

021-342-5003.pdf

**CENTER FOR DRUG EVALUATION AND RESEARCH**

**APPROVAL PACKAGE FOR:**

**APPLICATION NUMBER(S)**

**21-342/S-003**

**Trade Name:** Levo-T Tablets

**Generic Name(s):** (levothyroxine sodium)

**Sponsor:** Alara Pharmaceuticals, Inc.

**Agent:**

**Approval Date:** June 23, 2004

**Indication:** Demonstrates bioequivalence between Levo-T and Levoxyl in order to obtain an AB rating

**CENTER FOR DRUG EVALUATION AND  
RESEARCH**

**APPLICATION NUMBER:**

**21-342-S-003**

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**APPROVAL PACKAGE FOR:**

**APPLICATION NUMBER**

**21-342/S-003**

**Approval Letter(s)**



DEPARTMENT OF HEALTH & HUMAN SERVICES

Public Health Service

Food and Drug Administration  
Rockville, MD 20857

NDA 21-342/S-003

Alara Pharmaceuticals, Inc.  
Attention: Mayra Garcia  
Senior Regulatory Affairs Associate  
P.O. Box 7439  
Caguas, Puerto Rico 00726

Dear Ms. Garcia:

Please refer to your supplemental new drug application dated March 31, 2003, received April 2, 2003, submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act for Levo-T (levothyroxine sodium tablets, USP).

We acknowledge receipt of your submissions dated April 9, May 29, and November 19, 2003.

This supplemental new drug application proposes to demonstrate bioequivalence between Levo-T and Levoxyl in order to obtain an AB rating.

We have determined your Levo-T (levothyroxine sodium tablets, USP) 25, 50, 75, 88, 100, 112, 125, 137, 150, 175, 200, and 300 mcg tablets to be bioequivalent and therapeutically equivalent to the listed drug Levoxyl (levothyroxine sodium tablets, USP) 25, 50, 75, 88, 100, 112, 125, 137, 150, 175, 200, and 300 mcg tablets.

Our review concludes that the data establish bioequivalence between these products, and this supplement is approved. However, your supplement requested an "AB" rating for interchangeability between Levo-T and Levoxyl. That decision will be made by the Office of Generic Drugs, and any change in the rating of this product will be listed in the next monthly supplement to the "Approved Drug Products with Therapeutic Equivalence Evaluations" list (the "Orange Book") published by the Agency.

In addition, submit three copies of the introductory promotional materials that you propose to use for this product. Submit all proposed materials in draft or mock-up form, not final print. Send one copy to the Division of Metabolic and Endocrine Drug Products and two copies of both the promotional materials and the package insert directly to:

Division of Drug Marketing, Advertising, and Communications, HFD-42  
Food and Drug Administration  
5600 Fishers Lane  
Rockville, MD 20857

If you issue a letter communicating important information about this drug product (i.e., a "Dear Health Care Professional" letter), we request that you submit a copy of the letter to this NDA and a copy to the following address:

MEDWATCH, HFD-410  
FDA  
5600 Fishers Lane  
Rockville, MD 20857

We remind you that you must comply with reporting requirements for an approved NDA (21 CFR 314.80 and 314.81).

If you have any questions, call Oluchi Elekwachi, Pharm.D., M.P.H., Regulatory Project Manager, at (301) 827-6381.

Sincerely,

  
*{See appended electronic signature page}*

David G. Orloff, M.D.  
Director  
Division of Metabolic and Endocrine Drug Products  
Office of Drug Evaluation II  
Center for Drug Evaluation and Research

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

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David Orloff

6/23/04 04:23:20 PM

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**APPROVAL PACKAGE FOR:**

**APPLICATION NUMBER**

**21-342/S-003**

**Medical Review(s)**

**MEMO TO FILE**

**NDA:** 21-342/SE4-003  
**Sponsor:** Alara  
**Drug Name:** Levo-T  
**Date of Submission:** March 31, 2003  
**Subject:** Review of Financial Disclosure Information

In compliance with 21 CFR 54.2, the sponsor has submitted financial disclosure information for all clinical investigators participating in clinical studies whose results are relied upon for the approval of this supplement.

I have reviewed the documents submitted and all investigators have provided statements denying the following:

- entering into any financial arrangements with the sponsor of the clinical trial
- receiving significant payments of other sorts
- holding proprietary interest in the tested product
- having significant equity interest in the sponsor of the clinical trial

The sponsor has provided sufficient information for this reviewer to conclude that there are no financial conflicts of interest on the part of the investigator(s) to question the integrity of the data submitted.

**APPEARS THIS WAY  
ON ORIGINAL**

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

-----  
Mary Parks  
6/15/04 02:23:58 PM  
MEDICAL OFFICER

Levo-T™ (Levothyroxine Sodium Tablets, USP)

NDA 21-342

ALARA Pharmaceutical Corporation

Prior Approval Supplement

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## BIOAVAILABILITY/BIOEQUIVALENCE

### B. Financial Certification/Disclosure Statement

Completed FDA Form 3454 Certification: Financial Interests and Arrangements of Clinical Investigators is provided with the corresponding attachment.

We are also including Financial Disclosure signed by the Clinical Investigator at [redacted] who participated in Project AA01991.

APPEARS THIS WAY  
ON ORIGINAL

# 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).

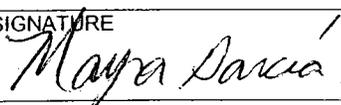
Please mark the applicable checkbox.

- (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 Mayra García	TITLE Sr. Reg. Affairs Associate
FIRM / ORGANIZATION ALARA Pharmaceutical Corporation	
SIGNATURE 	DATE 3/31/03

### 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

Levo-T™ (Levothyroxine Sodium Tablets, USP)

NDA 21-342

ALARA Pharmaceutical Corporation

Prior Approval Supplement

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ATTACHMENT TO FORM FDA 3454

CLINICAL INVESTIGATOR

[

]

**CERTIFICATION/DISCLOSURE FORM**  
**Financial Disclosure by Clinical Investigators**

Study Name: Comparative, Randomized, Single-Dose, 2-way Crossover Bioavailability Study of MOVA Pharmaceutical (Levo-T®) and Jones Pharma (Levoxyl®) 300 mcg Levothyroxine Sodium Tablets in Healthy Adult Volunteers under Fasting Conditions Following Administration of a 600 mcg Dose

Protocol number: AA01991

3. Investigator  Subinvestigator

4. Investigator/subinvestigator Name: \_\_\_\_\_

5. Address: \_\_\_\_\_

6. Telephone: \_\_\_\_\_ 7. Fax: \_\_\_\_\_

8. Indicate by marking Yes or No if any of the financial interests or arrangements with \_\_\_\_\_ of concern to FDA (and describe below) apply to you, your spouse, or dependent children:

Yes <input type="checkbox"/>	No <input type="checkbox"/>	Financial Arrangements whereby the value of the compensation could be influenced by the outcome of the study. This could include, for example, compensation that is explicitly greater for a favorable outcome, or compensation to the investigator in the form of an equity interest in the sponsor or in the form of compensation tied to sales of the product such as a royalty interest.  If yes, please describe: _____ _____
---------------------------------	--------------------------------	--

Yes <input type="checkbox"/>	No <input type="checkbox"/>	Significant payments of other sorts, excluding the costs of conducting the study or other clinical studies. This could include, for example, payments received by the investigator to support activities that have a monetary value greater than \$25,000 (i.e. a grant to the investigator or the institution to fund ongoing research, compensation in the form of equipment, or retainers for ongoing consultation or honoraria).  If yes, please describe: _____ _____
---------------------------------	--------------------------------	--

Yes <input type="checkbox"/>	No <input type="checkbox"/>	A proprietary or financial interest in the test product such as a patent, trademark, copyright, or licensing agreements.  If yes, please describe: _____ _____
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Yes <input type="checkbox"/>	No <input type="checkbox"/>	A significant equity interest in the sponsor of the study. This would include, for example, any ownership interest stock options, or other financial interest whose value cannot be easily determined through reference to public prices, or any equity interest in a publicly traded company exceeding \$50,000.  If yes, please describe: _____ _____
---------------------------------	--------------------------------	---

I hereby certify that none of the financial interest or arrangements listed above exist for myself, my spouse, or my dependent children.

In accordance with 21 CFR Parts 54.1 to 54.8, I declare that the information provided on this form is, to the best of my knowledge and belief, true, correct, and complete. Furthermore, if my financial interests and arrangements, or those of my spouse and dependent children, change from the information provided above during the course of the study or within one year of the last patient has completed the study as specified in the protocol, I will notify (company name) promptly.

9. Name: (please print) **ISI**

Signature \_\_\_\_\_ 10. Date **3 Sep 2002**

**Levo-T™ (Levothyroxine Sodium Tablets, USP)**

**NDA 21-342**

**ALARA Pharmaceutical Corporation**

**Prior Approval Supplement**

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**BIOAVAILABILITY/BIOEQUIVALENCE**

- C. Study AA01991 - Comparative, Randomized, Single-Dose, 2-Way Crossover Bioavailability Study of MOVA Pharmaceutical (Levo-T™) and Jones Pharma (Levoxyl®) 300 mcg Levothyroxine Sodium Tablets in Healthy Adult Volunteers Under Fasting Conditions Following Administration of a 600 mcg Dose**

Labeled diskettes containing electronic files of the concentration and PK data generated by this study along with hard copies are provided in the Archival and Review Copy immediately following this page.

**APPEARS THIS WAY  
ON ORIGINAL**

**CENTER FOR DRUG EVALUATION AND RESEARCH**

**APPROVAL PACKAGE FOR:**

**APPLICATION NUMBER**

**21-342/S-003**

**Clinical Pharmacology and Biopharmaceutics  
Review**

**OFFICE OF CLINICAL PHARMACOLOGY AND BIOPHARMACEUTICS  
REVIEW**

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NDA: 21-342  
 Submission Date(s): April 02, 2003, November 19, 2003  
 Brand Name Levo-T™  
 Generic Name Levothyroxine sodium tablets, USP  
 Reviewer Sang M. Chung, Ph.D.  
 Team Leader Hae-Young Ahn, Ph.D.  
 OCPB Division DPE-2  
 OND division Metabolic and Endocrine (HFD-510)  
 Sponsor ALARA Pharmaceuticals, Corp.  
 Submission Type Supplement (S-003) for AB rating  
 Strength(s) 25, 50, 75, 88, 100, 112, 125, 137, 150, 175, 200,  
 and 300 mcg tablets  
 Indication Hypothyroidism and suppression of thyroid-  
 stimulating hormone

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**1 Executive Summary**

The sponsor submitted this supplement to demonstrate interchangeability for Levo-T™ (test) with Levoxyl® (reference) manufactured by Jones Pharma (table 1). The tablet of 0.3mg Levoxyl® is listed as one of reference listed drugs in the Electronic Orange Book as of July 2003.

**Table 1 Information on test and reference products**

	Test	Reference
Name	Levo-T® 0.3 mg tablet	Levoxyl® 0.3 mg tablet
Lot No.	HT4691	7484
Manufactured Date	August 12, 2002	
Exp. Date		September, 2003
Assay*	99.2%	94.0%
Content Uniformity* (mean of 10 tablets)	98.7% (range L J)	94.3% (range L J)

\*: Specification was L J and C J for the assay and the content uniformity (each tablet), respectively.

A comparative bioavailability between two formulations was assessed in an open-label, single dose, crossover study in healthy volunteers (Protocol AA01991). Oral doses of 0.6mg (two 0.3mg tablets) were administered under overnight fasting condition and 18 blood samples (-0.5, -0.25, -0.083, 0.5, 1, 1.5, 2, 2.5, 3, 4, 6, 8, 10, 12, 16, 24, 48, and 72 hours postdose) were obtained including three pre-dose samples for baseline adjustment. There was 35 days washout period between the treatment periods.

Baseline was corrected with the average of the three serum concentrations at -0.5, -0.25, and -0.083 hour prior to dosing in each period. Negative values after the correction were set to zero. Ratios of  $AUC_{0-48}$  and  $C_{max}$  (test/reference), and 90% confidence interval (CI) were calculated with the corrected serum concentrations based on the current recommendation on statistical methods in Guidance for Industry\*\*

- \*\*:
1. Guidance for Industry, Bioavailability and Bioequivalence Studies for Orally Administered Drug Products-General Considerations.
  2. Guidance for Industry; Levothyroxine sodium tablets – In vivo pharmacokinetic and bioavailability studies and in vitro dissolution testing

The *in vivo* study results (n=24) met the current statistical criteria for the BE between the test (Levo-T™) and the reference (Levoxyl®) formulation with  $AUC_{0-48}$  (CI) and  $C_{max}$  (CI) ratios of 97.7 (87.7-108.8) and 101.4 (95.0-108.2), respectively. Results of statistical analyses are summarized in the figure 1 and table 2.

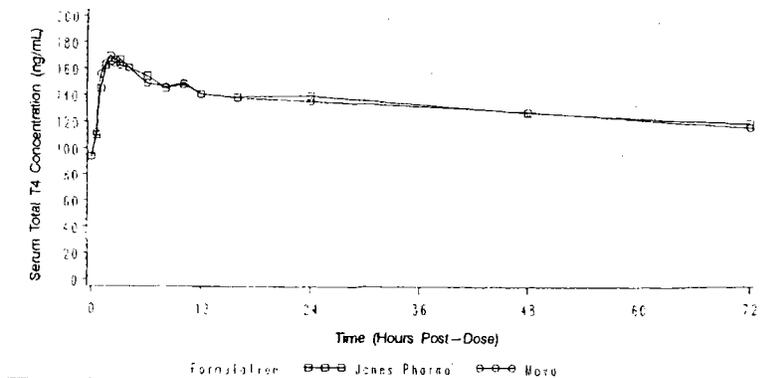


Figure 1 Mean serum total T4 concentration-time profiles of uncorrected data (square is for Levoxyl and circle is for Levo-T)

**Table 2** Statistical results for BE assessment based on the baseline corrected data

Parameter	Ratio of T/R (%)	90% CI
AUC <sub>0-24</sub>	99.6	90.5-109.6
AUC <sub>0-48</sub>	97.7	87.7-108.8
AUC <sub>0-72</sub>	96.7	85.3-110.4
C <sub>max</sub>	101.4	95.0-108.2

Arithmetic means (SD) of baseline adjusted AUC<sub>0-48</sub> were 2154.3 (542.61) and 2199.9 (537.31) ng h/ml for the test and the reference, respectively.

The sponsor indicated that primary exposure data were AUC<sub>0-72</sub>, and others (i.e., AUC<sub>0-24</sub> and AUC<sub>0-48</sub>) were supportive data for BE assessment. It should be noted that the primary recommended exposure data for BE are AUC<sub>0-24</sub> and AUC<sub>0-48</sub>.

The serum total levothyroxine (T4) was analyzed using the [ ] with a validated range of [ ] ng/ml. Three nominal concentrations for QC were [ ] (LQC), [ ] (MQC), and [ ] (HQC) ng/ml. Between-batch accuracy (%nominal) and precision (%CV) are summarized in the following table.

**Table 3** Between-batch precision and accuracy from 11 QC samples

QC (ng/ml)	LQC	MQC	HQC
% nominal	[ ]	[ ]	[ ]
% CV	8.9	5.2	5.4

In addition, the sponsor requested a waiver of *in vivo* bioequivalence (BE) studies for the 25, 50, 75, 88, 100, 112, 125, 137, 150, 175, and 200 microgram strengths by referencing for dosage form equivalence and comparative dissolution data. The review of the original NDA concluded that dosage form equivalence was established among 50, 100, and 300 microgram strengths and dissolution profiles were comparable among all the strengths with proportionality in its active and inactive ingredients. In conclusion, the request of waiver can be granted.

The sponsor conducted a comparative dissolution test between the test and the reference product. However, similarity calculations ( $f_2$ ) per strength for the sameness can not be calculated based on the data (table 4) because of fast dissolution; dissolution of test and reference products showed more than or equal to [ ] at 15 minute.

**Table 4 In-Vitro Dissolution data comparison (mean of 12 tablets)**

Time	Test				Reference			
	5	10	15	20	5	10	15	20
25mcg	79	87	89	87	92	92	92	92
50mcg	91	94	94	94	89	88	88	89
75mcg	77	82	85	85	90	89	89	87
88mcg	87	92	93	93	95	95	95	94
100mcg	92	98	98	96	96	95	95	95
112mcg	84	91	94	95	96	95	95	95
125mcg	86	91	97	98	94	94	94	94
137mcg	88	94	95	96	92	92	92	92
150mcg	89	95	97	96	95	95	95	95
175mcg	87	94	100	100	93	94	93	93
200mcg	83	91	95	95	95	94	93	93
300mcg	82	94	98	99	96	95	95	95

Dissolution conditions were USP apparatus II (paddle) at 50 rpm in 500 ml of 0.01 N HCl containing 0.2% sodium lauryl sulfate. Dissolution specification was that NLT  $\geq$  80% (Q=80%) of levothyroxine sodium was dissolved in 15 minutes.

The Division of Scientific Investigations (DSI) conducted audits of clinical study site and analytical study site, and recommended accepting the data from the study. The transmittal memo from DSI is in the attachment 2.

Optional Intra-Division CPB briefing was held on 3 December, 2003 at 13B17 (Attendee: Drs. Henry Malinowski, John Hunt, Hae-Young Ahn, Solomon Sobel, Sam Haidar, Robert Lionberger, and Sang M. Chung) and it was concluded that there was no major regulatory issues.

**APPEARS THIS WAY  
ON ORIGINAL**

Studies were conducted at the following facilities:

- Clinical study
  - C

1

- Analytical study and statistical analysis
  - C

1

### 1.1 Recommendation

The Office of Clinical Pharmacology and Biopharmaceutics, Division of Pharmaceutical Evaluation II (OCPB/DPE-2) reviewed the supplemental NDA 21-342 S003. and finds it acceptable. This recommendation should be sent to the sponsor as appropriate.

APPEARS THIS WAY  
ON ORIGINAL

List of Attachments

1. Synopsis
2. Transmittal memo from DSI

Attachment starts here.

## 2 Synopsis

300 mcg LEVOTHYROXINE TABLETS  
FINAL REPORT

NO. AA01991

### V. STUDY SYNOPSIS

**TITLE:** Comparative, Randomized, Single-Dose, 2-Way Crossover Bioavailability Study of Mova Pharmaceutical (Levo-T<sup>®</sup>) and Jones Pharma (Levoxyl<sup>®</sup>) 300 mcg Levothyroxine Sodium Tablets in Healthy Adult Volunteers Under Fasting Conditions Following Administration of a 600 mcg Dose.

**Objective:** The objective of this study was to compare the single-dose relative bioavailability of Mova Pharmaceutical (Levo-T<sup>®</sup>) and Jones Pharma (Levoxyl<sup>®</sup>) 300 mcg levothyroxine sodium tablets under fasting conditions following a 600 mcg dose.

**Study Design:** Open-label, randomized, 2-way crossover bioavailability study performed in 24 healthy adult volunteers and 4 alternates (see Subject Disposition and Demographics section of the Clinical Conduct of Study Report in Appendix 6 for exceptions). A total of 27 subjects (19 females and 8 males) completed the crossover. In each period, subjects were housed from at least 10 hours before dosing until after their 24-hour blood draw and returned for the 48- and 72-hour blood draws. Each dose was separated by a washout period of 35 days.

**Methods:** The AUC 0-72, C<sub>max</sub> and t<sub>max</sub> pharmacokinetic parameters were calculated for Total T4 (levothyroxine) in serum. Analyses of variance (ANOVA) and analyses of covariance (ANCOVA) were performed on the ln-transformed Total T4 serum pharmacokinetic parameters AUC 0-72 and C<sub>max</sub>, adjusted and unadjusted for baseline. The ANOVA and ANCOVA model used to reach the conclusions included sequence, period, and drug formulation as fixed effects, and subject nested within sequence, as a random effect. The ANCOVA was performed with the ln-transformed mean baseline as a covariate. The 90% confidence intervals for the ratios of drug formulation were derived by exponentiation of the confidence intervals obtained for the difference between formulation least-squares means (LSM) resulting from the analyses on the ln-transformed AUC 0-72 and C<sub>max</sub> parameters, adjusted and unadjusted for baseline.

As supportive data, AUC 0-24 and AUC 0-48 pharmacokinetic parameters were calculated for Total T4 in serum. ANOVA were performed on the ln-transformed Total T4 in serum pharmacokinetic parameters AUC 0-24 and AUC 0-48, adjusted and unadjusted for baseline. The 90% confidence intervals for the ratios of drug formulation were derived by exponentiation of the confidence intervals obtained for the difference between formulation least-squares means (LSM) resulting from the analyses on the ln-transformed AUC 0-24 and AUC 0-48 parameters, adjusted and unadjusted for baseline.

**Results:** The pharmacokinetic results are listed below for Total T4 in serum:

Mova (A) vs Jones Pharma (B)  
Ratios of LSM (A/B)% (90% Confidence Intervals)  
(ANOVA)

Parameter	Total T4	Total T4 - Baseline Adjusted
AUC 0-72	99.0% (95.9-102.2%)	96.7% (84.5-110.5%)
Cmax	100.1% (96.4-103.8%)	101.4% (95.0-108.2%)

Mova (A) vs Jones Pharma (B)  
Ratios of LSM (A/B)% (90% Confidence Intervals)  
(ANCOVA)

Parameter	Total T4	Total T4 - Baseline Adjusted
AUC 0-72	99.5% (96.8-102.3%)	94.6% (84.4-106.1%)
Cmax	100.6% (97.2-104.0%)	101.1% (94.6%-108.0%)

**Conclusions:** From the ANOVA, the ratios of least-squares means and 90% confidence intervals derived from the analyses of the In-transformed parameters AUC 0-72 and Cmax for Total T4 were within the 80-125% FDA acceptance range. Based on these results, the Mova Pharmaceutical (Levo-T<sup>®</sup>) and Jones Pharma (Levoxyl<sup>®</sup>) 300 mcg levothyroxine sodium tablets are bioequivalent under fasting conditions, following a 600 mcg oral dose. Furthermore, from the ANCOVA, the ratios of least-squares means and 90% confidence intervals derived from the analyses of the In-transformed parameters AUC 0-72 and Cmax for Total T4 were also within the 80-125% FDA acceptance range.

After correction for baseline, the ratios of least-squares means and 90% confidence intervals derived from the analyses of the In-transformed parameters AUC 0-72 and Cmax for Total T4 (from the ANOVA and ANCOVA) were again within the 80-125% FDA acceptance range.

As supportive data, ANOVA were also performed on the In-transformed parameters AUC 0-24 and AUC 0-48 adjusted and unadjusted for baseline. Results showed that the ratios of least-squares means and 90% confidence intervals were also within the 80-125% FDA acceptance range (see Appendix 8).

2 Page(s) Withheld



§ 552(b)(4) Trade Secret / Confidential

§ 552(b)(5) Deliberative Process

§ 552(b)(5) Draft Labeling

**CENTER FOR DRUG EVALUATION AND RESEARCH**

**APPROVAL PACKAGE FOR:**

**APPLICATION NUMBER**

**21-342/S-003**

**Administrative/Correspondence**

Levo-T™ (Levothyroxine Sodium Tablets, USP)  
NDA 21-342  
ALARA Pharmaceutical Corporation  
Prior Approval Supplement

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**PATENT CERTIFICATION**

**NO RELEVANT PATENTS**

In the opinion and to the best knowledge of ALARA Pharmaceutical Corporation, there are no patents that claim the listed drug referred to in this supplement or that claim a use of the listed drug.

Mayra García  
Mayra García  
Sr. Reg. Affairs Associate

3/31/03  
Date

Levo-T™ (Levothyroxine Sodium Tablets, USP)  
NDA 21-342  
ALARA Pharmaceutical Corporation  
Prior Approval Supplement

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**EXCLUSIVITY STATEMENT**

**EXCLUSIVITY STATEMENT**

According to the information published in the Electronic Approved Drug Products with Therapeutic Equivalence Evaluations, current through January 2003, the reference listed drug Levoxyl® (Levothyroxine Sodium Tablets, USP) is not entitled to a period of marketing exclusivity under section 505(j)(4)(D) of the Federal Food, Drug, and Cosmetic Act, as amended.



Mayra Garcia  
Sr. Reg. Affairs Associate



Date

EXCLUSIVITY SUMMARY FOR NDA # 21-342 SUPPL # -003

Trade Name: Levo-T      Generic Name: levothyroxine sodium tablets, USP

Applicant Name: Alara Pharmaceuticals, Inc. HFD # 510

Approval Date If Known \_\_\_\_\_

**PART I IS AN EXCLUSIVITY DETERMINATION NEEDED?**

1. An exclusivity determination will be made for all original applications, and all efficacy supplements. Complete PARTS II and III of this Exclusivity Summary only if you answer "yes" to one or more of the following question about the submission.

a) Is it a 505(b)(1) efficacy supplement?  
YES /X/ NO /\_\_\_/

If yes, what type? Specify 505(b)(1), 505(b)(2), SE1, SE2, SE3, SE4, SE5, SE6, SE7, SE8

SE4

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.

     This supplement sought an AB rating to Levoxyl.

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:

     N/A

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 the answer to the above question in YES, is this approval a result of the studies submitted in response to the Pediatric Written Request?

\_\_\_\_\_

IF YOU HAVE ANSWERED "NO" TO ALL OF THE ABOVE QUESTIONS, GO DIRECTLY TO THE SIGNATURE BLOCKS AT THE END OF THIS DOCUMENT.

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

YES /\_\_\_/ NO /\_\_\_/

IF THE ANSWER TO QUESTION 2 IS "YES," GO DIRECTLY TO THE SIGNATURE BLOCKS ON PAGE 8 (even if a study was required for the upgrade).

## **PART II FIVE-YEAR EXCLUSIVITY FOR NEW CHEMICAL ENTITIES**

(Answer either #1 or #2 as appropriate)

1. Single active ingredient product.

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

YES /\_\_\_/ NO /\_\_\_/

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

NDA# \_\_\_\_\_

NDA# \_\_\_\_\_

NDA# \_\_\_\_\_

2. Combination product.

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

YES /\_\_\_/      NO /\_\_\_/

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

NDA# \_\_\_\_\_

NDA# \_\_\_\_\_

NDA# \_\_\_\_\_

IF THE ANSWER TO QUESTION 1 OR 2 UNDER PART II IS "NO," GO DIRECTLY TO THE SIGNATURE BLOCKS ON PAGE 8. (Caution: The questions in part II of the summary should only be answered "NO" for original approvals of new molecular entities.) IF "YES" GO TO PART III.

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

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

1. Does the application contain reports of clinical

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

YES /\_\_\_/ NO /\_\_\_/

IF "NO," GO DIRECTLY TO THE SIGNATURE BLOCKS ON PAGE 8.

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.

(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 8:

---

(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:

---

---

Studies comparing two products with the same ingredient(s) are considered to be bioavailability studies for the purpose of this section.

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



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 Oluchi Elekwachi, PharmD, MPH  
Title: Regulatory Project Manager

Date 6/15/04

Signature of  
Division Director: David G. Orloff

Date

Form OGD-011347 Revised 05/10/2004

# PEDIATRIC PAGE

(Complete for all filed original applications and efficacy supplements)

DA/BLA #: 21-342 Supplement Type (e.g. SE5): SE4 Supplement Number: -003

Stamp Date: April 2, 2003 Action Date: February 2, 2004

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

Applicant: Alara Pharmaceuticals, Inc. Therapeutic Class: Thyroid

Indication(s) previously approved: 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(s): 2

Indication #1: \_\_\_\_\_

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

- Yes: Please proceed to Section A.
- No: Please check all that apply:  Partial Waiver  Deferred  Completed  
NOTE: More than one may apply  
Please proceed to Section B, Section C, and/or Section D and complete as necessary.

## Section A: Fully Waived Studies

Reason(s) for full waiver:

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

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

## Section B: Partially Waived Studies

Age/weight range being partially waived:

Min \_\_\_\_\_ kg \_\_\_\_\_ mo. \_\_\_\_\_ yr. \_\_\_\_\_ Tanner Stage \_\_\_\_\_  
Max \_\_\_\_\_ kg \_\_\_\_\_ mo. \_\_\_\_\_ yr. \_\_\_\_\_ Tanner Stage \_\_\_\_\_

Reason(s) for partial waiver:

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

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

**Section C: Deferred Studies**

Age/weight range being deferred:

Min \_\_\_\_\_ kg \_\_\_\_\_ mo. \_\_\_\_\_ yr. \_\_\_\_\_ Tanner Stage \_\_\_\_\_  
Max \_\_\_\_\_ kg \_\_\_\_\_ mo. \_\_\_\_\_ yr. \_\_\_\_\_ Tanner Stage \_\_\_\_\_

Reason(s) for deferral:

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

Other: \_\_\_\_\_

Date studies are due (mm/dd/yy): \_\_\_\_\_

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

**Section D: Completed Studies**

Age/weight range of completed studies:

Min \_\_\_\_\_ kg \_\_\_\_\_ mo. \_\_\_\_\_ yr. \_\_\_\_\_ Tanner Stage \_\_\_\_\_  
Max \_\_\_\_\_ kg \_\_\_\_\_ mo. \_\_\_\_\_ yr. \_\_\_\_\_ Tanner Stage \_\_\_\_\_

Comments:

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

This page was completed by:

{See appended electronic signature page}

\_\_\_\_\_  
Regulatory Project Manager

cc: NDA 21-210  
HFD-960/ Grace Carmouze

FOR QUESTIONS ON COMPLETING THIS FORM CONTACT THE DIVISION OF PEDIATRIC DRUG DEVELOPMENT, HFD-960, 301-594-7337.

(revised 12-22-03)

**Attachment A**

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

Indication #2: \_\_\_\_\_

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

- Yes: Please proceed to Section A.
- No: Please check all that apply: \_\_\_ Partial Waiver \_\_\_ Deferred \_\_\_ Completed

NOTE: More than one may apply

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

**Section A: Fully Waived Studies**

Reason(s) for full waiver:

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

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

**Section B: Partially Waived Studies**

Age/weight range being partially waived:

Min \_\_\_\_\_ kg \_\_\_\_\_ mo. \_\_\_\_\_ yr. \_\_\_\_\_ Tanner Stage \_\_\_\_\_  
Max \_\_\_\_\_ kg \_\_\_\_\_ mo. \_\_\_\_\_ yr. \_\_\_\_\_ Tanner Stage \_\_\_\_\_

Reason(s) for partial waiver:

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

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

**Section C: Deferred Studies**

Age/weight range being deferred:

Min \_\_\_\_\_ kg \_\_\_\_\_ mo. \_\_\_\_\_ yr. \_\_\_\_\_ Tanner Stage \_\_\_\_\_  
Max \_\_\_\_\_ kg \_\_\_\_\_ mo. \_\_\_\_\_ yr. \_\_\_\_\_ Tanner Stage \_\_\_\_\_

Reason(s) for deferral:

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

Date studies are due (mm/dd/yy): \_\_\_\_\_

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

**Section D: Completed Studies**

Age/weight range of completed studies:

Min \_\_\_\_\_ kg \_\_\_\_\_ mo. \_\_\_\_\_ yr. \_\_\_\_\_ Tanner Stage \_\_\_\_\_  
Max \_\_\_\_\_ kg \_\_\_\_\_ mo. \_\_\_\_\_ yr. \_\_\_\_\_ Tanner Stage \_\_\_\_\_

Comments:

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

This page was completed by:

*{See appended electronic signature page}*

\_\_\_\_\_  
Regulatory Project Manager

cc: NDA ###-###  
HFD-960/ Grace Carmouze

**FOR QUESTIONS ON COMPLETING THIS FORM CONTACT THE DIVISION OF PEDIATRIC DRUG DEVELOPMENT, HFD-960, 301-594-7337.**

(revised 10-14-03)

**ALARA Pharmaceutical Corporation**

P.O.Box 7439

Caguas, P.R. 00726

Telephone (787) 746-8500

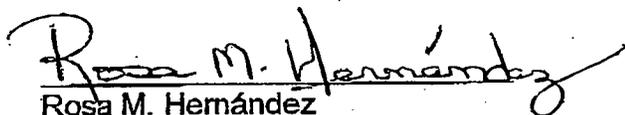
Fax (787) 745-4310

**DEBARMENT CERTIFICATION**

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

ALARA Pharmaceutical also certifies, 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 at any time after submission or approval of this application, ALARA Pharmaceutical Corporation becomes aware of any person employed hereby or any affiliate person/firm is in the process of being debarred, ALARA hereby certifies that it will so notify the Food and Drug Administration immediately.



Rosa M. Hernández

President &amp; COO

ALARA Pharmaceutical Corporation

5/29/03

Date

**MEMORANDUM**

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

DATE: June 22, 2004

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

TO: NDA 21-342/S-003  
Levo-T (levothyroxine sodium) tablets  
Alara Pharmaceuticals Corporation  
Bioequivalence to Levoxyl (Jones Pharma)

SUBJECT: sNDA review issues and recommended action

**Background**

This application was submitted on March 31, 2003, and included the results of a bioequivalence study comparing Levo-T to Levoxyl. The sponsor proposed that the results of the study supported bioequivalence of the test and reference products and that an AB rating in the *Approved Drug Products with Therapeutic Equivalence Evaluations (Orange Book)* publication be granted.

**Biopharmaceutics**

The review by Dr. Chung of OCPB is in the action package. The results of the open-label, single dose, crossover study in healthy volunteers were reviewed and analyzed. The study was conducted according to guidance issued by the Agency. Using the baseline correction method recommended by the Agency (correction with the average of three pre-dose determinations of serum T4 with negative values after correction set to zero), the data clearly demonstrate bioequivalence of the two products. Analysis of the data from the 24 subjects completing the crossover study shows that the 90% confidence intervals for the ratios of levothyroxine AUC (0-24), AUC (0-48), AUC (0-72), and Cmax for Levo-T to Levoxyl are all within the range of 0.8 to 1.25.

The methods validation for the [ ] was acceptable, and the request for a waiver of in vivo bioequivalence studies for the dosage strengths other than the 0.3 mg tablet formally tested was granted based on dosage form equivalence and dissolution data submitted and reviewed with the original NDA for Levo-T.

**DSI/Data Integrity**

DSI conducted audits of the clinical site and of the analytical site found no deficiencies, and recommended that the data be accepted for review.

**Financial disclosure**

NDA # 21-342/S-003  
Drug: Levo-T (LT4, Alara)  
Proposal: AB rating to Levoxyl  
06/22/04

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.

**Recommendation**

In concurrence with the conclusions of the review by OCPB, the Division will approve this sNDA and recommends the granting of AB rating of Levo-T to Levoxyl by the Office of Generic Drugs.

**APPEARS THIS WAY  
ON ORIGINAL**

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

-----  
David Orloff  
6/22/04 05:59:10 PM  
MEDICAL OFFICER

# NDA/EFFICACY SUPPLEMENT ACTION PACKAGE CHECKLIST

NDA 21-342	Efficacy Supplement Type SE-4	Supplement Number -003
Drug: Levo-T (levothyroxine sodium, USP)		Applicant: Alara Pharmaceuticals
RPM: Oluchi Elekwachi, Pharm.D., M.P.H.		HFD-510 <span style="float: right;">Phone # 301-827-6381</span>
Application Type: <input checked="" type="checkbox"/> 505(b)(1)		Reference Listed Drug (NDA #, Drug name):
❖ Application Classifications:		
• Review priority		<input checked="" type="checkbox"/> Standard <input type="checkbox"/> Priority
• Chem class (NDAs only)		N/A
• Other (e.g., orphan, OTC)		N/A
❖ User Fee Goal Dates		2FEB04 (as soon as CP issues) <span style="float: right;">6/23/04</span>
❖ Special programs (indicate all that apply)		<input checked="" type="checkbox"/> None Subpart H <input type="checkbox"/> 21 CFR 314.510 (accelerated approval) <input type="checkbox"/> 21 CFR 314.520 (restricted distribution) <input type="checkbox"/> Fast Track <input type="checkbox"/> Rolling Review <input type="checkbox"/> CMA Pilot 1 <input type="checkbox"/> CMA Pilot 2
User Fee Information		
• User Fee		<input type="checkbox"/> Paid
• User Fee waiver		<input type="checkbox"/> Small business <input type="checkbox"/> Public health <input type="checkbox"/> Barrier-to-Innovation <input type="checkbox"/> Other
• User Fee exception		<input type="checkbox"/> Orphan designation <input type="checkbox"/> No-fee 505(b)(2) <input checked="" type="checkbox"/> Other – No Clinical Data
❖ Application Integrity Policy (AIP)		
• Applicant is on the AIP		<input type="checkbox"/> Yes <input checked="" type="checkbox"/> No
• This application is on the AIP		<input type="checkbox"/> Yes <input checked="" type="checkbox"/> No
• Exception for review (Center Director's memo)		
• OC clearance for approval		
❖ Debarment certification: verified that qualifying language (e.g., willingly, knowingly) was not used in certification & certifications from foreign applicants are cosigned by US agent.		<input type="checkbox"/> Verified
❖ Patent		
• Information: Verify that form FDA-3542a was submitted.		N/A
• Patent certification [505(b)(2) applications]: Verify type of certifications submitted.		21 CFR 314.50(i)(1)(i)(A) <input type="checkbox"/> I <input type="checkbox"/> II <input type="checkbox"/> III <input type="checkbox"/> IV  21 CFR 314.50(i)(1) <input type="checkbox"/> (ii) <input type="checkbox"/> (iii)
• For paragraph IV certification, verify that the applicant notified the patent holder(s) of their certification that the patent(s) is invalid, unenforceable, or will not be infringed (certification of notification and documentation of receipt of notice).		<input type="checkbox"/> Verified

❖ Exclusivity (approvals only)	
• Exclusivity summary	X
• Is there an existing orphan drug exclusivity protection for the active moiety for the proposed indication(s)? Refer to 21 CFR 316.3(b)(13) for the definition of sameness for an orphan drug (i.e., active moiety). This definition is NOT the same as that used for NDA chemical classification!	( ) Yes, Application # _____ (X) No
❖ Administrative Reviews (Project Manager, ADRA) (indicate date of each review)	5/24/03
<b>General Information</b>	
❖ Actions	
• Proposed action	(X) AP ( ) TA ( ) AE ( ) NA
• Previous actions (specify type and date for each action taken)	
• Status of advertising (approvals only)	( ) Materials requested in AP letter ( ) Reviewed for Subpart H
❖ Public communications	
• Press Office notified of action (approval only)	( ) Yes (X) Not applicable
• Indicate what types (if any) of information dissemination are anticipated	(X) None ( ) Press Release ( ) Talk Paper ( ) Dear Health Care Professional Letter
❖ Labeling (package insert, patient package insert (if applicable), MedGuide (if applicable))	
• Division's proposed labeling (only if generated after latest applicant submission of labeling)	N/A
• Most recent applicant-proposed labeling	N/A
• Original applicant-proposed labeling	N/A
• Labeling reviews (including DDMAC, DMETS, DSRCS) and minutes of labeling meetings (indicate dates of reviews and meetings)	N/A
• Other relevant labeling (e.g., most recent 3 in class, class labeling)	N/A
❖ Labels (immediate container & carton labels)	
• Division proposed (only if generated after latest applicant submission)	N/A
• Applicant proposed	N/A
• Reviews	N/A
❖ Post-marketing commitments	
• Agency request for post-marketing commitments	N/A
• Documentation of discussions and/or agreements relating to post-marketing commitments	N/A
❖ Outgoing correspondence (i.e., letters, E-mails, faxes)	X
❖ Memoranda and Telecons	X
❖ Minutes of Meetings	
• EOP2 meeting (indicate date)	N/A
• Pre-NDA meeting (indicate date)	N/A
• Pre-Approval Safety Conference (indicate date; approvals only)	N/A
• Other	N/A

❖ Advisory Committee Meeting	
• Date of Meeting	N/A
• 48-hour alert	N/A
❖ Federal Register Notices, DESI documents, NAS/NRC reports (if applicable)	N/A
<b>Summary Application Review</b>	
❖ Summary Reviews (e.g., Office Director, Division Director, Medical Team Leader) <i>(indicate date for each review)</i>	
<b>Clinical Information</b>	
❖ Clinical review(s) <i>(indicate date for each review)</i>	N/A
❖ Microbiology (efficacy) review(s) <i>(indicate date for each review)</i>	N/A
❖ Safety Update review(s) <i>(indicate date or location if incorporated in another review)</i>	N/A
❖ Risk Management Plan review(s) <i>(indicate date/location if incorporated in another rev)</i>	N/A
❖ Pediatric Page (separate page for each indication addressing status of all age groups)	N/A
❖ Demographic Worksheet <i>(NME approvals only)</i>	N/A
❖ Statistical review(s) <i>(indicate date for each review)</i>	N/A
❖ Biopharmaceutical review(s) <i>(indicate date for each review)</i>	4/29/04
❖ Controlled Substance Staff review(s) and recommendation for scheduling <i>(indicate date for each review)</i>	N/A
❖ Clinical Inspection Review Summary (DSI)	
• Clinical studies	N/A
• Bioequivalence studies	3/8/04
<b>CMC Information</b>	
❖ CMC review(s) <i>(indicate date for each review)</i>	N/A
❖ Environmental Assessment	
• Categorical Exclusion <i>(indicate review date)</i>	N/A
• Review & FONSI <i>(indicate date of review)</i>	N/A
• Review & Environmental Impact Statement <i>(indicate date of each review)</i>	N/A
❖ Microbiology (validation of sterilization & product sterility) review(s) <i>(indicate date for each review)</i>	N/A
❖ Facilities inspection (provide EER report)	Date completed: N/A ( ) Acceptable ( ) Withhold recommendation
❖ Methods validation	( ) Completed N/A ( ) Requested ( ) Not yet requested
<b>Nonclinical Pharm/Tox Information</b>	
❖ Pharm/tox review(s), including referenced IND reviews <i>(indicate date for each review)</i>	N/A
❖ Nonclinical inspection review summary	N/A
❖ Statistical review(s) of carcinogenicity studies <i>(indicate date for each review)</i>	N/A
❖ CAC/ECAC report	N/A

3 Page(s) Withheld

       § 552(b)(4) Trade Secret / Confidential

✓ § 552(b)(5) Deliberative Process

       § 552(b)(5) Draft Labeling

**Redacted** 9

**page(s) of trade secret.**

**and/or confidential**

**commercial information**

**(b4)**



ALARA Pharmaceutical Corporation

P.O. Box 7439

Caguas, P.R. 00726

Telephone (787) 746-8500

Fax (787) 745-4310

ORIGINAL

RECEIVED

NOV 20 2003

FDR/CDER

November 19, 2003

David Orloff, M.D., Director  
FDA/CDER/OND/ODE II  
Division of Metabolic and Endocrine Drug Products, HFD-510  
Attention: Fishers Document Room, 8B45  
5600 Fishers Lane  
Rockville, MD 20857

NDA SUPPL AMENDMENT

**NDA 21-342/S-003: Levo-T® (Levothyroxine Sodium Tablets, USP)  
AMENDMENT SUPPLEMENT 003 – BIOPHARMACEUTICS DATA**

Dear Dr. Orloff:

This submission provides for additional data requested by Mr. Sang Chung, Biopharmaceutic Reviewer, in a telephone conversation on the afternoon of November 7, 2003 for our above mentioned supplement.

As requested in the telephone conversation, negative values in the PK data after baseline correction have been recalculated as 0.

An original and review copy is being provided.

If you should require additional information or assistance, please contact me at (787) 746-8500 Ext. 2119 or by fax (787) 745-4310.

Sincerely,

Mayra García  
Sr. Reg. Affairs Associate

Enclosure

DEPARTMENT OF HEALTH AND HUMAN SERVICES  
FOOD AND DRUG ADMINISTRATION

Form Approved: OMB No. 0910-0338  
Expiration Date: August 31, 2005  
See OMB Statement on page 2.

**APPLICATION TO MARKET A NEW DRUG, BIOLOGIC,  
OR AN ANTIBIOTIC DRUG FOR HUMAN USE**

(Title 21, Code of Federal Regulations, Parts 314 & 601)

FOR FDA USE ONLY

APPLICATION NUMBER

**APPLICANT INFORMATION**

NAME OF APPLICANT

ALARA Pharmaceutical Corporation

DATE OF SUBMISSION

November 19, 2003

TELEPHONE NO. (Include Area Code)

787-746-8500

FACSIMILE (FAX) Number (Include Area Code)

787-745-4310

APPLICANT ADDRESS (Number, Street, City, State, Country, ZIP Code or Mail Code, and U.S. License number if previously issued):

P.O. Box 7439  
Caguas, PR 00726

AUTHORIZED U.S. AGENT NAME & ADDRESS (Number, Street, City, State, ZIP Code, telephone & FAX number) IF APPLICABLE

Not applicable

**PRODUCT DESCRIPTION**

NEW DRUG OR ANTIBIOTIC APPLICATION NUMBER, OR BIOLOGICS LICENSE APPLICATION NUMBER (If previously issued) 21-342

ESTABLISHED NAME (e.g., Proper name, USP/USAN name)

Levothyroxine Sodium; L-3,3',5,5',tetraiodothyronine Sodium Salt

PROPRIETARY NAME (trade name) IF ANY

Levo-T®

CHEMICAL/BIOCHEMICAL/BLOOD PRODUCT NAME (If any)

Not applicable

CODE NAME (If any)

Not Applicable

DOSAGE FORM:

Tablet

STRENGTHS: 25 mcg, 50 mcg, 75 mcg, 88 mcg, 100 mcg, 112 mcg, 125 mcg, 137 mcg, 150 mcg, 175 mcg, 200 mcg, 300 mcg

ROUTE OF ADMINISTRATION:

Oral

(PROPOSED) INDICATION(S) FOR USE:

Hypothyroidism and Pituitary TSH Suppression

**APPLICATION INFORMATION**

APPLICATION TYPE

(check one)

NEW DRUG APPLICATION (21 CFR 314.50)

ABBREVIATED NEW DRUG APPLICATION (ANDA, 21 CFR 314.94)

BIOLOGICS LICENSE APPLICATION (21 CFR Part 601)

IF AN NDA, IDENTIFY THE APPROPRIATE TYPE

505 (b)(1)

505 (b)(2)

IF AN ANDA, OR 505(b)(2), IDENTIFY THE REFERENCE LISTED DRUG PRODUCT THAT IS THE BASIS FOR THE SUBMISSION

Name of Drug

Holder of Approved Application

TYPE OF SUBMISSION (check one)

ORIGINAL APPLICATION

AMENDMENT TO PENDING APPLICATION

RESUBMISSION

PRESUBMISSION

ANNUAL REPORT

ESTABLISHMENT DESCRIPTION SUPPLEMENT

EFFICACY SUPPLEMENT

LABELING SUPPLEMENT

CHEMISTRY MANUFACTURING AND CONTROLS SUPPLEMENT

OTHER

IF A SUBMISSION OF PARTIAL APPLICATION, PROVIDE LETTER DATE OF AGREEMENT TO PARTIAL SUBMISSION:

IF A SUPPLEMENT, IDENTIFY THE APPROPRIATE CATEGORY

CBE

CBE-30

Prior Approval (PA)

REASON FOR SUBMISSION

Amendment S-003 (Biopharmaceutics Data)

PROPOSED MARKETING STATUS (check one)

PRESCRIPTION PRODUCT (Rx)

OVER THE COUNTER PRODUCT (OTC)

NUMBER OF VOLUMES SUBMITTED 1

THIS APPLICATION IS

PAPER

PAPER AND ELECTRONIC

ELECTRONIC

**ESTABLISHMENT INFORMATION (Full establishment information should be provided in the body of the Application.)**

Provide locations of all manufacturing, packaging and control sites for drug substance and drug product (continuation sheets may be used if necessary). Include name, address, contact, telephone number, registration number (CFN), DMF number, and manufacturing steps and/or type of testing (e.g. Final dosage form, Stability testing) conducted at the site. Please indicate whether the site is ready for inspection or, if not, when it will be ready.

Refer to original application

**Cross References (list related License Applications, INDs, NDAs, PMAs, 510(k)s, IDEs, BMFs, and DMFs referenced in the current application)**

Refer to original application

This application contains the following items: (Check all that apply)

<input type="checkbox"/>	1. Index
<input type="checkbox"/>	2. Labeling (check one) <input type="checkbox"/> Draft Labeling <input type="checkbox"/> Final Printed Labeling
<input type="checkbox"/>	3. Summary (21 CFR 314.50 (c))
<input type="checkbox"/>	4. Chemistry section
<input type="checkbox"/>	A. Chemistry, manufacturing, and controls information (e.g., 21 CFR 314.50(d)(1); 21 CFR 601.2)
<input type="checkbox"/>	B. Samples (21 CFR 314.50 (e)(1); 21 CFR 601.2 (a)) (Submit only upon FDA's request)
<input type="checkbox"/>	C. Methods validation package (e.g., 21 CFR 314.50(e)(2)(i); 21 CFR 601.2)
<input type="checkbox"/>	5. Nonclinical pharmacology and toxicology section (e.g., 21 CFR 314.50(d)(2); 21 CFR 601.2)
<input type="checkbox"/>	6. Human pharmacokinetics and bioavailability section (e.g., 21 CFR 314.50(d)(3); 21 CFR 601.2)
<input type="checkbox"/>	7. Clinical Microbiology (e.g., 21 CFR 314.50(d)(4))
<input type="checkbox"/>	8. Clinical data section (e.g., 21 CFR 314.50(d)(5); 21 CFR 601.2)
<input type="checkbox"/>	9. Safety update report (e.g., 21 CFR 314.50(d)(5)(vi)(b); 21 CFR 601.2)
<input type="checkbox"/>	10. Statistical section (e.g., 21 CFR 314.50(d)(6); 21 CFR 601.2)
<input type="checkbox"/>	11. Case report tabulations (e.g., 21 CFR 314.50(f)(1); 21 CFR 601.2)
<input type="checkbox"/>	12. Case report forms (e.g., 21 CFR 314.50 (f)(2); 21 CFR 601.2)
<input type="checkbox"/>	13. Patent information on any patent which claims the drug (21 U.S.C. 355(b) or (c))
<input type="checkbox"/>	14. A patent certification with respect to any patent which claims the drug (21 U.S.C. 355 (b)(2) or (j)(2)(A))
<input type="checkbox"/>	15. Establishment description (21 CFR Part 600, if applicable)
<input type="checkbox"/>	16. Debarment certification (FD&C Act 306 (k)(1))
<input type="checkbox"/>	17. Field copy certification (21 CFR 314.50 (i)(3))
<input type="checkbox"/>	18. User Fee Cover Sheet (Form FDA 3397)
<input type="checkbox"/>	19. Financial Information (21 CFR Part 54)
<input checked="" type="checkbox"/>	20. OTHER (Specify) Data Recalculation Requested by Telephone Conversation 11/7/03

**CERTIFICATION**

I agree to update this application with new safety information about the product that may reasonably affect the statement of contraindications, warnings, precautions, or adverse reactions in the draft labeling. I agree to submit safety update reports as provided for by regulation or as requested by FDA. If this application is approved, I agree to comply with all applicable laws and regulations that apply to approved applications, including, but not limited to the following:

1. Good manufacturing practice regulations in 21 CFR Parts 210, 211 or applicable regulations, Parts 606, and/or 820.
2. Biological establishment standards in 21 CFR Part 600.
3. Labeling regulations in 21 CFR Parts 201, 606, 610, 660, and/or 809.
4. In the case of a prescription drug or biological product, prescription drug advertising regulations in 21 CFR Part 202.
5. Regulations on making changes in application in FD&C Act Section 506A, 21 CFR 314.71, 314.72, 314.97, 314.99, and 601.12.
6. Regulations on Reports in 21 CFR 314.80, 314.81, 600.80, and 600.81.
7. Local, state and Federal environmental impact laws.

If this application applies to a drug product that FDA has proposed for scheduling under the Controlled Substances Act, I agree not to market the product until the Drug Enforcement Administration makes a final scheduling decision.

The data and information in this submission have been reviewed and, to the best of my knowledge are certified to be true and accurate.

**Warning:** A willfully false statement is a criminal offense, U.S. Code, title 18, section 1001.

SIGNATURE OF RESPONSIBLE OFFICIAL OR AGENT <i>Mayra Garcia</i>	TYPED NAME AND TITLE Mayra Garcia, Sr. Reg. Affairs Associate	DATE: 11/19/03
---	--	-------------------

ADDRESS (Street, City, State, and ZIP Code) P.O. Box 7439 Caguas, Puerto Rico 00726	Telephone Number ( 787 ) 746-8500 Ext. 2119
--	--

Public reporting burden for this collection of information is estimated to average 24 hours per response, including the time for reviewing instructions, searching existing data sources, gathering and maintaining the data needed, and completing and reviewing the collection of information. Send comments regarding this burden estimate or any other aspect of this collection of information, including suggestions for reducing this burden to:

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

Food and Drug Administration  
CDER (HFD-94)  
12229 Wilkins Avenue  
Rockville, MD 20852

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

**SUMMARY OF RESULTS  
USING A BASELINE ADJUSTMENT METHOD REQUESTED BY THE FDA**

AA01991

**STUDY TITLE:** COMPARATIVE, RANDOMIZED, SINGLE-DOSE, 2-WAY CROSSOVER BIOAVAILABILITY STUDY OF MOVA PHARMACEUTICAL (LEVO-T<sup>®</sup>) AND JONES PHARMA (LEVOXYL<sup>®</sup>) 300 MCG LEVOTHYROXINE SODIUM TABLETS IN HEALTHY ADULT VOLUNTEERS UNDER FASTING CONDITIONS FOLLOWING ADMINISTRATION OF A 600 MCG DOSE

**DATE:** 13/NOV/2003

In the above-mentioned study, the baseline adjustment on serum Total T4 was performed by subtracting the average of the three pre-dose samples (0.5, 0.25 and 0.083 h before dosing) collected in each dosing period from the concentrations at all time points. Negative concentration values that occurred following the baseline adjustment of serum Total T4 post-dose were included in the calculation of the pharmacokinetic (PK) parameters. This method of adjusting baseline concentrations is the most common and consistent approach [ ] for adjusting plasma, serum, and blood concentrations values to baseline values, as per [ ]

However, we have complied with the FDA's request to test an alternate method of baseline adjustment by setting negative values of adjusted Total T4 serum concentrations to zero. The following patient profiles contained negative values for the adjusted Total T4 serum concentrations at the following timepoints:

ID	Period	Time (h)	Adjusted Concentration (ng/mL)
4	1	0.5	-2.0247
13	1	72	-9.2873
19	1	0.5	-1.709
23	2	0.5	-0.246
24	2	0.5	-0.8487

As previously explained, these negative values were set to zero for the purpose of pharmacokinetic and statistical analyses. Statistical outputs are retained on file [ ]

The pharmacokinetic results are listed below for the baseline adjusted Total T4 in serum:

Mova (A) vs Jones Pharma (B)  
Ratios of LSM (A/B)% (90% Confidence Intervals)  
(ANOVA)

Parameter	Total T4 – Baseline Adjusted	
	[ ] Method	FDA Method
AUC 0-24	99.6%(90.5-109.6%)	99.6% (90.5-109.6%)
AUC 0-48	97.7% (87.8-108.8%)	97.7%(87.8-108.8%)
AUC 0-72	96.7% (84.5-110.5%)	97.0% (85.3-110.4%)
Cmax	101.4% (95.0-108.2%)	101.4% (95.0-108.2%)

**SUMMARY OF RESULTS  
USING A BASELINE ADJUSTMENT METHOD REQUESTED BY THE FDA**

L

1AA01991

Mova (A) vs Jones Pharma (B)  
Ratios of LSM (A/B)% (90% Confidence Intervals)  
(ANCOVA)

Parameter	Total T4 – Baseline Adjusted	
	[ ] Method	FDA Method
AUC 0-24	98.3% (90.1-107.3%)	98.3% (90.1-107.3%)
AUC 0-48	96.4% (87.3-106.4%)	96.4% (87.3-106.4%)
AUC 0-72	94.6% (84.4-106.1%)	95.1% (85.1-106.3%)
Cmax	101.1% (94.6%-108.0%)	101.1% (94.6%-108.0%)

The new results for the adjusted serum Total T4 concentrations, presented under the column labelled "FDA method", still meet the standards to determine bioequivalence in this comparative bioavailability study. After correction for baseline using the FDA method, the ratios of least-squares means and 90% confidence intervals derived from the analyses of the ln-transformed parameters AUC 0-72 and Cmax for the adjusted Total T4 (from the ANOVA and ANCOVA) were again within the 80-125% FDA acceptance range.

As supportive data, ANOVA and ANCOVA were performed on the ln-transformed parameters AUC 0-24 and AUC 0-48 adjusted and unadjusted for baseline. Results show that the ratios of least-squares means and 90% confidence intervals were also within the 80-125% FDA acceptance range.

As previously presented in the Final Report for PN AA01991, based on the ANOVA for the unadjusted Total T4, the Mova Pharmaceutical (Levo-T®) and Jones Pharma (Levoxyll®) 300 mcg levothyroxine sodium tablets are bioequivalent under fasting conditions, following a 600 mcg oral dose. The ratios of least-squares means and 90% confidence intervals derived from the analyses of the ln-transformed parameters AUC 0-72 and Cmax for the unadjusted Total T4 were within the 80-125% FDA acceptance range. Furthermore, from the ANCOVA, the ratios of least-squares means and 90% confidence intervals derived from the analyses of the ln-transformed parameters AUC 0-72 and Cmax for the unadjusted Total T4 were also within the 80-125% FDA acceptance range.



**Redacted** 2

**page(s) of trade secret.**

**and/or confidential**

**commercial information**

**(b4)**

**Galliers, Enid M**

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**From:** Galliers, Enid M  
**Sent:** Tuesday, August 26, 2003 7:39 PM  
**To:** 'mayra.garcia@movapharm.com'  
**Cc:** Dettelbach, Kim; Buehler, Gary J  
**Subject:** Regarding FDA request for a patent certification for NDA 21-342/S-004(wrong) ---> S-003

Dear Ms. Garcia: (The firm called back to say that this should have been S-003.)

This message confirms the August 26, 2003, message I left on your voice mail regarding the Agency's response to your inquiry regarding my August 4, 2003, telephone voice mail request to submit a patent certification to pending Supplement-004, which requests an AB rating (therapeutic equivalence) between Alara's Levo-T and Jones Pharmaceuticals' Levoxyl.

Subsequent to the August 12, 2003, phone call between Claribell Velez and you of Mova/Alara Pharmaceuticals and me, a patent certification is not required when an applicant is seeking to establish equivalence between two approved 505(b)(2) applications. Therefore, I am rescinding my request for a patent certification and extend my apologies for the inconvenience.

Very truly yours,

Enid Galliers  
Chief, Project Management Staff  
Division of Metabolic and Endocrine Drug Products, HFD-510  
Office of Drug Evaluation II

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

-----  
Enid Galliers  
9/10/03 06:44:29 PM  
CSO



**ALARA Pharmaceutical Corporation**

P.O. Box 7439  
Caguas, P.R. 00726  
Telephone (787) 746-8500  
Fax (787) 745-4310

May 29, 2003

David Orloff, M.D., Director  
FDA/CDER/OND/ODE II  
Division of Metabolic and Endocrine Drug Products, HFD-510  
Attention: Fishers Document Room, 8B45  
5600 Fishers Lane  
Rockville, MD 20857

**RE: SUPPLEMENT NEW CORRESPONDENCE**  
**NDA 21-342/S-003 - Levo-T<sup>TM</sup> (Levothyroxine Sodium Tablets, USP)**

Dear Dr. Orloff:

Reference is made to correspondence from the Agency dated May 19, 2003, received yesterday May 28, 2003, where Filing Issues were identified for the above mentioned supplement. The following potential review issue was identified:

"This supplemental application does not contain a Debarment Certification."

This new correspondence provides for the submission of a Debarment Certification signed by an authorized official requested in the referenced letter. An archival copy and review copy is provided.

Please contact me if you have questions or need additional information at Ext. 2119.

Sincerely,

A handwritten signature in cursive script that reads "Mayra Garcia".

Mayra Garcia  
Sr. Regulatory Affairs Associate

Enclosure: Debarment Certification

**NDA REGULATORY FILING REVIEW**  
(Including Memo of Filing Meeting)

NDA # **21-342** Supplement # **003** SE4

Trade Name: **Levo-T**  
Generic Name: levothyroxine sodium tablets, USP  
Strengths: (12) 25, 50, 75, 88, 100, 112, 125, 137, 150, 175, 200, 300 mcg

Applicant: **ALARA Pharmaceutical Corp.**

Date of Application: March 31, 2003  
Date of Receipt: April 2, 2003  
Date clock started after UN:  
Date of Filing Meeting: April 30, 2003  
Filing Date: June 1, 2003  
Action Goal Date (optional): **30-OCT-2003** User Fee Goal Date: 02-FEB-2004

CHANGE requested: **To show comparability between Levo-T and Levoxyl and obtain an AB rating**

Type of Application: Original (b)(1) NDA \_\_\_\_\_ Original (b)(2) NDA \_\_\_\_\_  
(b)(1) Supplement \_\_\_\_\_ (b)(2) Supplement   X    
[If the Original NDA was a (b)(2), all supplements are (b)(2)s; if the Original NDA was a (b)(1), the supplement can be either a (b)(1) or a (b)(2).]

NOTE: If the application is a 505(b)(2) application, complete the 505(b)(2) section at the end of this summary.

Therapeutic Classification: S   X   P \_\_\_\_\_  
Resubmission after a withdrawal? \_\_\_\_\_ Resubmission after a refuse to file? \_\_\_\_\_  
Chemical Classification: (1,2,3 etc.)   N/A    
Other (orphan, OTC, etc.) \_\_\_\_\_

User Fee Status: Paid   N/A   Waived (e.g., small business, public health) \_\_\_\_\_  
Exempt (orphan, government) \_\_\_\_\_

Form 3397 (User Fee Cover Sheet) submitted: YES NO  
User Fee ID # N/A  
Clinical data? YES   NO  , Referenced to NDA #   N/A  

Is there any 5-year or 3-year exclusivity on this active moiety in either a (b)(1) or a (b)(2) application?

YES   NO  

If yes, explain:

Does another drug have orphan drug exclusivity for the same indication? YES   NO  

If yes, is the drug considered to be the same drug according to the orphan drug definition of sameness [21 CFR 316.3(b)(13)]?

  N/A   YES NO

Is the application affected by the Application Integrity Policy (AIP)? YES NO  
 If yes, explain.

If yes, has OC/DMPQ been notified of the submission? YES NO

• Does the submission contain an accurate comprehensive index? YES NO

• Was form 356h included with an authorized signature? YES NO  
**If foreign applicant, both the applicant and the U.S. agent must sign.**

• Submission complete as required under 21 CFR 314.50? YES NO  
 If no, explain:

• If an electronic NDA, does it follow the Guidance? N/A YES NO  
**If an electronic NDA, all certifications must be in paper and require a signature.**  
 Which parts of the application were submitted in electronic format?

Additional comments:

• If in Common Technical Document format, does it follow the guidance? N/A YES NO

• Is it an electronic CTD? N/A YES NO  
**If an electronic CTD, all certifications must be in paper and require a signature.**  
 Which parts of the application were submitted in electronic format?

Additional comments:

• Patent information included with authorized signature? YES NO

• Exclusivity requested? YES, \_\_\_\_\_ years NO  
 Note: An applicant can receive exclusivity without requesting it; therefore, requesting exclusivity is not required.

• Correctly worded Debarment Certification included with authorized signature? YES NO  
**If foreign applicant, both the applicant and the U.S. Agent must sign the certification.**

**NOTE:** Debarment Certification must have correct wording, e.g.: "I, the undersigned, hereby certify that \_\_\_\_\_ Co. did not and will not use in any capacity the services of any person debarred under section 306 of the Federal Food, Drug and Cosmetic Act in connection with the studies listed in Appendix \_\_\_\_." Applicant may not use wording such as "To the best of my knowledge . . . ."

• Financial Disclosure information included with authorized signature? YES NO  
**(Forms 3454 and/or 3455 must be used and must be signed by the APPLICANT.)**

• Field Copy Certification (that it is a true copy of the CMC technical section)? YES N/A NO

**Refer to 21 CFR 314.101(d) for Filing Requirements**

- **PDUFA** and Action Goal dates correct in COMIS? YES NO  
 If not, have the document room staff correct them immediately. These are the dates EES uses for calculating inspection dates.
- Drug name/Applicant name correct in COMIS? If not, have the Document Room make the corrections. Y
- List referenced IND numbers: None
- End-of-Phase 2 Meeting(s)? Date(s) \_\_\_\_\_ NO  
 If yes, distribute minutes before filing meeting.
- Pre-NDA Meeting(s)? Date(s) \_\_\_\_\_ NO  
 If yes, distribute minutes before filing meeting.

**Project Management**

- Package insert consulted to DDMAC? N/A YES NO
- Trade name (plus PI and all labels and labeling) consulted to ODS/Div. of Medication Errors and Technical Support? N/A YES NO
- MedGuide and/or PPI (plus PI) consulted to ODS/Div. of Surveillance, Research and Communication Support? N/A YES NO
- If a drug with abuse potential, was an Abuse Liability Assessment, including a proposal for scheduling, submitted? N/A YES NO

**If Rx-to-OTC Switch application:**

- OTC label comprehension studies, all OTC labeling, and current approved PI consulted to ODS/ Div. of Surveillance, Research and Communication Support? N/A YES NO
- Has DOTCDP been notified of the OTC switch application? YES NO

**Clinical**

- If a controlled substance, has a consult been sent to the Controlled Substance Staff? N/A YES NO

**Chemistry**

- Did applicant request categorical exclusion for environmental assessment? YES N/A NO  
 If no, did applicant submit a complete environmental assessment? YES NO  
 If EA submitted, consulted to Nancy Sager (HFD-357)? YES NO
- Establishment Evaluation Request (EER) submitted to DMPQ? YES NO

- If parenteral product, consulted to Microbiology Team (HFD-805)? YES N/A NO

**If 505(b)(2) application, complete the following section:**

- Name of listed drug(s) and NDA/ANDA #: N/A
- Describe the change from the listed drug(s) provided for in this (b)(2) application (for example, "This application provides for a new indication, otitis media" or "This application provides for a change in dosage form, from capsules to solution").

**Requests AB rating to Levoxyl**

- Is the application for a duplicate of a listed drug and eligible for approval under section 505(j) as an ANDA? (Normally, FDA will refuse-to-file such NDAs.) YES NO
- Is the extent to which the active ingredient(s) is absorbed or otherwise made available to the site of action less than that of the reference listed drug (RLD)? (See 314.54(b)(1)). If yes, the application should be refused for filing under 314.101(d)(9). YES N/A NO
- Is the rate at which the product's active ingredient(s) is absorbed or otherwise made available to the site of action unintentionally less than that of the RLD? (See 314.54(b)(2)). If yes, the application should be refused for filing under 314.101(d)(9). YES N/A NO
- Which of the following patent certifications does the application contain? Note that a patent certification must contain an authorized signature.

21 CFR 314.50(i)(1)(i)(A)(1): The patent information has not been submitted to FDA.

21 CFR 314.50(i)(1)(i)(A)(2): The patent has expired.

21 CFR 314.50(i)(1)(i)(A)(3): The date on which the patent will expire.

21 CFR 314.50(i)(1)(i)(A)(4): The patent is invalid, unenforceable, or will not be infringed by the manufacture, use, or sale of the drug product for which the application is submitted.

*IF FILED, and if the applicant made a "Paragraph IV" certification [21 CFR 314.50(i)(1)(i)(A)(4)], the applicant must submit a signed certification that the patent holder was notified the NDA was filed [21 CFR 314.52(b)]. Subsequently, the applicant must submit documentation that the patent holder(s) received the notification ([21 CFR 314.52(e)].*

21 CFR 314.50(i)(1)(ii): No relevant patents.

21 CFR 314.50(i)(1)(iii): The patent on the listed drug is a method of use patent and the labeling for the drug product for which the applicant is seeking approval does not include any indications that are covered by the use patent. Applicant must provide a statement that the method of use patent does not claim any of the proposed indications.

21 CFR 314.50(i)(3): Statement that applicant has a licensing agreement with the patent owner (must also submit certification under 21 CFR 314.50(i)(1)(i)(A)(4) above.)

\_\_\_\_\_ Written statement from patent owner that it consents to an immediate effective date upon approval of the application.

- Did the applicant:
  - Identify which parts of the application rely on information the applicant does not own or to which the applicant does not have a right of reference?  
YES NO
  - Submit a statement as to whether the listed drug(s) identified has received a period of marketing exclusivity?  
N/A YES NO
  - Submit a bioavailability/bioequivalence (BA/BE) study comparing the proposed product to the listed drug? **It compares one approved product to another approved product.**  
N/A YES NO
  - Certify that it is seeking approval only for a new indication and not for the indications approved for the listed drug if the listed drug has patent protection for the approved indications and the applicant is requesting only the new indication (21 CFR 314.54(a)(1)(iv).?  
N/A YES NO
- If the (b)(2) applicant is requesting exclusivity, did the applicant submit the following information required by 21 CFR 314.50(j)(4):
  - Certification that each of the investigations included meets the definition of "new clinical investigation" as set forth at 314.108(a).  
YES NO
  - A list of all published studies or publicly available reports that are relevant to the conditions for which the applicant is seeking approval.  
YES NO
  - EITHER  
The number of the applicant's IND under which the studies essential to approval were conducted.  
YES, IND # 54,672 NO  
OR  
A certification that it provided substantial support of the clinical investigation(s) essential to approval if it was not the sponsor of the IND under which those clinical studies were conducted?  
YES NO
- Has the Director, Div. of Regulatory Policy II, HFD-007, been notified of the existence of the (b)(2) application?  
YES NO

ATTACHMENT

MEMO OF FILING MEETING

DATE: April 30, 2003

BACKGROUND: Unithroid was the first levothyroxine sodium tablets NDA approved. This supplement provides a comparative bioavailability study to obtain an AB rating to Levoxyl.

ATTENDEES: Dr. David Orloff, Dr. Hank Malinowski, Dr. Hae-Young Ahn, Dr. Mamta Gautam-Basak, Dr. Sang Chung, Dr. David Lewis, Enid Galliers.

ASSIGNED REVIEWERS:

<u>Discipline</u>	<u>Reviewer</u>
Medical: (Financial Disclosure only)	J. Temeck
Secondary Medical:	
Statistical:	----
Pharmacology:	----
Statistical Pharmacology:	----
Chemist:	----
Environmental Assessment (if needed):	----
Biopharmaceutical:	Sang Chung
Microbiology, sterility:	----
Microbiology, clinical (for antimicrobial products only):	----
DSI:	Vishwanathan
Regulatory Project Manager:	Enid Galliers
Other Consults:	----

Per reviewers, are all parts in English or English translation? YES NO  
 If no, explain:

CLINICAL FILE \_\_\_\_\_ REFUSE TO FILE \_\_\_\_\_ N/A

- Clinical site inspection needed: YES NO
- Advisory Committee Meeting needed? YES, date if known \_\_\_\_\_ NO
- If the application is affected by the AIP, has the division made a recommendation regarding whether or not an exception to the AIP should be granted to permit review based on medical necessity or public health significance? N/A YES NO

CLINICAL MICROBIOLOGY FILE \_\_\_\_\_ REFUSE TO FILE \_\_\_\_\_ N/A

STATISTICS FILE \_\_\_\_\_ REFUSE TO FILE \_\_\_\_\_ N/A

BIOPHARMACEUTICS FILE X REFUSE TO FILE \_\_\_\_\_

	• Biopharm. inspection needed: (Consult sent)	<u>YES</u>	NO
PHARMACOLOGY	FILE _____	REFUSE TO FILE _____	<u>N/A</u>
	• GLP inspection needed:	YES	NO
CHEMISTRY	FILE _____	REFUSE TO FILE _____	<u>N/A</u>
	• Establishment(s) ready for inspection?	YES	NO
	• Microbiology	YES	NO

ELECTRONIC SUBMISSION:  
Any comments:

REGULATORY CONCLUSIONS/DEFICIENCIES:

\_\_\_\_\_ The application is unsuitable for filing. Explain why:

X The application, on its face, appears to be well organized and indexed. The application appears to be suitable for filing.

\_\_\_\_\_ No filing issues have been identified.

X Filing issues to be communicated by Day 74. List (optional):  
**Submit a debarment statement.**

**ACTION ITEMS:**

1. If RTF, notify everybody who already received a consult request of the RTF action. Cancel the EER.
2. If filed and the application is under the AIP, prepare a letter either granting (for signature by Center Director) or denying (for signature by ODE Director) an exception for review.
3. Document filing issues/no filing issues conveyed to applicant by Day 74. **FI sent 05.19.03**

Enid Galliers  
Chief, Project Management Staff, HFD-510

C:\Data\Wpfiles\FilingSummary2.doc  
LRipper/1-13-03

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

-----  
Enid Galliers  
5/24/03 08:02:14 PM  
CSO

FI 5.19.03



DEPARTMENT OF HEALTH & HUMAN SERVICES

Public Health Service

Food and Drug Administration  
Rockville, MD 20857

**FILING ISSUES IDENTIFIED**

NDA 21-342/S-003

Alara Pharmaceutical Corporation  
Attention: Mayra García  
Senior Regulatory Affairs Associate  
P.O. Box 7439  
Caguas, Puerto Rico 00726

Dear Ms. García:

Please refer to your March 31, 2003, new drug application (NDA) submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act for Levo-T<sup>TM</sup> (levothyroxine sodium tablets, USP).

We also refer to your submission dated April 9, 2003.

We have completed our filing review and have determined that your application is sufficiently complete to permit a substantive review. Therefore, this application will be filed under section 505(b) of the Act on June 1, 2003, in accordance with 21 CFR 314.101(a).

In our filing review, we have identified the following potential review issues:

This supplemental application does not contain a Debarment Certification.

We are providing the above comments to give you preliminary notice of potential review issues. Our filing review is only a preliminary evaluation of the application and is not indicative of deficiencies that may be identified during our review. Issues may be added, deleted, expanded upon, or modified as we review the application.

We request that you submit the following information:

A Debarment Certification signed by an authorized official.

Please respond only to the above requests for additional information. While we anticipate that any response submitted in a timely manner will be reviewed during this review cycle, such review decisions will be made on a case-by-case basis at the time of receipt of the submission.

NDA 21-342

Page 2

If you have any questions, call me at (301) 827-6429.

Sincerely,

*{See  appended electronic signature page}*

Enid Galliers  
Chief, Project Management Staff  
Division of Metabolic and Endocrine Drug Products  
(HFD-510)  
Office of Drug Evaluation II  
Center for Drug Evaluation and Research

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

/s/

-----  
Enid Galliers  
5/19/03 01:27:02 PM



ACK

4.16.03

Food and Drug Administration  
Rockville, MD 20857

NDA 21-342/S-003

**PRIOR APPROVAL SUPPLEMENT**

ALARA Pharmaceutical Corporation  
Attn: Mayra Garcia  
Senior Regulatory Affairs Associate  
P.O. Box 7439  
Caguas, PR 00726

Dear Ms. Garcia:

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

Name of Drug Product:	Levo-T™ (levothyroxine sodium tablets, USP)
NDA Number:	21-342
Supplement number:	S-003
Review Priority Classification:	Standard
Date of supplement:	March 31, 2003
Date of receipt:	April 2, 2003

This supplemental application proposes to demonstrate bioequivalence between Levo-T™ (levothyroxine sodium tablets, USP) 25, 50, 75, 88, 100, 112, 125, 137, 150, 175, 200, and 300 mcg and Levoxyl® (levothyroxine sodium tablets, USP) with the same dosages, in order to obtain an AB rating in the *Approved Drug Products with Therapeutic Equivalence Evaluations* publication.

Unless we notify you within 60 days of the receipt date that the application is not sufficiently complete to permit a substantive review, we will file the application on June 1, 2003 in accordance with 21 CFR 314.101(a). If the application is filed, the user fee goal date will be February 2, 2004.

All communications concerning this supplement 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 & Endocrine Drug Products, HFD-510  
Attention: Fishers Document Room, 8B45  
5600 Fishers Lane  
Rockville, Maryland 20857

If you have any question, call me at (301) 827-6429.

Sincerely,

{See  appended electronic signature page}

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

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

/s/

-----  
Enid Galliers

4/16/03 03:07:36 PM



ORIGINAL

ALARA Pharmaceutical Corporation

P.O. Box 7439  
Caguas, P.R. 00726  
Telephone (787) 746-8500  
Fax (787) 745-4310

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APR 11 2003

FDR/CDER

SUPPL NEW CORRESP

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APR 10 2003

CDR/CDER

SEL 003 C  
SUPPL NEW CORRESP

April 9, 2003

Central Document Room (HFD-94)  
Center for Drug Evaluation and Research  
Food and Drug Administration  
12229 Wilkins Ave.  
Rockville, MD 20852-1833

**RE: AMENDMENT - NDA 21-342 - Levo-T<sup>TM</sup> (Levothyroxine Sodium Tablets, USP)  
BIOEQUIVALENCE SUPPLEMENT 3/31/03  
RESUBMISSION OF ELECTRONIC FILES**

Dear Sir or Madam:

As per fax received on April 3, 2003 from the Electronic Document Room Staff, we are resubmitting one 3.5" floppy disk containing datasets in electronic format for the Bioequivalence Prior Approval Supplement submitted March 31, 2003, along with hard copies.

The disk contains SAS Transport Files for the concentration and PK data (adjusted and unadjusted) for Study AA01991 provided in the supplement.

We hope these files satisfy FDA requirements.

If you have additional requests or comments, please do not hesitate to contact me at Ext. 2119.

Sincerely,

Mayra Garcia  
Sr. Regulatory Affairs Associate

Enclosures: One 3.5" Floppy Disk  
Form FDA 356h

DEPARTMENT OF HEALTH AND HUMAN SERVICES  
FOOD AND DRUG ADMINISTRATION

Form Approved: OMB No. 0910-0338  
Expiration Date: August 31, 2005  
See OMB Statement on page 2.

**APPLICATION TO MARKET A NEW DRUG, BIOLOGIC,  
OR AN ANTIBIOTIC DRUG FOR HUMAN USE**  
(Title 21, Code of Federal Regulations, Parts 314 & 601)

FOR FDA USE ONLY

APPLICATION NUMBER

**APPLICANT INFORMATION**

NAME OF APPLICANT ALARA Pharmaceutical Corporation	DATE OF SUBMISSION April 9, 2003
TELEPHONE NO. (Include Area Code) 787-746-8500	FACSIMILE (FAX) Number (Include Area Code) 787-745-4310
APPLICANT ADDRESS (Number, Street, City, State, Country, ZIP Code or Mail Code, and U.S. License number if previously issued): P.O. Box 7439 Caguas, PR 00726	AUTHORIZED U.S. AGENT NAME & ADDRESS (Number, Street, City, State, ZIP Code, telephone & FAX number) IF APPLICABLE Not applicable

**PRODUCT DESCRIPTION**

NEW DRUG OR ANTIBIOTIC APPLICATION NUMBER, OR BIOLOGICS LICENSE APPLICATION NUMBER (If previously issued) 21-342		
ESTABLISHED NAME (e.g., Proper name, USP/USAN name) Levothyroxine Sodium; L-3,3',5,5',tetraiodothyronine Sodium Salt	PROPRIETARY NAME (trade name) IF ANY Levo-T™	
CHEMICAL/BIOCHEMICAL/BLOOD PRODUCT NAME (If any) Not applicable	CODE NAME (If any) Not Applicable	
DOSAGE FORM: Tablet	STRENGTHS: 25 mcg, 50 mcg, 75 mcg, 88 mcg, 100 mcg, 112 mcg, 125 mcg, 137 mcg, 150 mcg, 175 mcg, 200 mcg, 300 mcg	ROUTE OF ADMINISTRATION: Oral

(PROPOSED) INDICATION(S) FOR USE:

Hypothyroidism and Pituitary TSH Suppression

**APPLICATION INFORMATION**

APPLICATION TYPE (check one) <input checked="" type="checkbox"/> NEW DRUG APPLICATION (21 CFR 314.50) <input type="checkbox"/> ABBREVIATED NEW DRUG APPLICATION (ANDA, 21 CFR 314.94) <input type="checkbox"/> BIOLOGICS LICENSE APPLICATION (21 CFR Part 601)
IF AN NDA, IDENTIFY THE APPROPRIATE TYPE <input type="checkbox"/> 505 (b)(1) <input checked="" type="checkbox"/> 505 (b)(2)
IF AN ANDA, OR 505(b)(2), IDENTIFY THE REFERENCE LISTED DRUG PRODUCT THAT IS THE BASIS FOR THE SUBMISSION Name of Drug _____ Holder of Approved Application _____
TYPE OF SUBMISSION (check one) <input type="checkbox"/> PRESUBMISSION <input type="checkbox"/> ANNUAL REPORT <input type="checkbox"/> ESTABLISHMENT DESCRIPTION SUPPLEMENT <input type="checkbox"/> EFFICACY SUPPLEMENT <input type="checkbox"/> LABELING SUPPLEMENT <input type="checkbox"/> CHEMISTRY MANUFACTURING AND CONTROLS SUPPLEMENT <input type="checkbox"/> OTHER
IF A SUBMISSION OF PARTIAL APPLICATION, PROVIDE LETTER DATE OF AGREEMENT TO PARTIAL SUBMISSION: _____
IF A SUPPLEMENT, IDENTIFY THE APPROPRIATE CATEGORY <input type="checkbox"/> CBE <input type="checkbox"/> CBE-30 <input type="checkbox"/> Prior Approval (PA)
REASON FOR SUBMISSION Amendment – Resubmission of Electronic Files
PROPOSED MARKETING STATUS (check one) <input checked="" type="checkbox"/> PRESCRIPTION PRODUCT (Rx) <input type="checkbox"/> OVER THE COUNTER PRODUCT (OTC)
NUMBER OF VOLUMES SUBMITTED <u>1</u> THIS APPLICATION IS <input type="checkbox"/> PAPER <input checked="" type="checkbox"/> PAPER AND ELECTRONIC <input type="checkbox"/> ELECTRONIC
ESTABLISHMENT INFORMATION (Full establishment information should be provided in the body of the Application.) Provide locations of all manufacturing, packaging and control sites for drug substance and drug product (continuation sheets may be used if necessary). Include name, address, contact, telephone number, registration number (CFN), DMF number, and manufacturing steps and/or type of testing (e.g. Final dosage form, Stability testing) conducted at the site. Please indicate whether the site is ready for inspection or, if not, when it will be ready. Refer to original application

Cross References (list related License Applications, INDs, NDAs, PMAs, 510(k)s, IDEs, BMFs, and DMFs referenced in the current application)

Refer to original application

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This application contains the following items: (Check all that apply)

- 1. Index
- 2. Labeling (check one)       Draft Labeling       Final Printed Labeling
- 3. Summary (21 CFR 314.50 (c))
- 4. Chemistry section
  - A. Chemistry, manufacturing, and controls information (e.g., 21 CFR 314.50(d)(1); 21 CFR 601.2)
  - B. Samples (21 CFR 314.50 (e)(1); 21 CFR 601.2 (a)) (Submit only upon FDA's request)
  - C. Methods validation package (e.g., 21 CFR 314.50(e)(2)(i); 21 CFR 601.2)
- 5. Nonclinical pharmacology and toxicology section (e.g., 21 CFR 314.50(d)(2); 21 CFR 601.2)
- 6. Human pharmacokinetics and bioavailability section (e.g., 21 CFR 314.50(d)(3); 21 CFR 601.2)
- 7. Clinical Microbiology (e.g., 21 CFR 314.50(d)(4))
- 8. Clinical data section (e.g., 21 CFR 314.50(d)(5); 21 CFR 601.2)
- 9. Safety update report (e.g., 21 CFR 314.50(d)(5)(vi)(b); 21 CFR 601.2)
- 10. Statistical section (e.g., 21 CFR 314.50(d)(6); 21 CFR 601.2)
- 11. Case report tabulations (e.g., 21 CFR 314.50(f)(1); 21 CFR 601.2)
- 12. Case report forms (e.g., 21 CFR 314.50 (f)(2); 21 CFR 601.2)
- 13. Patent information on any patent which claims the drug (21 U.S.C. 355(b) or (c))
- 14. A patent certification with respect to any patent which claims the drug (21 U.S.C. 355 (b)(2) or (j)(2)(A))
- 15. Establishment description (21 CFR Part 600, if applicable)
- 16. Debarment certification (FD&C Act 306 (k)(1))
- 17. Field copy certification (21 CFR 314.50 (l)(3))
- 18. User Fee Cover Sheet (Form FDA 3397)
- 19. Financial Information (21 CFR Part 54)
- 20. OTHER (Specify) SAS Transport Files for Concentration and PK Data - Study AA01991

**CERTIFICATION**

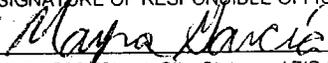
I agree to update this application with new safety information about the product that may reasonably affect the statement of contraindications, warnings, precautions, or adverse reactions in the draft labeling. I agree to submit safety update reports as provided for by regulation or as requested by FDA. If this application is approved, I agree to comply with all applicable laws and regulations that apply to approved applications, including, but not limited to the following:

- 1. Good manufacturing practice regulations in 21 CFR Parts 210, 211 or applicable regulations, Parts 606, and/or 820.
- 2. Biological establishment standards in 21 CFR Part 600.
- 3. Labeling regulations in 21 CFR Parts 201, 606, 610, 660, and/or 809.
- 4. In the case of a prescription drug or biological product, prescription drug advertising regulations in 21 CFR Part 202.
- 5. Regulations on making changes in application in FD&C Act Section 506A, 21 CFR 314.71, 314.72, 314.97, 314.99, and 601.12.
- 6. Regulations on Reports in 21 CFR 314.80, 314.81, 600.80, and 600.81.
- 7. Local, state and Federal environmental impact laws.

If this application applies to a drug product that FDA has proposed for scheduling under the Controlled Substances Act, I agree not to market the product until the Drug Enforcement Administration makes a final scheduling decision.

The data and information in this submission have been reviewed and, to the best of my knowledge are certified to be true and accurate.

**Warning:** A willfully false statement is a criminal offense, U.S. Code, title 18, section 1001.

SIGNATURE OF RESPONSIBLE OFFICIAL OR AGENT 	TYPED NAME AND TITLE Mayra Garcia, Sr. Reg. Affairs Associate	DATE: 04/09/03
ADDRESS (Street, City, State, and ZIP Code) P.O. Box 7439 Caguas, Puerto Rico 00726		Telephone Number ( 787 ) 746-8500 Ext. 2119

Public reporting burden for this collection of information is estimated to average 24 hours per response, including the time for reviewing instructions, searching existing data sources, gathering and maintaining the data needed, and completing and reviewing the collection of information. Send comments regarding this burden estimate or any other aspect of this collection of information, including suggestions for reducing this burden to:

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

Food and Drug Administration  
CDER (HFD-94)  
12229 Wilkins Avenue  
Rockville, MD 20852

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APR 10 2003

**Redacted 15**

**page(s) of trade secret.**

**and/or confidential**

**commercial information**

**(b4)**



ORIGINAL ALARA Pharmaceutical Corporation

P.O. Box 7439  
Caguas, P.R. 00726  
Telephone (787) 746-8500  
Fax (787) 745-4310

NDA NO. 21342 REF NO. 003  
NDA SUPPL FOR SELF

*Standard*

March 31, 2003

David Orloff, M.D., Director  
Division of Metabolic and Endocrine Drug Products, HFD-510  
FDA/CDER/OND/ODE II  
Attention: Fishers Document Room, 8B45  
5600 Fishers Lane  
Rockville, MD 20857

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APR 02 2003

FDR/CDER

*UF<sub>10</sub> = 2/2/04*

*Filing date = 6/1/03*

**PRIOR APPROVAL SUPPLEMENT – BIOEQUIVALENCE**  
**NDA 21-342: Levo-T™ (Levothyroxine Sodium Tablets, USP)**

Dear Dr. Orloff:

This submission provides for a Prior Approval Supplement, where ALARA Pharmaceutical Corporation is demonstrating bioequivalence between Levo-T™ (Levothyroxine Sodium Tablets, USP) 25 mcg, 50 mcg, 75 mcg, 88 mcg, 100 mcg, 112 mcg, 125 mcg, 137 mcg, 150 mcg, 175 mcg, 200 mcg and 300 mcg and Levoxyl® (Levothyroxine Sodium Tablets, USP) 25 mcg, 50 mcg, 75 mcg, 88 mcg, 100 mcg, 112 mcg, 125 mcg, 137 mcg, 150 mcg, 175 mcg, 200 mcg and 300 mcg, in order (to obtain an AB rating) in the *Approved Drug Products with Therapeutic Equivalence Evaluations* publication.

This supplement is being submitted based on the recommendations provided by the Agency in communication dated February 4, 2003 (copy included).

In order to meet bioequivalence requirements the following *in vivo* study was performed: **AA01991** - Comparative, Randomized, Single-Dose, 2-Way Crossover Bioavailability Study of MOVA Pharmaceutical (Levo-T™) and Jones Pharma (Levoxyl®) 300 mcg Levothyroxine Sodium Tablets in Healthy Adult Volunteers Under Fasting Conditions Following Administration of a 600 mcg Dose by [

] Also, *in vitro* dissolution profile data for all strengths has been generated.

Chemistry and Manufacturing Controls information regarding the lots used in this bioequivalency supplement have already been provided in NDA 21-342/S-002.

The following criteria has been met in order to classify Levo-T™ therapeutically equivalent to Levoxyl®:

- They are approved as safe and effective (Levo-T™ approved March 1, 2002 and Levoxyl® approved May 25, 2001)
- They are pharmaceutical equivalent:
  1. Contain identical amounts of the same active drug ingredient (Levothyroxine Sodium, USP), in the same dosage form (Tablet), and route of administration (Oral)
  2. Meet compendial standards of strength, quality, purity, and identity (Levothyroxine Sodium Tablets, USP)
- They are bioequivalent:
  1. They do not present a known or potential bioequivalence problem
  2. They meet an acceptable *in vitro* standard
- They are adequately labeled (Labeling template for Levothyroxine Sodium Tablets, USP has been provided by the Agency)
- They are manufactured in compliance with cGMP regulations.

One archival copy and one pharmacokinetics review copy, each of 5 volumes, have been provided.

If you should require additional information or assistance, please contact me at (787) 746-8500 Ext. 2119 or by fax (787) 745-4310.

Sincerely,



Mayra García  
Sr. Reg. Affairs Associate  
ALARA Pharmaceutical Corporation

Enclosures

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**Levo-T™ (Levothyroxine Sodium Tablets, USP)**  
**NDA 21-342**  
ALARA Pharmaceutical Corporation  
Prior Approval Supplement

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DEPARTMENT OF HEALTH AND HUMAN SERVICES  
FOOD AND DRUG ADMINISTRATION

Form Approved: OMB No. 0910-0338  
Expiration Date: August 31, 2005  
See OMB Statement on page 2.

**APPLICATION TO MARKET A NEW DRUG, BIOLOGIC,  
OR AN ANTIBIOTIC DRUG FOR HUMAN USE**  
(Title 21, Code of Federal Regulations, Parts 314 & 601)

FOR FDA USE ONLY

APPLICATION NUMBER

**APPLICANT INFORMATION**

NAME OF APPLICANT <b>ALARA Pharmaceutical Corporation</b>	DATE OF SUBMISSION <b>March 31, 2003</b>
TELEPHONE NO. (Include Area Code) <b>787-746-8500</b>	FACSIMILE (FAX) Number (Include Area Code) <b>787-745-4310</b>
APPLICANT ADDRESS (Number, Street, City, State, Country, ZIP Code or Mail Code, and U.S. License number if previously issued): <b>P.O. Box 7439 Caguas, PR 00726</b>	AUTHORIZED U.S. AGENT NAME & ADDRESS (Number, Street, City, State, ZIP Code, telephone & FAX number) IF APPLICABLE <b>Not applicable</b>

**PRODUCT DESCRIPTION**

NEW DRUG OR ANTIBIOTIC APPLICATION NUMBER, OR BIOLOGICS LICENSE APPLICATION NUMBER (If previously issued) <b>21-342</b>	
ESTABLISHED NAME (e.g., Proper name, USP/USAN name) <b>Levothyroxine Sodium; L-3,3',5,5',tetraiodothyronine Sodium Salt</b>	PROPRIETARY NAME (trade name) IF ANY <b>Levo-T™</b>
CHEMICAL/BIOCHEMICAL/BLOOD PRODUCT NAME (If any) <b>Not applicable</b>	CODE NAME (If any) <b>Not Applicable</b>
DOSAGE FORM: <b>Tablet</b>	STRENGTHS: 25 mcg, 50 mcg, 75 mcg, 88 mcg, 100 mcg, 112 mcg, 125 mcg, 137 mcg, 150 mcg, 175 mcg, 200 mcg, 300 mcg
ROUTE OF ADMINISTRATION: <b>Oral</b>	

(PROPOSED) INDICATION(S) FOR USE:

**Hypothyroidism and Pituitary TSH Suppression**

**APPLICATION INFORMATION**

APPLICATION TYPE (check one)  NEW DRUG APPLICATION (21 CFR 314.50)  ABBREVIATED NEW DRUG APPLICATION (ANDA, 21 CFR 314.94)  
 BIOLOGICS LICENSE APPLICATION (21 CFR Part 601)

IF AN NDA, IDENTIFY THE APPROPRIATE TYPE  505 (b)(1)  505 (b)(2)

IF AN ANDA, OR 505(b)(2), IDENTIFY THE REFERENCE LISTED DRUG PRODUCT THAT IS THE BASIS FOR THE SUBMISSION  
Name of Drug \_\_\_\_\_ Holder of Approved Application \_\_\_\_\_

TYPE OF SUBMISSION (check one)  ORIGINAL APPLICATION  AMENDMENT TO PENDING APPLICATION  RESUBMISSION  
 PRESUBMISSION  ANNUAL REPORT  ESTABLISHMENT DESCRIPTION SUPPLEMENT  EFFICACY SUPPLEMENT  
 LABELING SUPPLEMENT  CHEMISTRY MANUFACTURING AND CONTROLS SUPPLEMENT  OTHER

IF A SUBMISSION OF PARTIAL APPLICATION, PROVIDE LETTER DATE OF AGREEMENT TO PARTIAL SUBMISSION: \_\_\_\_\_

IF A SUPPLEMENT, IDENTIFY THE APPROPRIATE CATEGORY  CBE  CBE-30  Prior Approval (PA)

REASON FOR SUBMISSION  
**Bioequivalency Supplement**

PROPOSED MARKETING STATUS (check one)  PRESCRIPTION PRODUCT (Rx)  OVER THE COUNTER PRODUCT (OTC)

NUMBER OF VOLUMES SUBMITTED 5 THIS APPLICATION IS  PAPER  PAPER AND ELECTRONIC  ELECTRONIC

**ESTABLISHMENT INFORMATION (Full establishment information should be provided in the body of the Application.)**  
Provide locations of all manufacturing, packaging and control sites for drug substance and drug product (continuation sheets may be used if necessary). Include name, address, contact, telephone number, registration number (CFN), DMF number, and manufacturing steps and/or type of testing (e.g. Final dosage form, Stability testing) conducted at the site. Please indicate whether the site is ready for inspection or, if not, when it will be ready.  
Refer to original application

**Cross References (list related License Applications, INDs, NDAs, PMAs, 510(k)s, IDEs, BMFs, and DMFs referenced in the current application)**

Refer to original application

This application contains the following items: (Check all that apply)

- |                                     |   |
|-------------------------------------|---|
| <input checked="" type="checkbox"/> | 1. Index  |
| <input type="checkbox"/>            | 2. Labeling (check one) <input type="checkbox"/> Draft Labeling <input type="checkbox"/> Final Printed Labeling |
| <input type="checkbox"/>            | 3. Summary (21 CFR 314.50 (c))  |
| <input type="checkbox"/>            | 4. Chemistry section  |
| <input type="checkbox"/>            | A. Chemistry, manufacturing, and controls information (e.g., 21 CFR 314.50(d)(1); 21 CFR 601.2)                 |
| <input type="checkbox"/>            | B. Samples (21 CFR 314.50 (e)(1); 21 CFR 601.2 (a)) (Submit only upon FDA's request)                            |
| <input type="checkbox"/>            | C. Methods validation package (e.g., 21 CFR 314.50(e)(2)(i); 21 CFR 601.2)                                      |
| <input type="checkbox"/>            | 5. Nonclinical pharmacology and toxicology section (e.g., 21 CFR 314.50(d)(2); 21 CFR 601.2)                    |
| <input checked="" type="checkbox"/> | 6. Human pharmacokinetics and bioavailability section (e.g., 21 CFR 314.50(d)(3); 21 CFR 601.2)                 |
| <input type="checkbox"/>            | 7. Clinical Microbiology (e.g., 21 CFR 314.50(d)(4))  |
| <input type="checkbox"/>            | 8. Clinical data section (e.g., 21 CFR 314.50(d)(5); 21 CFR 601.2)  |
| <input type="checkbox"/>            | 9. Safety update report (e.g., 21 CFR 314.50(d)(5)(vi)(b); 21 CFR 601.2)  |
| <input type="checkbox"/>            | 10. Statistical section (e.g., 21 CFR 314.50(d)(6); 21 CFR 601.2)   |
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| <input type="checkbox"/>            | 12. Case report forms (e.g., 21 CFR 314.50 (f)(2); 21 CFR 601.2)  |
| <input type="checkbox"/>            | 13. Patent information on any patent which claims the drug (21 U.S.C. 355(b) or (c))                            |
| <input type="checkbox"/>            | 14. A patent certification with respect to any patent which claims the drug (21 U.S.C. 355 (b)(2) or (j)(2)(A)) |
| <input type="checkbox"/>            | 15. Establishment description (21 CFR Part 600, if applicable)  |
| <input type="checkbox"/>            | 16. Debarment certification (FD&C Act 306 (k)(1))   |
| <input type="checkbox"/>            | 17. Field copy certification (21 CFR 314.50 (l)(3))   |
| <input type="checkbox"/>            | 18. User Fee Cover Sheet (Form FDA 3397)  |
| <input type="checkbox"/>            | 19. Financial Information (21 CFR Part 54)  |
| <input checked="" type="checkbox"/> | 20. OTHER (Specify) Basis for Submission  |

**CERTIFICATION**

I agree to update this application with new safety information about the product that may reasonably affect the statement of contraindications, warnings, precautions, or adverse reactions in the draft labeling. I agree to submit safety update reports as provided for by regulation or as requested by FDA. If this application is approved, I agree to comply with all applicable laws and regulations that apply to approved applications, including, but not limited to the following:

1. Good manufacturing practice regulations in 21 CFR Parts 210, 211 or applicable regulations, Parts 606, and/or 820.
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3. Labeling regulations in 21 CFR Parts 201, 606, 610, 660, and/or 809.
4. In the case of a prescription drug or biological product, prescription drug advertising regulations in 21 CFR Part 202.
5. Regulations on making changes in application in FD&C Act Section 506A, 21 CFR 314.71, 314.72, 314.97, 314.99, and 601.12.
6. Regulations on Reports in 21 CFR 314.80, 314.81, 600.80, and 600.81.
7. Local, state and Federal environmental impact laws.

If this application applies to a drug product that FDA has proposed for scheduling under the Controlled Substances Act, I agree not to market the product until the Drug Enforcement Administration makes a final scheduling decision.

The data and information in this submission have been reviewed and, to the best of my knowledge are certified to be true and accurate.

**Warning:** A willfully false statement is a criminal offense, U.S. Code, title 18, section 1001.

SIGNATURE OF RESPONSIBLE OFFICIAL OR AGENT <i>Mayra Garcia</i>	TYPED NAME AND TITLE Mayra Garcia, Sr. Reg. Affairs Associate	DATE: 03/31/03
ADDRESS (Street, City, State, and ZIP Code) P.O. Box 7439 Caguas, Puerto Rico 00726		Telephone Number ( 787 ) 746-8500 Ext. 2119

Public reporting burden for this collection of information is estimated to average 24 hours per response, including the time for reviewing instructions, searching existing data sources, gathering and maintaining the data needed, and completing and reviewing the collection of information. Send comments regarding this burden estimate or any other aspect of this collection of information, including suggestions for reducing this burden to:

Department of Health and Human Services Food and Drug Administration D.E.R., HFD-99 401 Rockville Pike Rockville, MD 20852-1448	Food and Drug Administration CDER (HFD-94) 12229 Wilkins Avenue Rockville, MD 20852
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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.

1-002



## DEPARTMENT OF HEALTH &amp; HUMAN SERVICES

Public Health Service

Food and Drug Administration  
Rockville, MD 20857

NDA 21-342

Mova Pharmaceutical Corporation  
Attention: Claribel Velez  
Regulatory Affairs & Compliance Director  
P.O. Box 8639  
Caguas, Puerto Rico 00726

Dear Ms. Velez:

Please refer to your New Drug Application (NDA) submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act for Levo-T (levothyroxine sodium tablets, USP).

We also refer to your July 16, 2002, letter (fax) in which you made several inquiries regarding the demonstration of bioequivalence (i.e., to obtain an AB rating) between Levo-T and Levoxyl as well as the recently approved Synthroid.

We are enclosing a "Protocol - Bioequivalence of levothyroxine sodium tablets" to assist you. We recommend that you submit a protocol to your IND and request comments before initiating your study.

We also have the following responses to your questions.

1(a). Can the bioequivalence (BE) study be submitted as a CBE-30 supplement?

This must be submitted as a prior approval supplement to your NDA.

1(b). Can you use only the highest strength (300 mcg) tablets to conduct the in vivo BE study or should other strengths be included?

The 0.3 mg strengths should be used in the BE study (also see the enclosed protocol.)

1(c). Is it necessary to use all strengths of Levo-T to conduct an in vitro study?

All the strengths of Levo-T should be used in an in vitro dissolution study.

1(d). Is it possible to market Levo-T as the generic version of Levoxyl once Levo-T achieves an AB rating to Levoxyl?

Levo-T tablets will be listed as AB rated to Levoxyl in the Orange Book, indicating that Levo-T is therapeutically equivalent to Levoxyl.

2. Because the in vitro study submitted to the NDA compared Levo-T and Synthroid Solution, is it necessary to conduct in vivo studies with Synthroid tablets to demonstrate BE or is an in vitro study adequate?

Because Levo-T tablets will be listed as AB rated to Synthroid tablets, not to Synthroid solution, a BE study with Synthroid tablets is required in order to obtain an AB rating for Levo-T to Synthroid.

If you have any questions, call Enid Galliers, Chief, Project Management Staff, at (301) 827-6429.

Sincerely,

*{See attached electronic signature page}*

David G. Orloff, M.D.  
Director  
Division of Metabolic and Endocrine Drug Products  
Office of Drug Evaluation II  
Center for Drug Evaluation and Research

**ENCLOSURE**

## PROTOCOL -- Bioequivalence of levothyroxine sodium tablets

**OBJECTIVE:** The objective of this study is to determine if bioequivalence can be conferred between Product A and Product B.

**METHODOLOGY:** Single-dose, two-treatment, two-sequence, crossover design. The total administered dose given for each regimen will be 600 mcg levothyroxine sodium. Subjects will receive one of two sequences of Regimen A (two 300 mcg Product A tablets) and Regimen B (two 300 mcg Product B tablets) under fasting conditions in the morning of study day 1 of each period. A washout interval of at least 35 days will separate the doses in consecutive study periods.

Blood samples for total (free + bound) thyroxine ( $T_4$ ) assay will be collected at -0.5, -0.25, 0, 0.5, 1, 1.5, 2, 2.5, 3, 4, 6, 8, 10, 12, 18, 24, 36, and 48 hours post dose.

**SUBJECTS:** Refer to Guidance for Industry: Levothyroxine Sodium Tablets - In Vivo Pharmacokinetic and Bioavailability Studies and In Vitro Dissolution Testing

### EVALUATION:

**Pharmacokinetic:** The pharmacokinetic parameter values of total thyroxine ( $T_4$ ) will be estimated using non-compartmental methods. These will include the maximum serum concentration ( $C_{max}$ ) and time to  $C_{max}$  ( $T_{max}$ ), the area under the concentration-time curve (AUC) from time 0 to 24 hours ( $AUC_{24}$ ) and time 0 to 48 hours ( $AUC_{48}$ ).

Values of these parameters ( $C_{max}$ ,  $T_{max}$ ,  $AUC_{24}$ , and  $AUC_{48}$ ) will be determined after correcting all post-dose concentrations using the following method:

**Correction Method:** The pre-dose baseline value on the day of dosing will be subtracted from each post-dose concentration. The pre-dose baseline value will be calculated as the average of the three concentrations at -0.5, -0.25, and 0 hours prior to dosing in each period.

**Statistical:** Analysis of variance (ANOVA) will be performed for log-transformed  $C_{max}$ ,  $AUC_{24}$ , and  $AUC_{48}$ , using the SAS General Linear Models (GLM) procedure. The geometric means and 90% confidence intervals of the geometric mean ratio of  $C_{max}$  and  $AUC_{0-t}$  will be presented for each pair-wise comparison. Bioequivalence is demonstrated if the 90% confidence intervals fall within the 80 - 125 percent range for corrected  $T_4$ .

**SAFETY:** Refer to appropriate *Guidance for Industry* documents.

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

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David Orloff  
2/4/03 03:35:42 PM