CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

21-116

ADMINISTRATIVE DOCUMENTS

Patent Certification

In the opinion and to the best knowledge of LLOYD, Inc., there are no patents that claim the drug product levothyroxine sodium tablets (25 µg, 50 µg, 75 µg, 100 µg, 125 µg, 150 µg, 175 µg, 200 µg, 300 µg) on which investigations that are relied upon in this application were conducted or that claim a use of such drug.

W.E. Lloyd, DVM, PhD
Chief Executive Officer
LLOYD, Inc.

11 August 1999
Date

16. Debarment Certification

A Debarment Certification as specified by Section 306 (k) of the Food, Drug, and Cosmetic Act, as amended by the Generic Drug Enforcement Act of 1992, is provided.

Certification of Compliance

OYD, Inc., hereby certifies that it did not and will not use in any capacity the
s of any person debarred under Section 306 of the Federal Food, Drug, and
metic Act in connection with this application.

N L Lloyd

. Lloyd, DVM, PhD
f Executive Officer
YD, Inc.

11 August 1999
Date

10.30.02

EXCLUSIVITY SUMMARY for NDA # 21-116 SUPPL #

Trade Name Thyro-Tabs® Generic Name levothyroxine sodium tablets

Applicant Name Lloyd Inc. HFD- 510

Approval Date October 24, 2002

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.

      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 # 21-210	Drug Name Unithroid
	NDA # 21-301	Levoxyl
	NDA # 21-402	Synthroid
	NDA # 21-342	Levo-T

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 /_x__/ NO /___/

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

NDA # 21-210	Unitroid
NDA # 21-301	Levoxy
NDA # 21-402	Synthroid
NDA # 21-342	Levo-T

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 /_x__/

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: <u>THREE-YEAR EXCLUSIVITY FOR NDA'S AND SUPPLEMENTS</u>

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 /_x__/

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: _____

_____

_____

_____
Signature of Preparer Date
Title:

Signature of Office or Division Director Date

CC:
Archival NDA
HFD- /Division File
HFD- /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/

David Orloff
10/30/02 12:44:42 PM

PEDIATRIC PAGE

(Complete for all original application and all efficacy supplements)

NDA/BLA Number:	21116	**Trade Name:**	THYRO TABS(LEVOTHYROXINE SODIUM TABLETS)
Supplement Number:		**Generic Name:**	LEVOTHYROXINE SODIUM TABLETS
Supplement Type:		**Dosage Form:**	TAB
Regulatory Action:	PN	**Proposed Indication:**	

ARE THERE PEDIATRIC STUDIES IN THIS SUBMISSION?

NO, No waiver and no pediatric data

What are the INTENDED Pediatric Age Groups for this submission?

X NeoNates (0-30 Days) X Children (25 Months-12 years)

X Infants (1-24 Months) X Adolescents (13-16 Years)

Label Adequacy	Does Not Apply
Formulation Status	-
Studies Needed	-
Study Status	-

Are there any Pediatric Phase 4 Commitments in the Action Letter for the Original Submission? NO

COMMENTS:

The approval of the labeling including pediatric labeing is still pending. June 2, 2000. sMcCort

Application still pending.

This Page was completed based on information from a PROJECT MANAGER/CONSUMER SAFETY OFFICER, :
STEPHEN MCCORT

Signature 6-2-00 Date

PEDIATRIC PAGE

(Complete for all APPROVED original applications and efficacy supplements)

NDA/BLA # : 21-116 **Supplement Type (e.g. SE5):** _____ **Supplement Number:**

Stamp Date: August 19, 1999 **Action Date:** October 24, 2002

HFD 510 **Trade and generic names/dosage form:** Thyrotabs (levothyroxine sodium Tablets, USP)

Applicant: Lloyd Inc. **Therapeutic Class:** 5S

Indication(s) previously approved: Treatment of hypothyroidism and suppression of thyroid-stimulating hormone

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

Number of indications for this application: 2

Indication #1: Treatment of hypothroidism

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

X 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
X 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:_____

Attachment A

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

Indication #2: Suppression of thyroid stimulating hormone

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

X **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
X **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:

_____
Seve McCort
Regulatory Project Manager

cc: NDA 21-116
HFD-960/ Terrie Crescenzi

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

/s/

Stephen McCort
10/23/02 09:33:00 AM
CSO

MEMORANDUM

DATE: June 19, 2000

FROM: John K. Jenkins, M.D.
Acting Director
Division of Drug Products, HFD-510
Director
Office of D-102

6/19/2000

TO: NDA 21-116

SUBJECT: Overview of review issues

Administrative

NDA 21-116 for Thyro-Tabs (levothyroxine sodium tablets) was submitted by Lloyd Incorporated on August 20, 1999. This application was submitted in response to the August 14, 1997, Federal Register Notice announcing that orally administered drug products containing levothyroxine sodium are new drugs. The FR notice required that sponsors who wished to continue to market orally administered drug products containing levothyroxine sodium have an approved NDA by August 14, 2000 (this date was recently extended to August 14, 2001). This NDA was assigned for a standard review. The current 10-month user fee due date for this application is June 20, 2000.

Clinical/Statistical

The 1997 FR notice stated that the active ingredient, levothyroxine sodium, is effective in treating hypothyroidism and is safe when carefully and consistently manufactured and stored, and prescribed in the correct amount to replace the deficiency of thyroid hormone in a particular patient. Therefore, no clinical safety and effectiveness studies were required to support approval of these formulations, only a submission of literature references to support the safety and effectiveness of levothyroxine sodium. The sponsor submitted a review of the available literature for this purpose. Please refer to the review prepared by Dr. Temeck for a detailed review of the available literature on the safety and effectiveness of levothyroxine sodium.

This application is approvable from a clinical/statistical perspective pending agreement with the sponsor on labeling. A class-labeling document is being prepared by the division for the orally administered levothyroxine drug products.

Pharmacology/Toxicology

No preclinical studies were included in the NDA and none were required given the long marketing history of levothyroxine containing products and the determination as stated in

the 1997 FR notice that the active ingredient, levothyroxine sodium is safe and effective when manufactured, stored, and prescribed correctly. The sponsor submitted literature references to address preclinical sections of labeling.

This application is approvable from a pharmacology/toxicology perspective pending agreement with the sponsor on labeling. A class-labeling document is being prepared by the division for the orally administered levothyroxine drug products.

Chemistry, Manufacturing, and Controls

The sponsor proposes to market tablets containing 25 mcg, 50 mcg, 75 mcg, 100 mcg, 125 mcg, 150 mcg, 175 mcg, 200 mcg, and 300 mcg. Please see the review prepared by Dr. Lewis for a detailed review of the CMC information provided by the sponsor. The sponsor utilized a bracketing approach for the testing of stability of the drug product. This is an acceptable approach; however, the data provided in support of the 25-mcg strength was unacceptable and inadequate to support the bracket of strengths that included 25, 50, and 75 mcg. There were other minor deficiencies in the CMC information that will be communicated to the sponsor in the action letter.

This application is approvable from a CMC perspective for the tablet strengths of 100 mcg and above pending resolution of several minor deficiencies and agreement with the sponsor on adequate labeling.

Clinical Pharmacology and Biopharmaceutics

The Agency's guidance for submission of an NDA for orally administered levothyroxine drug products recommended two in vivo BA/BE studies (a comparison of the tablet formulation to an oral solution and a comparison of low, medium, and high strength tablets) and in vitro dissolution studies. These studies were submitted by the sponsor. Please refer to the review prepared by Dr. Johnson for a detailed review of these studies. In summary, the tablet formulation was demonstrated to be equivalent to an oral solution of levothyroxine sodium and the 50 mcg, 100 mcg, and 300 mcg tablets were demonstrated to be equivalent to each other. The dissolution data submitted by the sponsor do not meet the current USP 24 monograph tolerances; thus the product may not be labeled as conforming to USP. In addition the proposed dissolution tolerances are not supported by the data and a biowaiver cannot be granted to the 25, 125, and 150 mcg products.

This application is approvable from a clinical pharmacology and biopharmaceutics perspective for all strengths other than the 25, 125, and 150 mcg products.

Data Integrity

The Division of Scientific Investigations audited the analytical portions of the two pivotal BA/BE studies and noted minor deficiencies that resulted in a VAI rating. These

deficiencies are not felt to adversely affect the interpretation of the data derived from these studies.

Labeling and Nomenclature

The proposed tradename "Thyro-Tabs" was reviewed by OPDRA and found to be acceptable at this time. The Division has no objections to this name. Since there are expected to be numerous applications for orally administered levothyroxine drug products in response to the 1997 FR Notice and since most of the information that will be included in labeling will be based on literature references, the Division is developing class labeling for these products that will be individualized as appropriate for each sponsor (e.g., Description, How Supplied, PK sections). Since this application is not being approved at this time, labeling comments will be deferred until the other deficiencies noted in this application have been adequately addressed.

Conclusions

From a CMC perspective all tablet strengths of 100 mcg and above are approvable. The tablet strengths below 100 mcg are not approvable from a CMC perspective and additional stability data will be required for the 25-mcg strength to support approval of this bracket. From a clinical pharmacology and biopharmaceutics perspective all tablet strengths with the exception of 25, 125, and 150 mcg are approvable. Thus, the following strengths are considered approvable by both disciplines at this time: 100 mcg, 175 mcg, 200 mcg, and 300 mcg. This range of tablet strengths is not considered adequate to allow for labeling of this product for safe and effective use. This is because while the "average" replacement levothyroxine dose for adult is approximately 100 mcg/day, it is necessary to titrate patients to achieve the correct dosage and often increments of as little as 12.5 mcg/day are required. It is also important to note that the elderly and children often require reduced doses and careful titration in these age groups is essential for safety reasons. The absence of a 25-mcg-strength tablet, therefore, makes it impossible to adequately titrate this product. Since the levothyroxine products currently marketed are not considered to be directly interchangeable, it is not possible to write labeling for the safe and effective us of Thyro-Tabs. It will be necessary for the sponsor to address the deficiencies related to the 25-mg tablet before this application may be approved. The sponsor should receive an APPROVABLE letter. Labeling comments will be deferred to a later date.

cc:

NDA 21-116
HFD-510/Division File
HFD-510/McCort
HFD-102/Jenkins

NDA # 21-116
Thyro-Tabs (levothyroxine sodium tablets)
Lloyd, Inc.
Date submitted: August 19, 1999
Date of review: June 9, 2000

Medical Team Leader review of NDA

Administrative background

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. 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.

Because of the medical necessity of these products, manufacturers of levothyroxine-containing products were given 3 years, until August 14, 2000, to obtain NDA approval. This deadline has recently been extended to August 14, 2001.

Manufacturers wishing to continue to market oral T4 products after August 14, 2001 are expected to submit NDAs, including 505(b)(2) applications, that contain literature references supporting the safety and effectiveness of LT4 for the proposed indications. In addition, bioavailability and *in vitro* dissolution studies are required. In short, this approach to development of levothyroxine-containing new drug products relies on the fact that levothyroxine itself is a safe and effective treatment for supplementation or replacement in patients with insufficient endogenous thyroid hormone and for suppression to TSH in patients with thyroid nodules or cancer. Therefore, the approvability of an oral T4 product depends upon demonstration of acceptable quality, quantity, and performance as assessed by manufacturing information, data from stability studies, and the results of bioequivalence/bioavailability and dissolution studies.

The Levolet NDA was submitted with the clinical section in accordance with the August 1997 FR notice, with the required section 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.

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 class 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 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).

From discussion with the reviewers from ONDC involved with this NDA, it is apparent that, because of poor performance on stability testing, no dosage strengths under 100 mcg are approvable (see Chemistry review). In addition, the 125 and 150 mcg dosage strengths are not approvable due to unacceptable dissolution profiles (see Biopharmaceutics review).

Summary and conclusions

Levothyroxine is a safe and effective option for the treatment of thyroid deficiency states and for suppression of pituitary TSH secretion in goiter, nodular thyroid disease, and thyroid cancer. This does not imply that all (or indeed any) currently available levothyroxine-containing oral drug products are safe and effective. Indeed, because of instances of failure of available products to maintain potency through the expiration date, because of lot-to-lot inconsistencies in the amount of active ingredient present in tablets of the same nominal dosage strength, problems related to both safety and efficacy have arisen. Chronic underdosing with T4 as well as both acute and chronic overdosing with T4 can have serious health consequences. Thus, only high-quality T4-containing

products will be both safe and effective. In addition, as different LT4 products are not necessarily interchangeable, it is further necessary that the available range of dosage strengths for any given product permit titration of daily dose in increments of 12 or 12.5 mcg. In order to accomplish this, at a minimum, a 25 mcg dosage strength is required.

The current application contains adequate information to support the clinical use of LT4 for the proposed indications.

The recommendations of OCPB and DNDC are contained in their reviews. It appears that because of poor stability as well as unacceptable dissolution characteristics, the 25 mcg dosage strength is not approvable. The stability and functional profiles of the 100, 175, 200, and 300 mcg dosage strengths are acceptable.

Recommendation
This NDA is approvable, once the deficiencies regarding the stability and biopharm issues raised are addressed and, at the least, the 25 mcg dosage strength meets CMC and biopharmaceutical specifications.

David G. Orloff, M.D.
Deputy Director, DMEDP (HFD-510)
CDER/FDA

Recommendation code: AE

151, 6-5-00

MEMORANDUM OF TELECON

DATE: October 23, 2002

APPLICATION NUMBER: NDA 21-116, Thyro-Tabs (levothyroxine sodium tablets, USP)

BETWEEN:

Name: W.E. Lloyd, DVM, PhD, CEO
Phone: 712-246-4000
Representing: Lloyd Inc.

AND

Name: Enid Galliers, Chief, Project Management Staff
Division of Metabolic and Endocrine Drug Products, HFD-510

SUBJECT: Labeling changes for bottle and shipper carton labels

Background: The most recently submitted draft labels for Thyro-Tabs need one additional minor change before the application can be approved. The UF goal date is Oct. 24, 2002.

Discussion: I called the firm to ask for their agreement to use the "Rx only" legend on the bottle and shipper labels instead of the old "Caution: Federal law . . ." statement as required by FDAMA. Dr. Lloyd agreed that the firm would replace the "Caution: Federal law . . ." statement on the bottle and shipper labels with the "Rx only" statement.

{See appended electronic signature.}

Enid Galliers
Chief, Project Management Staff, DMEDP

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/s/

Enid Galliers
10/24/02 06:27:19 PM
CSO

MEMORANDUM OF TELECON

DATE: October 22, 2002

APPLICATION NUMBER: NDA 21-116, Thyro-Tabs (levothyroxine sodium tablets, USP)

BETWEEN:

Name:	Stuart Johnson, Vice President of Operations W.E. Lloyd, DVM, PhD, CEO Carolyn Larson
Phone:	712-246-4000
Representing:	Lloyd Inc.

AND

Name:	Enid Galliers, Chief, Project Management Staff Steve McCort, Project Manager Division of Metabolic and Endocrine Drug Products, HFD-510

SUBJECT: Labeling changes for PI and bottles

Background: The most recently submitted draft labeling and labels for Thyro-Tabs need additional minor changes before the application can be approved. Also, we needed to learn whether the firm intended to [redacted] because two different PI's submitted in October referred to [redacted] The firm has not submitted [redacted]. The UF goal date is Oct. 24, 2002.

Discussion: The firm confirmed that it would change the storage statement on the PI and bottle and shipper labels as indicated in the faxes dated October 21 and 22, 2002. They agreed to move the "Rx only" statement to the top of the PI. They confirmed that they had not submitted [redacted] remove [redacted] from the HOW SUPPLIED section of the PI.

We told the firm that they needed to submit the stability data and draft labeling for the [redacted] with the description of the packaging materials, and that this could be done in a supplement after approval of the NDA. We also said that Physicians and Patients Samples had to be submitted and approved but the samples did not need to be added to the HOW SUPPLIED section of the PI. However, [redacted] for trade use (hospital or pharmacy) did need to be added to the PI HOW SUPPLIED.

We agreed that their previously mentioned faxes would be added to the NDA file and that the firm did not need to make additional labeling submissions to confirm these agreements.

{See appended electronic signature.}
Enid Galliers
Chief, Project Management Staff, DMEDP

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/s/

Enid Galliers
10/23/02 08:21:35 PM
CSO

Enid Galliers
10/23/02 08:25:30 PM
CSO

Summary of understanding to FDA teleconference of 15 June 2001, 1 PM EST

FDA attendees:
Enid Galliers, Project Management Team Leader
Steve McCort, Project Manager
Hae Young Ahn, Ph.D., Biopharmaceutics Team Leader
Steven B. Johnson, Ph.D., Biopharmaceutics Reviewer
Duu-Gong Wu, Ph.D., Chemistry Team Leader
David Lewis, Ph.D., Chemistry Reviewer

LLOYD attendees:
W.E. Lloyd, DVM, Ph.D., Chairman/CEO
Ronald Ketcham, Executive Vice President
Joseph Denhart, DVM, MS, V.P. Regulatory Affairs/Quality Assurance
Charles M. Siegfried, Ph.D., V.P. Research and Development
Rob Davis, Validation and Stability Specialist
Joanne Cowen, Associate Laboratory Resource Manager
Stuart Johnson, V.P. Operations, Project Manager
Carolyn Larson, Quality Assurance Reviewer and scribe

Meeting Purpose:
The purpose of the teleconference meeting was to follow up on unresolved issues from the teleconference of 5 June 2001. The specific issues were the adequacy of the multi-point dissolution proposal (question 8(b)) and use of the USP designation (question 8(d)(1)).

USP designation (question 8(d)(1))

Drs. Lewis and Woo stated that the USP issue was unresolved at this time. Follow up with LLOYD will be made once it is internally resolved within FDA. No timeline for a response could be given at this time.

Multi-point dissolution (question 8(b))

Dr. Ahn indicated that the change LLOYD was proposing was actually two changes: a formulation change (PH101 to PH200) and a process change (i.e. ——). She stated that according to SUPAC, which the Agency would apply in this case, both tablet changes were level 2 and required f2 comparisons. Since the dissolution profiles of the old vs new tablets will be different (as previously stated by LLOYD), the Agency cannot grant a biowaver using the clinical studies from the old tablets. There must be a link between the original bioformulation and the modified formulation.

Dr. Ahn suggested that LLOYD conduct a bioequivalence study (2-way crossover, old vs new tablet, dose-2X300) and then, if equivalent, the Agency could waive the bioequivalence requirement down to the 25 ug tablet based upon equality of the dissolution f2 values using the 300 ug tablet as the reference for f2 comparisons. LLOYD indicated that they would like to consider this suggestion for a few days before responding and perhaps offer alternate suggestions if appropriate. Dr. Ahn was agreeable.

Dr. Ahn indicated that the previous requirement for 3 dissolution media (previous teleconference) was predicated on there being no further bioequivalence study. If LLOYD conducts the

bioequivalence study, then the requirement for multi-point dissolution testing would be to test one lot only for each strength in one media (not 3).

For any bioquivalence study with old tablets, Dr. Lloyd stated that there may be a decreased potency and asked if potency corrections were acceptable. Dr. Ahn stated that the Biopharmaceutics group did not accept potency adjustments in the calculation of confidence intervals. If there was a difference in potency, this fact should be simply noted in the final report and would be taken into account in the review.

Ms — asked how firm was the — for the f2 comparisons since the old tablets had a — , but in-vivo no difference was found in the bioequivalence study. Dr. Ahn stated that even though the acceptable limit was arbitrary, the limit that the Agency would accept was —

MEMORANDUM OF TELECON

DATE: October 15, 1999

APPLICATION NUMBER: NDA 21-116; Levothyroxine

BETWEEN:

Name: W.E. Lloyd, DVM, Ph.D.
Phone: 712-246-4000
Representing: Lloyd Inc.

AND

Name: Steve McCort
Division of Metabolic and Endocrine Drug Products, HFD-510

SUBJECT: Response to FAX dated October 14, 1999

In a Faxed letter dated October 14, 1999 the Sponsor had requested clarification regarding the FAXEd information sent on October 8, 1999, **"Recommendations for submission data to support preclinical data for Levothyroxine products for replacement therapy."** In the letter the Sponsor had indicated that they did not obtain results of pertinent articles of published preclinical data and they also indicated that a statement to that effect was included in the Nonclinical section of their NDA.

After consultation with Dr. Ron Steigerwalt, Pharmacology Team Leader, the Sponsor was called and advised that their reference to "No formal nonclinical toxicology studies were identified in the literature search", in the Nonclinical section of their NDA was sufficient." However the Sponsor was reminded that the need for preclinical studies might be considered in cases where the formulation might change (e.g., inactive ingredients, excipients,etc.). In such cases published data which support the safety of the excipient may be acceptable in leu of new preclinical studies.

In addition the Sponsor was told that the Agency would be doing a "class labeling review" and may make additional recommendations in the labeling. The labeling recommendations from this review will pertain to the entire label for levothyroxine tablets and not just to the sections that pertain to Pharm/Tox.

The Sponsor will send a correspondence to the NDA file documenting this call.

LS/

Steve McCort
Project Manager, HFD-510

cc: Original NDA 21-116
HFD-510/Div. File
HFD-510/Steve McCort
HFD-510/RSteigerwalt

TELECON

5/1/31 5

JAN 25 1999

T/CON
DIVISION OF METABOLISM AND ENDOCRINE DRUG PRODUCTS (HFD-510) AND LLOYD INC.

T/CON DATE: January 25, 1999 TIME: 10:00 am PLACE: Parklawn 14-56

DRUG: Levothyroxine Sodium Tablets

IND: 57,315

TYPE OF MEETING: T/CON - Advice IND/Pre-NDA

MEETING CHAIR: Steve McCort

MEETING RECORDER: Steve McCort, Project Manager

LIST OF FDA ATTENDEES:

Jean Temeck, M.D., Medical Reviewer, DMEDP
Mike Fossler, Ph.D., Biopharmaceutics Reviewer, OCPB, HFD-870
Duu-Gong Wu, Ph.D., Chemistry Team Leader, DMEDP, HFD-510
David Lewis, Ph.D., Chemistry Reviewer, DMEDP, HFD-510
Steve McCort, Project Manager, DMEDP, HFD-510

LLOYD, INC

W. E. Lloyd, D.V.M., Ph.D., Chief Executive Officer
Joseph W. Denhart, D.V.M., M.S., Vice President Regulatory Affairs and Quality Assurance
Carolyn Larson, Project Manager

MEETING OBJECTIVE:

To respond to Lloyd's written follow-up dated January 12, 1999 to the meeting held December 14, 1998 with FDA and to the comments FAXED to the firm December 28, 1999.

BACKGROUND:

A Meeting with the firm was held on December 14, 1998.

Comments (Medical) were FAXED to the firm on December 28, 1998.

The firm FAXED to the Division dated January 12, 1999, in reponse to the December 28, 1998, FAXED comments from FDA, and to additonal questions from the December 14, 1998 meeting.

The Division FAXED a reply to questions #1 and #2 on January 14, 1999.

The purpose of this T/CON with the firm was to further clarify questions #2 and to get answers to questions #3 and #4 of the January 12, 1999 communcation from the Sponsor.

DISCUSSION/CONCLUSIONS:

From the January 12, 1999 FAXED communication, the following questions were addressed:

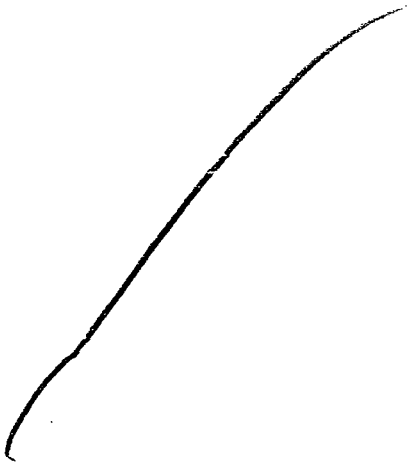
Question 1. We indicated that our reference solution for the two-way cross over study would be levothyroxine sodium for injection, USP, 200 mg/vial fro Knoll Pharmaceuticals. Our question was what is the number of vials that should be available at the clinical site as retention samples. We are not aware of the number of vials required for release testing of this product but had proposed — vials. Dr. Fossler had indicated that he would check with OGD as to whether — vials were an adequate number. Since we are starting our studies the last of this month (January) we need a response on this proposal as soon as possible.

FDA Response: This answer to this question has been provided in an earlier FAX for the Division dated January 14, 1998. The question will not be addressed at this time.

Question 2. The medical comments FAXED to the firm on December 28, 1998, pertaining to the submitted protocols -LLOY9801 and 9802 stated that *"1. Exclusion criteria should include: . . . C. Subjects taking any prescription or OTC medication within 1 month of study dosing."*

The firm indicates in their reply that they will make every attempt to limit medications after the study has commenced. However, they propose that should a subject take a medication during a washout period that each case be handled individually or a case by case basis to determine whether the medication would adversely affect the study and not that a subject would automatically be eliminated from the study.

FDA Response: From the previous t/con with the firm on January 5, 1998, Dr. Temeck, medical reviewer, had stated that the exclusion criteria of one month for patients taking prescription or OTC medication, before the study commences, is to allow an adequate washout period for these products. The one month washout period is preferable to a shorter period since it reduces the risk of an interaction between these products and the T4 tablets used in the study. The firm suggested that certain drugs may not interfere potentially with the administration of L-thyroxine, due to the short half lives of these products and that would justify whether or not these patients were excluded from the study. Dr. Temeck suggested that the Sponsor will need to check to see whether the drugs that had been taken do not interfere with L-thyroxine from a list of drugs that influence L-thyroxine metabolism; if they do, there should be a 30 day wash-out period before T_4 adminstration. If the drug is included on the list, the specific PK characteristic including half-life of the drug in question would then have to be evaluated by the firm. Dr. Temeck stated that she will FAX an article from the New England Journal of Medicine that the firm can use as a reference. Dr. Lloyd asked if the estimation of concentration of the concomitant drugs could be used in their evaluation. Dr. Fossler answered that the levels of T3, T4, TSH are not necessarily dependent on the concentration or PK characteristics of a particular drug. After the Sponsor's evaluation, it is up to the Sponsor whether to follow the 30 day exclusion criteria for patients taking OTC or prescription medications.



Question 4. Dr. Wu had indicated during the December 14, 1998 meeting with FDA that he would review the post-approval stability matrix design the Sponsor had proposed and would respond to at a later date. In addition he gave some indication at the conference that perhaps our proposal for stability testing that we proposed to file with our NDA might have been excessive. Dr. Wu indicated 3 low strengths, 3 high strengths and 2 or 3 in the middle would probably be adequate. We had proposed that 3 low strengths would have at least — stability data at filing the NDA and that the middle and high strengths would each have two more stability tests started on post-approval batches. We would like Dr. Wu's comments on our stability proposals for NDA filing as soon as possible as we are manufacturing batches now an need the minimum stability information that would be expected for filing the NDA.

FDA Response:

Dr. Wu responded by saying that 3 of the lowest concentration, 3 of the highest concentration and three middle concentrations of the stability batches would be needed for the NDA. The firm indicated that they have at this time one batch each of the three highest batches - 300 mcg, 200 mcg and 175 mcg; three batches at the lowest concentration 25 mcg, and five batches of one each for intermediate strengths (50, 75, 100 125 and 150 mcg). The firm asked whether this would suffice for the filing of an NDA? Dr. Wu indicated that this would be satisfactory.

CONCLUSIONS:

1. The answers to questions 1, 2, and 4 FAX communication from the firm have been satisfactorily addressed.

2. —

3. Steve McCort faxed to the sponsor a copy of the December 21, 1996 NEJM article entitled "Drugs and Thyroid Function" (See attached)

151

Steve McCort
Project Manager, HFD-510

Comments Cleared for FAX.

151

[illegible] Sobel, M.D.
Division Director, HFD-510

Concurrence: JTemeck 2-9-99/MFossler 2-8-99/DLewis 2-10-99/DWu 2-17-99/CRogers 2-12-99

cc: IND 57,315
HFD-510/DivFiles
HFD-510/JTemeck/SSobel/DWu/DLewis
HFD-870/MFossler/HAhn
HFD-007/CRogers

MEETING MINUTES

RECORD OF TELEPHONE CONVERSATION/MEETING	Date: 23 Aug. 1999
BACKGROUND: The firm's cover letter stated that the user fee had been waived by FDA on Aug. 18, but there was no copy of the Waiver letter in the the tan review jacket. **DISCUSSION:** I said that I was calling for steve McCort who would return tomorrow and I explained that I needed to see a copy of the waiver letter today. Dr. Denhart said he was sure the waiver letter was in the archival jacket. I noted that if the firm had included the waiver letter in the archival copy, I would not see the archival jacket for several days. Dr. Denhart agreed to fax me a copy of the waiver letter within the next half hour. I gave him my direct phone and fax numbers and thanked him. Cc: arch. NDA + fax HFD-510/division HFD-510/SMcCort +fax 151 **Name: Enid Galliers**	NDA 21-116 **Telecon/Meeting initiated by:** ○ Applicant/Sponsor ● FDA **By:** Telephone **Product Name:** Thyro-Tabs (levothyroxine Sodium) tablets (9 strengths) **Firm Name:** LLOYD, INC. **Name and Title of Person with whom conversation was held:** Dr. Joseph W. Denhart VP, Reg. Aff & QA **Phone:** 712-246-4000 x 202

McCort
21-116

MEMORANDUM OF A MEETING
DIVISION OF METABOLISM AND
ENDOCRINE DRUG PRODUCTS (HFD-510)

MEETING DATE: October 4, 1999 TIME: 2:30 PM PLACE: Parklawn Rm 14B-56

DRUG: Levothyroxine Sodium Tablets

SPONSOR: Lloyd Inc.

NDA: 21-116

TYPE OF MEETING: Filing/Planning Meeting

MEETING CHAIR: Solomon Sobel, M.D., Division Director

MEETING RECORDER: Steve McCort, Regulatory Project Manager

FDA STAFF:

Solomon Sobel, M.D., Division Director (HFD-510)
David Orloff, M.D., Medical Team Leader (HFD-510)
David Lewis, Ph.D., Chemistry Reviewer (HFD-820)
Hae Young Ahn, Ph.D., Biopharmaceutics Reviewer (HFD-870)
Mike Fossler, Ph.D., Biopharmaceutics Reviewer (HFD-870)
Steve Johnson, Ph.D., Biopharmaceutics Reviewer (HFD-870)
Ron Steigerwalt, Ph.D., Pharmacacology Reviewer (HFD-5100
Chris Rogers, Policy Management, (HFD-007)
Steve McCort, Regulatory Project Manager (HFD-510)

Meeting Objectives:

1. To discuss whether the application is fileable.
2. To discuss planning dates for the review and action for the application

CONCLUSIONS AND DECISIONS REACHED:

1. **IS THE APPLICATION FILEABLE?**

Project Manager- Yes. It is fileable.

Medical: Yes.

Biopharmaceutics: Yes

Chemistry: Yes

Pharmacology: Yes.

2. **PLANNING:**

- Application is a Standard Review
- Filing date: October 19, 1999
- Date of Labeling Meeting: CLASS LABELING January 18, 2000 [same date as labeling meeting for NDA 21-137, Vintage Pharmaceuticals]
- Date Reviews Signed Off: July 10, 2000
- Date to Dr. Sobel: August 1, 2000
- Action Performance Goal Date: August 14, 2000
- 10 Mth. User Fee Date: June 20, 2000
- 12 Mth. User Fee Date: August 20, 2000

CONCLUSIONS:

1. The application is fileable.

2. The Action Performance Goal Date is August 14, 2000 for the application.

3. A CLASS LABELING meeting for L-thyroxine products will be held on January 18, 2000. It will be held at the same time as the labeling for the Vintage Pharmaceuticals pending NDA 21-137 labeling meeting.

4. The Action performance Goal Date for NDA 21-137, Vintage Pharmaceuticals has been reset for May 10, 1999 [twelve month clock]. A memo to the file to reflect the new planning date will be drafted.

Signature of Minutes preparer: /S/ 9-99

Steve McCort
Project Manager, HFD-510

Signature of Chair: /S/ 10-7-99

Solomon Sobel. M.D.,
Division Director, HFD-510

cc: NDA 21-116
HFD-510/DivFile
HFD-510/CSO/SMcCort
HFD-510/SSobel/JTemeck/DOrloff/MFossler/HAhn/RSteigerwalt
HFD-DLewis/DWu
HFD-870/HAhn/MFossler/SJohnson
HFD-007/CRogers

MEMORANDUM OF MEETING MINUTES

MEETING DATE: October 9, 2002

TIME: 1:00 pm.

LOCATION: Room 14B-45

APPLICATION: NDA 21-116

DRUG NAME: THYRO-TABS

TYPE OF MEETING: T/CON

MEETING CHAIR: David, Lewis, Ph.D., Chemistry Reviewer

MEETING RECORDER: Steve McCort, Project Manager

FDA ATTENDEES, TITLES, AND OFFICE/DIVISION

Name of FDA Attendee	Title	Division Name & HFD#
1. David Lewis, Ph.D.	Chemistry Reviewer	ONDC, DNDC II, HFD-820
2. Sheldon Markofsky, Ph.D.	Acting Chemistry Team Leader	ONDC, DNDC II, HFD-820
3. Steve McCort	Regulatory Project Manager	DMEDP, HFD-510
4. Enid Galliers	Chief, Project Management Staff	DMEDP, HFD-510
5. Steve Johnson, Pharm. D.	Biopharmaceutics Reviewer	OCPB, DPE II, HFD-870

EXTERNAL CONSTITUENT ATTENDEES AND TITLES:

External Attendee	Title	Sponsor/Firm Name
1. Eugene Lloyd, DVM, Ph.D.	President and Executive Vice President, Scientific Affairs	Lloyd Inc.
2. Joseph W. Denhart, DVM, MS.	Vice President Regulatory Affairs And Quality Assurance	Lloyd Inc.
3. Mark Heininger, Ph.D.	Vice President, Scientific Affairs	Lloyd Inc.
4. Charles M. Siegfried, Ph.D.	Vice President, Research and Development	Lloyd Inc.
5. Roger Buhman	Laboratory Resources Manager	Lloyd Inc.
6. Rob Davis	Stability Manager and Laboratory Chemist	Lloyd Inc.
7. Todd Delahanty, Ph.D.	New Products Project Manager	Lloyd Inc.
8. Ronald D. Ketcham	Executive Vice President Marketing, Principle Operations Officer	Lloyd Inc.

BACKGROUND:

The sponsor submitted NDA 21-116 for Thyro-Tabs (levothyroxine sodium tablets, USP) on August 19, 1999. The sponsor received an approvable letter dated June 20, 2000, for chemistry and biopharmaceutical deficiencies. The sponsor submitted a complete response dated April 22, 2002, to the June 20, 2000, letter.

On October 4, 2002, the sponsor requested a teleconference to discuss the outstanding chemistry and biopharmaceutics issues in the pending application. The teleconference was granted on October 7, 2002.

MEETING OBJECTIVES:

1. Confirmation that the submitted information on the dissolution method and specification is acceptable.

2. Resolution of the GMP issues for the drug product

3. USP designation for Thyro-Tabs

CONCLUSIONS:

1. The (tolerances) for dissolution testing are acceptable to the Agency.

2. Resolution of GMP issues for the drug product-
   A Form 483 was issued by the Office of Compliance with a withhold recommendation on September 20, 2002. The "483" consisted of two parts: (a) GMP issues at the facilities site and (b) analytical methods for stability testing.
   The Agency stated that the resolution of the GMP facility issue will be decided by CDER Office of Compliance (Item a). The analytical methods are not a Compliance issue and should be handled by the review division, and they should not have been included in the "483" report. The Division has no objections to the analytical methods for assay and dissolution at this time.

3. USP designation for Thyro-Tabs-

   The product meets USP specifications and may be designated "USP".

ACTION ITEMS:

None.

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

Chair Concurrence: _____
David Lewis, Ph.D.
Chemistry Reviewer

Filename: \21116\21116mot.10092002.doc

Drafted by: S McCort/October 23, 2002
Initialed by: E. Galliers/ 12.08.2002/ S. Johnson/ 01.16.2003/ H-Y. Ahn/ 01.16.2003/ S. Markofsky/ 01.18.2003/D. Lewis/ 01.15,22.2003/

Final: E. Galliers/ 01.24.2003/

MEETING MINUTES

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/s/

David Lewis
1/31/03 02:42:54 PM
I see No problems with the minutes, as written.

M E M O R A N D U M

DEPARTMENT OF HEALTH AND HUMAN SERVICES
PUBLIC HEALTH SERVICE
FOOD AND DRUG ADMINISTRATION
CENTER FOR DRUG EVALUATION AND RESEARCH

DATE: October 23rd, 2002

FROM: David B. Lewis, Ph.D.

SUBJECT: cGMP status of application and final ONDC recommendation.

TO: NDA 21-116 Division File

The CMC Review of NDA 21-116 dated October 21st, 2002 had a recommendation of "approval, pending satisfactory cGMP status". On October 22nd, 2002, an EER Summary Report with the recommendation "ACCEPTABLE" was entered into the EES System by the Office of Compliance (see Memorandum dated October 22nd, 2002). An action may now be taken on NDA 21-116, and the ONDC recommendation is changed to "Approval, from the standpoint of chemistry".

Conclusion: NDA 21-116 may be approved from the standpoint of chemistry.

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/s/

David Lewis
10/23/02 09:29:52 AM
CHEMIST
Approval, from the standpoint of chemistry
Shelly and I thought that you should be the
secondary signatory, since you did the secondary review
of the CMC review.

Duu-gong Wu
10/23/02 01:08:03 PM
CHEMIST

M E M O R A N D U M

DEPARTMENT OF HEALTH AND HUMAN SERVICES
PUBLIC HEALTH SERVICE
FOOD AND DRUG ADMINISTRATION
CENTER FOR DRUG EVALUATION AND RESEARCH

DATE: October 22nd, 2002

FROM: David B. Lewis, Ph.D.

SUBJECT: cGMP status of application

TO: NDA 21-116 Division File

The Establishment Evaluation Request (EER) Summary Report for NDA 21-116 [Thyro-tabs (levothyroxine sodium tablets, USP), Lloyd, Inc.] was posted by the Office of Compliance with the overall recommendation of ACCEPTABLE, dated October 22nd, 2002 (S. Ferguson, HFD-324). A scanned representation of the EER Summary Report is attached at the end of this memorandum.

Conclusion: An action may be taken on NDA 21-116, since there is an acceptable cGMP status for all of the pertinent manufacturing and testing facilities.

MEMO TO THE FILE

NDA 21-116
Drug product: Thyro-Tabs (levothyroxine sodium tablets)
Sponsor: Lloyd, Inc.
Date: October 22, 2002

Subject: Financial Disclosure Information faxed to Agency on 10/22/02

In accordance with 21 CFR 314.50(k) the sponsor submitted Form 3454 certifying that the two clinical investigators, Drs. Krishna Talluri and Aziz Laurent, have not received any significant compensation, hold proprietary interests, or received significant payments of other sorts (e.g., honoraria, research grants) which may bias or alter the outcomes of the clinical pharmacology studies submitted in support of this application.

In the opinion of this reviewer, the financial disclosure information provided is adequate.

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/s/

Mary Parks
10/22/02 04:41:46 PM
MEDICAL OFFICER

10.29.02

DIVISION OF METABOLIC AND ENDOCRINE DRUG PRODUCTS

LABEL REVIEW

Application Number: NDA 21-116

Name of Drug: Thyro-Tabs® (levothyroxine sodium tablets, USP)

Applicant: Lloyd Inc.

Material Reviewed:

Submission Dates: May 27 and October 14, 2002

Receipt Dates: June 5 and October 15, 2002

Background and Summary

The drug Thyro-Tabs was submitted on August 19, 1999 in response to a Federal Register Notice dated August 14, 1997, requiring all manufacturers of L-thyroxine sodium to submit new drug applications (NDAs) for this product. The original application dated August 19, 1999, included draft labeling for 11 strengths: 25, 50, 75, 88, 100, 112, 125, 150, 175, 200 and 300 mcg strengths. The labeling included the draft package insert, the bottle labels for the 100-count and 1000 count bottles and shipper labels (cartons of 12 bottles of 100 and 1000).

The sponsor submitted draft labeling in a submission dated April 22, 2002, for the package insert and bottle in response to the approvable letter sent by the Agency dated June 20, 2000.

The sponsor submitted revised labeling dated May 27, 2002, for the package insert in response to the Agency's revised template labeling for L-Thyroxine dated February 9, 2002. In the same package the sponsor submitted draft labeling for the bottle labeling for all strengths.

On October 14, 2002 the sponsor submitted a revised draft package insert in response to the September 25, 2002, letter containing L-thyroxine template labeling (revision dated July 9, 2002).

In a fax submission dated October 21, 2002, the firm responded to requested modifications by Dr. David Lewis, the chemistry reviewer, to modify the Storage statement for Thyro-Tabs. In the fax the firm submitted a package insert and a representative bottle label for the 25 mcg strength.

The revised Storage statement read as follows:

"Store at 25°C (77°F) with excursions permitted to 15-30°C (59-86°F)."

In an October 22, 2002, submission the firm agreed to revise the storage statement as submitted above for the other bottle labels.

In a separate t/con the firm agreed to make two additional labeling revisions as follows.

1. The "**R_x Only**" statement that is listed after **Storage Conditions** should be moved under the trade name Thyro-Tabs and before the **DESCRIPTION** section of the package insert.

2. In the **HOW SUPPLIED** section, the column referring to [redacted] should be deleted.

On October 23, 2002, Enid Galliers of this Agency communicated by telephone with Dr. Eugene Lloyd of Lloyd Inc., additional labeling revisions as follows:

To the Bottle and Shipper labels (bottles of 100 and 1000; cartons of 12 bottles [100-ct and 1000-ct]) submitted May 27, 2002:

1. Replace the "Caution:Federal law prohibits. . ."statement on the main panel of the bottle and shipper labels with **"Rx Only."**

2. On the side panel of the bottle and shipper labels, replace the phrase " [redacted] . . ." with the phrase **"Store at 25°C (77°F) with excursions permitted to15°-30°C (59° –86°F), protect from moisture and light."**

Review

PACKAGE INSERT

The draft package insert dated October 14, 2002, was compared with the template labeling revision dated July 9, 2002 The following changes are noted and were agreed upon:

1. The **Storage** statement should be revised to read **"Store at 25 °C (77 °F) with excursions permitted to 15°-30 °C (59° –86°F) . Protect from moisture and light."**

2 . The "**R_x Only**" statement that is listed after **Storage Conditions** should be moved under the trade name Thyro-Tabs and before the **DESCRIPTION** section of the package insert.

3. In the **HOW SUPPLIED** section, the column referring to "— — should be deleted.

4. Insert the title, "**DESCRIPTION**" at the beginning of that section as in the package insert submitted on May 27, 2002.

REVIEWER'S RESPONSE:

The labeling submitted by the sponsor in the October 14, 2002, submission for the package insert will be revised per agreement with FDA to reflect the revisions described above. A copy of the agreed upon labeling has been included with the approval letter for NDA 21-116.

BOTTLE AND SHIPPER LABELS

The bottle and shipper labels (bottles of 100 and 1000; cartons of 12 bottles [100-ct and 1000-ct]) submitted May 27, 2002, will be revised per agreement with the sponsor. The following changes are noted and were communicated to the firm in the action letter dated October 24, 2002 for NDA 21-116 as follows:

1. Replace the "Caution: Federal law prohibits . . ." statement on the main panel of the bottle and shipper labels with **"Rx Only."**

2. On the side panel of the bottle and shipper labels, replace the phrase " — — ." with the phrase **"Store at 25°C (77°F) with excursions permitted to 15°-30°C (59°-86°F), protect from moisture and light."**

Conclusions

The labeling as submitted on May 27, 2002, for the bottle labels and the October 14, 2002, submission for the package insert are approvable with the labeling revisions agreed upon with the Agency. The reviewer recommends an approval letter for NDA 21-116 be drafted.

Steve McCort
Regulatory Project Manager, HFD-510

Supervisory Comment/Concurrence:

Enid Galliers
Chief, Project Management Staff, HFD-510

Drafted: S McCort/October 24, 2002
Revised/Initialed: E Galliers/Oct. 27, 28,2002
Finalized: S McCort/October 29, 2002
Filename: n21116lab.doc

CSO LABELING REVIEW

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

/s/

Stephen McCort
10/29/02 04:02:34 PM
CSO

Enid Galliers
10/29/02 04:11:29 PM
CSO