CENTER FOR DRUG EVALUATION AND RESEARCH

Approval Package for:

APPLICATION NUMBER:

85-755

Generic Name: Liothyronine Sodium Tablets, 25mcg

Sponsor: Bolar Pharmaceutical Co., Inc.

Approval Date: January 25, 1982

CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

85-755

CONTENTS

Reviews / Information Included in this ANDA Review.

CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

85-755

APPROVAL LETTER

JAN 25 1982

NDA 85-755

Solar Pharmaceutical Co., Inc.
Attention: Robert Shulman
130 Lincoln Street
Copiague, New York 11726

Gentlemen:

Reference is made to your abbreviated new drug application dated April 12, 1977, submitted pursuant to Section 505(b) of the Federal Food, Drug, and Cosmetic Act for Liothyronine Sodium Tablets, 25 mcg.

We acknowledge receipt of your communication dated September 23, 1981, October 20, 1981 and November 3, 1981.

We have completed the review of this abbreviated new drug application and have concluded that the drug is safe and effective for use as recommended in the submitted labeling. Accordingly, the application is approved.

Since the analytical methods have not been validated by our laboratories, this Administration expects you to work to resolve any technical issues which may result with regard to these methods.

Any significant change in the conditions outlined in this abbreviated new drug application requires an approved supplemental application before the change may be made, except for changes made in conformance with other provisions of Section 314.8 of the new drug regulations.

This Administration should be advised of any change in the marketing status of this drug.

We request that you submit, in duplicate, any proposed advertising or promotional copy which you intend to use in your immediate advertising or promotional campaigns. Please submit both copies and a completed Form FD-2253, together with a copy of the Final Printed Labeling, to the Division of Drug Advertising, (HFD-170). A copy of Form FD-2253 is enclosed for your convenience.

We call your attention to Regulation 21 CFR 310.300 (b)(3) (or 431.60 (b)(3) if Form 6) which requires that material for any subsequent advertising or promotional campaigns, at the time of their initial use be submitted to our Division of Drug Advertising (HFD-170) with a completed Form FD-2253.

APPEARS THIS WAY
ON ORIGINAL

The enclosures summarize the conditions relating to the approval of this application.

Sincerely yours,

Marvin Seife 1/25/82

Marvin Seife, M.D.
Director
Division of Generic Drug Monographs
Office of Drug Monographs
Bureau of Drugs

Enclosures:
Conditions of Approval of a New Drug Application
Records & Reports Requirements
Form FD 2253

cc: NYK-DO

HFD-616
HFD-534 (HZELL)
HZell/BArnwine B. J. Arnwine 1/22/82 HC Zell 1/22/82
R/D INITIAL HZell/MSeife
mstephens: 1/22/82(7245A)
Approved

APPEARS THIS WAY
ON ORIGINAL

CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

85-755

FINAL PRINTED LABELING

Q.2.4.

[redacted]

LIOTHYRONINE SODIUM

DESCRIPTION: Liothyronine Sodium contains liothyronine (L-triiodothyronine or LT_3) as the sodium salt. 25 mcg of liothyronine is equivalent to approximately 1 grain of desiccated thyroid or thyroglobulin and 0.1 mg of L-thyroxine.

ACTIONS: Liothyronine Sodium is a synthetic form of a natural thyroid hormone, with all pharmacologic activities of the natural substance. Thyroid hormone acts to promote the synthesis of protein. It increases the metabolic rate of the body, presumably by, among other things, increasing oxygen consumption, altering enzymes (particularly those that affect growth), and altering the permeability of the mitochondrial membranes of cells.

APPROVED

JAN 25 1982

Since liothyronine sodium is not firmly bound to serum protein, it is readily available to body tissues. Following oral administration, about 85% of the dose is absorbed from the gastrointestinal tract. The onset of activity of liothyronine sodium is rapid, occurring within a few hours. Maximum pharmacologic response occurs within two or three days, providing early clinical response. The biological half-life is about 2 1/2 days. The drug has a rapid cutoff of activity which permits quick dosage adjustment and facilitates control of the effects of overdosage, should they occur.

Liothyronine sodium can be used in patients allergic to desiccated thyroid or thyroid extract derived from pork or beef.

INDICATIONS: Liothyronine sodium, is indicated for thyroid replacement or supplementation in patients with inadequate endogenous thyroid hormone production. These include:

a) HYPOTHYROIDISM, all gradations from frank myxedema to mild hypofunction; cretinism.

b) SIMPLE (NON-TOXIC) GOITER, liothyronine sodium may be tried therapeutically in an attempt to reduce the size of such a goiter.

Liothyronine sodium may be used in the T_3 suppression test to differentiate suspected hyperthroidism from euthyroidism. (See special instructions under Dosage and Administration).

CONTRAINDICATION: Uncorrected adrenal insufficiency.

WARNINGS:

> Drugs with thyroid hormone activity, alone or together with other therapeutic agents, have been used for the treatment of obesity. In euthyroid patients, doses within the range of daily hormonal requirements are ineffective for weight reduction. Larger doses may produce serious or even life-threatening manifestations of toxicity, particularly when given in association with sympathomimetic amines such as those used for their anorectic effects.

Liothyronine sodium should not be used in the presence of cardiovascular disease unless thyroid replacement therapy is clearly indicated. In such cases it should be used with caution and initiated at a low dosage, with due consideration for its relatively rapid onset of action. Starting dosage is 5 mcg daily, and should be increased by no more than 5 mcg increments at two-week intervals.

Morphologic hypogonadism and nephrosis should be ruled out before the drug is administered. If hypopituitarism is present, the adrenal deficiency must be corrected prior to starting the drug.

Myxedematous patients are very sensitive to thyroid; dosage should be started at a very low level and increased gradually.

Severe and prolonged hypothyroidism can lead to a decreased level of adrenocortical activity commensurate with the lowered metabolic state. When thyroid-replacement therapy is administered, the metabolism increases at a greater rate than adrenocortical activity. This can precipitate adrenocortical insufficiency. Therefore, in severe and prolonged hypothyroidism, supplemental adrenocortical steroids may be necessary.

In rare instances the administration of thyroid hormone may precipitate a hyperthyroid state or may aggravate existing hyperthyroidism.

PRECAUTIONS: Since liothyronine sodium is not as firmly bound to serum protein as thyroxine, the PBI usually remains at levels below normal during full replacement therapy using [redacted] sodium.

[redacted]

As with all thyroid preparations, thyroid gland function reflected by ^{131}I thyroid uptake may be depressed by liothyronine sodium, particularly when dosage exceeds 75 mcg daily. This effect disappears rapidly, and useful ^{131}I thyroid uptake values may be obtained usually within two weeks following discontinuance of the drug.

ADVERSE REACTIONS: Overdosage will produce signs and symptoms of hyperthyroidism, such as nervousness, cardiac arrhythmias, angina pectoris, and menstrual irregularities. (See OVERDOSAGE section) Medication should be interrupted until symptoms disappear, then resumed in smaller doses. Therapy can usually be resumed after one or two days.

In rare instances, allergic skin reactions have been reported.

DOSAGE AND ADMINISTRATION: Optimum dosage is usually determined by the patient's clinical response. Confirmatory tests include; Radioactive Iodine T_3 Resin Uptake, BMR, Thyro Binding Index (TBI), and the Achilles Tendon Reflex Test.

Once-a-day dosage is recommended, although liothyronine sodium has a rapid cutoff, its metabolic effects persist for a few days following discontinuance.

MILD HYPOTHYROIDISM: Recommended starting dosage is 25 mcg daily. Daily dosage then may be increased by 12.5 or 25 mcg every one or two weeks. Usual maintenance dose is 25 - 75 mcg daily. Smaller doses may be fully effective in some patients, while dosage of 100 mcg daily may be required in others.

MYXEDEMA: Recommended starting dosage is 5 mcg daily. This may be increased by 5 to 10 mcg daily every one or two weeks. When 25 mcg daily is reached, dosage may often be increased by 12.5 or 25 mcg every one or two weeks. Usual maintenance dose is 50 to 100 mcg daily.

CRETINISM: Since the mother provides little or no thyroid hormone to the fetus, infants with thyroid dysfunction will require replacement therapy from birth. Treatment should be initiated as early as possible to avoid permanent physical and mental changes.

Recommended starting dosage is 5 mcg daily, with a 5 mcg increment every three to four days until the desired response is achieved. Infants a few months old may require only 20 mcg daily maintenance. At 1 year 50 mcg daily may be required. Above 3 years, full adult dosage may be necessary.

SIMPLE (NON-TOXIC) GOITER: Recommended starting dosage is 5 mcg daily. This dosage may be increased by 5 to 10 mcg daily every one or two weeks. When 25 mcg daily is reached, dosage may be increased every week or two by 12.5 or 25 mcg. Usual maintenance dosage is 75 mcg daily.

IN THE ELDERLY OR IN CHILDREN: Therapy should be started with 5 mcg daily and increased only by 5 mcg increments at the recommended intervals.

WHEN SWITCHING A PATIENT TO LIOTHYRONINE SODIUM FROM: thyroid, L-thyroxine or thyroglobulin, discontinue the other medication, initiate liothyronine sodium at a low dosage, and increase gradually according to the patient's response. When selecting a starting dosage, bear in mind that this drug has a rapid onset of action, and that residual effects of the other thyroid preparation may persist for the first several weeks of therapy.

SPECIAL INSTRUCTIONS FOR T_3 SUPPRESSION TEST: When ^{131}I Thyroid Uptake is in the borderline-high range, administer 75 - 100 mcg of liothyronine sodium daily for 7 days, then repeat ^{131}I Thyroid Uptake Test. In the hyperthyroid patient, 24-hour ^{131}I Thyroid Uptake will not be affected significantly. In the euthyroid patient, 24 hour ^{131}I Thyroid Uptake will drop to less than 20%.

OVERDOSAGE: *Symptoms:* Headache, irritability, nervousness, sweating, tachycardia, increased bowel motility, and menstrual irregularities. Angina pectoris or congestive heart failure may be induced or aggravated. Shock may also develop. Massive overdosage may result in symptoms resembling thyroid storm. Chronic excessive dosage will produce the signs and symptoms of hyperthyroidism.

Treatment: In shock, supportive measures and treatment of unrecognized adrenal insufficiency should be considered.

HOW SUPPLIED: In two dosage forms:

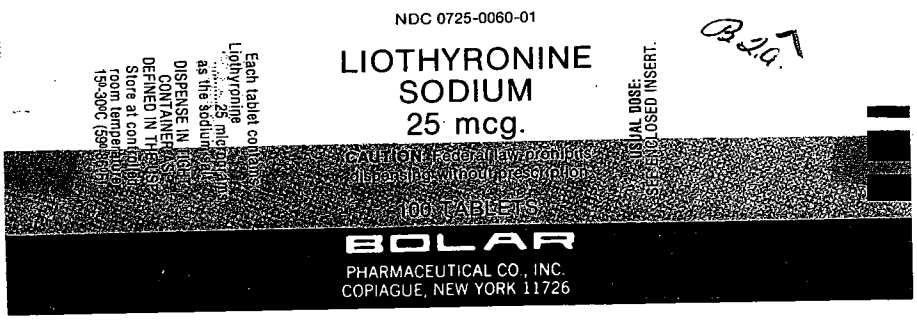
25 mcg tablets in bottles of 100 and 1000.
50 mcg tablets in bottles of 100 and 1000.

DATE OF ISSUE: October 23, 1981

[redacted]

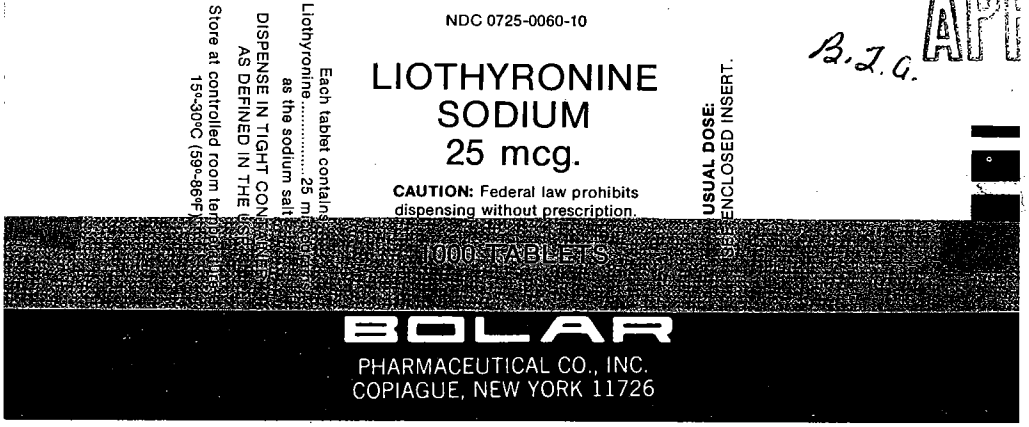
APPROVED

JAN 25 1982



B.J.G.

APPROVED
JAN 25 1982



B.J.G. APPROVED

JAN 25 198

CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

85-755

CHEMISTRY REVIEW(S)

ABBREVIATED NEW DRUG APPLICATION OR SUPPLEMENT

Statement Date

NDA Number

85-755

AF Number

Name and Address of Applicant (City and State)

bolar pharmaceutical CO., Inc
copiague, NY

Original
Amendment
Supplement
Resubmission
Correspondance
Report
Other

Purpose of Amendment/Supplement

orig abbr NDA

Date(s) of Submission(s)

4/12/77

Pharmacological Category	Name of Drug	How Dispensed
thyroid hormone	liothyronine sodium	R_x xxx OTC
Dosage Form(s): oral	Potency(ies): 25 mcg.	
Packaging/Sterilization: requested	Samples: requested	Related IND/NDA/MF: 85-756 = 50 mcg.

Labeling

as per MO(rbarzilai)

Biologic Availability

in vivvo/in vitro requirement currently deferred
as per HFD-500 list dated 3/11/77

Establishment Inspection

requseted

Components, Composition, Manufacturing and Controls

as per letter to issue

APPEARS THIS WAY ON ORIGINAL

Remarks

rev w/f

gmillar
6/20/77

Conclusion

REVIEWER

DATE

REVIEW OF ANDAS

DATE COMPLETED: 5-2-77

ANDA #s: ~~85-755 25 mcg~~
85-753 50 mcg

NAME OF DRUG: Liothyronine Sodium Tablets

DATE OF SUBMISSION: 4-14-77

TYPE OF SUBMISSION: ANDA

CLINICAL EVALUATION:

1. Review of Studies: EIAR - for review by assigned chemist
   Bio studies - deferred

2. Review of Labeling:

   a) Container labels: Acceptable draft copies of labels for containers of 100 and 1000's in three strengths.

   b) Package insert: Acceptable drafts for three strengths.

CONCLUSION: Acceptable draft labeling.

RECOMMENDATIONS:
1. Needs chemist's review.
2. Request FPL as per submitted drafts.

R. Barzilai

R. Barzilai, M.D.

cc:dup
REB/wlb/5-3-77

ABBREVIATED NEW DRUG APPLICATION OR SUPPLEMENT

Statement Date

85-755
AF Number

Name and Address of Applicant (City and State)
bolar pharmaceutical co., inc
copiague, NY 11726

Original
Amendment
Supplement
Resubmission
Correspondance
Report
Other

Purpose of Amendment/Supplement
amend

Date(s) of Submission(s)
7/26/77.

Pharmacological Category	Name of Drug	How Dispensed
thyroid hormone	liothyronine NA	R_x xx OTC
Dosage Form(s)	**Potency(ies)**	**Related IND/NDA/MF**
oral	25 mcg.	85-753 = 50 mcg
Packaging/Sterilization	**Samples**	
requested	requested	

Labeling
as per MO

Biologic Availability
NC

Establishment Inspection
requested for [redacted]

APPEARS THIS WAY
ON ORIGINAL

Components, Composition, Manufacturing and Controls
as per letter to issue

Remarks
rev w/f

gmillar
10/6/77

Conclusion

REVIEW

DATE

ABBREVIATED NEW DRUG APPLICATION OR SUPPLEMENT

Statement Date

AF Number 85-755

Name and Address of Applicant (City and State)

[illegible] [illegible]eutical CO., Inc

[illegible]

Original	
Amendment	
Supplement	
Resubmission	
Correspondance	
Report	
Other	

Purpose of Amendment/Supplement

[illegible]

amend

Date(s) of Submission

1/13/77

7/26/77 + 9/6/77

Pharmacological Category	Name of Drug
[illegible]	[illegible] sodium

Dosage Form(s)	Potency(ies)	How Dispensed
oral	25 mcg.	Rx xxx OTC

Packaging/Sterilization	Samples	Related IND/NDA/MF
[illegible]	requested	85-755 - 50 mcg

Labeling

as per [illegible]

Biologic Availability

in vivo/in vitro requirement currently deferred as per [illegible] 3/11/77

Establishment Inspection

[illegible]

Components, Composition, Manufacturing and Controls

APPEARS THIS WAY ON ORIGINAL

[illegible]

Remarks

[illegible] [illegible]

11/1/77

Conclusion

REVIEWER

DATE

ABBREVIATED NEW DRUG APPLICATION OR SUPPLEMENT	Statement Date:	NDA NUMBER: 85-755

NAME AND ADDRESS OF APPLICANT

Bolar Pharmaceutical Co., Inc.
Copiague, NY 11726

ORIGINAL
AMENDMENT xx
SUPPLEMENT
RESUBMISSION
CORRESPONDENCE
REPORT
OTHER

PURPOSE OF AMENDMENT/SUPPLEMENT

bio protocol

DATE(s) of SUBMISSION(s)
10-24-78

PHARMACOLOGICAL CATEGORY	NAME OF DRUG	HOW DISPENSED
thyroid hormone	liothyronine sodium	RX XXX OTC
DOSAGE FORM(S)	POTENCY(IES)	RELATED IND/NDA/DMF
tablet	25 mcg	
STERILIZATION	SAMPLES	
	re-requested	

LABELING

na

BIOLOGIC AVAILABILITY

protocol to HFD-522 for review

ESTABLISHMENT INSPECTION

requested

COMPONENTS, COMPOSITION, MANUFACTURING, CONTROLS

re-requested; updated specs for active ingredient with next letter

PACKAGING

requested

STABILITY

Protocol: revision needed

Exp. Date: requested

REMARKS AND CONCLUSION: rev w/f

GMillar

CHEMIST'S REVIEW
(If necessary, continue any item on 8" x 10½" paper. Key continuation to item by number.)

1. ORGANIZATION

2. NDA NUMBER: 85-755

3. NAME AND ADDRESS OF APPLICANT *(City and State)*
Bolar Pharmaceutical Co. Inc.
Copiague,LI,NY 11726

4. AF NUMBER

5. SUPPLEMENT (S)
NUMBER(S) | DATE(S)

6. NAME OF DRUG: Sodium Liothyronine

7. NONPROPRIETARY NAME

8. SUPPLEMENT(S) PROVIDES FOR:
submission of additional control information and bioavailability ☒ information

9. AMENDMENTS AND OTHER *(Reports, etc.)* DATES
5/16/79,10/15/79

10. PHARMACOLOGICAL CATEGORY: thyroid hormone

11. HOW DISPENSED
☒ RX ☐ OTC

12. RELATED IND/NDA/DMF(S)
85-753 50 mcg.
Cytomel Tablets
Smith,Kline &French
Labs. 10-379

13. DOSAGE FORM (S): tablet

14. POTENCY *(Iss)*: 25 mcg.

15. CHEMICAL NAME AND STRUCTURE

16. RECORDS AND REPORTS
CURRENT ☐ YES ☐ NO
REVIEWED ☐ YES ☐ NO

17. COMMENTS

Pending: an approved bioavailability study
satisfactory analysis of samples

APPEARS THIS WAY
ON ORIGINAL

18. CONCLUSIONS AND RECOMMENDATIONS

Requested: Update application as per tests and specifications / current compendia
submit samples for analysis

rev w/f

19. REVIEWER

NAME	SIGNATURE	DATE COMPLETED
J.M.Ross	J.M.Ross	9/26/80

DISTRIBUTION ☐ ORIGINAL JACKET ☐ REVIEWER ☐ DIVISION FILE

FORM FDA 2246 (7/75) PREVIOUS EDITION MAY BE USED UNTIL SUPPLY IS EXHAUSTED.

CHEMIST'S REVIEW, Page 2

Enter evaluation or comments for each item. If necessary, continue on 8" x 10½" paper. Key continuation to item by number. Enter "NC" if no change or "NA" if not applicable.

NDA NUMBER 87-755

20. COMPONENTS AND COMPOSITION *(5, 7)*

see application

21. FACILITIES AND PERSONNEL *(8a,b)*

22. SYNTHESIS *(8c)*

23. RAW MATERIAL CONTROLS *(8d,e)*

a. NEW DRUG SUBSTANCE

is tested as per USP
Requested: update tests and specifications as per current USP

b. OTHER INGREDIENTS

are tested as per USP/NF
Requested: update tests and specifications

24. OTHER FIRM(s) *(8f)*

25. MANUFACTURING AND PROCESSING *(8g,h,j,k)*

26. CONTAINER *(8i)*

opaque white high density polyethylene containers

27. PACKAGING AND LABELING *(8l,m)*

28. LABORATORY CONTROLS *(In-Process and Finished Dosage Form) (8n)*

is tested as per USP..... Requested: update tests and specifications

29. STABILITY *(8p)*

protocol submitted and some challenge studies

30. CONTROL NUMBERS *(8c)*

31. SAMPLES AND RESULTS *(9)*

a. VALIDATION requested b. MARKET PACKAGE

32. LABELING *(6)*

Satisfactory(RBarzilai)

33. ESTABLISHMENT INSPECTION

Bolar Pharmaceutical Co. Inc. incompliance 7/31./79

34. RECALLS

CHEMIST'S REVIEW FOR ABBREVIATED NEW DRUG APPLICATION OR SUPPLEMENT	Statement Date:	NDA # 85-755
NAME AND ADDRESS OF APPLICANT: Bolar Pharmaceutical		ORIGINAL 4/12/77 AMENDMENT SUPPLEMENT RESUBMISSION CORRESPONDENCE REPORT OTHER
PURPOSE OF AMENDMENT/SUPPLEMENT		DATE(s) of SUBMISSION(s) 5/29/81
PHARMACOLOGICAL CATEGORY: Thyroid hormone	NAME OF DRUG: Liothyronine sodium	HOW DISPENSED RX XXX OTC _____
DOSAGE FORM: Tablet	POTENCY(IES): 25 mcg.	RELATED IND/NDA/DMF
STERILIZATION: NA	SAMPLES: USP product - not required	

LABELING

Acceptable per M.O. review 5/3/77

BIOLOGIC AVAILABILITY

Under review

ESTABLISHMENT INSPECTION

Satisfactory per 8/14/81

COMPONENTS, COMPOSITION, MANUFACTURING, CONTROLS

Submit update of compendium status

PACKAGING

STABILITY: Request current stability data

Protocol:

Exp. Date:

REMARKS & CONCLUSION:

Rev w/f letter R.E.Joyce

CHEMIST'S REVIEW NDA NUMBER 85-755

NAME AND ADDRESS OF APPLICANT
Bolar Pharmaceutical Co., Inc.
Copiague, New York 11726

ORIGINAL 4/12/77

AMENDMENT 9/23/81, 11/3/81

CORRESPONDENCE 10/20/81

PHARMACOLOGICAL CATEGORY
Thyroid hormone

NAME OF DRUG
Liothyronine Sodium

HOW DISPENSED
RX OTC

RELATED IND/NDA/DMF(s)
85-753

DOSAGE FORM(s)	POTENCY
Tablet	25 mcg

STERILZATION
NA

SAMPLES
To be sent for methods validation

LABELING
Satisfactory as per M.S. 11/10/81

BIOLOGIC AVAILABILITY
Acceptable as per Memo 10/1/81

ESTABLISHMENT INSPECTION
Satisfactory as per Alert List 1/4/82

COMPONENTS, COMPOSITION, MANUFACTURING, CONTROLS
Satisfactory - Updated excipient specifications in accord with current compendias. An [redacted] Method submitted for content uniformity and assay of active ingredient and finished dosage form.

STABILITY
Satisfactory - Updated room temperature stability data are sufficient for requested 3 year expiration dating.

PROTOCOL:	EXP. DATE:
	36 Months.

REMARKS AND CONCLUSION:
Approval B.T. Arnwine
Brenda T. Arnwine 1/22/82 JMC 1/22/82

CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

85-755

BIOEQUIVALENCE REVIEW(S)

Liothyronine Sodium
25 microgram Tablet
ANDA 85-755

Bolar Pharmaceutical Co.
Copiague, New York
Submission Dated:
May 29, 1981

REVIEW OF A BIOAVAILABILITY STUDY

1. Bolar Pharmaceutical Company has submitted a bioequivalence study comparing the triiodothyronine (T_3) serum levels obtained after administration of liothyronine sodium tablets, 25 mcgm. The study compares liothyronine sodium tablet, 25 mcgm, manufactured by Bolar with Cytomel, 25 mcgm, manufactured by Smith, Kline and French Company. The dose was 2 X 25 mcgm tablets. The study was conducted by [redacted] under the supervision of [redacted] The study protocol was reviewed and approved by the Peer Review Committee for [redacted] on April 2, 1981.

2. The bioequivalence study was a randomized 2-way crossover study employing 23 subjects. Six subjects dropped out of the study for reasons of refusing to spend the night of check-in, abnormal laboratory value, and personal difficulties. A total of 17 subjects completed the study. The subjects were healthy male adults ranging in age from 19 to 35 years and conforming to ideal weight for height as defined by Metropolitan Life Insurance Company Statistical Bulletin. Good health of subjects was ensured from medical history, physical examination and clinical laboratory tests. The subjects were housed in the [redacted] live-in facility from 12 hours before until 24 hours after drug administration. They were free of any medication including aspirin and OTC preparations for 2 weeks prior to the first administration until after the study. After an overnight fast subjects were administered a single dose of 2 X 25 mcgm tablets of the test or the reference drug (Cytomel) with 180 ml water. Blood samples were collected at -72, -48, -24, 0, 0.25, 0.5, 0.75, 1, 1.5, 2, 2.5, 3, 3.5, 4, 5, 6, 8, 12 and 24 hours. Serum was separated and kept frozen until assayed. The serum samples were assayed for T_3 by a [redacted] using the [redacted] produced by [redacted] The assays were performed by Bruce Hamilton, M.D. at the laboratories of the Veterans Administration Hospital, Loch Raven Boulevard, Baltimore, Maryland. A washout period of one week was observed between the two legs of crossover study.

Results and Comments:

3. Table I shows the mean bioavailability parameters for the test and reference drugs. The concentrations are in terms of ng/100 ml.

Table I

Mean Bioavailability Parameters for Liothyronine Sodium

Drug A: Bolar's 25 mcgm Tablet.
Drug B: SKF's Cytomel, 25 mcgm Tablet.
Dose: 2 X 25 mcgm Tablets.

Parameter	Drug A	Drug B
Base line T_3 Conc. (ng/100 ml)	144.65 (18%)*	147.22 (15%)*
C_{max}(ng/100 ml)	422 (17%)	477 (22%)
T_{max} (hrs)	2.47 (27%)	2.03 (33%)
AUC_{0-24}(ng.hrs/100 ml)	5564 (16%)	5799 (15%)
AUC_{0-24}(corrected for baseline)	2022 (29%)	2266 (26%)

* Coefficient of variation.

The normal baseline value for T_3 in healthy subjects is 80-200 ng/100 ml. The baseline values in this study are 144.65 and 147.22 ng/100 ml with coefficients of variation of 18 and 15 percent respectively. The small coefficient of variation shows good baseline value from day to day. The Bolar product has mean C_{max} 12 percent below that of the SKF product. The difference is statistically significant. The uncorrected AUC_{0-24} shows that the Bolar product is 96 percent as bioavailable as the SKF product. The AUC_{0-24} value when corrected for baseline demonstrates that the Bolar product, on an average, is 89 percent as bioavailable as the SKF product. The difference between mean baseline corrected values of AUC_{0-24} is statistically not significant. The power of the study to detect significant differences of 20 percent between drugs for this parameter is 0.96. The statistically significant differences are not clinically significant.

4. Table II enumerates mean serum levels of T_3 at various sampling for the test and reference products.

Table II

T_3 Levels in Serum by RIA after 50 mcgm Dose

Time	Bolar: Lot #083269 Bolar	SKF: Lot #550016 SKF
0	144.6 (28.5)*	146.0 (17.2)*
15 min.	152.4 (31.9)	145.9 (24.4)
30	181.6 (36.8)	184.9 (37.5)
45	226.8 (50.6)	263.8 (74.4)
1 hr.	301.5 (64.7)	344.7 (118.4)
1.5	357.4 (64.1)	408.8 (122.7)
2.0	387.9 (76.2)	425.6 (93.9)
2.5	393.2 (57.2)	425.9 (75.6)
3.0	386.2 (56.9)	425.3 (95.5)
3.5	357.6 (73.1)	377.1 (76.9)
4.0	332.6 (72.3)	352.9 (74.2)
5.0	300.9 (60.1)	316.4 (68.5)
6.0	271.2 (48.7)	274.4 (44.7)
8.0	239.2 (39.8)	240.4 (31.1)
12.0	203.4 (39.6)	207.5 (41.8)
24.0	179.9 (31.2)	182.9 (28.1)

* Values in parenthesis are standard deviations.

The standard deviations for the SKF product are much greater than the Bolar product for T_3 levels from 1 hour to 3 hours sampling times, indicating greater inter-subject variability for the reference product.

At the end of 24 hours the serum levels of T_3 for both the products fall within the range of base value of endogenous T_3 in normal subjects. The half-life of T_3 is about 1 day. A bioavailability study is normally conducted for 3-5 half-lives. However, in the presence of endogenous T_3 a bioavailability study for 1 half-life is feasible, logical and rational. The half-lives of the test drug and reference drugs, calculated from the mean data are about 1 day, in agreement with the reported literature value.

5. Table III shown base-line corrected values of AUC_{0-24} of individual subjects for both the test and reference products. The fourth column shows the ratio AUC_{Test} to $AUC_{Reference}$. Only in three subjects out of 17, the Bolar product has bioavailability lower than 70 percent in comparison to that of SKF product (63, 51 and 68 percent). In one subject it is 166 percent. In all other subjects the bioavailability of Bolar product ranges from 77 to 110 percent of that of the SKF product. The Bolar product has, thus been demonstrated to be bioequivalent with SKF's Cytomel.

Table III

Comparison of AUC(test) and AUC(reference) Products

AUC's corrected for base-line T_3 levels

Subject #	Bolar (T)	SKF (R)	Ratio (T/R)
1	1397.5	1805.6	0.77
2	1778.1	1995.0	0.89
3	1881.3	2222.5	0.85
4	1670.0	1848.8	0.90
5	2602.5	2483.1	1.05
6	1311.3	2094.4	0.63*
8	2043.8	2431.1	0.84
10	1890.6	3693.1	0.51*
11	2593.1	2998.8	0.86
12	3063.8	2762.5	1.10
14	1299.0	1183.4	1.10
15	1963.1	1957.0	1.00
16	2166.1	2740.0	0.79
17	3252.5	1949.4	1.66*
18	2329.1	2696.3	0.86
19	1370.3	2007.4	0.68*
20	1768.5	1649.8	1.07

6. The present submission contains no dissolution testing data. The firm should be asked to conduct dissolution testing as described below:

> USP XX Method II, 50 rpm.
> 500 ml water (deionized), 37°C.
> Specification: Not less than — in 30 minutes.

The dissolution testing should be conducted on 12 dosage units in comparison to that of 12 dosage units of Cytomel, 25 mcgm tablets.

7. Deficiencies:

1. Bioequivalence study - None.
2. Dissolution testing: See Comment under 6.

RECOMMENDATION:

1. The bioequivalence study conducted by Bolar Pharmaceutical Company on its Liothyronine sodium (lot #083269) in comparison to Cytomel, manufactured by Smith, Kline and French (lot #550016) demonstrates that Bolar's 25 microgram tablet is bioequivalent with Cytomel, 25 microgram tablet. The study is acceptable.

2. The firm should be informed of comment under 6.

3. Samples (<—— tablets) of Bolar's Liothyronine sodium (lot #083269) should be sent to:

Mrs. Ting Eng Ong Chen (Chemist)
Department of Health and Human Services
Food and Drug Administration
Bureau of Drugs, HFD-522
Division of Biopharmaceutics, Rm. 16B08
5600 Fishers Lane
Rockville, MD 20857

Shrikant V. Dighe

Shrikant V. Dighe, Ph.D.
Biopharmaceutics Review Branch

cc: ANDA 85-755 Orig., HFD-530 (4), HFD-522 (Dr. Dighe), Drug File, HFD-503 (Mr. Hare), HFD-522 (Dr. Ise), Review File, Chron File

SVDIGHE/mrs/9/28/81 (6560E)
RD INITIALED BY CMISE
FT INITIALED BY CMISE C. M. Ise 9-28-81

APPEARS THIS WAY
ON ORIGINAL

Liothyronine Sodium
25 microgram Tablet
ANDA 85-755

Bolar Pharmaceutical Co.
Copiague, New York
Submission Date:
September 23, 1981

Review of Dissolution

1. Bolar Pharmaceutical Company reports in this submission that dissolution data on its Liothyronine Sodium, 25 mg, tablet, is not available at this time. The firm also reports attempts to conduct dissolution in — 500 and — ml water, and with variety of paddle speeds. Although the tablets were completely dissolved in most cases after 60 minutes, the level of detection was too low to allow for accurate determination of concentration.

Comment:

2. The laboratory branch of the Division of Biopharmaceutics is developing a methodology for dissolution testing of T_3 (trirodothyronine sodium) tablets. The methodology would become available to interested investigators in about a month. Bolar should be asked to give written commitment to undertake dissolution testing of its liothyronine sodium drug product in comparison to Smith, Kline and French Company's Cytomel, 25 mcgm tablet, using the new methodology when it becomes available.

Recommendation:

1. The firm should be informed of the above comment.
2. Bolar Pharmaceutical Company will be required to meet dissolution specifications developed by the Agency in the future.

Shrikant V. Dighe

Shrikant V. Dighe, Ph.D.
Biopharmaceutics Review Branch

cc: Orig., HFD-530(4), HFD-522 (Dr. Dighe), Drug File, HFD-503 (Mr. Hare), HFD-522 (Dr. Ise), Review File, Chron File

DIGHE/rjb/10/03/81(6789E) RD
DIGHE/vmp/10/7/81(6789E) FT

RD INITIALED CMISE
FT INITIALED BY CMISE C.M. Ise 10-8-81

Liothyronine Sodium
Tablets, 25 and 50 mcg
ANDA 85-755
ANDA 85-753

Bolar Pharmaceuctical Co., Inc.
Copiague, New York
Submissions Dated:
October 12, 1981
November 4, 1981

REVIEW OF CORRESPONDENCE

Bolar conducted an acceptable bioequivalence study comparing its liothyronine sodium tablets, 25mcg (lot #083269) to Cytomel 25mcg tablets (lot #550016) manufactured by Smith, Kline and French.

With respect to dissolution testing, the firm was advised that the Laboratory Branch (HFD-524) is developing a methodology for dissolution testing of liothyronine sodium tablets. When the methodology becomes available the firm would be expected to undertake dissolution testing of its products in comparison with Cytomel using the new methodology.

The purpose of this communication (Bolar letters to Dr. Seife dated October 12 and November 4, 1981; see attachments) was to advise the Agency that:

> "Bolar will undertake dissolution testing of its liothyronine sodium drug product(s) in comparison to Smith, Kline and French Company's Cytomel, 25 (and 50)mcg tablets(s), using the new methodology when it become available."

COMMENTS:

1. The Division (HFD-520) received —— liothyronine tablets, 25mcg (lot #061073) from Bolar on October 24, 1981.

2. I called Mr. Jack Rivers (Bolar) to inform him that the development of dissolution test methodology was running behind schedule; the method should be ready in about 6 months. I also asked Mr. Rivers to send a sample (200 tablets) of the liothyronine sodium tablets, 25 and 50mcg for HFD-524 to use in methodology development. I specifically requested some samples of lot #083269 which was use in the in vivo bioavailability study.

3. Samples —— tablets) of liothyronine sodium tablets, 25 and 50mcg should be forwarded to:

   Ms. Ting E. O. Chen (Chemist)
   Food and Drug Administration (HFD-522)
   Room 16B-08
   5600 Fishers Lane
   Rockville, MD 20857

RECOMMENDATION:

The firm's commitment to do dissolution testing, when methodology becomes available, is acceptable.

From a biopharmaceutical point of view the applications for liothyronine sodium tablets, 25 and 50mcg-strength are approvable.

The above recommendations above as well as comments (#2 and 3) should be forwarded to the firm.

Francis R. Pelsor 1/6/82

Francis R. Pelsor, Pharm. D.
Biopharmaceutics Review Branch

cc: ANDA 85-755 orig., ANDA 85-753, HFD-530(4), HFD-522(Pelsor, Ise), Chron File, Drug File, Review File, HFD-503(Mr. Hare)

FRPELSOR/mk/12/23/81 (8036E)
FRP/mrs/1/6/82 FT

RD INITIALED BY CMISE
FT INITIALED BY CMISE C.M. Ise 1-7-82

CONCUR: Bernard E. Cabana Date 1/19/82
Bernard E. Cabana, Ph.D.
Director, Division of Biopharmaceutics

APPEARS THIS WAY
ON ORIGINAL

Liothyronine Sodium
25 microgram Tablet
ANDA 85-755

Bolar Pharmaceutical Company
Copiague, L.I., New York
Submission Dated:
April 30, 1979
October 15, 1979

REVIEW OF A BIOAVAILABILITY STUDY

1. Bolar Pharmaceutical Company has submitted a bioavailability study for its liothyronine sodium, 25 microgram tablet, comparing it with Cytomel manufactured by Smith, Kline and French. The study compares the concentrations of T_3 (tri-iodothyronine), T_4 (thyroxine) and TSH (thyroid stimulating hormone) in blood after an administration of a single dose of 75 (3 X 25) micrograms of the test or the reference product. The study was conducted by [redacted] under the supervision of [redacted]

2. The rationale for the study is based on considerations of the physiological activity of the thyroid gland. This gland secretes two active hormones, T_3 and T_4. Other factors such as iodine etc. being normal the secretion of these hormones by the thyroid is controlled by the pituitary gland through a feedback mechanism controlling the secretion of TSH. It is TSH which controls the secretion of T_3 and T_4. The investigators in this study hypothesize that the administration of extraneous T_3 should depress the secretion of the endogenous hormones in normal subjects through the pituitary feedback mechanism. Thus the concentration of TSH and the ratio of T_4 to T_3 in the circulation should decrease. The investigators claim that such an effect is easily demonstrable in individual cases with large (100 micrograms) doses of T_3. They further claim that a 75 micrograms dose would produce the same effect qualitatively but quantitatively the intensity of the effect would be less.

3. The study employed 16 healthy male euthyroid subjects in a two-way crossover. Subjects were selected on the basis of physical examination, medical history and clinical laboratory tests (SMA 12) including T_3, T_4 and TSH determination. Written informed consent was obtained from the subjects. On the study day 1 of each leg of the crossover the subjects were confined to the clinical facility for 12 hours. Each subject was administered a single dose of 75 micrograms of the test or the reference product. Blood samples were collected at 0, 1, 2, 3, 4, 6, 8, 12, 24, 36, 48, 60, and 72 hours after dose administration. The crossover period was one week.

The blood samples were assayed for T_3, T_4 and TSH by use of [redacted] assay techniques.

At the conclusion of the study each subject was given a physical examination and SMA-12 laboratory tests.

COMMENTS:

1. In Table I are shown the mean values for the concentration of T_3 and T_4 at various sampling times. Inspection of the data shows that there is hardly any change from the mean base values for T_3 and T_4 obtained at 0 hour before administration of the drug. The data strongly demonstrate that the presence of endogenous T_3 and T_4 there is no significantly discernible change in the concentration of T_3 and T_4 in blood upon administration of 75 micrograms of T_3. This is not surprising and should be expected in view of the fact that 99.5 percent of T_3 is protein bound.* The volume of distribution (Vd) of T_3 is about 42 liters for a normal individual (70 Kg).* Even a totally absorbed and unbound drug would add only about 0.0018 mcg/ml to the already existing pool of T_3 in the body. To detect changes in the concentration of this magnitude and quantitate them one needs an analytical methodology with sensitivity in picograms per milliliter. The method employed does not have that kind of sensitivity.

* "Handbood of Clinical Pharmacology", F. Bochner, et al., Little, Brown and Company, Boston, 1978; p. 291.

Similarly T_4 is 99.95 percent protein-bound and has a volume of distribution of 6-12 liters. The normal value for T_4 is 4-13 mcg/100 ml. The ~~~ method is not sensitive enough to detect any minute changes in concentrations.

Table I

Mean Blood Levels at Each Collection Time (Groups Pooled)

Drug A: Bolar Liothyronine

Drug B: Cytomel

	T_3 (mg %)		T_4 (mcg %)	
Hr.	Drug A	Drug B	Drug A	Drug B
0	44.2 ± 3.0	44.8 ± 2.7	9.3 ± 2.0	9.0 ± 1.7
1	45.2 ± 3.2	44.9 ± 2.8	9.3 ± 2.0	8.9 ± 2.1
2	44.7 ± 3.2	44.9 ± 2.7	9.2 ± 2.2	9.3 ± 2.1
3	44.9 ± 3.4	45.0 ± 2.9	9.0 ± 2.3	9.2 ± 2.6
4	44.5 ± 3.6	44.5 ± 2.8	9.4 ± 2.1	9.8 ± 3.0
6	44.6 ± 2.9	44.7 ± 3.1	8.9 ± 2.4	9.1 ± 2.3
8	45.3 ± 2.8	44.0 ± 2.7	9.1 ± 2.5	9.8 ± 2.9
12	43.9 ± 3.5	43.8 ± 3.1	9.1 ± 2.2	9.3 ± 2.7
24	44.8 ± 3.3	44.0 ± 2.9	8.7 ± 2.3	8.4 ± 1.9
36	43.2 ± 3.1	43.5 ± 3.0	9.0 ± 2.3	8.4 ± 1.5
48	44.9 ± 3.5	44.5 ± 2.5	7.7 ± 2.3	7.9 ± 1.4
60	42.3 ± 3.8	43.0 ± 4.1	7.9 ± 2.0	7.8 ± 1.4
72	43.4 ± 3.6	43.1 ± 2.4	7.6 ± 1.6	8.4 ± 1.7

2. Table II shows the individual values for the baseline of T_3 for the test and the reference product; it also shows blood levels of T_3 averaged over a period of 72 hours for each individual upon administration of the test or the reference product (Average blood level = (Concentrations of 12 sampling times divided by 12)). If the hypothesis of investigators is correct there should be a drop in the value of T_3 concentration after administration of exogenous T_3. In the case of Cytomel (the reference product) one sees a very small drop in T_3 concentration in 12 out of 16 subjects; for the Bolar product only in 5 subjects out of 16, there is a small drop in T_3 value in comparison to the baseline value.

3. Table III enumerates baseline concentration, and average concentration (1 to 72 hours) of TSH for each individual upon administration of Cytomel and Bolar product. There is a small drop in TSH concentraton upon Cytomel administration in 12 out of 16 subjects

but TSH concentration actually increases in 11 out of 16 subjects upon administration of Bolar product. The magnitude of decrease in concentration is too small to use this parameter to demonstrate the bioequivalence of the two products.

Table II

	T_3 Cytomel (%)		T_3 - Bolar (%)	
	Baseline	Ave. Level	Baseline	Ave. Level
1	45.7	43.8	44.8	44.8
2	47.1	49.3	49.7	52.3
3	48.9	49.1	46.6	44.4
4	41.9	42.9	38.7	40.8
5	37.8	41.1	42.4	41.6
6	45.7	44.6	42.3	43.1
7	45.4	43.9	43.4	45.1
8	47.9	46.8	45.0	45.5
9	47.2	45.4	42.1	44.7
10	44.7	43.0	44.0	44.4
11	43.2	42.8	40.4	40.6
12	45.5	44.4	47.1	47.1
13	42.6	41.2	43.0	41.7
14	46.1	45.4	46.0	45.3
15	44.5	43.1	47.6	45.0
16	42.6	41.4	41.8	42.5

Table III

TSH Concentraton in IU/ml

	TSH - Cytomel		TSH - Bolar	
Subject #	Baseline	Ave/Level	Baseline	Ave/Level
1	4.6	2.52	1.6	2.73
2	2.3	1.78	1.6	2.11
3	3.4	2.15	1.8	1.69
4	1.8	1.29	1.0	1.36
5	3.1	3.23	1.7	3.83
6	2.8	2.49	2.6	3.09
7	3.6	3.21	0.9	1.33
8	2.2	3.16	4.7	3.79
9	1.3	2.66	2.0	3.73
10	3.7	2.99	2.2	2.10
11	1.8	2.53	4.6	2.90
12	4.8	3.22	2.8	1.82
13	4.3	3.28	1.7	2.53
14	3.3	2.29	2.0	1.43
15	5.0	2.76	0.7	1.96
16	2.1	2.46	1.7	2.02

DEFICIENCIES:

1. The data based on blood concentrations of T_3, T_4 and TSH upon administration liothyromine sodium and its comparison to the baseline values for these parameters do not substantiate the hypothesis of the investigators that the drop in values for these parameters would quantitatively demonstrate the bioequivalence the test product with the reference product. In view of the presence of endogenous T_3, T_4 and TSH in euthyroid subjects and the extremely small amount of the drug (75 mcg) administered, and the high protein-binding and volume of distributiion of T_3, the use of subjects with normal thyroid function is not appropriate to demonstrate bioequivalence of the test product to the reference product.

2. The report does not contain validation of the assay methodology employed to analyze the blood samples.

3. The concentration units for T_3 are not described anywhere in the report.

RECOMMENDATION:

1. The study is unacceptable to demonstrate bioequivalence of Bolar's liothyronine sodium 25 mcg tablet with Cytomel (manufactured by Smith, Kline and French).

2. Use of subjects with normal thyroid functions appears to be inappropriate. A study comparing steady-state blood levels of T_3, T_4 and TSH in hypothyroid patient upon administration of the test and reference products will be appropriate and desirable.

The firm should be informed of COMMENTS 1, 2, and 3, and DEFICIENCIES 1, 2, and 3.

Shrikant V. Dighe

Shrikant V. Dighe, Ph.D.
Biopharmaceutics Review Branch

cc: ANDA 85-755 Orig., HFD-530 (4), HFD-522 (Dr. Dighe), Drug File, Review File, Chron File

SVDIGHE/mrs/12/11/80 (0089E)
RD INITIALED BY CMISE
FT INITIALED BY SVDIGHE C. M Ise

APPEARS THIS WAY
ON ORIGINAL

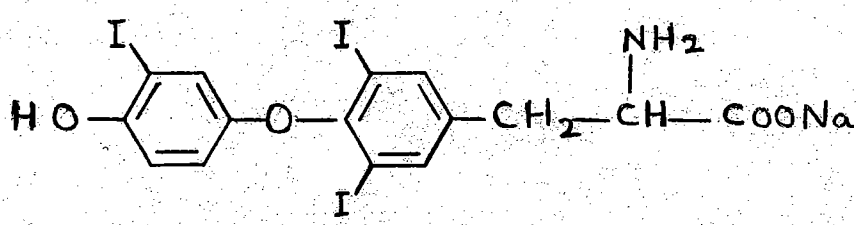
Liothyronine Sodium
25 mcg Tablet
ANDA 85-755

Bolar Pharmaceutical Co.
Copiague, New York
Submission Dated:
October 24, 1978

REVIEW OF A BIOAVAILABILITY PROTOCOL

1. The purpose of the proposed study in this protocol is to compare a new formulation of liothyronine sodium (sodium salt of L-triiodothyronine, T3) with a commercially available formulation (Cytomel) in order to establish bioequivalence.

2. Sodium liothyronine is a sodium salt of L-isomer of 3, 3^1, 5-triiodothyronine. The chemical structure of the compound is shown below:



The drug is indicated in hypothyroidism and the usual initial dose for adults is 25 mcg daily.

3. The study will employ 16 healthy male subjects with normal thyroid function, in a two-way crossover design study. They will be chosen from the general population on the basis of physical examination and clinical laboratory tests (SMA 12) including determination of T_3, T_4 and TSH. On study day subjects will ingest a single dose of 3 x 25 mcg tablets of the test product or the reference product (cytomel). Blood samples will be drawn at 0, 1, 2, 3, 4, 6, 8, 12, 24, 36, 48, 60 and 72 hours after dose administration. The washout period will be one week, after which the subjects will be crossed over. The study will close with a physical examination of each subject and a repeat of clinical laboratory tests. The analysis of blood samples will be carried out by a hospital laboratory, located at the [redacted] The blood level data will be subjected to appropriate statistical analysis. Severe adverse experiences including symptoms of hyperthyroidism e.g. nervousness, cardiac arrythmia, etc. will be reported immediately to the sponsor. The study will be conducted by [redacted]

COMMENTS:

1. Blood samples should be analyzed by a method specific for T_3 and T_4. The analyst should validate the method for its specificity, sensitivity and linearity. We suggest a pilot study employing four subjects be conducted.

2. The protocol does not contain any description of the facility where the study will be conducted. A full description of the clinical and laboratory facilities should be provided.

3. The protocol does not contain the name and curriculum vitae of the principal investigator for the study. These should be included in the protocol.

4. Written, informed consent should be signed by each participant in the study, after the protocol, purpose of study and adverse reactions have been fully and satisfactorily explained to the subjects.

5. The firm should conduct dissolution testing on both the test and the reference product. Dissolution testing should be conducted in 500 ml deionized water using USP paddle at 50 rpm. Samples should be collected at 10, 20, 30, 45 and 60 minutes to generate dissolution profiles for both test and reference products.

6. All compendial tests such as disintegration, content uniformity, etc., should be performed on test and reference products used in the study and reported.

7. The study report should contain all raw data, physical examination and clinical laboratory test data, standard curves, etc. A complete, step by step description of analytical method and recovery data should be part of the study report.

8. The study report should include pharmacokinetic analysis of the blood level data. Pharmacokinetic parameters such as Cmax, Tmax, AUC, half-life of absorption and elimination should be computed and reported.

9. The blood level data should be analyzed statistically using the Analysis of Variance technique. All blood level data for individuals should be reported in tabular form. The mean data should be reported in a graphical display.

RECOMMENDATION:

The study protocol as written is incomplete and unacceptable. The company should be informed of comments 1 through 9 and asked to submit a revised protocol incorporating the comments.

Shrikant V. Dighe

Shrikant V. Dighe, Ph.D.
Biopharmaceutics Review Branch

cc: ANDA Orig., HFD-530, HFD-522, HFD-525, Chron File

SVDIGHE/mrs/12/22/78
RD INITIALED BY SVDIGHE
FINAL TYPE INITIALED BY SVD
12/28/78

CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

85-755

ADMINISTRATIVE DOCUMENTS

MEMO RECORD	AVOID ERRORS PUT IT IN WRITING	DATE 10/25/78
FROM: Marvin Seife, M.D.		OFFICE HFD-500
TO: Division of Biopharmaceutics		DIVISION HFD-530
SUBJECT:		

SUMMARY

ATTENTION: Dr. Jerome P. Skelly

ANDA #: 85-755

Liothyronine Sodium Tablets 25mcg

Bolar Pharmaceutical Co.

Please review the bioavailability protocol on the above drug.

Thank you,

Marvin Seife

Marvin Seife, M.D.

APPEARS THIS WAY
ON ORIGINAL

SIGNATURE	DOCUMENT NUMBER

FD FORM 2034 (2/73)

MEMO RECORD	AVOID ERRORS PUT IT IN WRITING	DATE 9/23
FROM: J. M. Ross		OFFICE
TO:		DIVISION

SUBJECT: Review of Bioavailability Studies

SUMMARY

85-753 + 85-755 Sodium Liothyronine Tabs.
Bolar Pharm. Co. Inc.

In a conversation today (9/23/80) with Dr. Isci, I was told that so far their bio-studies are not satisfactory. In fact they have been in touch with Bolar representatives recently. Bolar's representatives were to send their studies to _____ for a second opinion. As of yet our Div. of Pharm. has received no reply from Bolar concerning this.
Presently Dr. Isci indicated that based on the information we have, the study will not be approved.

SIGNATURE J M Ross

DOCUMENT NUMBER 85-755/753

FD FORM 2034 (2/72)

MEMORANDUM

DEPARTMENT OF HEALTH, EDUCATION, AND WELFARE
PUBLIC HEALTH SERVICE
FOOD AND DRUG ADMINISTRATION

DATE: July 31, 1979

TO : Director
Division of Generic Drug Monographs (HFD-530)
Attn: G. Millar

FROM : Chief, Manufacturing Review Branch (HFD-322)
Division of Drug Manufacturing

SUBJECT: Approvable ANDAs -
85-755 - Liothyronine Sodium Tablets

APPLICANT: Bolar Pharmaceutical Co., Inc.,
Copiague, New York

[redacted]

We have evaluated the operations of [redacted] as they relate to compliance with Current Good Manufacturing Practice Regulations (21 CFR 211) and the referenced New Drug Applications. We conclude that there is no reason to withhold approval of the referenced pending ANDAs insofar as they relate to this firm and the type of operations as specified in these pending new drug applications.

Our evaluation is based in part on an inspection concudted November 29, 30, 1977.

David H. Bryant

cc: NYK-DO (HFR-2100)
HFD-322 Firm File
HFD-300 R/F
HFD-530 (2)
HFD-530 (ANDA Orig)
WSKletch:hjh:7/31/79
WSKletch 7/31/79

85-755

MEMORANDUM

DEPARTMENT OF HEALTH, EDUCATION, AND WELFARE
PUBLIC HEALTH SERVICE
FOOD AND DRUG ADMINISTRATION

TO : Marvin Seife, M.D.
Director, Division of Generic Drug Monographs (HFD-530)

DATE: January 25, 1982

THROUGH: Bernard E. Cabana, Ph.D.,
Director, Division of Biopharmaceutics (HFD-520) B E Cabana

FROM : Chief, Biopharmaceutics Review Branch (HFD-522)

SUBJECT: Deferral of In Vitro Dissolution Testing for Sodium Liothyronine Tablets.

1. In September 1981 the Division of Biopharmaceutics approved an in vivo bioequivalence study conducted by Bolar Pharmaceutical Company on its 25 microgram tablet. At that time the firm was asked to conduct dissolution testing on the test product in comparison with Cytomel, manufactured by Smith, Kline and French Company. In response the firm furnished information that even though the drug product visually went in solution completely, it was not possible to measure the quantity in solution in view of the small amount of active ingredient (25 microgram) in the drug product.

2. A [redacted] method, developed by the Laboratory Branch of the Division of Biopharmaceutics, for assay of sodium liothyronine in solution shows about [redacted] percent dissolution in 60 minutes for the active ingredient. With the present state of the art the assay method is not sufficiently discriminating and needs further refinement.

3. In the absence of sensitive, discriminating assay methodology for the active ingredient, in vitro dissolution testing requirement for sodium liothyronine should be deferred. The basis of approval of abbreviated new drug application should be: (i) an acceptable in vivo bioequivalence study, (ii) acceptable stability data and manufacturing controls, (iii) chemistry, and (iv) good manufacturing practices.

4. Applicant firms should be informed that they will be required to conduct in vitro dissolution testing on sodium liothyronine drug products when an adequate assay methodology becomes available, and meet the dissolution specifications imposed by the Agency. A written commitment to this effect should be requested from the firms.

Shrikant V. Dighe

Shrikant V. Dighe, Ph.D.

NOTICE OF APPROVAL
NEW DRUG APPLICATION OR SUPPLEMENT

NDA NUMBER: 85-755

DATE APPROVAL LETTER ISSUED:

TO: Press Relations Staff (HFI-40)

FROM:
- [X] Bureau of Drugs
- [ ] Bureau of Veterinary Medicine

ATTENTION

Forward original of this form for publication only after approval letter has been issued and the date of approval has been entered above.

ORIGINAL ABBREVIATED

TYPE OF APPLICATION
- [ ] ORIGINAL NDA
- [ ] SUPPLEMENT TO NDA
- [X] ABBREVIATED ORIGINAL NDA
- [ ] SUPPLEMENT TO ANDA

CATEGORY
- [X] HUMAN
- [ ] VETERINA

TRADE NAME (or other designated name) AND ESTABLISHED OR NONPROPRIETARY NAME (if any) OF DRUG:
Liothyronine Sodium

DOSAGE FORM: Tablet

HOW DISPENSED
- [X] RX
- [ ] OTC

ACTIVE INGREDIENT(S) (as declared on label. List by established or nonproprietary name(s) and include amount(s), if amount is declared on label.)

Liothyronine Sodium, 25 mcg

APPEARS THIS WAY
ON ORIGINAL

NAME OF APPLICANT (Include City and State)

Bolar Pharmaceutical Company, Inc.
130 Lincoln Street
Copiague, New York 11726

PRINCIPAL INDICATION OR PHARMACOLOGICAL CATEGORY

Thyroid hormone

COMPLETE FOR VETERINARY ONLY

ANIMAL SPECIES FOR WHICH APPROVED

COMPLETE FOR SUPPLEMENT ONLY

CHANGE APPROVED TO PROVIDE FOR

FORM PREPARED BY

NAME: Brenda T. Arnwine — Brenda T. Arnwine — DATE: 1/25/82

FORM APPROVED BY

NAME: Howard C. Zell — Howard C. Zell — DATE: 1/25/82

FORM FD 1642 (2/75) PREVIOUS EDITION MAY BE USED UNTIL SUPPLY IS EXHAUSTED.

CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

85-755

CORRESPONDENCE

FEB 1 1982

NDA 85-753
NDA 85-755

Solar Pharmaceutical Co., Inc.
Attention: Mr. Robert Shulman
130 Lincoln Street
Copiague, NY 11726

Gentlemen:

Reference is made to your correspondence dated October 20, 1981 and November 4, 1981 regarding Liothyronine Sodium Tablets, 25 and 50 mcg.

The letter was reviewed by our Division of Biopharmaceutics and they have the following comments:

"1. Mr. Jack Rivers (Solar) was informed that the development of dissolution test methodology was running behind schedule; the method should be ready in about 6 months. Mr. Rivers was asked to send a sample (— tablets) of the liothyronine sodium tablets, 25 and 50 mcg for HFD-624 to use in methodology development. Samples of lot #083269 which was used in the in vivo bioavailability study were specifically requested.

2. Samples (— tablets) of liothyronine sodium tablets, 25 and 50 mcg should be forwarded to:

Ms. Ting E.O. Chen
FDA/Division of Biopharmaceutics (HFD-522)
5600 Fishers Lane
Rockville, MD 20857

RECOMMENDATIONS: The firm's commitment to do dissolution testing, when methodology becomes available, is acceptable."

Sincerely yours,

Marvin Seife, M.D.
Director
Division of Generic Drug Monographs
Office of Drug Monographs
Bureau of Drugs

cc:
NYK-DO DUP
HFD-530
HFD-520
MSeife/wh/2-1-82
bio

FEB 1 1982

NDA 85-755

Bolar Pharmaceutical Co.
Attention: Mr. Robert Shulman
130 Lincoln St.
Copiague, NY 11726

Gentlemen:

Reference is made to the dissolution data you submitted for Sodium Liothyronine Tablets, 25 mcg.

The data have been reviewed by our Division of Biopharmaceutics and they have the following comments:

"1. In September 1981 the Division of Biopharmaceutics approved an *in vivo* bioequivalence study conducted by Bolar Pharmaceutical Company on its 25 microgram tablet. At that time the firm was asked to conduct dissolution testing on the test product in comparison with Cytomel, manufactured by Smith, Kline and French Company. In response the firm furnished information that even though the drug product visually went in solution completely, it was not possible to measure the quantity in solution in view of the small amount of active ingredient (25 microgram) in the drug product.

2. A [redacted] method, developed by the Laboratory Branch of the Division of Biopharmaceutics, for assay of sodium liothyronine in solution shows about [redacted] percent dissolution in 60 minutes for the active ingredient. With the present state of the art the assay method is not sufficiently discriminating and needs further refinement.

3. In the absence of sensitive, discriminating assay methodology for the active ingredient, *in vitro* dissolution testing requirement for sodium liothyronine should be deferred.

4. Applicant firms will be required to conduct *in vitro* dissolution testing on sodium liothyronine drug products when ad adequate assay methodology becomes available, and meet the dissolution specifications imposed by the Agency. A written commitment to this effect is requested."

Sincerely yours,

Marvin Seife 1/29/82

Marvin Seife, M.D.
Director
Division of Generic Drug Monographs
Office of Drug Monographs
Bureau of Drugs

cc:
NYK-DO DUP
HFD-530
HFD-520
MSeife/wh/1-29-82
bio

Oii

11/10/81
THE SUBMITTED FPL IS SATISFACTORY.
M.B.

BOLAR PHARMACEUTICAL CO., INC.
130 Lincoln Street, Copiague, New York 11726
(516) 842-8383

November 3, 1981

NDA # 85-755

Bureau of Drugs
Food and Drug Administration
HFD # 530
Room # 16-72
5600 Fishers Lane
Rockville, Maryland 20857

NDA ORIG AMENDMENT

ATTN: Dr. Marvin Seife

FPL

Dear Dr. Seife,

In reference to our Abbreviated New Drug Application for Liothyronine Sodium Tablets, 25 mcg, enclosed please find the following:

1. Our Revised Package Insert as per your letter of October 14, 1981.

2. Our Final Printed Container Labels.

Sincerely,

Robert Shulman, President
ENCLS:
RS/fn

RECEIVED
NOV 06 1981
GENERIC DRUGS

orig

BOLAR PHARMACEUTICAL CO., INC.

130 Lincoln Street, Copiague, New York 11726

(516) 842-8383

October 20, 1981

NDA # 85-755

ORIG NEW CORRES

Bureau of Drugs
Food and Drug Administration
HFD # 530
Room # 16-72
5600 Fishers Lane
Rockville, Maryland 20857

ATTN: Dr. Marvin Seife,

Dear Dr. Seife,

In reference to our Abbreviated New Drug Application for Liothyronine Sodium Tablets, 25 mcg and your letter of October 13, 1981, please be advised of the following:

> Bolar will undertake dissolution testing of its liothyronine sodium drug product in comparison to Smith, Kline and French Company's Cytomel, 25 mcgm tablet, using the new methodology when it becomes available.

Sincerely,

Robert Shulman

Robert Shulman, President
RS/fn

RECEIVED
OCT 26 1981
GENERIC DRUGS

NDA 85-755

Bolar Pharmaceutical Co.
Attention: Robert Shulman
130 Lincoln Street
Copiague, NY 11726

Gentlemen:

Reference is made to the bioavailability study you submitted for Liothyronine Sodium Tablets, 25 mg.

The study has been reviewed by our Division of Biopharmaceutics and they have the following comments:

"1. The bioequivalence study conducted by Bolar Pharmaceutical Company on its Liothyronine sodium (lot #083269) in comparison to Cytomel, m manufactured by Smith, Kline and French (lot #550016) demonstrates that Bolar's 25 microgram tablet is bioequivalent with Cytomel, 25 microgram tablet. The study is acceptable.

2. The present submission contains no dissolution testing data. The firm is requested to conduct dissolution testing as described below:

USP XX Method II, 50 rpm
500 ml. water (deionized), 37°C
Specification: Not less than —— in 30 minutes.

The dissolution testing should be conducted on 12 dosage units in comparison to that of 12 dosage units of Cytomel, 25 mcgm tablets.

3. Samples (—— tablets) of Bolar's Liothyronine sodium (lot #083269) should be sent to:

Mrs. Ting Eng Ong Chen
FDA/BD/Division of Biopharmaceutics (HFD-522)
5600 Fishers Lane
Rockville, MD 20857"

Sincerely yours,

Marvin Seife 10/1/81

Marvin Seife, M.D.
Director
Division of Generic Drug Monographs
Office of Drug Monographs
Bureau of Drugs

cc:
NYK-DO
DUP
HFD-530 HFD-520
MSeife/wh/9-30-81
bio

OCT 14 1981

NDA 85-755

Bolar Pharmaceutical Co., Inc.
Attention: Robert Shulman
130 Lincoln Street
Copiague, NY 11726

Gentlemen:

Reference is made to your communication dated September 23, 1981 regarding your abbreviated new drug application sbbmitted pursuant to Section 505(b) of the Federal Food, Drug, and Cosmetic Act for Liothyronine Sodium Tablets, 25 mcg.

The labeling submitted with this communication has been reviewed and we have the following comments:

Package insert:

1. WARNING section: Include a box warning referable to use in obesity as per the enclosed Federal Register statement.

2. DOSAGE AND ADMINISTRATION section: Delete the subsection headed "_____" as this is not an approved Indication.

Please submit twelve final printed inserts, revised as above, when available.

Sincerely yours,

Marvin Seife 10/13/81

Marvin Seife, M.D.
Director
Division of Generic Drug Monographs
Office of Drug Monographs
Bureau of Drugs

Enclosure:
F.R. 5-23-78

cc:
NYK-DO DUP
HFD-530
HFD-614
MSeife/wh/10-13-81
labeling letter

OCT 13 1981

NDA 85-755

Bolar Pharmaceutical Co., Inc.
Attention: Robert Shulman
130 Lincoln Street
Copiague, NY 11726

Gentlemen:

Reference is made to the dissolution data you submitted for Liothyronine Sodium Tablets, 25 mcg.

The data have been reviewed by our Division of Biopharmaceutics and they have the following comments:

> "The laboratory branch of the Division of Biopharmaceutics is developing a methodology for dissolution testing of T_3 (triiodothyronine sodium) tablets. The methodology should become available to interested investigators in about a month. Bolar is to submit a written commitment to undertake dissolution testing of its liothyronine sodium drug product in comparison to Smith, Kline and French Company's Cytomel, 25 mcgm tablet, using the new methodology when it becomes available.
>
> RECOMMENDATIONS: Bolar Pharmaceutical Company will be required to meet dissolution specifications developed by the Agency in the future."

Sincerely yours,

Marvin Seife 10/9/81

Marvin Seife, M.D.
Director
Division of Generic Drug Monographs
Office of Drug Monographs
Bureau of Drugs

cc:
NYK-DO DUP
HFD-530
HFD-614
HFD-520
Mseife/wh/10-9-81
bio

10/13/81
The TPP package insert is satisfactory except for 2 items,
a) include a box warning in the WARNING section referable to use in obesity &
b). delete from the DOSAGE AND ADMINISTRATION section, the subsection headed "..." as this is not an approved INDICATION M.S.

ORIG

BOLAR PHARMACEUTICAL CO., INC.

130 Lincoln Street, Copiague, New York 11726

(516) 842-8383

September 23, 1981

NDA # 85-755

Bureau of Drugs
Food and Drug Administration
HFD # 530
Room # 16-72
5600 Fishers Lane
Rockville, Maryland 20857

NDA ORIG AMENDMENT

EPL

ATTN: Dr. Marvin Seife,

BIOAVAILABILITY MATERIAL

Dear Dr. Seife,

In reference to our Abbreviated New Drug Application for Liothyronine Sodium Tablets, 25 mcg and your letters of September 29, 1980 and September 8, 1981, please be advised of the following:

1. Current final printed inserts are enclosed. Final printed labels will be forwarded as soon as available.

2. A revised raw material specification for Liothyronine Sodium is enclosed. The enclosed method is an [redacted] analysis developed by our Analytical Research and Development Section under the Direction of Ms. Gena Finelli. It was ascertained that the USP assay for Liothyronine is based upon total iodine content and therefore is not specific for Liothyronine. The enclosed [redacted] analysis allows for specific quantitation of Liothyronine as well as Diiodothyronine and Thyroxine.

3. Revised excipient specifications in accord with current compendia requirements are enclosed.

4. Finished dosage form specifications including Content Uniformity and Stability Testing Procedures along with Precision and Recovery Data are enclosed.

5. Samples of the active ingredient and dosage form along with analytical results of all tests performed are enclosed.

6. Challenge Condition Stability Data is enclosed.

RECEIVED
SEP 24 1981
GENERIC DRUGS

BOLAR PHARMACEUTICAL CO., INC.

130 Lincoln Street, Copiague, New York 11726

(516) 842-8383

7. Updated Stability Data for the two lots submitted on October 24, 1977 is enclosed.

Based upon the enclosed data we are requesting a 36 month expiration date.

Dissolution data at this point in time is not available. In our efforts to establish a Dissolution Procedure, we reduced the dissolution media from ___ to 500 ml and finally to ___. We used a number of dissolution media including water, and varied the paddle speed. Although the tablets were completely dissolved in most cases after 60 minutes, the level of detection was too low to allow for accurate, reproducable results.

Sincerely,

Robert Shulman, President
ENCLS:
RS/fn

SEP 8 1981

ANDA 85-755

Bolar Pharmaceutical Company
Attention: Robert Shulman
130 Lincoln Street
Copiague, New York 11726

Gentlemen:

Reference is made to your abbreviated new drug application dated April 12, 1977, submitted pursuant to Section 505(b) of the Federal Food, Drug, and Cosmetic Act for Liothyronine Sodium Tablets, 25 mcg.

After a further review of your application, we have the following comments:

1. Your bioavailability study submitted May 29, 1981 is currently under review by our Division of Biopharmaceutics.

2. Submit revised specification for the finished dosage form and ingredients in accord with current compendia (USP XX and NF XV) requirements.

3. Submit current stability data.

4. Submit current final printed labeling of the package insert and container label.

Your response is requested.

Sincerely yours,

Marvin Seife 9/8/81

Marvin Seife, M.D.
Director
Division of Generic Drug Monographs
Office of Drug Monographs
Bureau of Drugs

cc: NYK-DO
HFD-616
HCZell/RJoyce
R/D INITIAL HCZell/MSeife
ms 9/3/81
rev w/f (6253E)

Orig

Dupon Bx

BOLAR PHARMACEUTICAL CO., INC.

130 Lincoln Street, Copiague, New York 11726

(516) 842-8383

May 29, 1981

NDA # 85-755

Bureau of Drugs
Food and Drug Administration
HFD # 530
Room # 16-72
5600 Fishers Lane
Rockville, Maryland 20857

NDA ORIG AMENDMENT

ATTN: Dr. Marvin Seife

BIOAVAILABILITY MATERIAL

Dear Dr. Seife,

In reference to our Abbreviated New Drug Application for Liothyronine Sodium Tablets, 25 mcg., please be advised of the following:

Our Completed Bioavailability Study is enclosed.

Sincerely,

Robert Shulman

Robert Shulman, President
ENCLS:
RS/fn

RECEIVED
JUN 01 1981
GENERIC DRUGS

NDA 85-755

DEC 12 1980

Bolar Pharmaceutical Co., Inc.
Attention: Mr. Robert Shulman
130 Lincoln Street
Copiague, NY 11726

Gentlemen:

Reference is made to the bioavailability studies you submitted for Liothyronine Sodium Tablets, 25 mcg.

The studies have been reviewed by our Division of Biopharmaceutics and they have the following comments:

"1. In Table I are shown the mean values for the concentration of T_3 and T_4 at various sampling times. Inspection of the data shows that there is hardly any change from the mean base values for T_3 and T_4 obtained at 0 hour before administration of the drug. The data strongly demonstrate that the presence of endogenous T_3 and T_4 there is no significantly discernible change in the concentration of T_3 and T_4 in blood upon administration of 75 micrograms of T_3. This is not surprising and should be expected in view of the fact that 99.5 percent of T_3 is protein bound.* The volume of distribution (Vd) of T_3 is about 42 liters for a normal individual (70 Kg).* Even a totally absorbed and unbound drug would add only about 0.0018 mcg/ml to the already existing pool of T_3 in the body. To detect changes in the concentration of this magnitude and quantitate them one needs an analytical methodology with sensitivity in picograms per milliliter. The RIA method employed does not have that kind of sensitivity.

APPEARS THIS WAY
ON ORIGINAL

* "Handbook of Clinical Pharmacology", F. Bochner, et al., Little, Brown and Company, Boston, 1978; p. 291.

Similarly T_4 is 99.95 percent protein-bound and has a volume of distribution of 6-12 liters. The normal value for T_4 is 4-13 mcg/100 ml. The RIA method is not sensitive enough to detect any minute changes in concentrations.

Table 1

Mean Blood Levels at Each Collection Time (Groups Pooled)

Drug A: Bolar Liothyronine

Drug B: Cytomel

	T (mg %)		T (mcg %)	
Hr.	Drug A	Drug B	Drug A	Drug B
0	44.2 ± 3.0	44.8 ± 2.7	9.3 ± 2.0	9.0 ± 1.7
1	45.2 ± 3.2	44.9 ± 2.8	9.3 ± 2.0	8.9 ± 2.1
2	44.7 ± 3.2	44.9 ± 2.7	9.2 ± 2.2	9.3 ± 2.1
3	44.9 ± 3.4	45.0 ± 2.9	9.0 ± 2.3	9.2 ± 2.6
4	44.5 ± 3.6	44.5 ± 2.8	9.4 ± 2.1	9.8 ± 3.0
6	44.6 ± 2.9	44.7 ± 3.1	8.9 ± 2.4	9.1 ± 2.3
8	45.3 ± 2.8	44.0 ± 2.7	9.1 ± 2.5	9.8 ± 2.9
12	43.9 ± 3.5	43.8 ± 3.0	9.1 ± 2.2	9.3 ± 2.7
24	44.8 ± 3.3	44.0 ± 2.9	8.7 ± 2.3	8.4 ± 1.9
36	43.2 ± 3.1	43.5 ± 3.0	9.0 ± 2.3	8.4 ± 1.5
48	44.9 ± 3.5	44.5 ± 2.5	7.7 ± 2.3	7.9 ± 1.4
60	42.3 ± 3.8	43.0 ± 4.1	7.9 ± 2.0	7.8 ± 1.4
72	43.4 ± 3.6	43.1 ± 2.4	7.6 ± 1.6	8.4 ± 1.7

2. Table II shows the individual values for the baseline of T_3 for the test and the reference product; it also shows blood levels of T_3 averaged over a period of 72 hours for each individual upon administration of the test or ther reference product (Average blood level = (Concentrations of 12 sampling times divided by 12)). If the hypothesis of investigators is correct there should be a drop in the value of T_3 concentration after administration of exogenous T_3. In the case of Cytomel (the reference product) one sees a very small drop in T_3 concentration in 12 out of 16 subjects; for the Bolar product only in 5 subjects out of 16, there is a small drop in T_3 value in comparison to the baseline value.

3. Table III enumerates baseline concentration, and average concentration (1 to 72 hours) of TSH for each individual upon administration of Cytomel and Bolar product. There is a small drop in TSH concentration upon Cytomel administration in 12 out of 16 subjects but TSH concentration actually increases

in 11 out of 16 subjects upon administration of Bolar product. The magnitude of decrease in concentration is too small to use this parameter to demonstrate the bioequivalence of the two products.

Table II

	T Cytomel (%)		T - Bolar (%)	
	Baseline	Ave. Level	Baseline	Ave. Level
1	45.7	43.8	44.8	44.8
2	47.1	49.3	49.7	52.3
3	48.9	49.1	46.6	44.4
4	41.9	42.9	38.7	40.8
5	37.8	41.1	42.4	41.6
6	45.7	44.6	42.3	43.1
7	45.4	43.9	43.4	45.1
8	47.9	46.8	45.0	45.5
9	47.2	45.4	42.1	44.7
10	44.7	43.0	44.0	44.4
11	43.2	42.8	40.4	40.6
12	45.5	44.4	47.1	47.1
13	42.6	41.2	43.0	41.7
14	46.1	45.4	46.0	45.3
15	44.5	43.1	47.6	45.0
16	42.6	41.4	41.8	42.5

Table III

TSH Concentration in IU/ml

	TSH - Cytomel		TSH - Bolar	
Subject #	Baseline	Ave/Level	Baseline	Ave/Level
1	4.6	2.52	1.6	2.73
2	2.3	1.78	1.6	2.11
3	3.4	2.15	1.8	1.69
4	1.8	1.29	1.0	1.36
5	3.1	3.23	1.7	3.83
6	2.8	2.49	2.6	3.09
7	3.6	3.21	0.9	1.33
8	2.2	3.16	4.7	3.79
9	1.3	2.66	2.0	3.73
10	3.7	2.99	2.2	2.10
11	1.8	2.53	4.6	2.90
12	4.8	3.22	2.8	1.82
13	4.3	3.28	1.7	2.53
14	3.3	2.29	2.0	1.43
15	5.0	2.76	0.7	1.96
16	2.1	2.46	1.7	2.02

DEFICIENCIES:

1. The data based on blood concentrations of T_3, $T_4$and TSH upon administration liothyromine sodium and its comparison to the baseline values for these parameters do not substantiate the hypothesis of the investigators that the drop in values for these parameters would quantitatively demonstrate the bioequivalence the test product with the reference product. In view of the presence of endogenous T_3, T_4 and TSH in euthyroid subjects and the extremely small amount of the drug (75 mcg) administered, and the high protein-binding and volume of distribution of T_3, the use of subjects with normal thyroid function is not appropriate to demonstrate bioequivalence of the test product to the reference product.

2. The report does not contain validation of the assay methodology employed to analyze the blood samples.

3. The concentration units for T_3 are not described anywhere in the report.

RECOMMENDATION:

1. The study is unacceptable to demonstrate bioequivalence of Bolar's liothyronine sodium 25 mcg tablet with Cytomel (manufactured by Smith, Kline & French).

2. Use of subjects with normal thyroid functions appears to be inappropriate. A study comparing steady-state blood levels of T_3, T_4 and TSH in hypothyroid patient upon administration of the test and reference products will be appropriate and desirable."

Sincerely yours,

Marvin Seife 12/12/80

Marvin Seife, M.D.
Director
Division of Generic Drug Monographs
Office of Drug Monographs
Bureau of Drugs

cc: NYK-DO DUP HFD-614
HFD-530/HFD-520
MS/cjl/12-12-80 bio

APPEARS THIS WAY
ON ORIGINAL

SEP 29 1980

NDA 85-755

Bolar Pharmaceutical Co., Inc.
Attention: Mr. Robert Shulman
130 Lincoln Street
Copiague, L.I. NY 11726

Gentlemen:

Reference is made to your abbreviated new drug application submitted pursuant to Section 505(b) of the Federal Food, Drug, and Cosmetic Act for Sodium Lioythronine Tablets, 25 mcg.

We acknowledge receipt of your communication dated October 15, 1980 and May 16, 1979 enclosing additional control and bioavailability information.

We have completed the review of this abbreviated new drug application. However, before we can reach a final conclusion the following information is necessary:

1. Appropriately update your application as to tests and specifications for the active ingredient, excipients and finished dosage form per current compendium.

2. Submit samples of the active ingredient and finished dosage form with the analytical results of all tests performed for the lot submitted.

We call to your attention that your bioavailability studies are under review by our Division of Biopharmaceutics and a reply will be issued, when commented upon.

Please submit the above information promptly.

Sincerely yours,

Marvin Seife 9/29/80

Marvin Seife, M.D.
Director
Division of Generic Drug Monographs
Office of Drug Monographs
Bureau of Drugs

NYK-DO DUP HFD-614
JLMeyer/JMRoss
R/DinitJMeyer/MSeife
ft/cjl/9-24-80 rev w/f

JMeyer 9/26/80

JMeyer 9/26/80

Drug

BOLAR PHARMACEUTICAL CO., INC.

130 LINCOLN STREET • COPIAGUE, L. I., N. Y. 11726 • 516-842-8383

October 15, 1979

NDA # 85-755

ORIG NEW CORRES

Bureau of Drugs
Food and Drug Administration
HFD #530
Room # 16-72
5600 Fishers Lane
Rockville, Maryland 20857

ATTN: Dr. Shrikant V. Dighe

Dear Dr. Dighe,

In reference to our Abbreviated New Drug Application for Liothyronine Sodium Tablets, 25 mcg, enclosed please find typed tables and individual results as per your request.

Sincerely,

Robert Shulman

Robert Shulman, President
ENCLS:
RS/fn

Dup in Bio Drug

BOLAR PHARMACEUTICAL CO., INC.

130 LINCOLN STREET • COPIAGUE, L. I., N. Y. 11726 • 516-842-8383

April 26, 1979

NDA # 85-755

ORIG NEW CORRES

Bureau of Drugs
Food and Drug Administration
HFD # 530
Room # 16-72
5600 Fishers Lane
Rockville, Maryland 20857

BIOAVAILABILITY MATERIAL

ATTN: Dr. Marvin Seife

Dear Dr. Seife,

In reference to our Abbreviated New Drug Application for Liothyronine Sodium Tablets, 25 mcg, enclosed please find the following:

1. Completed bioavailability study.

Samples and other information requested in your letter of December 11, 1978 will be sent under separate cover.

Sincerely,

Robert Shulman, President
ENCLS:
RS/fn

RECEIVED
APR 30 1979
GENERIC DRUGS

JAN 3 1979

NDA 85-755

Bolar Pharmaceutical Co., Inc.
Attention: Mr. Robert Shulman
130 Lincoln Street
Copiague, NY 11726

Gentlemen:

Reference is made to the protocol you submitted for bioavailability studies for Liothyronine Sodium Tablets, 25 mcg.

The protocol has been reviewed by our Division of Biopharmaceutics and they have the following comments:

"1. Blood samples should be analyzed by a method specific for T_3 and T_4. The analyst should validate the method for its specificity, sensitivity and linearity. We suggest a pilot study employing four subjects be conducted.

2. The protocol does not contain any description of the facility where the study will be conducted. A full description of the clinical and laboratory facilities should be provided.

3. The protocol does not contain the name and curriculum vitae of the principal investigator for the study. These should be included in the protocol.

4. Written, informed consent should be signed by each participant in the study after the protocol, purpose of study and adverse reactions have been fully and satisfactorily explained to the subjects.

5. The firm should conduct dissolution testing on both the test and the reference product. Dissolution testing should be conducted in 500 ml deionized water using USP paddle at 50 rpm. Samples should be collected at 10, 20, 30, 45 and 60 minutes to generate dissolution profiles for both test and reference products.

6. All compendial tests such as disintegration, content uniformity, etc., should be performed on test and reference products used in the study and reported.

7. The study report should contain all raw data, physical examination and clinical laboratory test data, standard curves, etc. A complete, step by step description of analytical method and recovery data should be part of the study report.

8. The study report should include pharmacokinetic analysis of the blood level data. Pharmacokinetic parameters such as Cmax, Tmax, AUC, half-life of absorption and elimination should be computed and reported.

9. The blood level data should be analyzed statistically using the Analysis of Variance technique. All blood level data for individuals should be reported in tabular form. The mean data should be reported in a graphical display."

RECOMMENDATION: The study protocol as written is incomplete and unacceptable. The firm is requested to submit a revised protocol incorporating the above comments.

Sincerely yours,

Marvin Seife 1/3/79

Marvin Seife, M.D.
Director
Division of Generic Drug Monographs
Office of Drug Monographs
Bureau of Drugs

cc:
NYK-DO DUP HFD-614
HFD-520 HFD-530
MSeife/wlh/1-3-79
bio

APPEARS THIS WAY
ON ORIGINAL

DEC 1 1 1978

NDA 85-755

Bolar Pharmaceutical Co., Inc.
Attention: Mr. Robert Shulman
130 Lincoln Street
Copiague, NY 11726

Gentlemen:

Reference is made to your abbreviated new drug application submitted pursuant to Section 505(b) of the Federal Food, Drug, and Cosmetic Act for Liothyronine Sodium Tablets, 25 mcg.

We acknowledge receipt of your communication dated October 24, 1978, proposing a bioavailability protocol.

We have completed the review of this abbreviated new drug application. However, before we are able to reach a final conclusion the following additional information is necessary:

1. An updating of manufacturing and control information where/when necessary.

2. Samples of the active ingredient and drug dosage form you propose to use in your bioavailability study.

3. For stability provide (for this product):
   a) A we-written protocol for stability studies for this product which include:

      test procedures:for: [redacted]

      sampling procedures: usually the first three production batches are sampled and representative batches thereafter (at least once a year).

      testing stations:
      1. on the first three production batches; 3 month intervals the first year; 6 month intervals the second year; yearly thereafter
      2. on check batches: 6-12 month intervals

storage conditions:
1. for long term studies usually controlled room temperature.
2. for challenge studies see b)

b) Data from challenge studies, i.e., samples stored for one month into and out of 37-40°C and 75% relative humidity.

c) A revised reporting format which includes:

the name and potency of the product
the formula
the lot/batch number
the manufacturing procedure: e.g., research, pilot or production batch
the container-closure system in which the product is to be marketed
the dates: manufactured; released by quality control; packaged; placed on stability
a continuous tabulation of data at the indicated test stations and storage conditions

d) A realistic expiration date to appear on labeling.

4. A commitment to submit analytical results for the first several batches manufactured (after approval of this application).

That part of your submission pertaining to bioavailability is being reviewed by our Division of Biopharmaceutics and will be commented upon at a later date.

Please let us have your response promptly.

Sincerely yours,

Marvin Seife, M.D.
Director
Division of Generic Drug Monographs
Office of Drug Monographs
Bureau of Drugs

cc: NYK-DO DUP HFD-614
JMeyer/GMillar
r/d/ init. GMillar/MSeife 12-7-78
f/t/wlh/12-7-78
rev w/f

BOLAR PHARMACEUTICAL CO., INC.
130 LINCOLN STREET • COPIAGUE, L. I., N. Y. 11726 • 516-842-8383

October 24, 1978

Drug

Supp B

NDA 85-755

ORIG NEW CORRES

Bureau of Drugs
Food and Drug Administration
HFD # 530
Room # 16-72
5600 Fishers Lane
Rockville, Maryland 20857

BIOAVAILABILITY MATERIAL

ATTN: Dr. Marvin Seife

Dear Dr. Seife,

In reference to our Abbreviated New Drug Application for Liothyronine Sodium Tablets, 25 mcg, enclosed please find a proposed bioavailability study for your review.

Sincerely,

Robert Shulman
ENCLS:
RS/fn

RECEIVED
OCT 25 1978
GENERIC DRUGS

JAN 23 1978

NDA 85-755

Bolar Pharmaceutical Co., Inc.
Attn: Mr. Robert Shulman
130 Lincoln St.
Copiague, NY 11726

Gentlemen:

Reference is made to you rabbreviated new drug application submitted pursuant to Section 505(b) of the Federal Food, Drug, and Cosmetic Act for Liothyronine Sodium Tablets, 25 mcg.

We acknowledge receipt of your communication dated October 24, 1977.

We note the material submitted. However, the Federal Register notice of December 2, 1977, provides updated guidelines to be included in an abbreviated new drug application.

If you elect to complete this application, the information so requested should be submitted.

Please let us have your response promptly.

Sincerely yours,

R. Douglas 1/23/78

Marvin Seife, M.D.
Director
Division of Generic Drug Monographs
Office of Drug Monographs
Bureau of Drugs

Enclosure:
F.R. 12-2-77

cc:
NYK-DO
DUP HFD-614
JMeyer/GMillar 1-19-78
r/d/ init. JMeyer/MSeife 1-20-78
f/t/wlb/1-20-78
rev w/f

JMeyer 1/23/78
1/20/78

al law prohibits dispensing without prescription."

(b) The drug product is labeled to comply with all requirements of the act and regulations, and the labeling bears adequate information for safe and effective use of the drug. The indication is as follows:

For radiographic visualization of the bronchial tree.

3. *Marketing status.* (a) Marketing of such drug product which is now subject of an approved or effective new drug application may be continued provided that, on or before January 31, 1978, the holder of the application submits, if he has not already done so, (i) a supplement for revised labeling as needed to be in accord with the labeling conditions described in this notice, and complete container labeling if current container labeling has not been submitted, and (ii) a supplement to provide full updating information with respect to items 6 (components), 7 (composition), and 8 (methods, facilities, and controls) of new drug application form FD-356H (21 CFR 314.1(c)).

(b) Approval of an abbreviated new drug application (21 CFR 314.1(f)) must be obtained prior to marketing such products. The applications shall contain full information with respect to items 6 (components), 7 (composition) and 8 (methods, facilities, and controls) of new drug application form FD-356H (21 CFR 314.1(c)). Marketing prior to approval of a new drug application will subject such products, and those persons who caused the products to be marketed, to regulatory action.

This notice is issued under the Federal Food, Drug, and Cosmetic Act (secs. 502, 505, 52 Stat. 1050-1053, as amended (21 U.S.C. 352, 355)) and under the authority delegated to the Director of the Bureau of Drugs (21 CFR 5.70).

Dated: November 11, 1977.

J. RICHARD CROUT,
Director, Bureau of Drugs.

[FR Doc. 77-34268 Filed 12-1-77; 8:45 am]

[4110-03]

[Docket No. 76N-0451; DESI 2245]

SODIUM LIOTHYRONINE

Drugs for Human Use; Drug Efficacy Study Implementation; Followup Notice and Opportunity for Hearing

AGENCY: Food and Drug Administration.

ACTION: Notice.

SUMMARY: This notice sets forth the conditions for marketing sodium liothyronine tablets for the indications for which it continues to be regarded as effective and offers an opportunity for a hearing concerning indications reassified to lacking substantial evidence of effectiveness. This drug is used for certin conditions of inadequate endogenous thyroid production.

DATES: Hearing requests due on or before January 3, 1978. Supplements due on or before January 31, 1978.

ADDRESSES: Communications forwarded in response to this notice should be identified with reference number DESI 2245, directed to the attention of the appropriate office named below, and addressed to the Food and Drug Administration, 5600 Fishers Lane, Rockville, Md. 20857.

Supplements (identify with NDA number): Division of Metabolism and Endocrine Drug Products (HFD-130), Room 14B-04, Bureau of Drugs.

Abbreviated new drug applications and notices of claimed investigational exemption for a new drug (IND) (identify as such): Division of Generic Drug Monographs (HFD-[illegible]), Bureau of Drugs.

Requests for hearing (identify with Docket number appearing in the heading of this notice): Hearing Clerk, Food and Drug Administration (HFC-20), Room 4-65.

Requests for the report of the National Academy of Sciences-National Research Council: Public Records and Documents Center (HFC-18) Room 4-62.

Request for opinion of the applicability of this notice to a specific product: Division of Drug Labeling Compliance (HFD-310), Bureau of Drugs.

FOR FURTHER INFORMATION CONTACT:

John H. Hazard, Jr., Bureau of Drugs (HFD-32), Food and Drug Administration, Department of Health, Education, and Welfare, 5600 Fishers Lane, Rockville, Md. 20857, (301-443-3650).

SUPPLEMENTARY INFORMATION: In a notice (DESI 2245) published in the FEDERAL REGISTER of September 25, 1969 (34 FR 14775), the Food and Drug Administration announced its conclusions that the drug product described below is (1) effective for certain conditions resulting from inadequate endogenous thyroid production, and (2) possibly effective for gynecological disorders associated with hypothyroidism. In addition, that notice should have stated that the drug product is effective for use in the T_3 suppression test to differentiate suspected hyperthyroidism from euthyroidism. No data in support of the less-than-effective indication were submitted, and it is now reclassified to lacking substantial evidence of effectiveness. This notice offers an opportunity for a hearing concerning that indication and sets forth the conditions for marketing the drug product for the indications for which it is regarded as effective. The other drug (thyroglobulin) included in the September 25, 1969, notice is not affected by this notice.

NDA 10-379; Cytomel Tablets containing sodium liothyronine; Smith Kline & French Laboratories, Division of SmithKline Corp., 1500 Spring Garden St., Philadelphia, Pa. 19101.

Such drugs are regarded as new drugs (21 U.S.C 321(p)). Supplemental new drug applications are required to revise the labeling in and to update previously approved applications providing for such drugs. An approved new drug application is a requirement for marketing such drug products.

In addition to the holder of the new drug application specifically named above, this notice applies to all persons who manufacture or distribute a drug product, not the subject of an approved new drug application, that is identical, related, or similar to the drug product named above, as defined in 21 CFR 310.6. It is the responsibility of every drug manufacturer or distributor to review this notice to determine whether it covers any drug product he manufactures or distributes. Any person may request an opinion of the applicability of this notice to a specific drug product he manufactures or distributes that may be identical, related, or similar to the drug product named in this notice by writing to the Division of Drug Labeling Compliance (address given above).

A. *Effectiveness classification.* The Food and Drug Administration has reviewed all available evidence and concludes that the drug is effective for the indications stated in the labeling conditions below. The drug now lacks substantial evidence of effectiveness for the indication evaluated as possibly effective in the September 25, 1969, notice.

B. *Conditions for approval and marketing.* The Food and Drug Administration is prepared to approve abbreviated new drug applications and abbreviated supplements to previously approved new drug applications under conditions described herein.

1. *Form of drug.* The drug is in tablet form suitable for oral administration.

2. *Labeling conditions.* (a) The label bears the statement, "Caution: Federal law prohibits dispensing without prescription." (b) The drug is labeled to comply with all requirements of the act and regulations, and the labeling bears adequate information for safe and effective use of the drug. The Indications are as follows:

(1) Thyroid replacement in patients with inadequate endogenous thyroid hormone production. These include mild hypofunction, cretinism, and myxedema. Replacement therapy will be effective only in manifestations of hypothyroidism.

(2) Simple (nontoxic) goiter. The drug may be used therapeutically in

an attempt to reduce the size of such a goiter.

(3) For use in the T_3 suppression test to differentiate suspected hyperthyroidism from euthyroidism.

3. *Marketing status of approved products.* Marketing of such drugs products that are now the subject of an approved or effective new drug application may be continued provided that, on or before January 31, 1978, the holder of the application submits the following if he has not previously done so: (i) a supplemental for revised labeling as needed to be in accord with the labeling conditions described in this notice, and complete container labeling if current container labeling has not been submitted, and (ii) a supplement to provide updating information with respect to items 6 (components), 7 (composition), 8 (methods, facilities, and controls) of new drug application form FD-356H (21 CFR 314.1(c)) to the extent required in abbreviated applications (21 CFR 314.1(f)).

4. *Marketing status of all other products.* Approval of an abbreviated new drug application (21 CFR 314.1(f)) must be obtained prior to marketing such drug products. The abbreviated new drug application is required to contain evidence from in vivo studies demonstrating bioequivalence to an appropriate reference standard. Such bioavailability studies shall consist of either single- and/or multiple-dose blood level studies or comparison of acute pharmacological activity to an appropriate reference material. Multiple-dose studies will require prior submission of a Notice of Claimed Investigational Exemption for a New Drug (IND) including a protocol for such studies. Because of inherent toxicological side effects associated with this drug, it is advisable that firms submit a protocol with the ANDA prior to undertaking a single-dose study in human subjects. Abbreviated new drug applications and notices of claimed investigational exemption for a new drug (IND) (identify as such) should be directed to the Division of Generic Drug Monographs (HFD-530), Bureau of Drugs (address given above). Marketing prior to approval of a new drug application will subject such products, and those persons who caused the products to be marketed, to regulatory action.

C. *Notice of opportunity for hearing.* On the basis of all the data and information available to him, the Director of the Bureau of Drugs is unaware of any adequate and well-controlled clinical investigation, conducted by experts qualified by scientific training and experience, meeting the requirements of section 505 of the Federal Food, Drug, and Cosmetic Act (21 U.S.C. 355) and 21 CFR 314.111(a)(5), demonstrating the effectiveness of the drug(s) for the indication(s) lacking substantial evidence of effectiveness referred to in paragraph A. of this notice.

Notice is given to the holder(s) of the new drug application(s), and to all other interested persons, that the Director of Bureau of Drugs proposes to issue an order under section 505(e) of the Federal Food, Drug, and Cosmetic Act (21 U.S.C. 355(e)), withdrawing approval of the new drug application(s) and all amendments and supplements thereto providing for the indication(s) lacking substantial evidence of effectiveness referred to in paragraph A. of this notice on the ground that new information before him with respect to the drug product(s), evaluated together with the evidence available to him at the time of approval of the application(s), shows there is a lack of substantial evidence that the drug product(s) will have all the effects it purports or is represented to have under the conditions of use prescribed, recommended, or suggested in the labeling. An order withdrawing approval will not issue with respect to any application(s) supplemented, in accord with this notice, to delete the claim(s) lacking substantial evidence of effectiveness. (In addition to the ground for the proposed withdrawal of approval stated above, this notice of opportunity for hearing encompasses all issues relating to the legal status of the drug products subject to it (including identical, related, or similar drug products as defined in 21 CFR 310.6), e.g., any contention that any such product is not a new drug because it is generally reognized as safe and effective within the meaning of section 201(p) of the act or because it is exempt from part or all of the new drug provisions of the act pursuant to the exemption for products marketed prior to June 25, 1938, contained in section 201(p) of the act, or pursuant to section 107(c) of the Drug Amendments of 1962; or for any other reson.

In accordance with the provisions of section 505 of the act (21 U.S.C. 355) and the regulations promulgated thereunder (21 CFR Parts 310, 314), the applicant(s) and all other persons who manufacture or distribute a drug product which is identical, related, or similar to a drug product named above (21 CFR 310.6), are hereby given an opportunity for a hearing to show why approval of the new drug application(s) providing for the claim(s) involved should not be withdrawn and an opportunity to raise, for administrative determination, all issues relating to the legal status of a drug product named above and all identical, related, or similar drug products.

If an applicant or any person subject to this notice pursuant to 21 CFR 310.6 elects to avail himself of the opportunity for a hearing, he shall file (1) on or before January 3, 1978, a written notice of appearance and request for hearing, and (2) on or before January 31, 1978, the data, information, and analyses on which he relies to justify a hearing, as specified in 21 CFR 314.200. Any other interested person may also submit comments on this proposal to withdraw approval. The procedures and requirements governing this notice of opportunity for hearing, a notice of appearance and request for hearing, a submission of data, information, and analyses to justify a hearing, other comments, and a grant or denial of hearing, are contained in 21 CFR 314.200.

The failure of an applicant or any other person subject to this notice pursuant to 21 CFR 310.6 to file timely written appearance and request for hearing as required by 21 CFR 314.200 constitutes an election by such person not to avail himself of the opportunity for a hearing concerning the action proposed with respect to such drug product and a waiver of any contentions concerning the legal status of such drug product. Any such drug product labeled for the indication(s) lacking substantial evidence of effectiveness referred to in paragraph A. of this notice may not thereafter lawfully be marketed, and the Food and Drug Administration will initiates appropriate regulatory action to remove such drug products from the market. Any new drug product marketed without an approved NDA is subject to regulatory action at any time.

A request for a hearing may not rest upon mere allegation or denials, but must set forth specific facts showing that there is a genuine and substantial issue of fact that requires a hearing. If it conclusively appears from the face of the data, information, and factual analyses in the request for the hearing that there is no genuine and substantial issue of fact which precludes the withdrawal of approval of the application, or when a request for hearing is not made in the required format or with the required analyses, the Commissioner will enter summary judgment against the person(s) who requests the hearing, making findings and conclusions, denying a hearing.

All submissions pursuant to this notice shall be filed in quintuplicate. Such submissions, except for data and information prohibited from public disclosure pursuant to 21 U.S.C. 331(j) or 18 U.S.C. 1905, may be seen in the office of the Hearing Clerk between the hourse of 9 a.m. and 4 p.m., Monday through Friday.

This notice is issued under the Federal Food, Drug, and Cosmetic Act (secs. 502, 505, 52 Stat. 1050-1053, as amended (21 U.S.C. 352, 355)) and under the authority delegated to the Director of the Bureau of Drugs (21 CFR 5.82).

NOV 3 1977

NDA 85-755

Bolar Pharmaceutical Co., Inc.
Attention: Mr. Robert Shulman
130 Lincoln Street
Copiague, NY 11726

Gentlemen:

Reference is made to your abbreviated new drug application submitted pursuant to Section 505(b) of the Federal Food, Drug, and Cosmetic Act for Liothyronine Sodium Tablets, 25 mcg.

We acknowledge receipt of your communication dated September 6, 1977, amending the application with copies printed labeling.

We have completed our review of this abbreviated new drug application. However, before we are able to reach a final conclusion the following additional information is necessary:

That requested in our letter of October 11, 1977 pertaining to stability and container/closure systems.

Please let us have your response promptly.

Sincerely yours,

Marvin Seife 11/3/77

Marvin Seife, M.D.
Director
Division of Generic Drug Monographs
Office of Drug Monographs
Bureau of Drugs

cc: 11/2/77
NYK-DO
HFD-614
RBarzilai/JMeyer/GMillar
R/D init JMeyer/MSeife/11/1/77
ps/11/1/77
rev w/f

11/1/77 JMeyer 11/2/77

ORIGINAL

BOLAR PHARMACEUTICAL CO., INC.

130 LINGOLN STREET • COPIAGUE, L. I., N. Y. 11726 • 516-842-8383

October 24, 1977

NDA 85-755

RESUBMISSION

NDA ORIG AMENDMENT

Bureau of Drugs
Food and Drug Administration
HFD # 530
Room # 16-72
5600 Fishers Lane
Rockville, Maryland 20857

ATTN: Dr. Marvin Seife

Dear Dr. Seife,

In reference to our Abbreviated New Drug Application for Liothyronine Sodium Tablets, 25 mcg and your letter of October 11, 1977, please be advised of the following:

1) Printed labeling has been previously submitted.

2) Regarding stability we are enclosing stability data on two production batches of tablets.

   a) Lot # 083269 was manufactured and initially assayed during September on 1973. The samples were kept at room temperature and were packaged in container/closure system in which they were marketed. The enclosed stability data summary shows 48 month data.

   b) Lot # 113479 was manufactured and initially assayed during February 1974. The samples were kept at room temperature and were packaged in the container/closure system in which they were marketed. The enclosed stability data summary show 44 months data.

   We have marketed this product since 1973, discontinuing the sale as a result of the Judge Green decision. The actual analytical work for both lots is available if needed.

3) Samples have been previously submitted. The submitted samples were manufactured October 1975.

RECEIVED
OCT 27 1977
BUREAU OF DRUGS

Sincerely,

Robert Shulman, President
ENCLS: MANUFACTURERS OF PHARMACEUTICAL TABLETS AND CAPSULES
RS/fa

OCT 11

NDA 85-755

Bolar Pharmaceutical Co., Inc.
Attention: Mr. Robert Shulman
130 Lincoln Street
Copiague, NY 11726

Gentlemen:

Reference is made to your abbreviated new drug application submitted pursuant to Section 505(b) of the Federal Food, Drug, and Cosmetic Act for Liothyronone Sodium Tablets, 25 mcg.

We acknowledge receipt of your communication dated July 26, 1977, amending the application.

We have completed our review of this abbreviated new drug application. However, before we are able to reach a final conclusion the following additional information is necessary:

1. Printed labeling, as per your commitment.

2. For stability:
   a) we are requesting a signed statement that you will check the stability of production batches (in the container/closure system in which it is to be marketed); submit results of these studies at 3, 6, 12, 18 and 24 months intervals and yearly thereafter; and promptly withdraw from the market any lots that may become subpotent.
   b) we are requesting studies at challenge conditions - especially with respect to humidity and cycling.
   c) we note your proposal for a 24 month expiration date.

3. For processing et al: we are requesting studies on the effect of _____.

4. We are requesting samples and your analytical results.

Please let us have your response promptly.

Sincerely yours,

Marvin Seife, M.D.
Director
Division of Generic Drug Monographs
Office of Drug Monographs
Bureau of Drugs

cc:
NYK-DD
Dup HFD-614
JLMeyer/GMillar 10-5-77
r/d/ init JMeyer/10-5-77
f/t/wlb/10-6-77
rev w/f

ORIG

Rec'd 9/6

BOLAR PHARMACEUTICAL CO., INC.

130 LINCOLN STREET • COPIAGUE, L. I., N. Y. 11726 • 516-842-8383

September 6, 1977

NDA 85-755

RESUBMISSION

NDA ORIG AMENDMENT

FPL 9/6

10/3/77

Bureau of Drugs
Food and Drug Administration
HFD # 530
Room # 16-72
5600 Fishers Lane
Rockville, Maryland 20857

ATTN: Dr. Marvin Seife

Dear Dr. Seife,

In reference to our Abbreviated New Drug Application for Liothyronine Sodium Tablets, 25 mg and our letter of July 26, 1977, enclosed please find:

1) Final printed package inserts and labels

Sincerely,

Robert Shulman, President
ENCLS:
RS/fa

RECEIVED
SEP 0 6 1977
FDA/BOD

Rsw·F
Ches

BOLAR PHARMACEUTICAL CO., INC.

130 LINCOLN STREET • COPIAGUE, L. I., N. Y. 11726 • 516-842-8383

July 26, 1977

NDA 85-755

RESUBMISSION

NDA ORIG AMENDMENT

Bureau of Drugs
Food and Drug Administration
HFD # 530
Room # 16-72
5600 Fishers Lane
Rockville, Maryland 20857

ATTN: Dr. Marvin Seife

Dear Dr. Seife,

In reference to our Abbreviated New Drug Application for Liothyronine Sodium Tablets, 25 mcg and your letter of June 21, 1977, enclosed please find the following:

1) Certificate of analysis from our [redacted]

2) Samples and our analytical results.

We will submit analytical results for production batches and lots of active ingredient used.

Since long term stability data is not available on the 25 mcg dosage form and based upon the 50 mcg dosage form stability data we propose a 24 month expiration date and will promptly remove from the market any lots that fall below specifications

The container closure system as described in our ANDA protects the contents from contamination by extraneous liquids, solids, and vapors.

The [redacted] of the Sodium Liothyronine is [redacted]

We will forward printed package inserts and container labels as soon as available from our printer.

Sincerely,

Robert Shulman, President
ENCLS:
RS/fa

RECEIVED
JUL 27 1977
BUREAU OF DRUGS

JUN 21 1977

NDA 85-755

Bolar Pharmaceutical Co., Inc.
Attention: Mr. Robert Shulman
130 Lincoln Street
Copiague, NY 11726

Gentlemen:

Reference is made to your abbreviated new drug application dated April 12, 1977, submitted pursuant to Section 505(b) of the Federal Food, Drug, and Cosmetic Act for Liothyronine Sodium Tablets, 25 mcg.

We have completed our review of this abbreviated new drug application. However, before we are able to reach a final conclusion the following additional information is necessary:

1. For labeling: copies of printed labeling in accord with the submitted drafts (containers and insert).

2. For the active ingredient:
   a) Identification of the actual manufacturer and submission of a certificate of analysis from your ———
   b) A commitment to submit analytical results for lots used.

3. For the drug dosage form:
   a) A commitment to submit analytical results for peoduction batches.
   b) stability data.
   c) Demonstration that the container/closures system is suitable for the intended use. Here we call your attention to the USP XIX requirement for "tight" containers.
   d) Samples and your analytical results.

Please let us have your response promptly.

Sincerely yours,

Marvin Seife 6/21/77

Marvin Seife, M.D.
Director
Division of Generic Drug Monographs
Office of Drug Monographs
Bureau of Drugs

RBarzilai 6/20/77

cc: NYK-DO JMeyer 6/20/77
Dup HFD-614 HFD-615 GMillar 6/21/77
RBarzilai/JMeyer/GMillar 6-14-77
r/d/ init. JMeyer/MSeife 6-20-77
f/t/wlb/6-20-77
rev w/f

NDA 85-755

Bolar Pharmaceutical Company, Inc.
Attention: Robert Shulman
130 Lincoln Street
Copiague, NY 11726

Gentlemen:

We acknowledge the receipt of your abbreviated new drug application submitted pursuant to Section 505(b) of the Federal Food, Drug, and Cosmetic Act for the following:

NAME OF DRUG: Liothyronine Sodium 25 mcg. Tablets

DATE OF APPLICATION: April 12, 1977

DATE OF RECEIPT: April 15, 1977

We will correspond with you further after we have had the opportunity to review the application.

Please identify any communications concerning this application with the NDA number shown above.

Sincerely yours,

NYK-DO DUP HFD-614,HFD-616

JLMeyer/cjb/4-26-77

ack JLMeyer 4/26/77

Marvin Seife, M.D.
Director
Division of Generic Drug Monographs
Office of Drug Monographs
Bureau of Drugs

required by law to be approved by the Secretary of Commerce.

.04 *Subpenas*—a. *Information under the control of the Civil Service Commission.* 1. If a subpena or other judicial order for information contained in an official personnel folder in the physical custody of the Department is served on an employee of the Department responsible for the folder, he shall disclose such information as is allowed under Part 294 of the Civil Service Regulations (5 CFR 294.101–294.1001). However, he should retain custody of the information and, as necessary, request permission of counsel or the court to furnish a certified copy for inclusion in the court record. (See 5 CFR 294.108(c).)

2. In an unusual situation or a situation in which information not available under Part 294 of the Civil Service Regulations is sought, the Department employee who received the subpena shall immediately forward it and the official personnel folder containing the information sought to the General Counsel of the Department for transmittal to the General Counsel, U.S. Civil Service Commission, Washington, D.C. 20415. When this is done, the Department employee shall inform the person who applied for the subpena that the subpena and the information sought have been sent to the Civil Service Commission pursuant to 5 CFR 294.108(c)(2) and, if necessary, and upon advice of the General Counsel of the Department, request a postponement of the scheduled appearance.*

b. *Other information within the purview of this order.* When a subpena duces tecum or other legal demand for the production of records or information relating to personnel other than as authorized pursuant to this order is served upon any officer or employee of the Department other than the Secretary, he shall comply with section 7, "Compulsory Process Requesting Documents or Testimony," of Department Order 64, "Public Information."

SEC. *12* *Saving provision.* This order shall be deemed consistent with Department Order 64. Any other orders or parts of orders or delegations of authority which are inconsistent herewith are hereby superseded.

LARRY A. JOBE,
Assistant Secretary for Administration.

[F.R. Doc. 69-11430; Filed, Sept. 24, 1969; 8:48 a.m.]

[Dept. Order 5-B, Amdt. 1]

ECONOMIC DEVELOPMENT ADMINISTRATION

Organization and Function [1]

SEPTEMBER 10, 1969.

The material appearing at 34 F.R. 6703 April 19, 1969, is amended as follows: Department Order 5-B of March 17, 1969, is hereby amended as follows:

1. SEC. 7. *Office of Administration and Program Analysis.* Paragraphs .01 and .02 are amended, and a new Paragraph .03 is added, to read:

.01 The *Program Analysis Division* shall: Develop and implement measures of resource utilization for programing and budgeting purposes, develop and conduct a systematic program evaluation effort for EDA; prepare the annual Program Memorandum and analytical studies required by the Bureau of the Budget; and develop cost benefits studies to aid the Assistant Secretary in making choices and decisions between alternative programs for economic development projects, activities, and programs in achieving the objectives of the Act and EDA.

.02 The *Management Analysis Division* shall: Conduct organization and management studies and surveys; plan and conduct a program for achieving maximum economy, effectiveness, and efficiency, and for obtaining optimum personnel utilization; develop and conduct a program for the efficient management of all official records, including an issuance system for administrative and program orders, and the design and control of official forms; and develop and administer a reports control system for all administrative and operational reports.

.03 The *Budget Division* shall: Develop and manage an integrated financial management and budgeting system for EDA. It shall develop and prepare the annual budget for EDA; be responsible for the total financial program of EDA, and for the fiscal aspects of EDA programs entrusted to other Federal agencies; and operate a fiscal control system for both program and administrative expenses consistent with the requirements of the Anti-Deficiency Act, which shall include but not be restricted to, allotment of funds, operating budgets, employment limitations, and analyses of reports and proposed actions relating thereto.

2. The remaining paragraphs of section 7 are renumbered paragraphs .04 through .08.

LARRY A. JOBE,
Assistant Secretary for Administration.

[F.R. Doc. 69-11431; Filed, Sept. 24, 1969; 8:48 a.m.]

DEPARTMENT OF AGRICULTURE

Office of the Secretary

WASHINGTON

Designation of Areas for Emergency Loans

For the purpose of making emergency loans pursuant to section 321 of the Consolidated Farmers Home Administration Act of 1961 (7 U.S.C. 1961), it has been determined that in the hereinafter-named counties in the State of Washington, natural disasters have caused a need for agricultural credit not readily available from commercial banks, cooperative lending agencies, or other responsible sources.

WASHINGTON

Chelan.	Okanogan.
Douglas.	

Pursuant to the authority set forth above, emergency loans will not be made in the above-named counties after June 30, 1970, except to applicants who previously received emergency or special livestock loan assistance and who can qualify under established policies and procedures.

Done at Washington, D.C., this 19th day of September, 1969.

CLIFFORD M. HARDIN,
Secretary of Agriculture.

[F.R. Doc. 69-11427; Filed, Sept. 24, 1969; 8:48 a.m.]

DEPARTMENT OF HEALTH, EDUCATION, AND WELFARE

Food and Drug Administration

[DESI 2245]

THYROGLOBULIN AND SODIUM LIOTHYRONINE

Drugs for Human Use; Drug Efficacy Study Implementation

The Food and Drug Administration has evaluated reports received from the National Academy of Sciences-National Research Council, Drug Efficacy Study Group, on the following drugs:

1. Thyroglobulin, marketed as Proloid, ¼, ½, 1, 1½, 3, and 5 grains per tablet, by Warner—Chilcott Laboratories Division of Warner-Lambert Pharmaceutical Co., 201 Tabor Road, Morris Plains, N.J. 07950 (NDA 2-245).

2. Sodium Liothyronine, marketed as Cytomel, 5 and 25 micrograms of base per tablet, by Smith Kline and French Laboratories, 1500 Spring Garden Street, Philadelphia, Pa. 19101 (NDA 10-379).

The drugs are regarded as new drugs (21 U.S.C. 321 (p)). Supplemental new drug applications are required to revise the labeling in and to update previously approved applications providing for such drugs. A new drug application is required from any person marketing such drugs without approval.

The Food and Drug Administration is prepared to approve new drug applications and supplements to previously approved new drug applications under conditions described in this announcement.

THYROGLOBULIN; SODIUM LIOTHYRONINE

A. Effectiveness classification. The Food and Drug Administration has considered the Academy reports, as well as other available evidence, and concludes that:

1. Both drugs are effective for certain conditions resulting from inadequate endogenous thyroid production.

---

[1] Organization chart filed as part of the original document.

2. Thyroglobulin lacks substantial evidence of effectiveness for the recommendation: "therapeutic trial for nonspecific symptoms, such as fatigue, depression, frequent colds, and low resistance when pharmacologic effects of a natural metabolic stimulant may be helpful." This claim was not part of any labeling provided for in the "deemed approved" new drug application.

3. Sodium liothyronine is regarded as possibly effective for the labeled indication "gynecological disorders associated with hypothyroidism". (This indication should be made more precise with adequate supporting data for each claim of therapeutic effectiveness.)

B. *Form of drug.* Thyroglobulin and sodium liothyronine preparations are in tablet form suitable for oral administration and contain per dosage unit an amount appropriate for administration in the dosage ranges described in the labeling conditions in this announcement.

C. *Labeling conditions.*

1. The label bears the statement "Caution: Federal law prohibits dispensing without prescription."

2. The drug is labeled to comply with all requirements of the Act and regulations and those parts of its labeling indicated below are substantially as follows: (Optional additional information, applicable to the drug, may be proposed under other appropriate paragraph heads and should follow the information set forth below.)

THYROGLOBULIN

DESCRIPTION

(Descriptive information to be included by the manufacturer or distributor should be confined to an appropriate description of the physical and chemical properties of the drug and the formulation.)

ACTIONS

(To be supplied by the manufacturer: This is to be confined to an appropriate statement of the demonstrated pharmacological/physiological actions of the active ingredient of the drug. When such actions are based on animal studies alone, this should be clearly stated. When the mode of action has not been determined, this should be clearly indicated.)

INDICATIONS

Conditions of inadequate endogenous thyroid production: E.g.

Replacement therapy in cretinism and myxedema.

Replacement therapy will be effective only in manifestations of hypothyroidism.

Simple (nontoxic) goiter, where in nonemergency situations the drug may be tried therapeutically in an attempt to reduce the size of such goiters.

CONTRAINDICATIONS

Uncorrected adrenal insufficiency.

WARNINGS

Thyroglobulin should not be used in the presence of cardiovascular disease unless thyroid-replacement therapy is clearly indicated. If the latter exists, low doses should be instituted beginning at 0.5 to 1.0 grain (32 to 64 mg.) and increasing by the same amount in increments at 2 week intervals. This demands careful clinical judgment.

Morphologic hypogonadism and nephroses should be ruled out before the drug is administered. If hypo-pituitarism is present, the adrenal deficiency must be corrected prior to starting the drug.

Myxedematous patients are very sensitive to thyroid and dosage should be started at a very low level and increased gradually.

PRECAUTION

As with all thyroid preparations, this drug will alter results of thyroid function tests.

ADVERSE REACTIONS

Overdosage or too rapid increase in dosage may result in signs and symptoms of hyperthyroidism such as nervousness, cardiac arrhythmias, and angina pectoris.

DOSAGE AND ADMINISTRATION

Optimal dosage is usually determined by the patient's clinical response. Confirmation tests include BMR, T_3I^{131} Resin sponge uptake, T_4I^{131} red cell uptake, Thyro Binding Index (TBI), and Achilles Tendon Reflex Test. Dosage should be started in small amounts and increased gradually, with increments at 1–2 week intervals. Usual maintenance does is 0.5 to 3.0 grains (32 to 190 mg.) daily.

OVERDOSAGE

Symptoms: Headache, instability, nervousness, sweating, tachycardia, with unusual bowel motility. Angina pectoris or congestive heart failure may be induced or aggravated. Shock may develop. Massive overdosage may result in symptoms resembling thyroid storm. Chronic excessive dosage will produce the signs and symptoms of hyperthyroidism.

(Treatment: In shock, supportive measures should be utilized. Treatment of unrecognized adrenal insufficiency should be considered.)

SODIUM LIOTHYRONINE

DESCRIPTION

(Descriptive information to be included by the manufacturer or distributor should be confined to an appropriate description of the physical and chemical properties of the drug and the formulation.)

ACTIONS

(To be supplied by the manufacturer: This is to be confined to an appropriate statement of the demonstrated pharmacological/physiological actions of the active ingredients of the drug. When such actions are based on animal studies alone, this should be clearly stated. When the mode of action has not been determined, this should be clearly indicated.)

INDICATIONS

(Use the same indications as are described for thyroglobulin.)

CONTRAINDICATIONS

Uncorrected adrenal insufficiency.

WARNINGS

Sodium liothyronine should not be used in the presence of cardiovascular disease unless thyroid-replacement therapy is clearly indicated. If the latter exists, low doses should be instituted beginning at 5 mcg. and increasing by 5 mcg. increments at 2-week intervals.

Morphologic hypogonadism and nephroses should be ruled out before the drug is administered. If hypo-pituitarism is present, the adrenal deficiency must be corrected prior to starting the drug.

Myxedematous patients are very sensitive to thyroid and dosage should be started at a very low level and increased gradually.

PRECAUTIONS

Since liothyronine is not as firmly bound to serum protein as thyroxine, the PBI may remain at hypothyroid levels even though the patient is euthyroid (liothyronine may lower the PBI when administered to normal patients). As with all thyroid preparations, thyroid gland function reflected by I^{131} thyroid uptake may be decreased by liothyronine. Useful I^{131} thyroid uptake values may be obtained, if necessary, usually within 2 weeks following withdrawal of the drug.

ADVERSE REACTIONS

Overdosage will produce signs and symptoms of hyperthyroidism, such as nervousness, cardiac arrhythmias, and angina pectoris.

DOSAGE AND ADMINISTRATION

Optimal dosage is usually determined by the patient's response. Confirmation tests include BMR, T_3I^{131} Resin sponge uptake, T_4I^{131} red cell uptake, Thyro Binding Index (TBI) and Achilles Tendon Reflex Test.

Mild hypothyroidism: recommended starting dose is 25 mcg. daily. Usual maintenance dose is 25–75 mcg. per day.

Myxedema: recommended starting dose is 5 mcg. daily. This may be increased by 5–10 mcg. daily every week or two until maintenance dose of 50–100 mcg. per day is reached. After a daily dosage of 25 mcg., dosage may often be increased by 12.5–25 mcg. every 1–2 weeks.

Cretinism: Therapy must be started as soon as possible. Recommended starting dose is 5 mcg. daily with an increase of 5 mcg. every 3–4 days until desired response is obtained.

Simple (nontoxic) goiter: Initial dosage is 5 mcg. daily and may be increased by 5–10 mcg. per day every 1–2 weeks, with usual maintenance dose of 25–75 mcg. daily.

In the elderly or in children, therapy should be started with 5 mcg. daily and increased only by 5 mcg. increments at the recommended intervals.

OVERDOSAGE

(Use same information as described for thyroglobulin.)

D. *Claims permitted during extended period for obtaining substantial evidence.* Those claims for which sodium liothyronine is described in paragraph A3 above as possibly effective (not included in the labeling conditions in paragraph C) may continue to be used for 6 months following the date of this publication to allow additional time within which holders of previously approved applications or persons marketing the drug without approval may obtain and submit to the Food and Drug Administration, data to provide substantial evidence of effectiveness.

E. *Previously approved applications.* 1. Each holder of a "deemed approved" new drug application (i.e., an application which became effective on the basis of safety prior to Oct. 10, 1962) for such drug is requested to seek approval of the claims of effectiveness and bring the application into conformance by submitting supplements containing:

a. Revised labeling as needed to conform to the labeling conditions described herein for the drug.

b. Adequate data to assure the biologic availability of the drug in the formulation which is marketed. If such data are already included in the application, specific reference thereto may be made.

c. A supplement containing updating information as needed to make the application current in regard to items 6 (components), 7 (composition), and 8 (methods, facilities, and controls) of the new

application form FD-356H to the extent described in the proposal for abbreviated new drug applications, § 130.4(f), published in the FEDERAL REGISTER February 27, 1969. (One supplement may contain all the information described in this paragraph.)

2. Such supplements should be submitted within the following time periods after the date of publication of this notice in the FEDERAL REGISTER:

a. 60 days for revised labeling—the supplement should be submitted under the provisions of section 130.9 (d) and (e) of the new drug regulations (21 CFR 130.9) which permit certain changes to be put into effect at the earliest possible time.

b. 180 days for biologic availability data.

c. 60 days for updating information.

3. Marketing of the drug may continue until the supplemental applications submitted in accord with the preceding paragraphs 1 and 2 are acted upon: *Provided*, That within 60 days after the date of this publication, the labeling of the preparation shipped within the jurisdiction of the Act is in accord with the labeling conditions described in this announcement. (The labeling of sodium liothyronine may continue to include the claims referenced in paragraph D for the period stated.)

F. *New applications.* 1. Any other person who distributes or intends to distribute such drug which is intended for conditions of use for which it has been shown to be effective, as described under A above, should submit an abbreviated new drug application meeting the conditions specified in the proposed regulation, section 130.4(f) (1), (2), and (3), published in the FEDERAL REGISTER of February 27, 1969. Such applications should include proposed labeling which is in accord with the labeling conditions described herein and adequate data to assure the biologic availability of the drug in the formulation which is marketed or proposed for marketing.

2. Distribution of any such preparation currently on the market without an approved new drug application may be continued provided that:

a. Within 60 days from the date of publication of this announcement in the FEDERAL REGISTER, the labeling of such preparation shipped within the jurisdiction of the Act is in accord with the labeling conditions described herein. (The labeling of sodium liothyronine may continue to include the claims referenced in paragraph D for the period stated.)

b. The manufacturer, packer, or distributor of such drug submits, within 180 days from the date of this publication, a new drug application to the Food and Drug Administration.

c. The applicant submits additional information that may be required for the approval of the application within a reasonable time as specified in a letter communication from the Food and Drug Administration.

d. The application has not been ruled incomplete or unapprovable.

G. *Exemption from periodic reporting.* The periodic reporting requirements of §§ 130.35(c) and 130.13(b)(4) are waived in regard to applications approved for these drugs solely for the conditions of use for which they are regarded as effective as described herein.

H. *Unapproved use or form of drug.* 1. If the article is labeled or advertised for use in any condition other than those provided for in this announcement, it may be regarded as an unapproved new drug subject to regulatory proceedings until such recommended use is approved in a new drug application, or is otherwise in accord with this announcement.

2. If the article is proposed for marketing in another form or for a use other than the use provided for in this announcement, appropriate additional information as described in section 130.4 or 130.9 of the regulations (21 CFR 130.4, 130.9) may be required, including results of animal and clinical tests intended to show whether the drug is safe and effective.

Representatives of the Administration are willing to meet with any interested person who desires to have a conference concerning proposed changes in the labeling set forth herein. Requests for such meetings should be made to the Office of Marketed Drugs (MD-300), Bureau of Medicine at the address given below, within 30 days after the publication of this notice in the FEDERAL REGISTER.

A copy of the NAS-NRC report has been furnished to each firm referred to above. Any other manufacturer, packer, or distributor of a drug of similar composition and labeling to the drug listed in this announcement or any other interested person may obtain a copy by request to the appropriate office named below.

Communications forwarded in response to this announcement should be identified with reference number DESI 2245, and directed to the attention of the following appropriate office and addressed to the Food and Drug Administration, 200 C Street SW., Washington, D.C. 20204:

Requests for NAS-NRC report: Press Relations Office (CE-300).

Supplements (identify with NDA number): Office of Marketed Drugs (MD-300), Bureau of Medicine.

Original abbreviated new drug applications: Office of Marketed Drugs (MD-300), Bureau of Medicine.

All other communications regarding this announcement: Special Assistant for Drug Efficacy Study Implementation (MD-16), Bureau of Medicine.

This notice is issued pursuant to the provisions of the Federal Food, Drug, and Cosmetic Act (secs. 502, 505, 52 Stat. 1050-53, as amended; 21 U.S.C. 352, 355) and under the authority delegated to the Commissioner of Food and Drugs (21 CFR 2.120).

Dated: September 18, 1969.

HERBERT L. LEY, JR.,
Commissioner of Food and Drugs.

[F.R. Doc. 69-11398; Filed, Sept. 24, 1969; 8:45 a.m.]

ABBOTT LABORATORIES

Tranvet; Notice of Withdrawal of Approval of New-Drug Application

Amdal Co., Agricultural Division, Abbott Laboratories, North Chicago, Ill. 60064, holder of new-drug application No. 12-800V and all amendments and supplements thereto for the drug Tranvet (propiopromazine hydrochloride), has waived opportunity for a hearing on the proposed withdrawal of approval of said application as announced in the FEDERAL REGISTER on February 19, 1969 (34 F.R. 2965).

The Commissioner of Food and Drugs, pursuant to the provisions of the Federal Food, Drug, and Cosmetic Act (sec. 505 (e), 52 Stat. 1053, as amended; 21 U.S.C. 355(e)) and under authority delegated to him (21 CFR 2.120), finds that new evidence of clinical experience not contained in the application and not available to him until after the application was approved shows that the drug is not safe under the conditions of use on the basis of which the application was approved.

Therefore, pursuant to the foregoing finding, approval of new-drug application No. 12-800V and all amendments and supplements thereto applying to the drug Tranvet is withdrawn, effective on the date of signature of this document.

Dated: September 18, 1969.

J. K. KIRK,
Associate Commissioner for Compliance.

[F.R. Doc. 69-11397; Filed, Sept. 24, 1969; 8:45 a.m.]

Office of the Secretary

CHILD AND HEALTH WELFARE PROGRAM

Reorganization

Correction

In F.R. Doc. 69-11316 published in the issue of Tuesday, September 23, 1969, the date following "Sec. 7." in the third column on page 14702 should be changed to "September 17, 1969".

DEPARTMENT OF TRANSPORTATION

Coast Guard

[CGFR 69-96]

EQUIPMENT, CONSTRUCTION, AND MATERIALS

Approval Notice

1. Certain laws and regulations (46 CFR, Ch. I) require that various items of lifesaving, firefighting, and miscellaneous equipment, construction, and materials used on board vessels subject to Coast Guard inspection, on certain motorboats and other recreational vessels, and on the artificial islands and