Committee Meeting NA
 Date of Meeting
 Questions considered by the committee
 Minutes or 48-hour alert or pertinent section of transcript
- ◆ Federal Register Notices, DESI documents 1997 2000 2001 ✓

CLINICAL INFORMATION:

Indicate N/A (not applicable),
 X (completed), or add a
 comment.

- ◆ Summary memoranda (e.g., Office Director's memo, Division Director's memo, Group Leader's memo) 7/23/02 ✓
- ◆ Clinical review(s) and memoranda 10/23/01 MEMO; 5/16/02 ✓

- ◆ Safety Update review(s) N/A
- ◆ Pediatric Information
 - ☒ Waiver/partial waiver (Indicate location of rationale for waiver) ☐ Deferred Pediatric Page..... ✓
 - ☐ Pediatric Exclusivity requested? ☐ Denied ☐ Granted ☐ Not Applicable
- ◆ Statistical review(s) and memoranda N/A
- ◆ Biopharmaceutical review(s) and memoranda 9/17/01, 7/22/02, 7/22/02 ✓
- ◆ Abuse Liability review(s) N/A
 - Recommendation for scheduling
- ◆ Microbiology (efficacy) review(s) and memoranda N/A
- ◆ DSI Audits in draft
 - ☐ Clinical studies ☒ bioequivalence studies

CMC INFORMATION:

Indicate N/A (not applicable),
X (completed), or add a
comment.

- ◆ CMC review(s) and memoranda 10/21/01 filing, 7/22/02 ✓
- ◆ Statistics review(s) and memoranda regarding dissolution and/or stability N/A
- ◆ DMF review(s) N/A
- ◆ Environmental Assessment review/FONSI/Categorical exemption Cat. Exemption ✓
- ◆ Micro (validation of sterilization) review(s) and memoranda N/A
- ◆ Facilities Inspection (include EES report)
 - Date completed March 21, 2002 ☒ Acceptable ☐ Not Acceptable
- ◆ Methods Validation ☐ Completed ☒ Not Completed

PRECLINICAL PHARM/TOX INFORMATION:

Indicate N/A (not applicable),
X (completed), or add a
comment.

- ◆ Pharm/Tox review(s) and memoranda 9/17/01 4/23/02 ✓
- ◆ Memo from DSI regarding GLP inspection (if any) N/A

- ◆ Statistical review(s) of carcinogenicity studies NA
- ◆ CAC/ECAC report NA

**APPEARS THIS WAY
ON ORIGINAL**

PEDIATRIC PAGE

(Complete for all APPROVED original applications and efficacy supplements)

NDA/BLA #: 21-402 Supplement Type (e.g. SE5): _____ Supplement Number: _____

Stamp Date: Aug. 1, 2001 Action Date: July 24, 2002

HFD -510 Trade and generic names/dosage form: Synthroid (levothyroxine sodium tablets, USP)

Applicant: Abbott Laboratories Therapeutic Class: thyroid

Indication(s) previously approved: New NDA

Each approved indication must have pediatric studies: Completed, Deferred, and/or Waived.

Number of indications for this application(s): 2

Indication #1: treatment of hypothyroidism

Is there a full waiver for this indication (check one)?

☐ Yes: Please proceed to Section A.

☐ No: Please check all that apply: ☐ Partial Waiver ☐ Deferred ☐ Completed

NOTE: More than one may apply

Please proceed to Section B, Section C, and/or Section D and complete as necessary.

Section A: Fully Waived Studies

Reason(s) for full waiver:

- ☒ Products in this class for this indication have been studied/labeled for pediatric population
- ☐ Disease/condition does not exist in children
- ☐ Too few children with disease to study
- ☐ There are safety concerns
- ☐ Other: _____

If studies are fully waived, then pediatric information is complete for this indication. If there is another indication, please see Attachment A. Otherwise, this Pediatric Page is complete and should be entered into DFS.

Section B: Partially Waived Studies

Age/weight range being partially waived:

Min _____ kg _____ mo. _____ yr. _____ Tanner Stage _____
Max _____ kg _____ mo. _____ yr. _____ Tanner Stage _____

Reason(s) for partial waiver:

- ☐ Products in this class for this indication have been studied/labeled for pediatric population
- ☐ Disease/condition does not exist in children
- ☐ Too few children with disease to study
- ☐ There are safety concerns
- ☐ Adult studies ready for approval
- ☐ Formulation needed
- ☐ Other: _____

If studies are deferred, proceed to Section C. If studies are completed, proceed to Section D. Otherwise, this Pediatric Page is complete and should be entered into DFS.

Section C: Deferred Studies

Age/weight range being deferred:

Min _____ kg _____ mo. _____ yr. _____ Tanner Stage _____
Max _____ kg _____ mo. _____ yr. _____ Tanner Stage _____

Reason(s) for deferral:

- ☐ Products in this class for this indication have been studied/labeled for pediatric population
- ☐ Disease/condition does not exist in children
- ☐ Too few children with disease to study
- ☐ There are safety concerns
- ☐ Adult studies ready for approval
- ☐ Formulation needed

Other: _____

Date studies are due (mm/dd/yy): _____

If studies are completed, proceed to Section D. Otherwise, this Pediatric Page is complete and should be entered into DFS.

Section D: Completed Studies

Age/weight range of completed studies:

Min _____ kg _____ mo. _____ yr. _____ Tanner Stage _____
Max _____ kg _____ mo. _____ yr. _____ Tanner Stage _____

Comments:

If there are additional indications, please proceed to Attachment A. Otherwise, this Pediatric Page is complete and should be entered into DFS.

This page was completed by:

{See appended electronic signature page}

Regulatory Project Manager

cc: NDA

HFD-960/ Terrie Crescenzi

(revised 1-18-02)

FOR QUESTIONS ON COMPLETING THIS FORM CONTACT, PEDIATRIC TEAM, HFD-960
301-594-7337

Attachment A

(This attachment is to be completed for those applications with multiple indications only.)

Indication #2: suppression of thyroid-stimulating hormone (TSH)

Is there a full waiver for this indication (check one)?

☐ **YES: Please proceed to Section A.**☐ **No: Please check all that apply: Partial Waiver Deferred Completed****NOTE: More than one may apply****Please proceed to Section B, Section C, and/or Section D and complete as necessary.****Section A: Fully Waived Studies**

Reason(s) for full waiver:

- ☒ ✓ Products in this class for this indication have been studied/labeled for pediatric population
- ☐ Disease/condition does not exist in children
- ☐ Too few children with disease to study
- ☐ There are safety concerns
- ☐ Other: _____

If studies are fully waived, then pediatric information is complete for this indication. If there is another indication, please see Attachment A. Otherwise, this Pediatric Page is complete and should be entered into DFS.

Section B: Partially Waived Studies

Age/weight range being partially waived:

Min _____	kg _____	mo. _____	yr. _____	Tanner Stage _____
Max _____	kg _____	mo. _____	yr. _____	Tanner Stage _____

Reason(s) for partial waiver:

- ☐ Products in this class for this indication have been studied/labeled for pediatric population
- ☐ Disease/condition does not exist in children
- ☐ Too few children with disease to study
- ☐ There are safety concerns
- ☐ Adult studies ready for approval
- ☐ Formulation needed
- ☐ Other: _____

If studies are deferred, proceed to Section C. If studies are completed, proceed to Section D. Otherwise, this Pediatric Page is complete and should be entered into DFS.

Section C: Deferred Studies

Age/weight range being deferred:

Min _____	kg _____	mo. _____	yr. _____	Tanner Stage _____
Max _____	kg _____	mo. _____	yr. _____	Tanner Stage _____

Reason(s) for deferral:

- ☐ Products in this class for this indication have been studied/labeled for pediatric population
- ☐ Disease/condition does not exist in children
- ☐ Too few children with disease to study
- ☐ There are safety concerns
- ☐ Adult studies ready for approval
- ☐ Formulation needed
- ☐ Other: _____

Date studies are due (mm/dd/yy): _____

*If studies are completed, proceed to Section D. Otherwise, this Pediatric Page is complete and should be entered into DFS.***Section D: Completed Studies**

Age/weight range of completed studies:

Min _____	kg _____	mo. _____	yr. _____	Tanner Stage _____
Max _____	kg _____	mo. _____	yr. _____	Tanner Stage _____

Comments:

If there are additional indications, please copy the fields above and complete pediatric information as directed. If there are no other indications, this Pediatric Page is complete and should be entered into DFS.

This page was completed by:

{See appended electronic signature page}

Regulatory Project Manager

cc: NDA

HFD-960/ Terrie Crescenzi
(revised 1-18-02)FOR QUESTIONS ON COMPLETING THIS FORM CONTACT, PEDIATRIC TEAM, HFD-960
301-594-7337

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/s/

Enid Galliers
7/25/02 07:23:06 PM

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Division of Metabolic & Endocrine Drug Products

PROJECT MANAGER LABELING REVIEW

Application Numbers: NDA 21-402 Synthroid (levothyroxine sodium tablets, USP)
25, 50, 75, 88, 100, 112, 125, 137, 150, 175, 200, and 300 mcg.

Sponsor: Abbott Laboratories

Material Reviewed:

Submission Dates:

(Note: All container labels, blisters, and cartons were submitted as full-scale, color mock-ups.)

July 31, 2001

NDA 21-301 draft labeling :

1. package insert
2. hospital unit dose blisters of 10 tablets and cartons of 10 X 10 blisters (50 mcg, 75 mcg, 100 mcg, 125 mcg, 150 mcg, 200 mcg) [6 strengths]
3. 100-count stock bottles labels (25 mcg – 300 mcg)
4. 1000-count stock bottles labels (25 mcg – 300 mcg)
5. professional sample labeling: carton of 10 blisters and blister card of 7 tablets [two sides of blister card] (50 mcg through 200 mcg strengths; i.e., no packaging for 25 mcg or 300 mcg)

January 29, 2002

1. revised package insert

April 15, 2002

1. revised package insert
2. revised labeling for physician samples (carton and blister card)

May 23, 2002

1. revised package insert
2. revised sample- 100-count stock bottle label (25 mcg)

July 11, 2002

1. revised package insert (draft)
2. revised sample hospital unit dose carton (50 mcg)

Background and Summary

Synthroid (levothyroxine sodium tablets, USP) is approved for hypothyroidism and suppression of thyroid-stimulating hormone in 12 strengths. The product is approved in stock bottles of 100 and 1000 tablets, hospital unit dose cartons of 100 tablets, and professional samples of 7 tablets in a calendar blister card. There are no cartons for bottles.

Review

Package Insert

The package insert submitted on July 11, 2002, corresponds exactly with the levothyroxine sodium tablets template package insert developed by the Agency (Revision: July 9, 2002) except for the insertion of the following product-specific information:

DESCRIPTION: list of coloring agents and other inactive ingredients
CLINICAL PHARMACOLOGY, "Pharmacokinetics," "Absorption," section
supplies the product-specific bioavailability value of "93%"

HOW SUPPLIED:

"**SYNTHROID®** (levothyroxine sodium tablets, USP) are round, color coded, scored and debossed with "**SYNTHROID**" on one side and potency on the other side. They are supplied as follows:"

A table of strength, tablet color, and NDC numbers for each of three market presentations

STORAGE CONDITIONS: "Store at 25°C (77°F); excursions permitted to 15°-30°C (59°-86°F) [see USP Controlled Room Temperature]. **SYNTHROID** tablets should be protected from light and moisture."

Substitution of "**SYNTHROID**" in place of "**TRADEMARK**" throughout

The package insert (Identifier, **DN0663V5 CR22-02605, REV: NEW**) is identical to the template developed by the Agency except for the product-specific information.

The product-specific information in the DESCRIPTION, HOW SUPPLIED, and STORAGE CONDITIONS sections are acceptable to the review chemist.

The product-specific bioavailability value is acceptable to the biopharmaceutics reviewer.

Container Labels

The approval of SYNTHROID included the following container labels:

1. Blister cards of 7 tablets - Professional Sample - 50 mcg, 75 mcg, 88 mcg, 100 mcg, 112 mcg, 125 mcg, 137 mcg, 150 mcg, 175 mcg, 200 mcg (10 strengths)
2. Blister label (10 tablets) - Hospital Unit Dose - 50 mcg, 75 mcg, 100 mcg, 125 mcg, 150 mcg, 200 mcg (6 strengths)
3. 100-count stock bottle - 25 mcg, 50 mcg, 75 mcg, 88 mcg, 100 mcg, 112 mcg, 125 mcg, 137 mcg, 150 mcg, 175 mcg, 200 mcg, 300 mcg (12 strengths)
4. 1000-count stock bottles - 25 mcg, 50 mcg, 75 mcg, 88 mcg, 100 mcg, 112 mcg, 125 mcg, 137 mcg, 150 mcg, 175 mcg, 200 mcg, 300 mcg (12 strengths)

Carton Labeling

5. Cartons - Professional Sample - 50 mcg, 75 mcg, 88 mcg, 100 mcg, 112 mcg, 125 mcg, 137 mcg, 150 mcg, 175 mcg, 200 mcg (10 strengths)
6. Cartons - Hospital Unit Dose "Abbo-Pac" (100 tablets in unit dose blisters) - 50 mcg, 75 mcg, 100 mcg, 125 mcg, 150 mcg, 200 mcg (6 strengths)

The labels do not use the exact phrase: "See package insert for dosage information" as specified under 21 CFR 201.55. Instead the hospital unit dose cartons use the phrase,

The bottle labels and professional sample cartons and blister cards (reverse side only) use the phrase, "

The draft (mock-up) carton and container labels were modified or samples of revised labels were submitted during the review period. The modifications were made to add the following sentences to the labels:

"Tablet identification change adopted <<month>> 2002."

"Each tablet contains XXX mcg (X.XXX mg) levothyroxine sodium."

- The 100-count bottle labels, 1000-count bottle labels, and hospital unit dose cartons (100 tablets) submitted July 31, 2001, were modified as described in the July 11, 2002, submission to add those two statements. A sample 100-count label (25 mcg) was submitted May 23, 2002, and a sample hospital unit dose carton (50 mcg) was submitted July 11, 2002.

- Professional sample carton and blister cards submitted April 15, 2002, contained the changes.
- There were no changes to the hospital unit dose 10-tablet blister labels submitted July 31, 2001.

The consult review from the Office of Drug Safety (DMETS) recommended two labeling changes with which the review chemist concurred. The Division Director agreed to request those changes rather than require them for approval. The text of the changes requested for implementation at a subsequent printing follows:

- Blister Labels (Abbo-Pac): The expression of strength is not prominent and all strengths look similar. Since multiple strengths are marketed, it is important that colors and/or boxes are used to distinguish each strength. In addition, they should appear *consistent* with the colors for the same-strength container labels.
- Professional samples: In order to increase the prominence of the strength, we recommend _____
_____ We also recommend _____

Conclusions

The submitted draft package insert submitted July 11, 2002, is acceptable and may be approved.

The professional sample cartons and blister cards submitted April 15, 2002, are acceptable and may be approved.

The hospital unit dose blister labels submitted July 31, 2001, are acceptable and may be approved.

The 100-count stock bottle labels, 1000-count stock bottle labels, and hospital unit dose cartons (Abbo-Pac) submitted July 31, 2001, are acceptable and may be approved with the additions described in the July 11, 2002, submission.

{See appended electronic signature.}

Enid Galliers
Chief, PM Staff, HFD-510

PM LABELING REVIEW

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/s/

Enid Galliers
7/26/02 07:49:02 PM
CSO

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ON ORIGINAL**

Number of Pages
Redacted 72



Draft Labeling
(not releasable)

Number of Pages
Redacted 84



Draft Labeling
(not releasable)

CONSULTATION RESPONSE
Office of Post-Marketing Drug Risk Assessment
(OPDRA; HFD-400)

DATE RECEIVED: August 10, 2001

DUE DATE: December 1, 2001

OPDRA CONSULT #: 01-0173

TO: David Orloff, M.D.
Director, Division of Metabolic and Endocrine Drug Products
HFD-510

THROUGH: Steve McCort,
Project Manager
HFD-510

PRODUCT NAME:
Synthroid
(levothyroxine sodium tablets, USP;
25, 50, 75, 88, 100, 112, 125, 137, 150,
175, 200, and 300 mcg)

MANUFACTURER: Abbott Laboratories

NDA #: 21-402

SAFETY EVALUATOR: Hye-Joo Kim, Pharm.D.

SUMMARY: In response to a consult from the Division of Metabolic and Endocrine Drug Products (HFD-510), OPDRA conducted a review of the proposed proprietary name "Synthroid" to determine the potential for confusion with approved proprietary and generic names as well as pending names.

OPDRA RECOMMENDATION: OPDRA has no objection to the use of the name "Synthroid". OPDRA considers this a final review.

Jerry Phillips, R.Ph.
Associate Director for Medication Error Prevention
Office of Post-Marketing Drug Risk Assessment
Phone: (301) 827-3246
Fax: (301) 480-8173

Martin Himmel, M.D.
Deputy Director
Office of Post-Marketing Drug Risk Assessment
Center for Drug Evaluation and Research
Food and Drug Administration

Office of Postmarketing Drug Risk Assessment (OPDRA)

HFD-400; Parklawn Building Room 15B-32

FDA Center for Drug Evaluation and Research

PROPRIETARY NAME REVIEW

DATE OF REVIEW: August 20, 2001

NDA NUMBER: 21-402

NAME OF DRUG: Synthroid (levothyroxine sodium tablets, USP;
25, 50, 75, 88, 100, 112, 125, — 150, 175, 200, 300 mcg)

NDA HOLDER: Abbott Laboratories

I. INTRODUCTION

This consult was written in response to a request from the Division of Metabolic and Endocrine Drug Products (HFD-510) for assessment of the proprietary name, Synthroid. The container and blister labels, carton labeling, blister carton labeling, and the package inserts were also submitted for review of possible interventions in minimizing medication errors.

The sponsor, Abbott, currently markets Synthroid for the same active ingredient, levothyroxine. Historically, levothyroxine sodium products have been marketed in the U.S. without the NDAs. However, this NDA was submitted in response to a Federal Register Notice published August 14, 1997, which requires that the manufacturers of all levothyroxine-containing drug products submit an NDA to market these products.

PRODUCT INFORMATION:

Each Synthroid contains synthetic levothyroxine sodium. Levothyroxine is the hormone secreted by the thyroid gland. The principal effect of thyroid hormones is to increase the metabolic rate of most body tissues. Synthroid is indicated as replacement or supplemental therapy in congenital or acquired hypothyroidism of any etiology, except transient hypothyroidism during the recovery phase of subacute thyroiditis. It is also indicated in the treatment or prevention of various types of euthyroid goiters. Synthroid is available in 12 oral tablet strengths: 25 mcg, 50 mcg, 75 mcg, 88 mcg, 100 mcg, 112 mcg, 125 mcg, 137 mcg, 150 mcg, 175 mcg, 200 mcg, and 300 mcg.

II. RISK ASSESSMENT

AERS/DORS DATABASE SEARCHES

Since Synthroid is a product name already in use in the U.S. marketplace, the usual prescription analysis studies were not conducted. OPDRA searched the *FDA Adverse Event Reporting System*

(AERS) database in order to determine any post-marketing safety reports of medication errors associated with Synthroid. The Meddra Preferred Term (PT), "Drug Maladministration," and the drug names, "Synthroid%" and "levothyroxine%" were used to perform the searches. The *Drug Quality Reporting System (DQRS)* database was also searched for medication error reports with the search terms, "Synthroid%" and "levothyroxine%."

Seven (7) relevant reports were retrieved using this search strategy.

Date	Source AERS/DQRS	Intended Product	Dispensed Product	Outcome/Description
9/28/98	3135646-4	Synthroid	Premarin	An 81 year-old female took Premarin for 97 days. The patient became hypothyroid and eventually suffered a severe stroke that left her permanently confined to a nursing home.
8/18/99	3327499-6	Symmetrel	Synthroid	A prescription for Symmetrel 100 mg was filled with Synthroid 100 mcg. The patient discovered the error, because Synthroid looked different from Symmetrel.
11/09/99	3392865-X	Synthroid	Risperdal	The prescription bottle was labeled correctly as Levothyroxine, but it contained Risperdal. The error was discovered prior to dosing.
4/19/00	3495414-0	Synthroid	Lanoxin	An outpatient prescription for Synthroid 0.125 mg was refilled with Digoxin 0.125 mg tablets. The error was discovered prior to dosing.
1/22/01	3651665-3	Folic Acid	Synthroid	An outpatient pharmacy prescription for folic acid 1 mg was refilled with Synthroid 0.1 mg at a call-in refill window. The prescription was dispensed, but the error was discovered prior to dosing.
7/23/01	3762556-1	Flexeril	Synthroid	A patient received another patient's Synthroid instead of her cyclobenzaprine. She took 1 Synthroid tablet before discovering the error.
7/26/01	3765339-1	Synthroid	Remeron	The prescription bottle was labeled correctly as Synthroid 50 mcg, but it contained Remeron 30 mg. The error was discovered prior to ingestion.

B. SAFETY EVALUATOR RISK ASSESSMENT

To date, the Agency received 7 relevant medication error reports involving Synthroid. One report involved Synthroid and Premarin. The patient took Premarin for 97 days instead of Synthroid and suffered a stroke that left her permanently confined to a nursing home. Another medication error report confirmed erroneous filling of Synthroid 100 mcg instead of Symmetrel 100 mg. In the third report, Lanoxin 0.125 mg was refilled instead of Synthroid 0.125 mg. The last four reports involved confusion between Synthroid and folic acid, Flexeril, Risperdal or Remeron.

Synthroid has been available in the U.S. marketplace since 1963, but only seven (7) medication error reports involving Synthroid and various drug products were received by the Agency. Therefore, there is no substantial evidence to warrant a name change. OPDRA will continue to monitor post-marketing medication errors in association with the proprietary name, Synthroid.

For these reasons, OPDRA has no objection to the continued use of the proprietary name, Synthroid.

III. LABELING, PACKAGING, AND SAFETY RELATED ISSUES

In the review of the container and blister labels, carton labeling, blister carton labeling, and package insert of the proposed drug, Synthroid, OPDRA has reviewed the current labels/labeling and has identified several areas of possible improvement, which might minimize potential user error.

A. BLISTER LABELS (25, 50, 75, 88, 100, 112, 125, 137, 150, 175, 200, & 300 mcg)

The expression of strength is not prominent and all strengths look similar. Since multiple strengths are marketed, it is important that colors and/or boxes are used to distinguish each strength. In addition, they should appear *consistent* with the colors for the same-strength container labels.

B. PROFESSIONAL SAMPLES

In order to increase the prominence of the strength, we recommend relocating the strength to the center of the label, below the proprietary name. We also recommend increasing the font size of the strength.

C. PACKAGE INSERT

No comments.

IV. RECOMMENDATIONS

A. OPDRA has no objections to the use of the proprietary name, Synthroid.

B. OPDRA recommends the above labeling revisions that might lead to safer use of the product

We would be willing to meet with the Division for further discussion, if needed. In addition, OPDRA would appreciate feedback on the final outcome of this consult. If you have any questions concerning this review, please contact Hye-Joo Kim at (301) 827-0925.

Hye-Joo Kim, Pharm.D.
Safety Evaluator
Office of Postmarketing Drug Risk Assessment (OPDRA)

Concur:

Jerry Phillips, R.Ph.
Associate Director for Medication Error Prevention
Office of Postmarketing Drug Risk Assessment (OPDRA)

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/s/

Hye-Joo Kim
8/28/01 08:51:14 AM
PHARMACIST

Jerry Phillips
8/28/01 09:05:14 AM
DIRECTOR

Martin Himmel
8/28/01 03:06:17 PM
MEDICAL OFFICER

**APPEARS THIS WAY
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MEMORANDUM OF TELECON

DATE: May 28, 2002 @ 4:00 PM

APPLICATION: NDA 21-402, Synthroid (levothyroxine sodium tablets, USP)
25, 50, 75, 88, 100, 112, 125, 137, 150, 175, 200, 300 mcg.

BETWEEN:

ABBOTT LABORATORIES

Larry Roebel, Ph.D.

Vice President, Regulatory Affairs & Research Information Center

Todd E Chermak

Director, Regulatory Affairs, Chemistry, Manufacturing, and Controls

Julie Garren, Ph.D.

Project Manager, Pharmaceutical Analytical Research and Development

Ernesto J. Rivera, Pharm.D.

Regulatory Affairs Project Manager

AND

FDA, CDER

David Lewis, Ph.D., Review Chemist, DNCD II, ONDC

Sheldon Markofsky, Ph.D., Acting Chemistry Team Leader, DNCD II, ONDC

Enid Galliers, Chief, Project Management Staff

Division of Metabolic and Endocrine Drug Products, HFD-510 (DMEDP)

SUBJECT: Decision on possible adoption of 12-month goal date for Synthroid to allow firm to submit additional stability information and to assess dissolution tolerance established by the Agency.

BACKGROUND: The telecon was arranged to convey the decisions of the firm and the Agency and establish the action plan.

DISCUSSION AND CONCLUSIONS:

Abbott proposed to _____
expiry dating – by showing that the slope had leveled off. The Agency explained the requirements for extrapolation which could not be met by this class of product. The Agency reiterated that it needed data to support the expiry. The Agency indicated that data for the controlled room temperature stations (25°C, 60%RH) was adequate, and data for intermediate conditions would not be needed.

The firm proposed _____ The Agency commented that the firm would need to submit the data enough in advance of the 12-month goal date (August 1, 2002) to allow for review of the data and necessary administrative preparation for an action.

Abbott and the Agency agreed to a 12 month review clock.

ACTION ITEMS:

- Abbott planned to consider the Agency's dissolution tolerance and submit its decision and additional data subsequently.
- Abbott said it would _____
_____ could be submitted.

{See appended electronic signature}

Sheldon Markofsky, Ph.D.
Acting Chemistry Team Leader, DND II, ONDC

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/s/

Enid Galliers
7/28/02 04:50:57 PM
CSO

This version replaces the version signed 7/22/02 by S.
Markofsky. The earlier version incorrectly indicated that the
telecon occurred at 9:30 AM on 5/28/02.

Sheldon Markofsky
7/29/02 08:02:58 AM
CHEMIST

**APPEARS THIS WAY
ON ORIGINAL**

MEMORANDUM OF TELECON

DATE: May 28, 2002 @ 9:30 AM

APPLICATION: NDA 21-402, Synthroid (levothyroxine sodium tablets, USP)
25, 50, 75, 88, 100, 112, 125, 137, 150, 175, 200, 300 mcg.

BETWEEN:

ABBOTT LABORATORIES

Larry Roebel, Ph.D.

Vice President, Regulatory Affairs & Research Information Center

Todd E Chermak

Director, Regulatory Affairs, Chemistry, Manufacturing, and Controls

Julie Garren, Ph.D.

Project Manager, Pharmaceutical Analytical Research and Development

Ernesto J. Rivera, Pharm.D.

Regulatory Affairs Project Manager

AND

FDA, CDER

David Lewis, Ph.D., Review Chemist, DNCD II, ONDC

Sheldon Markofsky, Ph.D., Acting Chemistry Team Leader, DNCD II, ONDC

Enid Galliers, Chief, Project Management Staff

Division of Metabolic and Endocrine Drug Products, HFD-510 (DMEDP)

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- Abbott said it would _____ could be submitted.

{See appended electronic signature}

Sheldon Markofsky, Ph.D.
Acting Chemistry Team Leader, DND II, ONDC

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/s/

Sheldon Markofsky
7/22/02 03:16:01 PM

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MEMORANDUM OF TELECON

DATE: May 28, 2002 @ 9:30 AM

APPLICATION: NDA 21-402, Synthroid (levothyroxine sodium tablets, USP)
25, 50, 75, 88, 100, 112, 125, 137, 150, 175, 200, 300 mcg.

BETWEEN:

ABBOTT LABORATORIES

Walid Awni, Ph.D.

Director, Department of Clinical Pharmacokinetics

Vicky Blakešley, M.D., Ph.D.

Medical Director, Metabolism, Therapeutic Area, Global Pharmaceutical Research and Development

John Bauer, Ph.D.

Senior Research Fellow, Pharmaceutical Analytical Research and Development

Todd E Chermak

Director, Regulatory Affairs, Chemistry, Manufacturing, and Controls

Jean Gallery, Ph.D.

Group Leader, Pharmaceutical Analytical Research and Development,

Julie Garren, Ph.D.

Project Manager, Pharmaceutical Analytical Research and Development

Richard Granneman

Senior Director, Center for Clinical Assessments

Kathy McFarland, Ph.D.

Divisional Vice President, Synthroid Program Head

Richard Poska, R.Ph.

Director, Corporate Regulatory Affairs

Ernesto J. Rivera, Pharm.D.

Regulatory Affairs Project Manager

AND

FDA, CDER

David Lewis, Ph.D., Review Chemist, DNCD II, ONDC

Sheldon Markofsky, Ph.D., Acting Chemistry Team Leader, DNCD II, ONDC

Duu-Gong Wu, Ph.D., Deputy Director, DNDC II, ONDC

Eric Duffy, Ph.D., Director, DNDC II, ONDC

Steven Johnson, Pharm.D., DPE II, OCPB

Hae-Young Ahn, Ph.D., Team Leader, DPE II, OCPB

Enid Galliers, Chief, Project Management Staff,

Division of Metabolic and Endocrine Drug Products, HFD-510 (DMEDP)

SUBJECT: Dissolution tolerance specifications and stability data requirements for Synthroid

BACKGROUND: The action goal date for this application was May 31, 2002, and the 10-month user fee goal date was Saturday, June 1, 2002. Two significant issues remained unresolved: a chemistry, manufacturing, and controls (CMC) issue relating to differences between submitted duration of stability data and the expiration dating period requested by the applicant and a biopharmaceutics issue regarding the discrepancy between the dissolution tolerance requested by OCPB and that set by the firm. The telecon was arranged to discuss those issues and reach a plan of action.

SUMMARY OF DISCUSSION:

OCPB indicated that the data submitted by the firm supported a dissolution tolerance of $Q = \text{---}$ @ 45 min, which the Agency planned to establish for the application. The Agency indicated that most of the 6-month dissolution data would pass S1, and all submitted lots would pass S2.

The firm was not ready to agree to that without further internal analysis of the data, and OCPB proposed that the firm accept the tolerance of $Q @ 45 \text{ min}$ as an interim specification which could be challenged later with bioequivalence (BE) data that compared just released batches with aged batches.

The submitted 6-month dissolution data showed --- , potency of the initial values, but the firm expressed concern regarding the extent of additional losses and the effect on their ability to meet this criterion.

The firm mentioned that the 9-month dissolution data for the 137 mcg strength was --- and was concerned about what actions would be required if a lot did not meet stability at 18 months, for example. The Agency commented on the puzzling behavior of that strength since it showed a slowed release. The firm never marketed that strength before and had very little experience; three lots were made and only one of them was significantly lower at release.

The Agency reiterated the decision regarding the tolerance and told the firm that this performance issue might affect bioavailability of the product (refer to requirement for a BE study above). Abbott suggested that the --- data might change the Agency's perspective. The Agency declined that suggestion.

The firm had proposed expiry of --- months for some products and --- months for 1000-count bottles. The Agency was willing to entertain an expiry of --- months (based on the 9-month data and the small decrease in potency from the 6-month data) provided the stability trends are satisfactory, but no longer.

UNRESOLVED ISSUES:

- The firm proposed extending the review clock to 12 months to allow submission and review of — dissolution data.
- The Agency indicated the need to discuss such an extension with senior management, and Abbott wanted to evaluate the $Q = \text{—} @ 45 \text{ min tolerance}$.

ACTION ITEMS:

Therefore, it was agreed to have another telecon to announce those decisions at approximately 5:00 PM EDT that day.

{See appended electronic signature}

Eric Duffy, Ph.D.
Director, DNDC II, ONDC

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Eric Duffy
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MINUTES OF MEETING

MEETING DATE: September 17, 2001
TIME: 11:30 am
PLACE: Parklawn 14B-45
APPLICANT: Abbott Labs
DRUG: Synthroid (levothyroxine sodium tablets)
NDA NUMBER: 21-402
TYPE OF MEETING: 45-day Filing and Planning Meeting
MEETING CHAIR: David Orloff, M.D., Director, DMEDP
MEETING RECORDER: Steve McCort, Project Manager, DMEDP

LIST OF ATTENDEES:

David Orloff, M.D., Director, DMEDP, HFD-510
Jean Temeck, M.D., Medical Reviewer, DMEDP, HFD-510
Duu-Gong Wu, Ph.D., Chemistry Team Leader, DNDC II, HFD-820
Steve Johnson, Pharm.D., Biopharmaceutics Reviewer, OCPB, HFD-870
Hae-Young Ahn, Ph.D., Biopharmaceutics Team Leader, OCPB, HFD-870
Chris Rogers, Regulatory Counsel, ORP, HFD-007
Margie Kober, Regulatory Review Officer, DDMAC, HFD-842
David Lewis, Ph.D., Chemistry Reviewer, DNDC II, HFD-820
Karen Davis-Bruno, Ph.D., Pharmacology Supervisor, DMEDP, HFD-510
Enid Galliers, Chief, Project Management Staff, DMEDP, HFD-510
Steve McCort, Project Manager, DMEDP, HFD-510

FILING:

CHEMISTRY: Fileable. See summary from Dr. David Lewis in DFS.
BIOPHARMACEUTICS: Fileable. No additional comments.
MEDICAL: Fileable. No additional comments.
PHARMACOLOGY: Fileable. No additional comments.

CONCLUSION: The NDA is fileable.

PLANNING:

The following planning dates were proposed:

User fee Goal date (10 mth) June 1, 2002

Date to Division Director May 15, 2002

Final reviews signoff May 1, 2002

Cutoff date for amendments to be reviewed in this cycle April 1, 2002

CONCLUSION: The planning dates were agreed upon except for the cutoff date of amendments. The review of amendments submitted late in the review cycle will be discussed as needed.

{See appended electronic signature}

Steve McCort, Project Manager, DMEDP

{See appended electronic signature}

David G. Orloff, M.D., Director, DMEDP

Drafted by: S McCort/9.28.01/6.27.02

Concurrence: E.Galliers/10.28.01/5.02.02/7/19/02

Final by S McCort/7/19/02

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/s/

David Orloff
7/22/02 05:30:02 PM

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MEMORANDUM OF MEETING

MEETING DATE: June 27, 2001 **TIME:** 4:00 pm. – 6:00 pm.

LOCATION: Parklawn Conference Room M

SPONSOR: Abbott Laboratories

APPLICATION:

DRUG: Synthroid (levothyroxine sodium tablets)

TYPE OF MEETING: Pre-NDA

MEETING CHAIR: David Orloff, M.D., Division Director

MEETING RECORDER: Steve McCort, Project Manager

FDA ATTENDEES, TITLES, AND OFFICE/DIVISION

<u>Name of FDA Attendees</u>	<u>Title</u>	<u>Division Name & HFD#</u>
1. John Jenkins, M.D.	Office Director	ODE II, HFD-002
2. David Orloff, M.D.	Division Director	DMEDP, HFD-510
3. Jean Temeck, M.D.	Medical Reviewer	DMEDP, HFD-510
4. Duu-Gong Wu, Ph.D.	Chemistry Team Leader	ONDC, DNDC II, HFD-820
5. David Lewis, Ph.D.	Chemistry Reviewer	ONDC, DNDC II, HFD-820
6. Steve Johnson, Pharm.D.	Biopharmaceutics Reviewer	OPS, DPE II, HFD-870
7. Hae-Young Ahn, Ph.D.	Biopharmaceutics Supervisor	OPS, DPE II, HFD-870
8. Chris Rogers	Regulatory Counsel	CDER/ORP, DRPI, HFD-007
9. David Read	Div. Dir.	CDER/ORP/DRPI, HFD-007
10. Karen Davis-Bruno, Ph.D.	Pharmacology Supervisor	DMEDP, HFD-510
11. Jane Axelrad	Associate Director, RM Policy	CDER ORP, HFD-005
12. Hank Malinowski, Ph.D.	Director, Division of Pharm. Evaluation II	OPS, DPE 2, HFD-870
13. Yuan-Yuan Chiu, Ph.D.	Director, Office of New Drug Chemistry	CDE, OPS, HFD-830
14. Margie Kober, R.Ph.	Regulatory Review Officer, Division of Drug Marketing, Advertising and Communications	DDMAC, HFD-842
15. Enid Galliers	Chief, Management Staff	DMEDP, HFD-510
16. Steve McCort	Regulatory Project Manager	DMEDP, HFD-510

ABBOTT ATTENDEES AND TITLES:

<u>Abbott Attendees</u>	<u>Title</u>	<u>Sponsor/Firm Name</u>
1. Walid Awni, Ph.D.	Director, Clinical Pharmacokinetics	Abbott Laboratories
2. William Bracken, Ph.D.	Senior Manager, Regulatory Toxicology and Safety Pharmacology	Abbott Laboratories
3. Todd Chermak	Associate Director, PPD Regulatory Affairs	Abbott Laboratories
4. John Donaubauer, Ph.D.	Manager CMC Strategy	Abbott Laboratories
5. Julie Garren, Ph.D.	Project Manager Pharmaceutical and Analytical Research and Development	Abbott Laboratories
5. Richard Granneman, Ph.D.	Center Director Center of Clinical Pharmacology, Pharmacokinetics, Statistics and Data Management	Abbott Laboratories
6. Kathy McFarland, Ph.D.	Divisional Vice President Synthroid Program Head	Abbott Laboratories
7. David Pizzuti, M.D.	Vice President, Global Medical Affairs	Abbott Laboratories
8. Christopher Silber, M.D.	Senior Medical Director Global Marketed Product	Abbott Laboratories
9. Douglas Sporn	Divisional Vice President Corporate Regulatory Affairs	Abbott Laboratories
10. James Steck	Director, PDD Regulator Affairs	Abbott Laboratories

BACKGROUND:

In a letter dated June 4, 2001, the firm requested a Pre-NDA Type B meeting with FDA to discuss the upcoming new drug application for Synthroid (levothyroxine sodium, USP). The new drug application (NDA) is being submitted in response to the Federal Register notice, dated August 14, 1997, which required that all orally administered drug products containing levothyroxine sodium marketed after August 14, 2000, have an approved new drug application (NDA). The requirement for having approved NDAs to be marketed was extended to August 14, 2001, in a Federal Register notice dated April 26, 2000. The firm plans to submit a 505(b)(2) application for Synthroid oral tablets by August 1, 2001. On June 6, 2001, Abbott submitted IND —, for Synthroid; it included protocols for proposed biopharmaceutics studies.

MEETING OBJECTIVE:

To discuss the content, fileability, and reviewability of the NDA.

AGENDA:

1. Discussion of issues by review discipline by FDA
2. Discussion of pre-submitted questions by FDA and Abbott
3. Summary and Conclusions

DISCUSSION:

I. FDA Introductory Remarks (Dr. David Orloff)

Fileability of an NDA for a product to be released with a stability overage is a major issue. A refuse to file decision is possible. If the Agency refuses to file the application, the sponsor has the option of filing over protest.

II. Abbott Presentation (Dr. Kathryn McFarland)
(See copy of Abbott's slides for more details)

Abbott Laboratories acquired Synthroid from Knoll Pharmaceuticals on March 2, 2001. The firm informed FDA on April 30, 2001, of their intent to file an NDA by August 1, 2001.

The following information will be included in the NDA:

1. The firm plans to file an NDA for oral tablets as a 505(b)(2) application.
2. Abbott started bioavailability studies before the submission of the IND. The firm intends to file an amendment to the NDA with the required pharmacokinetics(PK)/bioavailability data sometime in February 2002.
3. The drug substance will be manufactured at the Kingstree, SC and the Wyandotte, MI, sites. The drug product will be manufactured in the _____ site. All three sites will be included in the August 1, 2001, NDA submission. The Wyandotte facility will be evaluated based upon the complete preapproval inspection and on historical batches for both real-time and accelerated stability studies. The finished drug product will be manufactured at the _____, facility. The sponsor plans to start stability studies on drug substance batches manufactured at the Wyandotte facility as soon as possible.

FDA Comments:

1. The proposed bioavailability study results should be submitted for review in a timely manner. The firm should consider a target submission date earlier than February 2002.
2. A refuse to file (RTF) decision is a possibility if the Synthroid NDA is submitted without ICH stability data for a drug product manufactured without a stability overage. However, if the application is not filed, the firm may choose to file over protest. The FDA is not obligated to review amendments on the first cycle for an application that is filed over protest.
3. The August 14, 2001, deadline is for having *approved NDAs* for oral levothyroxine products. It is not a deadline for the submission of a new NDA. In addition, FDA has 60 days after an application is submitted in which to make a filing decision.

III. FDA Discussion of Issues by Discipline:

A. CLINICAL (Dr. Jean Temeck, Medical Reviewer)

1. For a 505(b)(2) application, the firm should reference pertinent literature that supports safety and efficacy of the drug product. The literature contains many references to Synthroid. The firm should also cite pediatric studies from pertinent literature. Summaries of literature as well as an overall summary should be included in this section. It was recommended to Abbott that they not cross-reference previously approved levothyroxine sodium products as this would require additional comparative bioavailability studies with the referenced product.
2. The firm cannot include the _____ in the Synthroid draft label without submitting a separate NDA for the _____. The firm was encouraged to submit an NDA for _____.

B. PHARMACOLOGY (Dr. Karen Davis-Bruno, Pharmacology Supervisor)

The pharmacology section of the NDA may be supported by published literature on the drug substance. Support for the drug product may require qualification of any impurities > 1% as a consequence of the manufacturing process (see ICM Q3A). If qualification is needed, a one-month bridging toxicity study comparing qualified and unqualified drug product in one species would likely be sufficient.

C. CHEMISTRY (Dr. David Lewis, Chemistry Reviewer)
(Refer to chemistry reviewer's handouts for details)

1. General Remarks:

To meet primary chemistry, manufacturing, and control requirements (CMC), the lots submitted for approval must be manufactured without stability overage, i.e., targeted for release at 100 % of label claim. The primary stability data must be collected under ICH conditions. The rationale for requiring the targeting at 100% of label claim is so that overlapping potencies would not occur across strengths, to minimize degradation products, and to provide accuracy in labeling of strength. The requirement for having product tested under ICH stability storage conditions for all new NDAs is given in guidance document #ICH Q1A.

2. FDA response to sponsor's questions from the meeting background packet.

Question #3. The firm has proposed using a manufacturing overage appropriate for Synthroid. The specific proposal included a manufacturing overage of — at the time of NDA approval (see Appendix 4, Page 64, last paragraph for the new formulation). After one year the — excess would be evaluated post-approval to determine if further adjustments would be necessary.

FDA Response:

1. — manufacturing overage seems more appropriate than —
2. The firm should manufacture the product to release at 100% of labeled claim.
3. The shelf-life of the drug product must be based on the stability data generated under ICH conditions. The Agency will accept batches manufactured with equal to or less than — manufacturing overage as primary stability batches. However, in the case of batches being released at more than 100 % of label claim, a — loss of potency will be used to determine shelf life. Also, at the time of NDA submission, a certificate of analysis (zero time point data) on stability batches under ICH conditions should be provided.

4. Before the application may be approved, it must be amended with revised manufacturing batch formulae that will consistently produce batches targeted to a 100 % label claim at the time of release, with analytical data to support it. Variability of values is to be expected. However, the values of release data should be targeted at \bar{x} around the mean. The Agency cannot approve the drug product with a stability overage.

Question #4. Site-specific issues from firm's questions, page 2 of meeting package. See Dr. Lewis's handouts for more details.)

FDA Response:

The Wyandotte facility should be listed as a manufacturing site for the drug substance. The data could be submitted through a DMF or included in the NDA. Stability data can be submitted during the review cycle. The firm should submit stability data on lots for the proposed marketed strengths using a bracketed approach with 3 lots of the lowest strength, 2 lots of an intermediate strength, and 3 lots of the highest strength tablets. This reduced stability design should be used for both room temperature and accelerated stability studies utilizing ICH storage conditions. The stability protocol for both the Kingstree and Wyandotte facilities should be the same.

The firm has no plan to submit a DMF for the drug substance.

Question #5. Specifications and test methods for degradants from firm's questions, page 2 of meeting package.

FDA Response:

The development of specifications and test methods can be completed as a Phase 4 commitment. The firm should refer to ICH Q3B and Q6A Guidelines for guidance.

Question #6. Use of ICH conditions for stability studies for the transition of lots to ICH conditions. Can this information be submitted as a phase 4 commitment? Page 2 of meeting package.

FDA Response:

The firm cannot submit this information as a Phase 4 commitment. However, the firm can provide this information via amendments during the review cycle. The stability study must utilize ICH storage conditions. A bracketing design with a low, medium, and high strength may be utilized. The Agency will accept a stability protocol based on full design without bracketing.

Question #7. Is the use of USP criteria for both drug substance and drug product controls acceptable? Page 3 of meeting package.

The use of the USP monograph is not acceptable for both drug substance and product. The USP criteria do not address process impurities or degradation products. However, the tests, analytical procedures, and acceptance criteria, already included in the USP monograph, need no revision.

Question # 8. Would the FDA object to Abbott's submitting a representative batch production record for one of the stability lots for each tablet strength rather than submitting all batch production records for each stability lot submitted in the NDA? Question taken from the meeting package.

FDA Response:

One representative executed batch record for each tablet strength used in stability testing will be sufficient.

Question #13. Timing of pre-approval inspections. From page 5, meeting package.

FDA Response:

The inspection schedule is determined by FDA's Office of Compliance and not the Division. All facilities for both drug substance and drug product should be ready for inspection at the time of the NDA submission.

D. BIOPHARMACEUTICS (Dr. Steve Johnson, Biopharmaceutics Reviewer)

Assessment of the in vivo bioavailability studies - Two protocols were submitted to IND _____

Protocol M01-324: A Comparison of the Bioavailability of a Levothyroxine Sodium Tablet Formulation with that of a Reference Liquid Formulation.

Protocol M01-323: Dose Proportionality Study of Three Different Dosage-Form Strengths of Marketed Levothyroxine Sodium Products.

FDA Response:

The protocols appear adequate to meet their objective and are acceptable. The equivalence criteria applied to protocol M01-323 are needed. Historical bioavailability data will be considered as supportive information to the NDA.

For the In vitro dissolution studies

FDA Response:

1. The biowaiver is based in part upon f_2 comparison of dose strengths. The agency recommends using 50 mcg, 100 mcg, and 300 mcg as reference. (See table in Dr. Johnson's slides for details.)
2. The dissolution method should be appropriate for the Synthroid product. In addition to conducting dissolution testing using the method described in the USP 24 S1 monograph for levothyroxine sodium tablets, the firm should also consider submitting additional dissolution data whereby the USP 24 S1 method is altered (e.g., increased paddle speed of — RPM, with or without surfactant, etc.) Note: paddle speed should not exceed — RPM, and the pH of the dissolution media should not exceed —
3. The sponsor should submit the results of the proposed bioavailability studies in a timely manner (i.e., October or November 2001.)
4. The biopharmaceutics information needed in the NDA is not a fileability issue.

CONCLUSIONS

1. For approval of the NDA the drug product should be at manufactured without stability overage and with a target to release at 100 % of the label claim.

2. Stability data must be collected under ICH storage conditions. The Agency will accept batches manufactured with equal or less than — overage as primary stability batches. However, if the test results show that these batches are released at slightly over 100 % of label claim, a — loss of potency will be used to determine shelf life. At the time of NDA submission, a certificate of analysis (zero time point data) on all stability batches should be provided. The sponsor can submit amendments to provide additional stability data generated under ICH conditions. The shelf life of the product will be determined based on ICH stability data. Approval of the NDA cannot be based on Phase 4 commitments to submit stability data post-approval.
3. For filing of the NDA, a manufacturing overage of no more than — will be allowed. Before an application may be approved, it must be amended with revised manufacturing batch formulae that will consistently yield batches with 100 % of label claim at the time of release. The Agency cannot approve the product with a stability overage.
4. The lack of stability data submitted in the NDA could be a potential refuse to file issue. The sponsor has agreed to submit zero time data and any data for the batches manufactured with reduced overage (i.e., — or less) collected at the time of submission. The amount and quality of the data will be evaluated within 60 days after receipt of the submission of the NDA. At the end of the 60-day period, the Agency may refuse to file the application. If the Agency refuses to file, the sponsor can file over protest and the application will be reviewed.
5. The proposed biopharmaceutics, clinical, and pharmacology information for the NDA do not appear to be filing issues at this time, provided that the information required for review is in the NDA submission.
6. The firm will submit data for the drug substance, as manufactured at the Wyandotte, Michigan, facility to the NDA.
7. The firm cannot include the — in the oral tablet NDA. A separate NDA is necessary for —. However, the Agency encouraged Abbott to submit an NDA for that —.
8. The sponsor should be ready for inspection of all manufacturing facilities for both the drug substance and finished product at the time of the NDA submission.

9. The sponsor will contact the Agency regarding future meetings or telephone conferences regarding the chemistry requirements for product to be manufactured without stability overage for filing of the NDA.

Minutes Preparer: _____
Stephen McCort
Project Manager, HFD-510

Chair Concurrence: _____
David Orloff, M.D.
Division Director, HFD-510

ATTACHMENTS/HANDOUTS:

cc: IND _____
HFD-510/Div. Files
HFD-510/SubjectFile/Thyroid 2001
HFD-510/SMcCort
HFD-510/DOrloff/DWu/DLewis/JTemeck/K Davis-Bruno/EGalliers
HFD-007/JAxelrad/DRead/C.Rogers
HFD-870/HMalinowski/H.Ahn/SJohnson
HFD-830/Y.Chiu
HFD-842/MKober

Drafted by: S.McCort-7/05/01 filename: \minutes4.synthro.doc
Edited by Steve McCort- 7/9,13/01; D.Lewis -7.24.01; E.Galliers/7.29.01/
Final (emg) 7.31.01

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H.Ahn/7.11.01/ H.Malinowski/7.11.01/D.Lewis/7.13,24.01/Dwu/7.13.01/ D.Orloff/7.30.01/
J.Jenkins/7.31.01/

MEETING MINUTES