CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER: 21-301

ADMINISTRATIVE DOCUMENTS

SECTION 13

PATENT INFORMATION

There are no patents which claim Levoxyl (Levothyroxine Sodium Tablets, USP) or which claim a method of using Levoxyl.

JONES PHARMA INCORPORATED
1945 Craig Road, P.O. Box 46903
St. Louis, Missouri 63146
314 576-6100 Fax 314 469-5749
www.jmedpharma.com

SECTION 14

PATENT CERTIFICATION

JONES PHARMA INCORPORATED certifies to the best of its knowledge in accordance with 21 U.S.C. §355(b)(2)(A)(i) that there has been no patent information filed with the Food and Drug Administration in connection with Levothyroxine Sodium which claims the drug or which claims a use for such drug.

JONES PHARMA INCORPORATED

Nancy Cafmeyer
Nancy Cafmeyer
Vice President of Regulatory Affairs

7/27/2000
Date

APPEARS THIS WAY
ON ORIGINAL

JPI JONES

ORIGINAL

NEW CORRESP
N-000-C

JONES PHARMA INCORPORATED
1945 Craig Road, P.O. Box 46903
St. Louis, Missouri 63146
314 576-6100 Fax 314 469-5749
www.jmedpharma.com

May 14, 2001

SENT VIA FACSIMILE AND FEDERAL EXPRESS

John Jenkins, M.D. Acting Director
Division of Metabolism and Endocrine Drug Products (HFD-510)
Document Control Room 14B-19
Food and Drug Administration
5600 Fishers Lane
Rockville, MD 20857

RE: Debarment Certification
NDA 21-301
Levoxyl (levothyroxine sodium tablets, USP)

Reference is made to our New Drug Application for Levoxyl (Levothyroxine Sodium Tablets, USP) NDA 21-301 submitted July 28, 2000.

By this letter, it is certified that JONES PHARMA INCORPORATED (JPI) did not and will not use in any capacity the services of any person debarred under Section 306(k)(1) in connection with this NDA application for LEVOXYL (Levothyroxine Sodium Tablets, USP).

JPI also certifies that the company has not used any person or affiliate person/firm for whom convictions subject to debarment have occurred in the last five years in any capacity in connection with the development of this product.

If there are any questions concerning this submission, please do not hesitate to contact me by telephone at (314) 576-6100 or by fax at (314) 205-9497.

Sincerely,

JONES PHARMA INCORPORATED
(A subsidiary of King Pharmaceuticals, Inc.)

Nancy Cafmeyer

Nancy Cafmeyer
Director, Regulatory Affairs

EXCLUSIVITY SUMMARY for NDA # 21-210 SUPPL # __

Trade Name Levoxyl
Generic Name Levothyroxine Sodium Tablets, USP)
Applicant Name Jones Pharma Incorporated HFD-510

Approval Date May 25, 2001

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 /_x__/ NO /___/

      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 except for 137 Strength

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 Unithroid

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 /N/A

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.

This NDA relies on literature reports and the approval of NDA 21-210. It does not contain reports of new clinical investigations or right of references to such reports.

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 /_x__/

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: _____

_____

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ON ORIGINAL

(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

APPEARS THIS WAY
ON ORIGINAL

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
5/24/01 04:20:38 PM

APPEARS THIS WAY
ON ORIGINAL

PEDIATRIC PAGE (Complete for all original application and all efficacy supplements)

View as Word Document

NDA Number:	021301	**Trade Name:**	LEVOXYL (LEVOTHYROXINE SODIUM) 25/50/75
Supplement Number:	000	**Generic Name:**	LEVOTHYROXINE SODIUM
Supplement Type:	N	**Dosage Form:**	ORAL TABLETS
Regulatory Action:	OP	**COMIS Indication:**	THYROID REPLACEMENT
Action Date:	7/28/00		

Indication # 1 Treatment of Hypothroidism and Pituitary TSH Suppression

Label Adequacy:	Adequate for ALL pediatric age groups
Formulation Needed:	NO NEW FORMULATION is needed
Comments (if any):	The application was submitted as a 505(b)(2) application. The Sponsor has cited pertinent literature to support the safety and efficacy of the drug product for the pediatric population for all age groups. The recommedation was to waive the requirement for doing clinical studies.

Ranges for This Indication

Lower Range	Upper Range	Status	Date
0 years	Adult	Waived	

Comments: Published literature adequately support the safe and effective use of Levoxyl (Levothyroxine Sodium Tablets, USP) for the indications specified in FDA's levothyroxine template. Therfore a waiver should be granted.

This page was last edited on 5/10/01

/S/ — Signature

5-10-01 — Date

APPEARS THIS WAY
ON ORIGINAL

SECTION 18

USER FEE COVER SHEET

Please refer to the following pages which include the User Fee Cover Sheet (Form FDA 3397). Please note that a small business waiver of user fees has been granted to JONES PHARMA for this NDA application. A copy of the official FDA notification that the waiver has been granted is included following the User Fee Cover Sheet.

APPEARS THIS WAY
ON ORIGINAL

FOOD AND DRUG ADMINISTRATION

USER FEE COVER SHEET

See Instructions on Reverse Side Before Completing This Form

1. APPLICANT'S NAME AND ADDRESS

JONES PHARMA INCORPORATED
1945 Craig Rd.
St. Louis, MO 63146

2. TELEPHONE NUMBER *(Include Area Code)*

(314) 576-6100

3. PRODUCT NAME

LEVOXYL (levothyroxine sodium tablets, USP)

4. DOES THIS APPLICATION REQUIRE CLINICAL DATA FOR APPROVAL? 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).

5. USER FEE I.D. NUMBER

6. LICENSE NUMBER / NDA 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 COMMERCIALLY *(Self Explanatory)*

FOR BIOLOGICAL PRODUCTS ONLY

☐ WHOLE BLOOD OR BLOOD COMPONENT FOR TRANSFUSION

☐ A CRUDE ALLERGENIC EXTRACT PRODUCT

☐ AN APPLICATION FOR A BIOLOGICAL PRODUCT FOR FURTHER MANUFACTURING USE ONLY

☐ AN "IN VITRO" DIAGNOSTIC BIOLOGICAL PRODUCT LICENSED UNDER SECTION 351 OF THE PHS ACT

☐ BOVINE BLOOD PRODUCT FOR TOPICAL APPLICATION LICENSED BEFORE 9/1/92

8. HAS A WAIVER OF AN APPLICATION FEE BEEN GRANTED FOR THIS APPLICATION? ☒ YES ☐ NO *(See reverse side if answered YES)*

A completed form must be signed and accompany each new drug or biologic product application and each new supplement. If payment is sent by U.S. mail or courier, please include a copy of this completed form with payment.

SIGNATURE OF AUTHORIZED COMPANY REPRESENTATIVE	TITLE	DATE
Nancy Cafmeyer	V.P. Regulatory Affairs	7/27/2000

APR 13 2000

Food and Drug Administration
Rockville MD 20857

Nancy Cafmeyer
Vice President of Regulatory Affairs
Jones Pharma Incorporated
1945 Craig Road
P.O. Box 46903
St. Louis, MO 63146

RE: Jones Pharma, Incorporated's Levothyroxine Sodium Tablets Small Business Waiver Request 2000.020

Dear Ms. Cafmeyer:

This letter responds to your February 9, and March 17, 2000, letters requesting a waiver of the prescription drug application fee for levothyroxine sodium tablets under the small business waiver provision of section 736(d)(1)(E) of the Prescription Drug User Fee Act of 1992 (PDUFA) as amended by the Food and Drug Administration Modernization Act of 1997 (Modernization Act) (Waiver Request 2000.020). For the reasons described below, the Food and Drug Administration (FDA) grants the request from Jones Pharma, Incorporated (JPI) for a small business waiver.

According to your request for a waiver of fees, JPI has fewer than 500 employees, including the employees of your affiliates, JMI-Daniels Pharmaceuticals, Inc., Gentrac, and JMI-Canton Pharmaceuticals. You state that this NDA submission will be the first human drug application submitted by JPI or its subsidiaries. You list two NDAs (NDA 10-379, Cytomel Tablets and NDA 20-105, Triostat Injection) that JPI has acquired through purchase.

[redacted]

Under PDUFA as amended, a waiver of the application fee shall be granted to a small business for the first human drug application that a small business or its affiliate[1] submits to the FDA for review. The small business waiver provision entitles a qualified small business to a waiver when the business meets two criteria: first, a business must employ fewer than 500 persons, including employees of its affiliates; and second, the marketing application must be the first human drug application, within the meaning of PDUFA, that a company or its affiliate submits to FDA.

[1] "The term 'affiliate' means a business entity that has a relationship with a second business entity if, directly or indirectly — (A) one business entity controls, or has the power to control, the other business entity; or (B) a third party controls, or has the power to control, both of the business entities" (21 U.S.C. 379g(9)).

FDA's decision to grant a small business waiver to JPI is based on two findings. First, by letter dated March 30, 2000, the Small Business Administration (SBA) determined that as of March 20, 2000, JPI had fewer than 500 employees, including employees of its affiliates, and had three affiliates: JMI-Daniels Pharmaceuticals, Inc., JMI-Canton Pharmaceuticals, and Gentrac, Inc.

Second, according to FDA records, JPI or its affiliates did not submit NDA 10-379, Cytomel Tablets or NDA 20-105, Triostat Injection. Therefore, the marketing application for levothyroxine sodium tablets is the first human drug application, within the meaning of PDUFA, to be submitted to FDA by JPI or its affiliates.

Consequently, your request for a small business waiver of the application fee for levothyroxine sodium tablets is granted, provided that FDA receives the marketing application no later than March 20, 2001, one year after the effective date of the size determination made by the SBA. Please note that once the marketing application is submitted, if FDA refuses to file the marketing application or if JPI withdraws the marketing application before it is filed by FDA, and the company plans to resubmit its marketing application, a reevaluation of the waiver will be required. If this occurs, JPI should contact this office approximately 90 days before it expects to resubmit its marketing application to determine whether JPI continues to qualify for a small business waiver.

Please include a copy of this letter in the marketing application for levothyroxine sodium tablets. FDA's Office of Financial Management has been notified of this waiver. If any billing questions arise concerning the marketing application or if you have any questions about this small business waiver, please contact Beverly Friedman or Michael Jones at 301-594-2041.

FDA plans to disclose to the public information about its actions granting or denying waivers and reductions. This disclosure will be consistent with the laws and regulations governing the disclosure of confidential commercial or financial information.

Sincerely,

/S/

Jane A. Axelrad
Associate Director for Policy
Center for Drug Evaluation and Research

MEMORANDUM

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

DATE: May 11, 2001

TO: File for NDA 21-301

FROM: Steve McCort
Project Manager, HFD-510

SUBJECT: Financial Disclosure

The firm had submitted a financial disclosure (Form 3454) with their original NDA 21-301. The list of clinical investigators were cited for the Study "A Pharmakinetic Study To Assess the Single Oral Dose Bioavailability of Two Formulations of Levothyroxine.". Dr. Jean Temeck's medical review dated May 9, 2001, Page 12-13, states that *"Jones Pharma did not enter into any financial interests arrangements with either PIs or the subinvestigators of the bioavailability studies that would affect the outcome of these studies."*

/S/ 5-11-2001

Steve McCort, Project Manager, HFD-510

APPEARS THIS WAY
ON ORIGINAL

SECTION 19

FINANCIAL INFORMATION

As required in the regulations the following information is being submitted.

Form FDA 3454: Certification: Financial Interests and Arrangements of Clinical Investigators

Attachment to Form FDA 3454: List of Clinical Investigators

DEPARTMENT OF HEALTH AND HUMAN SERVICES
Public Health Service
Food and Drug Administration

Form Approved: OMB No. 0910-0396
Expiration Date: 3/31/02

CERTIFICATION: FINANCIAL INTERESTS AND ARRANGEMENTS OF CLINICAL INVESTIGATORS

TO BE COMPLETED BY APPLICANT

With respect to all covered clinical studies (or specific clinical studies listed below (if appropriate)) submitted in support of this application, I certify to one of the statements below as appropriate. I understand that this certification is made in compliance with 21 CFR part 54 and that for the purposes of this statement, a clinical investigator includes the spouse and each dependent child of the investigator as defined in 21 CFR 54.2(d).

Please mark the applicable checkbox.

(1) As the sponsor of the submitted studies, I certify that I have not entered into any financial arrangement with the listed clinical investigators (enter names of clinical investigators below or attach list of names to this form) whereby the value of compensation to the investigator could be affected by the outcome of the study as defined in 21 CFR 54.2(a). I also certify that each listed clinical investigator required to disclose to the sponsor whether the investigator had a proprietary interest in this product or a significant equity in the sponsor as defined in 21 CFR 54.2(b) did not disclose any such interests. I further certify that no listed investigator was the recipient of significant payments of other sorts as defined in 21 CFR 54.2(f).

Clinical investigators		

(2) As the applicant who is submitting a study or studies sponsored by a firm or party other than the applicant, I certify that based on information obtained from the sponsor or from participating clinical investigators, the listed clinical investigators (attach list of names to this form) did not participate in any financial arrangement with the sponsor of a covered study whereby the value of compensation to the investigator for conducting the study could be affected by the outcome of the study (as defined in 21 CFR 54.2(a)); had no proprietary interest in this product or significant equity interest in the sponsor of the covered study (as defined in 21 CFR 54.2(b)); and was not the recipient of significant payments of other sorts (as defined in 21 CFR 54.2(f)).

(3) As the applicant who is submitting a study or studies sponsored by a firm or party other than the applicant, I certify that I have acted with due diligence to obtain from the listed clinical investigators (attach list of names) or from the sponsor the information required under 54.4 and it was not possible to do so. The reason why this information could not be obtained is attached.

NAME	TITLE
NANCY CAFMEYER	Vice President of Regulatory Affairs
FIRM/ORGANIZATION	
JONES PHARMA INCORPORATED	
SIGNATURE	**DATE**
Nancy Cafmeyer	7/27/2000

Paperwork Reduction Act Statement

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. Public reporting burden for this collection of information is estimated to average 1 hour per response, including time for reviewing instructions, searching existing data sources, gathering and maintaining the necessary data, and completing and reviewing the collection of information. Send comments regarding this burden estimate or any other aspect of this collection of information to the address to the right:

Department of Health and Human Services
Food and Drug Administration
5600 Fishers Lane, Room 14C-03
Rockville, MD 20857

WITHHOLD 1 PAGE

JONES PHARMA INCORPORATED
1945 Craig Road, P.O. Box 46903
St. Louis, Missouri 63146
314 576-6100 Fax 314 469-5749
www.jmedpharma.com

May 14, 2001

SENT VIA FACSIMILE AND FEDERAL EXPRESS

John Jenkins, M.D. Acting Director
Division of Metabolism and Endocrine Drug Products (HFD-510)
Document Control Room 14B-19
Food and Drug Administration
5600 Fishers Lane
Rockville, MD 20857

RE: Debarment Certification
NDA 21-301
Levoxyl (levothyroxine sodium tablets, USP)

Reference is made to our New Drug Application for Levoxyl (Levothyroxine Sodium Tablets, USP) NDA 21-301 submitted July 28, 2000.

By this letter, it is certified that JONES PHARMA INCORPORATED (JPI) did not and will not use in any capacity the services of any person debarred under Section 306(k)(1) in connection with this NDA application for LEVOXYL (Levothyroxine Sodium Tablets, USP).

JPI also certifies that the company has not used any person or affiliate person/firm for whom convictions subject to debarment have occurred in the last five years in any capacity in connection with the development of this product.

If there are any questions concerning this submission, please do not hesitate to contact me by telephone at (314) 576-6100 or by fax at (314) 205-9497.

Sincerely,

JONES PHARMA INCORPORATED
(A subsidiary of King Pharmaceuticals, Inc.)

Nancy Cafmeyer

Nancy Cafmeyer
Director, Regulatory Affairs

APPEARS THIS WAY
ON ORIGINAL

JONES

JONES PHARMA INCORPORATED
1945 Craig Road, P.O. Box 46903
St. Louis, Missouri 63146
314 576-6100 Fax 314 469-5749
www.jmedpharma.com

SECTION 16

DEBARMENT CERTIFICATION

JONES PHARMA INCORPORATED (JPI) certifies that to the best of its knowledge, the company did not and will not use in any capacity the services of any person debarred under Section 306(k)(1) in connection with this NDA application for LEVOXYL (Levothyroxine Sodium Tablets, USP).

JPI also certifies that to the best of its knowledge, the company has not used any person or affiliate person/firm for whom convictions subject to debarment have occurred in the last five years in any capacity in connection with the development of this product.

JONES PHARMA INCORPORATED

Nancy Cafmeyer
Nancy Cafmeyer
Vice President of Regulatory Affairs

7/27/2000
Date

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: May 20, 2001

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

TO: NDA 21-301
Levoxyl (levothyroxine sodium)
Jones Pharma, Inc.

SUBJECT: NDA review issues and action

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 lot-to-lot 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 must 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 Levoxyl 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

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).

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.

[ ]

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.

Labeling
The levothyroxine sodium template labeling has been provided to the sponsor. The sponsor has resubmitted proposed labeling after inserting their product-specific information into the template. This revised labeling has been accepted.

Biopharmaceutics
The biopharmaceutics section is acceptable to OCPB. They have recommended a revised *in vitro* dissolution specification for the product.

Pharmacology/Toxicology
No issues.

Chemistry/ Microbiology
The chemistry, manufacturing, and controls are satisfactory and the application is approvable from the standpoint of ONDC.
The site inspections were all acceptable.
A categorical exclusion from the environmental assessment was claimed by the sponsor and accepted by the Agency.

DSI/Data Integrity
No issues.

Financial disclosure
The financial disclosure information is in order. The sponsor has certified that no investigator received outcome payments, that no investigator disclosed a proprietary interest in the product or an equity interest in the company, and that no investigator was the recipient of significant payments of other sorts.

OPDRA/nomenclature
The proprietary name, Levoxyl, is acceptable.

Recommendation
This application may be approved.

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
5/21/01 07:38:42 PM
MEDICAL OFFICER

APPEARS THIS WAY
ON ORIGINAL

FDA CDER EES
ESTABLISHMENT EVALUATION REQUEST
SUMMARY REPORT

Application: NDA 21301/000 Priority: SS Org Code: 510
Stamp: 28-JUL-2000 Regulatory Due: 28-MAY-2001 Action Goal: District Goal: 29-MAR-2001
Applicant: JONES PHARMA Brand Name: LEVOXYL (LEVOTHYROXINE SODIUM) 25/50/75
Established Name:
Generic Name: LEVOTHYROXINE SODIUM
Dosage Form: TAB (TABLET)
Strength: 25-300 MCG

FDA Contacts:			
S. MCCORT	(HFD-510)	301-827-6415	, Project Manager
D. LEWIS	(HFD-510)	301-827-6420	, Review Chemist
D. WU	(HFD-510)	301-827-6375	, Team Leader

Overall Recommendation:

ACCEPTABLE on 06-NOV-2000 by J. D AMBROGIO (HFD-324) 301-827-0062
ACCEPTABLE on 23-OCT-2000 by J. D AMBROGIO (HFD-324) 301-827-0062
ACCEPTABLE on 16-OCT-2000 by J. D AMBROGIO (HFD-324) 301-827-0062

Establishment: [redacted] DMF No:
AADA No:

Profile: CTL OAI Status: NONE Responsibilities: FINISHED DOSAGE OTHER TESTER
Last Milestone: OC RECOMMENDATION
Milestone Date: 24-AUG-2000
Decision: ACCEPTABLE
Reason: DISTRICT RECOMMENDATION

Establishment: [redacted] DMF No:
AADA No:

Profile: CSN OAI Status: NONE Responsibilities: DRUG SUBSTANCE MANUFACTURER
Last Milestone: OC RECOMMENDATION
Milestone Date: 24-AUG-2000
Decision: ACCEPTABLE
Reason: DISTRICT RECOMMENDATION

Establishment: [redacted] DMF No:
AADA No:

Profile: CTL OAI Status: NONE

ESTABLISHMENT EVALUATION REQUEST SUMMARY REPORT

Responsibilities: FINISHED DOSAGE OTHER TESTER

Last Milestone: OC RECOMMENDATION
Milestone Date: 18-AUG-2000
Decision: ACCEPTABLE
Reason: BASED ON PROFILE

Establishment: [redacted]

DMF No:
AADA No:

Profile: CTL OAI Status: NONE
Last Milestone: OC RECOMMENDATION
Milestone Date: 18-AUG-2000
Decision: ACCEPTABLE
Reason: BASED ON PROFILE

Responsibilities: FINISHED DOSAGE OTHER TESTER

Establishment: 1014630
JMI DANIELS PHARMACEUTICALS I
2527 25TH AVE, NORTH
ST PETERSBURG, FL 33713

DMF No:
AADA No:

Profile: TCM OAI Status: NONE
Last Milestone: OC RECOMMENDATION
Milestone Date: 06-NOV-2000
Decision: ACCEPTABLE
Reason: DISTRICT RECOMMENDATION

Responsibilities: FINISHED DOSAGE MANUFACTURER

Establishment: [redacted]

DMF No:
AADA No:

Profile: TCM OAI Status: NONE
Last Milestone: OC RECOMMENDATION
Milestone Date: 18-AUG-2000
Decision: ACCEPTABLE
Reason: BASED ON PROFILE

Responsibilities: FINISHED DOSAGE PACKAGER

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: 5-14-01

FROM: David B. Lewis, Ph.D.

SUBJECT: Categorical Exclusion from EA.

TO: NDA 21-301 File

The sponsor of NDA 21-301 (Jones Pharma, Inc.) neglected to claim a Categorical Exclusion from EA in the original NDA. NDA 21-301 would qualify for an exclusion under 21 CFR 25.31, parts a, b, or c. On May 11th, 2001, Ms. Nancy Cafmeyer sent a FAXed request for categorical exclusion under 21 CFR 25.31 (no sub-chapters cited). This claim is warranted, and is acceptable.

Conclusion: NDA 21-301 is categorically excluded from Environmental Impact assessment under 21 CFR 25.31 (a), (b), and/or (c).

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

/s/

David Lewis
5/14/01 12:19:21 PM
CHEMIST
The FAX dated 5-11-01 provided a claim for categorical exclusion from EA. This is acceptable.

APPEARS THIS WAY
ON ORIGINAL

JONES

DUPLICATE

JONES PHARMA INCORPORATED
1945 Craig Road, P.O. Box 46903
St. Louis, Missouri 63146
314 576-6100 Fax 314 469-5749
www.jmedpharma.com

NEW COMMISSP
N-000-C

May 11, 2001

SENT VIA FACSIMILE AND FEDERAL EXPRESS

John Jenkins, M.D. Acting Director
Division of Metabolism and Endocrine Drug Products (HFD-510)
Document Control Room 14B-19
Food and Drug Administration
5600 Fishers Lane
Rockville, MD 20857

RE: Request for Categorical Exclusion for an Environmental Impact
NDA 21-301
Levoxyl (levothyroxine sodium tablets, USP)

Reference is made to our New Drug Application for Levoxyl (Levothyroxine Sodium Tablets, USP) NDA 21-301 submitted July 28, 2000.

Jones Pharma Incorporated requests a categorical exclusion for an environmental impact under 21CFR § 25.31 for NDA 21-301.

If there are any questions concerning this submission, please do not hesitate to contact me by telephone at (314) 576-6100 or by fax at (314) 205-9497.

Sincerely,

JONES PHARMA INCORPORATED
(A subsidiary of King Pharmaceuticals, Inc.)

Nancy Cafmeyer

Nancy Cafmeyer
Director, Regulatory Affairs

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

DATE: August 24, 2000	DUE DATE: October 27, 2000	OPDRA CONSULT #: 00-0233

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

THROUGH: Steve McCort
Project Manager
(HFD-510)

PRODUCT NAME:
Levoxyl (levothyroxine sodium tablets, USP)
[25, 50, 75, 88, 100, 112, 125, 137, 150, 175, 200, & 300 mcg]

NDA #: 21-301

MANUFACTURER:
Jones Pharma Inc.

CASE REPORT NUMBER(S): Ten (See narratives)

SAFETY EVALUATOR: Lauren Lee, Pharm.D.

OPDRA RECOMMENDATION:

OPDRA has no objections to the use of the proprietary name, Levoxyl, at this time. See review for details.

☐ FOR NDA/ANDA WITH ACTION DATE BEYOND 90 DAYS OF THIS REVIEW
This name must be re-evaluated approximately 90 days prior to the expected approval of the NDA. A re-review of the name prior to NDA approval will rule out any objections based upon approvals of other proprietary names/NDA's from the signature date of this document. A re-review request of the name should be submitted via e-mail to "OPDRAREQUEST" with the NDA number, the proprietary name, and the goal date. OPDRA will respond back via e-mail with the final recommendation.

☒ FOR NDA/ANDA WITH ACTION DATE WITHIN 90 DAYS OF THIS REVIEW
OPDRA considers this a final review. However, if the approval of the NDA is delayed beyond 90 days from the date of this review, the name must be re-evaluated. A re-review of the name prior to NDA approval will rule out any objections based upon approvals of other proprietary names/NDA's from this date forward.

☐ FOR PRIORITY 6 MONTH REVIEWS
OPDRA will monitor this name until approximately 30 days before the approval of the NDA. The reviewing division need not submit a second consult for name review. OPDRA will notify the reviewing division of any changes in our recommendation of the name based upon the approvals of other proprietary names/NDA's from this date forward.

/S/ 10/24/2000
Jerry Phillips, R.Ph.
Associate Director for Medication Error Prevention
Office of Post-Marketing Drug Risk Assessment
Phone: (301) 827-3242
Fax: (301) 480-8173

/S/ 10/24/00
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 Post-Marketing Drug Risk Assessment
HFD-400; Rm 15B-03
Center for Drug Evaluation and Research

Proprietary Name Review

DATE REVIEWED: October 17, 2000

NDA: 21-301

NAMES OF DRUGS: Levoxyl (levothyroxine sodium tablets, USP)

NDA HOLDER: Jones Pharma Inc.

I. INTRODUCTION

This consult is in response to an August 24, 2000 request, by the Division of Metabolic and Endocrine Drug Products, to review the proprietary drug name, Levoxyl, regarding potential name confusion with other proprietary/generic drug names. The container labels, blister carton labeling, and the package insert were also submitted for review of possible interventions in minimizing medication errors.

Levoxyl has been commercially available since the mid-1980s. Historically, levothyroxine sodium products have been marketed in the U.S. without the NDAs. However, the applicant has submitted this NDA in response to a Federal Register Notice published in August 14, 1997, which requires that the manufacturers of orally administered levothyroxine-containing products submit a NDA to continue marketing these products. The Federal Register announced the classification of orally administered drug products containing levothyroxine sodium as *new drugs*. The reason for the reclassification of oral levothyroxine sodium products as new drugs is as follows:

"There is new information showing significant stability and potency problems with orally administered levothyroxine sodium products. Also, these products fail to maintain potency through the expiration date, and tablets of the same dosage strength from the same manufacturer vary from lot to lot in the amount of active ingredient present."

Daniels Pharmaceuticals, which is a subsidiary of Jones Pharma Inc., first marketed the proposed product as *Levoxine* in November 1986. However, due to the numerous medication error reports of name confusion between Levoxine and *Lanoxin* (digoxin), the U.S. Food and Drug Administration (FDA) issued a letter to the applicant, on May 18, 1994, with concerns regarding the continued marketing of the product under the proprietary name, Levoxine. Subsequently, the name, Levoxine, was changed to Levoxyl.

PRODUCT INFORMATION:
Each Levoxyl tablet contains synthetic crystalline levothyroxine sodium (L-thyroxine). L-thyroxine is the principle hormone secreted by the normal thyroid gland. The principal effect of thyroid hormones is to increase the metabolic rate of most body tissues. The thyroid hormones

are also concerned with growth and development of tissues in the young and are particularly important for the developing nervous system. Levoxyl tablets are indicated as replacement therapy for any form of diminished or absent thyroid function, a means of suppressing pituitary secretion of TSH in euthyroid patients in order to treat or prevent the recurrence of various types of goiter and as part of the management of thyroid cancer, [redacted] In healthy adults with primary hypothyroidism, the recommended initial dosage is 25 to 100 mcg daily, while the predicted maintenance dose of 100 to 200 mcg daily may be achieved in several months. Levoxyl tablets are available in 12 strengths: 25, 50, 75, 88, 100, 112, 125, 137, 150, 175, 200, and 300 mcg.

II. RISK ASSESSMENT

A. AERS/DORS DATABASE SEARCHES

Since Levoxyl is a marketed product, the steps in this review included searches in *the FDA Adverse Event Reporting System (AERS)* for any post-marketing safety reports of medication errors associated with Levoxyl products, using the Meddra Higher Level Terminology, "Drug Maladministration" and the drug names, "Levoxyl %" and "levothyroxine %". The *Drug Quality Reporting System (DQRS)* database was also searched for medication error reports with the search terms, "Levoxyl %" and "levothyroxine %".

These searches revealed ten (10) medication error reports involving Levoxyl. Three (3) of these reports involved Levoxyl and Lanoxin (digoxin). In two of these three cases, physicians wrote prescriptions for Levoxyl using the *old* name, *Levoxine*, which was interpreted by two pharmacists and a nurse as Lanoxin. However, these events occurred near the time of the name change from Levoxine to Levoxyl. The third report indicated that the names, Levoxyl and Lanoxin, are similar and that mistakes could be made.

Of the seven (7) remaining medication error reports, there were four (4) accounts of dispensing errors between Levoxyl and the following drugs: Lescol, Synthroid (2), and Zoloft. The last three (3) reports described the similarity in tablet appearance between Levoxyl and Monopril, and the difficulty of distinguishing the various Levoxyl strengths due to their similar labeling and packaging. The results are listed in Tables I & II. *(See Appendix A for full text narratives of these medication error reports.)*

Table I (Errors involving Levoxyl)

	Intended	Dispensed	Cause	Outcome	AERS/DQRS #
1	Levoxyl	Lanoxin	Name confusion: prescribed Levoxine instead of Levoxyl. Then Levoxine confused with Lanoxin	No harm: drug not taken	41735
2	Levoxyl	Lanoxin	Name confusion: prescribed Levoxine instead of Levoxyl. Then Levoxine confused with Lanoxin	No harm: drug taken	42106
3	Levoxyl	Lanoxin	Verbal miscommunication leads to dispensing Lanoxin instead of Levoxyl	Not reported	125621
4	Levoxyl	Lescol	Dispensing error due to lack of attention	No harm: drug taken	42047
5	Synthroid	Levoxyl	Dispensing error: cause not reported	No harm	80850
6	Synthroid or generic equivalent	Levoxyl	Written miscommunication: wrong strength dispensed	No harm: drug not taken	80515

7	Zoloft	Levoxyl	Dispensing error due to busy workload	No harm: drug not taken	3508625-2

Table II (Labeling & packaging concerns of Levoxyl products)

	Safety Concern	Type of error	AERS/DQRS #
1	Labeling is small, easy to confuse the strengths	Potential error	3445174-4
2	Similar labeling and packaging for different Levoxyl strengths	Potential error	3538179-6
3	Similar tablet shape and color between Monopril and Levoxyl	Potential error	50308

B. SAFETY EVALUATOR RISK ASSESSMENT

The review of the post-marketing medication error reports revealed three (3) accounts of name confusion involving Levoxyl and Lanoxin. However, in two of these three cases, the confusion was *not* due to the name similarity between Levoxyl and Lanoxin. The errors were due to the use of the old name, *Levoxine*, instead of Levoxyl by physicians who were not applying the name change in prescribing the drug. Moreover, these two cases were reported near the time of the name change from Levoxine to Levoxyl. The third report, however, indicated that the names, Levoxyl and Lanoxin, were *actually* confused for one another when a verbal prescription was ordered. Given that this is a single report of such name confusion and no additional reports were submitted since 1997, there is insufficient evidence to conclude that the safety risk of name confusion between Levoxyl and Lanoxin warrants a name change at this time. However, continued monitoring of post-marketing reports will be conducted.

Other medication error reports involving Levoxyl revealed dispensing errors, primarily due to the busy workload at the pharmacy or the lack of attention to detail when filling the prescription. Other causes for dispensing errors, particularly involving Synthroid, were not clearly identified. Since Synthroid is another levothyroxine product, the confusion could have occurred during a drug substitution for a generic equivalent or during the dispensing of an unusual prescribed dosage strength.

In addition, there were two reports that addressed the potential for medication errors due to the labeling and packaging similarities of the different Levoxyl strengths. The safety concern is that the colors used for the various strengths are similar, and that the labeling is too small to make a clear distinction of the different strengths. Another reporter also stated that Levoxyl and Monopril (fosinopril) tablets are similar in color and shape. These three reports were accounts of potential errors and did not result in adverse events. The recommendations for labeling changes are described in section IV of this review.

In conclusion, the above post-marketing accounts of name confusion did not reveal a consistent pattern of errors, and it is difficult to assess the magnitude of the name confusion between Levoxyl and other approved drug names in current practice from the limited number of medication error reports. OPDRA will continue to monitor post-marketing medication errors in association with the proprietary name, Levoxyl. However, based on the above mentioned reports, OPDRA has no objections to the use of the proprietary name, Levoxyl, at this time.

III. SAFETY RELATED PACKAGING AND LABELING ISSUES

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

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

IV. RECOMMENDATIONS

A. OPDRA has no objections to the use of the proprietary name, Levoxyl, at this time.

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 Sammie Beam at (301) 827-3161.

/S/

Lauren Lee, Pharm.D.
Safety Evaluator
Office of Post-Marketing Drug Risk Assessment

Concur:

/S/ 10/24/2000

Jerry Phillips, RPh
Associate Director for Medication Error Prevention
Office of Post-Marketing Drug Risk Assessment

APPENDIX I

(The following narratives were transcribed from the medication error reports that were submitted. Therefore, the description of the events may not be complete or relevant in all cases. Furthermore, since all reports do not provide the date of events, other dates (such as the date that the report was written or when it was received by MedWatch/USP/ISMP/DQRS) are listed below.)

A. Medication Error Reports of Name Confusion Involving Levoxyl and Lanoxin

- DQRS: U# 41735 (Date of Event 9/19/95)
  A physician wrote a prescription for Levoxyl using the old name, Levoxine. A pharmacist filled the prescription with Lanoxin for a 63 year old patient. The patient discovered the error.

- DQRS: U# 42106 (Date of Report 10/2/96)
  In a hospital setting, a physician ordered Levoxine 0.75 mg instead of Levoxyl 0.75 mg. A nurse interpreted as Lanoxin 0.25 mg. A pharmacist interpreted the order as Lanoxin as well and spoke to the nurse by phone that he was in doubt. The nurse said it was an order for Lanoxin. The pharmacist filled the order and Lanoxin was dispensed. The patient received four doses. The error was discovered by another pharmacist who was checking the administered doses of the unit dose cart. The physician was alerted about the change in the name of the drug, and the pharmacist was instructed to call the physician if he has any doubt.

- DQRS: M# 125621 (Date Received 12/17/97)
  A physician reported that a telephone renewal of Levoxyl was requested and the pharmacy dispensed Lanoxin. The reporter stated that the names are sufficiently similar so that this mistake is easily made. The patient reported that "she was taking her thyroid pills."

B. Dispensing Error Report Involving Levoxyl and Lescol

- DQRS: U# 42047 (Date of Report 8/3/96)
  A patient went to a retail pharmacy for a refill of her prescription. However, the pharmacist dispensed Lescol instead of Levoxyl. According to the reporter, the error was likely due to "inattention". No apparent adverse effects were reported.

C. Dispensing Error Reports Involving Levoxyl and Synthroid

- DQRS: U# 80850 (Date of Event 12/19/95)
  According to the reporter, Levoxyl 0.5 mcg was dispensed instead of Synthroid 0.17 mcg. No harm resulted from this dispensing error.

- DQRS: U# 80515 (Date of Event 12/23/95)
  A prescription for Synthroid 0.25 mg or its generic equivalent was dispensed with Levoxyl 0.025 mg. The pharmacist made an assumption that the physician meant to write 0.25 mg because Synthroid and its generic equivalent does not come in 0.25 mg strength. The error was discovered by the patient who has been taking 0.25 mg for several months.

D. Dispensing Error Report Involving Levoxyl and Zoloft

- AERS: ISR# 3508625-2 (Date of Event 1/12/00)
  Levoxyl tablets were in a prescription vial labeled Zoloft 100 mg. According to the reporter, the mixed-up occurred on their busiest day at a retail pharmacy when 20-30 prescriptions were all on the counter. The medication was not taken internally by a patient as the patient recognized the different shape and color. A prescription error course was recommended by the commission of pharmacy.

E. Medication Error Report Involving Levoxyl and Monopril

- DQRS: U# 50308 (Date of Report 7/9/97)
  The reporting pharmacist was alerted to the problem by a patient complaint. The patient brought to her attention that the tablet shapes of Monopril and Levoxyl are very similar and could easily be mistaken for the other. Because of her poor eye sight, the patient told the reporter that this is very problematic and a constant source of worry. The patient hopes this report may provoke a change in the tablet shape by either manufacturer in hopes of promoting good health. Also, the reporter stated that the color of the tablets is similar. Levoxyl is light beige in color and Monopril is white.

F. Medication Error Reports Involving the Labeling and Packaging of Levoxyl

- AERS: ISR# 3445174-4 (Date of Report 1/11/00)
  According the reporter, the labeling for Levoxyl is so small and it is very easy to mistake the strength and drug.

- AERS: ISR# 3538179-6 (Date of Report 7/31/00)
  According to the reporter, Levoxyl 0.112 mg and 0.2 mg look very similar in terms of its color. The bottles also look similar, and the NDC numbers are close for the two strengths.

MEMORANDUM

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

DATE: May 15, 2001

TO: File for NDA 21-301

FROM: Steve McCort, Project Manager

SUBJECT: Response to Package labeling Recommendations from OPTRA review for NDA 21-301, Levoxyl.

The Division of Metabolic and Endocrine Products, HfD-510, reviewed the labeling recommendations for the package labeling dated July 28, 2000, from the OPTRA review dated October 24, 2000. (see enclosed copy of the review. The Division did not agree to incorporate the revisions proposed by OPTRA. The labeling submitted in draft for the package labeling dated July 28, 20000,will incorporate no additional changes in the labeling. (see Dr. David Lewis's comments).

/S/ 5-15-2001

Steve McCort, Project Manager, HFD-510

Concurrence: D Lewis 5-14-01/J Temeck 5-14-01/ D Orloff 5-14-01

MEMORANDUM

APPEARS THIS WAY
ON ORIGINAL

NDA 21-301

AUG 1 2000

Jones Pharma Incorporated
Attention: Nancy Cafmeyer
Vice President, Regulatory Affairs
1945 Craig Rd.
St. Louis, Missouri 63146

Dear Ms. Cafmeyer:

We have received your new drug application (NDA) submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act for the following:

Name of Drug Product:	Levoxyl (levothyroxine sodium) Tablets, 25, 50, 75, 88, 100, 112, 125, 137, 150, 200, and 300 mcg
Therapeutic Classification:	Standard (S)
Date of Application:	July 28, 2000
Date of Receipt:	July 28, 2000
Our Reference Number:	NDA 21-301

Unless we notify you within 60 days of our receipt date that the application is not sufficiently complete to permit a substantive review, this application will be filed under section 505(b) of the Act on September 26, 2000, in accordance with 21 CFR 314.101(a). If the application is filed, the primary user fee goal date will be May 28, 2001, and the secondary user fee goal date will be July 28, 2001.

Be advised that, as of April 1, 1999, all applications for new active ingredients, new dosage forms, new indications, new routes of administration, and new dosing regimens are required to contain an assessment of the safety and effectiveness of the product in pediatric patients unless this requirement is waived or deferred (63 *FR* 66632). If you have not already fulfilled the requirements of 21 CFR 314.55 (or 601.27), please submit your plans for pediatric drug development within 120 days from the date of this letter unless you believe a waiver is appropriate. Within approximately 120 days of receipt of your pediatric drug development plan, we will review your plan and notify you of its adequacy.

If you believe that this drug qualifies for a waiver of the pediatric study requirement, you should submit a request for a waiver with supporting information and documentation in accordance with the provisions of 21 CFR 314.55 within 60 days from the date of this letter. We will make a determination whether to grant or deny a request for a waiver of pediatric studies during the review of the application. In no case, however, will the determination be made later than the date action is taken on the application. If a waiver is not granted, we will ask you to submit your pediatric drug development plans within 120 days from the date of denial of the waiver.

Pediatric studies conducted under the terms of section 505A of the Federal Food, Drug, and Cosmetic Act may result in additional marketing exclusivity for certain products (pediatric exclusivity). You should refer to the *Guidance for Industry on Qualifying for Pediatric Exclusivity* (available on our web site at www.fda.gov/cder/pediatric) for details. If you wish to qualify for pediatric exclusivity you should submit a "Proposed Pediatric Study Request" (PPSR) in addition to your plans for pediatric drug development described above. We recommend that you submit a Proposed Pediatric Study Request within 120 days from the date of this letter. If you are unable to meet this time frame but are interested in pediatric exclusivity, please notify the division in writing. FDA generally will not accept studies submitted to an NDA before issuance of a Written Request as responsive to a Written Request. Sponsors should obtain a Written Request before submitting pediatric studies to an NDA. If you do not submit a PPSR or indicate that you are interested in pediatric exclusivity, we will review your pediatric drug development plan and notify you of its adequacy. Please note that satisfaction of the requirements in 21 CFR 314.55 alone may not qualify you for pediatric exclusivity. FDA does not necessarily ask a sponsor to complete the same scope of studies to qualify for pediatric exclusivity as it does to fulfill the requirements of the pediatric rule.

Please cite the NDA number listed above at the top of the first page of any communications concerning this application. All communications concerning this NDA should be addressed as follows:

U.S. Postal Service/Courier/Overnight Mail:

Food and Drug Administration
Center for Drug Evaluation and Research
Division of Metabolic and Endocrine Drug Products, HFD-510
Attention: Division Document Room, 14B-19
5600 Fishers Lane
Rockville, Maryland 20857

If you have any questions, call Steve McCort, Regulatory Project Manager, at (301) 827-6415.

Sincerely,

/S/

Enid Galliers
Chief, Project Management Staff
Division of Metabolic and Endocrine Drug Products
Office of Drug Evaluation II
Center for Drug Evaluation and Research

APPEARS THIS WAY
ON ORIGINAL

DUPLICATE

JONES PHARMA INCORPORATED
1945 Craig Road, P.O. Box 46903
St. Louis, Missouri 63146
314 576-6100 Fax 314 469-5749
www.jmedpharma.com

March 19, 2001

VIA FEDERAL EXPRESS

John Jenkins, M.D. Acting Director
Division of Metabolism and Endocrine Drug Products (HFD-510)
Document Control Room 14B-19
Food and Drug Administration
5600 Fishers Lane
Rockville, MD 20857

N 000 BC
NDA ORIG AMENDMENT

RE: Amendment to NDA 21-301
Levoxyl (Levothyroxine Sodium Tablets, USP)

Dear Dr. Jenkins:

JONES PHARMA INCORPORATED is hereby submitting an amendment to our pending New Drug Application (NDA) for Levoxyl (Levothyroxine Sodium Tablets, USP) submitted July 28, 2000.

According to the Guidance for Industry – Levothyroxine Sodium Questions and Answers published by the Agency in February 2001, now that an NDA has been approved for levothyroxine sodium tablets and there is a listed drug (Unithroid), applications that have been submitted or filed, but not yet approved, must be amended to contain a patent certification for each patent listed for the listed drug.

By this letter, JONES PHARMA INCORPORATED certifies that in the opinion of and to the best of its knowledge there are no patents that claim the drug or drugs on which investigations that are relied upon in this application were conducted or that claim a use of such drug or drugs

This application consists of a single volume. An archival copy is being filed in a blue folder and a technical review copy is being filed in a red folder. By this letter it is certified that a true copy of this amendment (including a copy of FDA application form 356h and a certification that the contents are a true copy of the amendment filed with the Center for Drug Evaluation and Research) was sent to the Kansas City District office of the FDA. This "field copy" was contained in a burgundy folder.

Amendment to NDA 21-301
Levoxyl (Levothyroxine Sodium Tablets, USP)

We look forward to the approval of this NDA. Should any additional information be required, please do not hesitate to contact me at (314) 576-6100 ext. 3070.

Sincerely,
JONES PHARMA INCORPORATED
(A wholly owned subsidiary of King Pharmaceuticals, Inc.)

-Nancy Cafmeyer

Nancy Cafmeyer
Director, Regulatory Affairs

APPEARS THIS WAY
ON ORIGINAL