CENTER FOR DRUG EVALUATION AND RESEARCH

Approval Package for:

APPLICATION NUMBER:

ANDA 90-097

Name: Liothyronine Sodium Tablets

Sponsor: Coastal Pharmaceuticals

Approval Date: March 20, 2009

CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

ANDA 90-097

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CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

ANDA 90-097

APPROVAL LETTER

DEPARTMENT OF HEALTH & HUMAN SERVICES

Food and Drug Administration
Rockville, MD 20857

ANDA 90-097

Coastal Pharmaceuticals
Attention: William A. Tilghman, Jr.
Regulatory Affairs Manager
1240 Sugg Parkway
Greenville, NC 27834

Dear Sir:

This is in reference to your abbreviated new drug application (ANDA) dated October 31, 2007, submitted pursuant to section 505(j) of the Federal Food, Drug, and Cosmetic Act (the Act), for Liothyronine Sodium Tablets USP, 5 mcg, 25 mcg and 50 mcg.

Reference is also made to your amendments dated December 16, 2008; and January 15, 2009.

We have completed the review of this ANDA and have concluded that adequate information has been presented to demonstrate that the drug is safe and effective for use as recommended in the submitted labeling. Accordingly the ANDA is approved, effective on the date of this letter. The Division of Bioequivalence has determined your Liothyronine Sodium Tablets USP, 5 mcg, 25 mcg and 50 mcg to be bioequivalent and, therefore, therapeutically equivalent to the reference listed drug, Cytomel Tablets, 5 mcg, 25 mcg and 50 mcg, of King Pharmaceuticals, Inc. Your dissolution testing should be incorporated into the stability and quality control program using the same method proposed in your application.

Under section 506A of the Act, certain changes in the conditions described in this ANDA require an approved supplemental application before the change may be made.

We note that if FDA requires a Risk Evaluation & Mitigation Strategy (REMS) for a listed drug, an ANDA citing that listed drug also will be required to have a REMS, See 505-1(i).

Postmarketing reporting requirements for this ANDA are set forth in 21 CFR 314.80-81 and 314.98. The Office of Generic Drugs should be advised of any change in the marketing status of this drug.

Promotional materials may be submitted to FDA for comment prior to publication or dissemination. Please note that these submissions are voluntary. If you desire comments on proposed launch promotional materials with respect to compliance with applicable regulatory requirements, we recommend you submit, in draft or mock-up form, two copies of both the promotional materials and package insert(s) directly to:

Food and Drug Administration
Center for Drug Evaluation and Research
Division of Drug Marketing, Advertising, and Communications
5901-B Ammendale Road
Beltsville, MD 20705

We call your attention to 21 CFR 314.81(b)(3) which requires that all promotional materials be submitted to the Division of Drug Marketing, Advertising, and Communications with a completed Form FDA 2253 at the time of their initial use.

Within 14 days of the date of this letter, submit updated content of labeling [21 CFR 314.50(1)] in structured product labeling (SPL) format, as described at http://www.fda.gov/oc/datacouncil/spl.html, that is identical in content to the approved labeling. Upon receipt and verification, we will transmit that version to the National Library of Medicine for public dissemination. For administrative purposes, please designate this submission as "***Miscellaneous Correspondence - SPL for Approved ANDA 90-097***".

Sincerely yours,

{See appended electronic signature page}

Gary Buehler
Director
Office of Generic Drugs
Center for Drug Evaluation and Research

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

/s/

Gary Buehler

3/20/2009 11:53:20 AM

CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

ANDA 90-097

LABELING

Liothyronine Sodium
Tablets, USP
5 mcg
25 mcg
50 mcg

60509

60509

Liothyronine Sodium Tablets, USP
5 mcg
25 mcg
50 mcg

Liothyronine Sodium Tablets, USP

DESCRIPTION

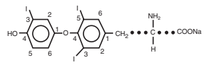
Thyroid hormone drugs are natural or synthetic preparations containing tetraiodothyronine (T_4, levothyroxine) sodium or triiodothyronine (T_3, liothyronine) sodium or both. T_4 and T_3 are produced in the human thyroid gland by the iodination and coupling of the amino acid tyrosine. T_4 contains four iodine atoms and is formed by the coupling of two molecules of diiodotyrosine (DIT). T_3 contains three atoms of iodine and is formed by the coupling of one molecule of DIT with one molecule of monoiodotyrosine (MIT). Both hormones are stored in the thyroid colloid as thyroglobulin.

Thyroid hormone preparations belong to two categories: (1) natural hormonal preparations derived from animal thyroid, and (2) synthetic preparations. Natural preparations include desiccated thyroid and thyroglobulin. Desiccated thyroid is derived from domesticated animals that are used for food by man (either beef or hog thyroid), and thyroglobulin is derived from thyroid glands of the hog. The United States Pharmacopeia (USP) has standardized the total iodine content of natural preparations. Thyroid USP contains not less than (NLT) 0.17 percent and not more than (NMT) 0.23 percent iodine, and thyroglobulin contains not less than (NLT) 0.7 percent of organically bound iodine. Iodine content is only an indirect indicator of true hormonal biologic activity.

Liothyronine Sodium Tablets, USP contain liothyronine (L-triiodothyronine or LT_3), a synthetic form of a natural thyroid hormone, and is available as the sodium salt.

The structural and empirical formulas and molecular weight of liothyronine sodium are given below.

Liothyronine Sodium



$C_{15}H_{11}I_3NNaO_4$ M.W. 672.96

L-Tyrosine, *O*-(4-hydroxy-3-iodophenyl)-3,5-diiodo-, monosodium salt

Twenty-five mcg of liothyronine is equivalent to approximately 1 grain of desiccated thyroid or thyroglobulin and 0.1 mg of L-thyroxine.

Each round, white Liothyronine Sodium Tablet, USP contains liothyronine sodium equivalent to liothyronine as follows: 5 mcg debossed 5 and 220; 25 mcg scored and debossed 25 and 222; 50 mcg scored and debossed 50 and 223. Inactive ingredients consist of calcium sulfate, microcrystalline cellulose, hypromellose, talc, and colloidal silicon dioxide.

CLINICAL PHARMACOLOGY

The mechanisms by which thyroid hormones exert their physiologic action are not well understood. These hormones enhance oxygen consumption by most tissues of the body, increase the basal metabolic rate and the metabolism of carbohydrates, lipids and proteins. Thus, they exert a profound influence on every organ system in the body and are of particular importance in the development of the central nervous system.

Pharmacokinetics

Since liothyronine sodium (T_3) is not firmly bound to serum protein, it is readily available to body tissues. The onset of activity of liothyronine sodium is rapid, occurring within a few hours. Maximum pharmacologic response occurs within 2 or 3 days, providing early clinical response. The biological half-life is about 2-1/2 days.

T_3 is almost totally absorbed, 95 percent in 4 hours. The hormones contained in the natural preparations are absorbed in a manner similar to the synthetic hormones.

Liothyronine sodium has a rapid cutoff of activity which permits quick dosage adjustment and facilitates control of the effects of overdosage, should they occur.

The higher affinity of levothyroxine (T_4) for both thyroid-binding globulin and thyroid-binding prealbumin as compared to triiodothyronine (T_3) partially explains the higher serum levels and longer half-life of the former hormone. Both protein-bound hormones exist in reverse equilibrium with minute amounts of free hormone, the latter accounting for the metabolic activity.

INDICATIONS AND USAGE

Thyroid hormone drugs are indicated:

1. As replacement or supplemental therapy in patients with hypothyroidism of any etiology, except transient hypothyroidism during the recovery phase of subacute thyroiditis. This category includes cretinism, myxedema and ordinary hypothyroidism in patients of any age (pediatric patients, adults, the elderly), or state (including pregnancy); primary hypothyroidism resulting from functional deficiency, primary atrophy, partial or total absence of thyroid gland, or the effects of surgery, radiation, or drugs, with or without the presence of goiter; and secondary (pituitary) or tertiary (hypothalamic) hypothyroidism (see **WARNINGS**).

2. As pituitary thyroid-stimulating hormone (TSH) suppressants, in the treatment or prevention of various types of euthyroid goiters, including thyroid nodules, subacute or chronic lymphocytic thyroiditis (Hashimoto's) and multinodular goiter.

3. As diagnostic agents in suppression tests to differentiate suspected mild hyperthyroidism or thyroid gland autonomy.

Liothyronine Sodium Tablets, USP can be used in patients allergic to desiccated thyroid or thyroid extract derived from pork or beef.

CONTRAINDICATIONS

Thyroid hormone preparations are generally contraindicated in patients with diagnosed but as yet uncorrected adrenal cortical insufficiency, untreated thyrotoxicosis and apparent hypersensitivity to any of their active or extraneous constituents. There is no well-documented evidence from the literature, however, of true allergic or idiosyncratic reactions to thyroid hormone.

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.

The use of thyroid hormones in the therapy of obesity, alone or combined with other drugs, is unjustified and has been shown to be ineffective. Neither is their use justified for the treatment of male or female infertility unless this condition is accompanied by hypothyroidism.

Thyroid hormones should be used with great caution in a number of circumstances where the integrity of the cardiovascular system, particularly the coronary arteries, is suspected. These include patients with angina pectoris or the elderly, in whom there is a greater likelihood of occult cardiac disease. In these patients, liothyronine sodium therapy should be initiated with low doses, with due consideration for its relatively rapid onset of action. Starting dosage of Liothyronine Sodium Tablets, USP is 5 mcg daily, and should be increased by no more than 5 mcg increments at 2-week intervals. When, in such patients, a euthyroid state can only be reached at the expense of an aggravation of the cardiovascular disease, thyroid hormone dosage should be reduced.

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

General – Thyroid hormone therapy in patients with concomitant diabetes mellitus or insipidus or adrenal cortical insufficiency aggravates the intensity of their symptoms. Appropriate adjustments of the various therapeutic measures directed at these concomitant endocrine diseases are required.

The therapy of myxedema coma requires simultaneous administration of glucocorticoids.

Hypothyroidism decreases and hyperthyroidism increases the sensitivity to oral anticoagulants. Prothrombin time should be closely monitored in thyroid-treated patients on oral anticoagulants and dosage of the latter agents adjusted on the basis of frequent prothrombin time determinations. In infants, excessive doses of thyroid hormone preparations may produce craniosynostosis.

Information for the Patient – Patients on thyroid hormone preparations and parents of pediatric patients on thyroid therapy should be informed that:

1. Replacement therapy is to be taken essentially for life, with the exception of cases of transient hypothyroidism, usually associated with thyroiditis, and in those patients receiving a therapeutic trial of the drug.

2. They should immediately report during the course of therapy any signs or symptoms of thyroid hormone toxicity, e.g., chest pain, increased pulse rate, palpitations, excessive sweating, heat intolerance, nervousness, or any other unusual event.

3. In case of concomitant diabetes mellitus, the daily dosage of antidiabetic medication may need readjustment as thyroid hormone replacement is achieved. If thyroid medication is stopped, a downward readjustment of the dosage of insulin or oral hypoglycemic agent may be necessary to avoid hypoglycemia. At all times, close monitoring of urinary glucose levels is mandatory in such patients.

4. In case of concomitant oral anticoagulant therapy, the prothrombin time should be measured frequently to determine if the dosage of oral anticoagulants is to be readjusted.

5. Partial loss of hair may be experienced by pediatric patients in the first few months of thyroid therapy, but this is usually a transient phenomenon and later recovery is usually the rule.

Laboratory Tests – Treatment of patients with thyroid hormones requires the periodic assessment of thyroid status by means of appropriate laboratory tests besides the full clinical evaluation. The TSH suppression test can be used to test the effectiveness of any thyroid preparation, bearing in mind the relative insensitivity of the infant pituitary to the negative feedback effect of thyroid hormones.

Serum T_4 levels can be used to test the effectiveness of all thyroid medications except products containing liothyronine sodium. When the total serum T_4 is low but TSH is normal, a test specific to assess unbound (free) T_4 levels is warranted. Specific measurements of T_4 and T_3 by competitive protein binding or radioimmunoassay are not influenced by blood levels of organic or inorganic iodine and have essentially replaced older tests of thyroid hormone measurements, i.e., PBI, BEI and T_4 by column.

Drug Interactions

Oral Anticoagulants – Thyroid hormones appear to increase catabolism of vitamin K-dependent clotting factors. If oral anticoagulants are also being given, compensatory increases in clotting factor synthesis are impaired. Patients stabilized on oral anticoagulants who are found to require thyroid replacement therapy should be watched very closely when thyroid is started. If a patient is truly hypothyroid, it is likely that a reduction in anticoagulant dosage will be required. No special precautions appear to be necessary when oral anticoagulant therapy is begun in a patient already stabilized on maintenance thyroid replacement therapy.

Insulin or Oral Hypoglycemics – Initiating thyroid replacement therapy may cause increases in insulin or oral hypoglycemic requirements. The effects seen are poorly understood and depend upon a variety of factors such as dose and type of thyroid preparations and endocrine status of the patient. Patients receiving insulin or oral hypoglycemics should be closely watched during initiation of thyroid replacement therapy.

Cholestyramine – Cholestyramine binds both T_4 and T_3 in the intestine, thus impairing absorption of these thyroid hormones. *In vitro* studies indicate that the binding is not easily removed. Therefore, 4 to 5 hours should elapse between administration of cholestyramine and thyroid hormones.

Estrogen, Oral Contraceptives – Estrogens tend to increase serum thyroxine-binding globulin (TBg). In a patient with a nonfunctioning thyroid gland who is receiving thyroid replacement therapy, free levothyroxine may be decreased when estrogens are started thus increasing thyroid requirements. However, if the patient's thyroid gland has sufficient function, the decreased free thyroxine will result in a compensatory increase in thyroxine output by the thyroid. Therefore, patients without a functioning thyroid gland who are on thyroid replacement therapy may need to increase their thyroid dose if estrogens or estrogen-containing oral contraceptives are given.

Tricyclic Antidepressants – Use of thyroid products with imipramine and other tricyclic antidepressants may increase receptor sensitivity and enhance antidepressant activity; transient cardiac arrhythmias have been observed. Thyroid hormone activity may also be enhanced.

Digitalis – Thyroid preparations may potentiate the toxic effects of digitalis. Thyroid hormonal replacement increases metabolic rate, which requires an increase in digitalis dosage.

Ketamine – When administered to patients on a thyroid preparation, this parenteral anesthetic may cause hypertension and tachycardia. Use with caution and be prepared to treat hypertension, if necessary.

Vasopressors – Thyroxine increases the adrenergic effect of catecholamines such as epinephrine and norepinephrine. Therefore, injection of these agents into patients receiving thyroid preparations increases the risk of precipitating coronary insufficiency, especially in patients with coronary artery disease. Careful observation is required.

Drug/Laboratory Test Interactions – The following drugs or moieties are known to interfere with laboratory tests performed in patients on thyroid hormone therapy: androgens, corticosteroids, estrogens, oral contraceptives containing estrogens, iodine-containing preparations and the numerous preparations containing salicylates.

1. Changes in TBg concentration should be taken into consideration in the interpretation of T_4 and T_3 values. In such cases, the unbound (free) hormone should be measured. Pregnancy, estrogens and estrogen-containing oral contraceptives increase TBg concentrations. TBg may also be increased during infectious hepatitis. Decreases in TBg concentrations are observed in nephrosis, acromegaly and after androgen or corticosteroid therapy. Familial hyper- or hypo-thyroxine-binding-globulinemias have been described. The incidence of TBg deficiency approximates 1 in 9000. The binding of thyroxine by thyroxine-binding prealbumin (TBPA) is inhibited by salicylates.

2. Medicinal or dietary iodine interferes with all *in vivo* tests of radioiodine uptake, producing low uptakes which may not be reflective of a true decrease in hormone synthesis.

3. The persistence of clinical and laboratory evidence of hypothyroidism in spite of adequate dosage replacement indicates either poor patient compliance, poor absorption, excessive fecal loss, or inactivity of the preparation. Intracellular resistance to thyroid hormone is quite rare.

Carcinogenesis, Mutagenesis and Impairment of Fertility – A reportedly apparent association between prolonged thyroid therapy and breast cancer has not been confirmed and patients on thyroid for established indications should not discontinue therapy. No confirmatory long-term studies in animals have been performed to evaluate carcinogenic potential, mutagenicity, or impairment of fertility in either males or females.

Pregnancy – Category A. Thyroid hormones do not readily cross the placental barrier. The clinical experience to date does not indicate any adverse effect on fetuses when thyroid hormones are administered to pregnant women. On the basis of current knowledge, thyroid replacement therapy to hypothyroid women should not be discontinued during pregnancy.

Nursing Mothers – Minimal amounts of thyroid hormones are excreted in human milk. Thyroid is not associated with serious adverse reactions and does not have a known tumorigenic potential. However, caution should be exercised when thyroid is administered to a nursing woman.

Geriatric Use – Clinical studies of liothyronine sodium did not include sufficient numbers of subjects aged 65 and over to determine whether they respond differently from younger subjects. Other reported clinical experience has not identified differences in responses between the elderly and younger patients. In general, dose selection for an elderly patient should be cautious, usually starting at the low end of the dosing range, reflecting the greater frequency of decreased hepatic, renal, or cardiac function, and of concomitant disease or other drug therapy. This drug is known to be substantially excreted by the kidney, and the risk of toxic reactions to this drug may be greater in patients with impaired renal function. Because elderly patients are more likely to have decreased renal function, care should be taken in dose selection, and it may be useful to monitor renal function.

Pediatric Use – Pregnant mothers provide little or no thyroid hormone to the fetus. The incidence of congenital hypothyroidism is relatively high (1:4000) and the hypothyroid fetus would not derive any benefit from the small amounts of hormone crossing the placental barrier. Routine determinations of serum T_4 and/or TSH is strongly advised in neonates in view of the deleterious effects of thyroid deficiency on growth and development.

Treatment should be initiated immediately upon diagnosis and maintained for life, unless transient hypothyroidism is suspected, in which case, therapy may be interrupted for 2 to 8 weeks after the age of 3 years to reassess the condition. Cessation of therapy is justified in patients who have maintained a normal TSH during those 2 to 8 weeks.

ADVERSE REACTIONS

Adverse reactions, other than those indicative of hyperthyroidism because of therapeutic overdosage, either initially or during the maintenance period are rare (see **OVERDOSAGE**).

In rare instances, allergic skin reactions have been reported with Liothyronine Sodium Tablets, USP.

OVERDOSAGE

Signs and Symptoms – Headache, irritability, nervousness, sweating, arrhythmia (including 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 Of Overdosage – Dosage should be reduced or therapy temporarily discontinued if signs and symptoms of overdosage appear. Treatment may be reinstituted at a lower dosage. In normal individuals, normal hypothalamic-pituitary-thyroid axis function is restored in 6 to 8 weeks after thyroid suppression.

Treatment of acute massive thyroid hormone overdosage is aimed at reducing gastrointestinal absorption of the drugs and counteracting central and peripheral effects, mainly those of increased sympathetic activity. Vomiting may be induced initially if further gastrointestinal absorption can reasonably be prevented and barring contraindications such as coma, convulsions, or loss of the gagging reflex. Treatment is symptomatic and supportive. Oxygen may be administered and ventilation maintained. Cardiac glycosides may be indicated if congestive heart failure develops. Measures to control fever, hypoglycemia, or fluid loss should be instituted if needed. Antiadrenergic agents, particularly propranolol, have been used advantageously in the treatment of increased sympathetic activity. Propranolol may be administered intravenously at a dosage of 1 to 3 mg over a 10-minute period or orally, 80 to 160 mg/day, especially when no contraindications exist for its use.

DOSAGE AND ADMINISTRATION

The dosage of thyroid hormones is determined by the indication and must in every case be individualized according to patient response and laboratory findings.

Liothyronine Sodium Tablets, USP are intended for oral administration; 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 up to 25 mcg every 1 or 2 weeks. Usual maintenance dose is 25 to 75 mcg daily.

The rapid onset and dissipation of action of liothyronine sodium (T_3), as compared with levothyroxine sodium (T_4), has led some clinicians to prefer its use in patients who might be more susceptible to the untoward effects of thyroid medication. However, the wide swings in serum T_3 levels that follow its administration and the possibility of more pronounced cardiovascular side effects tend to counterbalance the stated advantages.

Liothyronine Sodium Tablets, USP may be used in preference to levothyroxine (T_4) during radioisotope scanning procedures, since induction of hypothyroidism in those cases is more abrupt and can be of shorter duration. It may also be preferred when impairment of peripheral conversion of T_4 to T_3 is suspected.

Myxedema: Recommended starting dosage is 5 mcg daily. This may be increased by 5 to 10 mcg daily every 1 or 2 weeks. When 25 mcg daily is reached, dosage may be increased by 5 to 25 mcg every 1 or 2 weeks until a satisfactory therapeutic response is attained. Usual maintenance dose is 50 to 100 mcg daily.

Myxedema Coma: Myxedema coma is usually precipitated in the hypothyroid patient of long standing by intercurrent illness or drugs such as sedatives and anesthetics and should be considered a medical emergency.

An intravenous preparation of liothyronine sodium is marketed under the trade name Triostat® for use in myxedema coma/precoma.

Congenital Hypothyroidism: Recommended starting dosage is 5 mcg daily, with a 5 mcg increment every 3 to 4 days until the desired response is achieved. Infants a few months old may require only 20 mcg daily for maintenance. At 1 year, 50 mcg daily may be required. Above 3 years, full adult dosage may be necessary (see **PRECAUTIONS, Pediatric Use**).

Simple (non-toxic) Goiter: Recommended starting dosage is 5 mcg daily. This dosage may be increased by 5 to 10 mcg daily every 1 or 2 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 pediatric patients, 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 Tablets, USP from thyroid, L-thyroxine or thyroglobulin, discontinue the other medication, initiate *Liothyronine Sodium Tablets, USP* 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.

Thyroid Suppression Therapy: Administration of thyroid hormone in doses higher than those produced physiologically by the gland results in suppression of the production of endogenous hormone. This is the basis for the thyroid suppression test and is used as an aid in the diagnosis of patients with signs of mild hyperthyroidism in whom baseline laboratory tests appear normal or to demonstrate thyroid gland autonomy in patients with Graves' ophthalmopathy. ^{131}I uptake is determined before and after the administration of the exogenous hormone. A 50% or greater suppression of uptake indicates a normal thyroid-pituitary axis and thus rules out thyroid gland autonomy.

Liothyronine Sodium Tablets, USP are given in doses of 75 to 100 mcg/day for 7 days, and radioactive iodine uptake is determined before and after administration of the hormone. If thyroid function is under normal control, the radioiodine uptake will drop significantly after treatment. Liothyronine Sodium Tablets, USP should be administered cautiously to patients in whom there is a strong suspicion of thyroid gland autonomy, in view of the fact that the exogenous hormone effects will be additive to the endogenous source.

HOW SUPPLIED

Rx Only

Liothyronine Sodium Tablets, USP, 5 mcg, are white to off-white, round, flat, debossed "5" over "220" on one side and plain on the other in bottles of 100.

Liothyronine Sodium Tablets, USP, 25 mcg, are white to off-white, round, flat, debossed "25" above the score and "222" below the score on one side and plain on the other in bottles of 100.

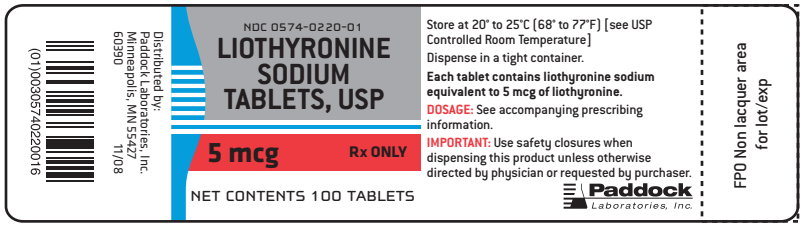
Liothyronine Sodium Tablets, USP, 50 mcg, are white to off-white, round, flat, debossed "50" above the score and "223" below the score on one side and plain on the other in bottles of 100.

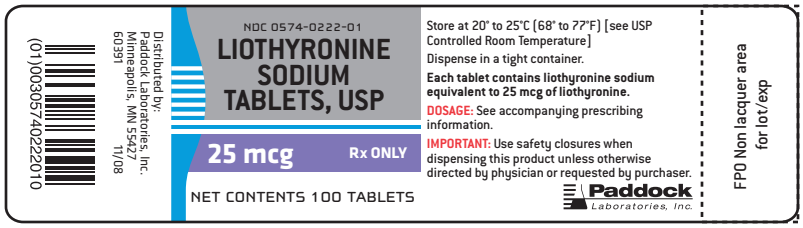
5 mcg 100's: NDC 0574-0220-01
25 mcg 100's: NDC 0574-0222-01
50 mcg 100's: NDC 0574-0223-01

Store at 20° to 25°C (68° to 77°F) [see USP Controlled Room Temperature]

Distributed by:
Paddock Laboratories, Inc.
Minneapolis, MN 55427
60509 11/08

Paddock Laboratories, Inc.


(01)00305740220016
Distributed by:
Paddock Laboratories, Inc.
Minneapolis, MN 55427
6030
11/08
NDC 0574-0220-01
LIOTHYRONINE SODIUM TABLETS, USP
5 mcg
Rx ONLY
NET CONTENTS 100 TABLETS
Store at 20° to 25°C (68° to 77°F) [see USP Controlled Room Temperature]
Dispense in a tight container.
Each tablet contains liothyronine sodium equivalent to 5 mcg of liothyronine.
DOSAGE: See accompanying prescribing information.
IMPORTANT: Use safety closures when dispensing this product unless otherwise directed by physician or requested by purchaser.
Paddock Laboratories, Inc.
FPO Non lacquer area
for lot/exp


(01)00305740222010
Distributed by:
Paddock Laboratories, Inc.
Minneapolis, MN 55427
60391
11/08
NDC 0574-0222-01
LIOTHYRONINE SODIUM TABLETS, USP
25 mcg
Rx ONLY
NET CONTENTS 100 TABLETS
Store at 20° to 25°C (68° to 77°F) [see USP Controlled Room Temperature]
Dispense in a tight container.
Each tablet contains liothyronine sodium equivalent to 25 mcg of liothyronine.
DOSAGE: See accompanying prescribing information.
IMPORTANT: Use safety closures when dispensing this product unless otherwise directed by physician or requested by purchaser.
Paddock Laboratories, Inc.
FPD Non lacquer area
for lot/exp

(01)00305740223017

Distributed by:
Paddock Laboratories, Inc.
Minneapolis, MN 55427
60392
11/08

NDC 0574-0223-01

LIOTHYRONINE SODIUM TABLETS, USP

50 mcg **Rx ONLY**

NET CONTENTS 100 TABLETS

Store at 20° to 25°C (68° to 77°F) [see USP Controlled Room Temperature]

Dispense in a tight container.

Each tablet contains liothyronine sodium equivalent to 50 mcg of liothyronine.

DOSAGE: See accompanying prescribing information.

IMPORTANT: Use safety closures when dispensing this product unless otherwise directed by physician or requested by purchaser.

Paddock Laboratories, Inc.

FPO Non lacquer area
for lot/exp

CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

ANDA 90-097

LABELING REVIEWS

APPROVAL SUMMARY 1
LABELING REVIEW BRANCH

1. APPLICANT INFORMATION:

ANDA Number	90-097
Date of Submission	16 DEC 2008
Applicant	Coastal Pharms
Drug Name	Liothyronine Sodium Tablets, USP
Strength(s)	5 mcg, 25 mcg, and 50 mcg * (as the base)

LABELS AND LABELING SUMMARY

Containers-
100s
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Insert
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2. NOTE TO CHEMIST: None

3. MODEL LABELING-This review was based on the labeling NDA- See above.

Reference Listed Drug

RLD on the 356(h) form	Cytomel
NDA Number	10-379
RLD established name	Liothyronine Sodium Tablet
Firm	King Pharms
Currently approved PI	SL-047
AP Date	May 17, 2002

RLD insert revised March 2004.

4. PATENTS/EXCLUSIVITIES: [Vol. A1.1 pg.] REFERENCE LISTED DRUG:

Patent Data For NDA 10-379

Patent No	Patent Expiration	Use Code	Description	How Filed	Labeling Impact
None				PI	

Exclusivity Data - 10-379

Code/sup	Expiration	Use Code	Description		Labeling Impact
None					

5. MANUFACTURING FACILITY OF FINISHED DOSAGE FORM - The drug substance is manu by (b) (4). The applicant and manufacturer of the finished dosage form is Coastal Pharmaceutical and the product will be disturbed by (b) (4). Metrics, Inc. (same address as the applicant, Coastal Pharmaceuticals, Inc.),1240 Sugg Parkway, Greenville, NC.

6. CONTAINER/CLOSURE/PACKAGING CONFIGURATIONS
NDA: 5 mc, 25 mcg, 50 mcg- 100s HDPE bottles
ANDA: same strengths package in 100s in HPDE

7. STORAGE AND DISPENSING STATEMENT
USP: USP item
NDA: Store at 20- 25°C (77°F); excursions permitted to 15°C-30°C (59°F-86°F).
ANDA: Store at 20° - 25°C (68° - 77°F) [see USP Controlled Room Temperature].

8. Active and INACTIVE INGREDIENTS -The description of the inactive ingredients in the insert labeling appears accurate according to the composition statement. [See lioqOS V001 10 in EDR]

Date of Review: 01/6/09 Date of Submission: 16 DEC 2008
Primary Reviewer: Angela Payne
Team Leader: John Grace

---

cc:
ANDA:
DUP/DIVISION FILE
HFD-613/APayne/JGrace (no cc)
V:\FIRMSAM\Coastal Pharm\LTRS&REV\90097ap1labdfsreview.doc
Review

4 Pages of Draft Labeling have been Withheld as b4 (CCI/TS) immediately following this page

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

/s/

Angela Payne
1/8/2009 12:15:37 PM
LABELING REVIEWER

John Grace
1/14/2009 09:17:52 AM
LABELING REVIEWER

REVIEW OF PROFESSIONAL LABELING #1
DIVISION OF LABELING AND PROGRAM SUPPORT
LABELING REVIEW

ANDA Number: 90-097 Date of Submission: 31 OCT 2007

Applicant's Name: Coastal Pharms

Established Name: Liothyronine Sodium Tablet USP 5 mcg*, 25 mcg*, and 50 mcg * (as the base)

Labeling Deficiencies:

1. CONTAINER - 100s - Please submit for review. Ensure that the RX only statement appears on the label.

2. INSERT - HOW SUPPLIED- Please include the description and distinguishing markings in this section as well as the "RX only" statement.

Please revise your labels and labeling, as instructed above, and submit electronic final printed labels and labeling according to the guidance for industry titled Providing Regulatory Submissions in Electronic Format – ANDA.

Prior to approval, it may be necessary to revise your labeling subsequent to approved changes for the reference listed drug. In order to keep ANDA labeling current, we suggest that you subscribe to the daily or weekly updates of new documents posted on the CDER web site at the following address - http://www.fda.gov/cder/cdernew/listserv.html

To facilitate review of your next submission, and in accordance with 21 CFR 314.94(a)(8)(iv), please provide a side-by-side comparison of your proposed labeling with the reference listed drug labeling with all differences annotated and explained.

FOR THE RECORD
LABELING REVIEW BRANCH

1. APPLICANT INFORMATION:

ANDA Number	90-326
Date of Submission	
Applicant	Coastal Pharms
Drug Name	Liothyronine Sodium Tablets, USP
Strength(s)	5 mcg, 25 mcg, and 50 mcg * (as the base)

LABELS AND LABELING SUMMARY

Containers- 100s
Insert

2. NOTE TO CHEMIST: None

3. MODEL LABELING-This review was based on the labeling NDA- See above.

Reference Listed Drug	
RLD on the 356(h) form	Cytomel
NDA Number	10-379
RLD established name	Liothyronine Sodium Tablet
Firm	King Pharms
Currently approved PI	SL-047
AP Date	May 17, 2002
RLD insert revised March 2004.	

4. PATENTS/EXCLUSIVITIES: [Vol. A1.1 pg.] REFERENCE LISTED DRUG:

Patent Data For NDA 10-379

Patent No	Patent Expiration	Use Code	Description	How Filed	Labeling Impact
None				PI	

Exclusivity Data - 10-379

Code/sup	Expiration	Use Code	Description		Labeling Impact
None					

5. MANUFACTURING FACILITY OF FINISHED DOSAGE FORM - The drug substance is manu by (b) (4). The applicant and manufacturer of the finished dosage form is Coastal Pharmaceutical and the product will be disturbed by (b) (4). Metrics, Inc. (same address as the applicant, Coastal Pharmaceuticals, Inc.),1240 Sugg Parkway, Greenville, NC.

6. CONTAINER/CLOSURE/PACKAGING CONFIGURATIONS
NDA: 5 mc, 25 mcg, 50 mcg- 100s HDPE bottles

ANDA: same strengths package in 100s in HPDE

7. STORAGE AND DISPENSING STATEMENT
   USP: USP item
   NDA: Store at 20- 25°C (77°F); excursions permitted to 15°C-30°C (59°F-86°F).
   ANDA: Store at 20° - 25°C (68° - 77°F) [see USP Controlled Room Temperature].

8. Active and INACTIVE INGREDIENTS -The description of the inactive ingredients in the insert labeling appears accurate according to the composition statement. [See lioqOS V001 10 in EDR]

Date of Review: 8/5/08 Date of Submission: 31 OCT 2007
Primary Reviewer: Angela Payne
Team Leader: John Grace

---

cc:

ANDA:
DUP/DIVISION FILE
HFD-613/APayne/JGrace (no cc)
V:\FIRMSAM\Coastal Pharm\LTRS&REV\90097na1labdfsreview.doc
Review

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

/s/

Angela Payne
8/7/2008 01:15:55 PM
LABELING REVIEWER

John Grace
8/11/2008 10:29:08 AM
LABELING REVIEWER

CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

ANDA 90-097

CHEMISTRY REVIEWS

ANDA 90-097

Liothyronine Sodium Tablets USP, 5 mcg, 25 mcg and 50 mcg

Coastal Pharmaceuticals

Eugene L. Schaefer, Ph.D.
Division of Chemistry I

Review #2

Table of Contents

Chemistry Review Data Sheet

1. ANDA 90-097

2. REVIEW #: 2

3. REVIEW DATE: 11/25/2008 REVISED: 12/02/2008

4. REVIEWER: Eugene L. Schaefer, Ph.D.

5. PREVIOUS DOCUMENTS:

Previous Documents	Volumes	Document Date
Original ANDA	A1.1 to A1.14 (1.6 to 1.14 are Bio only.)	10/31/07
Misc. correspondence	A2.1 (Bio only)	01/29/08

6. SUBMISSION(S) BEING REVIEWED:

Submission(s) Reviewed	Volumes	Document Date
Minor amendment	A3.1	09/30/08
Gratuitous amendment	Gateway	11/18/08

The ANDA is in CTD format. Module 2 (the QOS) of the original ANDA was electronic as Document 3177152 at Location \\Fdswa150\nonectd\N90097\N_000\2007-10-31 and Module 3 was paper only.

The minor amendment is electronic as Document 4022367 at Location \\FDSWA150\NONECTD\N90097\N_000\2008-09-30 .

The gratuitous amendment is electronic at Location \\FDSWA150\NONECTD\N90097\N_000\2008-11-18 . See Section P.3.3.

Chemistry Review Data Sheet

7. NAME & ADDRESS OF APPLICANT:

Name:	Coastal Pharmaceuticals
Address:	1240 Sugg Parkway Greenville, NC 27834
Representative:	William A. Tilghman, Jr. MSc, RAC
Telephone:	252-317-3804
Fax:	252-758-8522

8. DRUG PRODUCT NAME/CODE/TYPE:

a) Proprietary Name: None
b) Non-Proprietary Name (USAN): Liothyronine Sodium, USP
c) Code Name/# (ONDC only):
d) Chem. Type/Submission Priority (ONDC only):

- Chem. Type:
- Submission Priority:

9. LEGAL BASIS FOR SUBMISSION:

The RLD is Cytomel® Tablets 50 mcg, King Pharmaceuticals, Inc., NDA 10379. The NDA also covers the 5 mcg and 25 mcg strengths.

10. PHARMACOLOGIC CATEGORY: Thyroid hormone

11. DOSAGE FORM: Tablet

12. STRENGTH/POTENCY: 5 mcg, 25 mcg and 50 mcg

13. ROUTE OF ADMINISTRATION: Oral

14. Rx/OTC DISPENSED: _X__Rx ___OTC

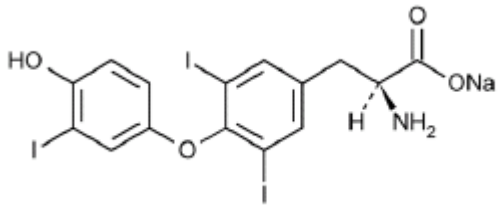
15. SPOTS (SPECIAL PRODUCTS ON-LINE TRACKING SYSTEM):

_____SPOTS product – Form Completed

___X___Not a SPOTS product

16. CHEMICAL NAME, STRUCTURAL FORMULA, MOLECULAR FORMULA, MOLECULAR WEIGHT:

IUPAC name: Sodium (2*S*)-2-amino-3-[4-(4-hydroxy-3-iodophenoxy)-3,5-diiodophenyl]propionate



Molecular formula: $C_{15}H_{11}I_3NNaO_4$

Molecular weight**:** 672.96

17. RELATED/SUPPORTING DOCUMENTS:

A. DMFs:

Chemistry Review Data Sheet

DMF #	TYPE	HOLDER (LoA Date)	ITEM REFERENCED	CODE [1]	STATUS [2]	DATE REVIEW COMPLETED	COMMENTS
(b) (4)	II	(b) (4)		3	Adequate but Info Request	08/05/08	Response has not been received as of 11/17/08 according to DARRTS.
	III			4	N/A		
	III			4	N/A		
	III			4	N/A		
	III			4	N/A		
	III			4	N/A		
	III			4	N/A		
	III			4	N/A		
	III			4	N/A		
	III			4	N/A		
	III			4	N/A		
	III			4	N/A		

* (b) (4) has indicated their DMF is inactive but they have provided a CoA letter stating the (b) (4) meets the applicable 21 CFR Indirect Food Additives regulations.

[1] Action codes for DMF Table:

1 – DMF Reviewed.
Other codes indicate why the DMF was not reviewed, as follows:
2 –Type 1 DMF
3 – Reviewed previously and no revision since last review
4 – Sufficient information in application
5 – Authority to reference not granted
6 – DMF not available
7 – Other (explain under "Comments")

[2] Adequate, Inadequate, or N/A (There is enough data in the application, therefore the DMF did not need to be reviewed)

B. Other Documents:

DOCUMENT	APPLICATION NUMBER	DESCRIPTION
None		

18. STATUS:

CONSULTS/ CMC RELATED REVIEWS	RECOMMENDATION	DATE	REVIEWER
Microbiology	N/A		
EES	Acceptable	3/19/08	S.Adams
Methods Validation	Not needed	6/30/08	E.L.Schaefer
Labeling	Deficient	8/11/08	A.Payne
Bioequivalence	Acceptable	10/08/08	Nam J. Chun
EA	Acceptable	6/30/08	E.L.Schaefer
Radiopharmaceutical	N/A		

19. ORDER OF REVIEW

The application submission(s) covered by this review was taken in the date order of receipt. ____ Yes __X__ No If no, explain reason(s) below:

The application was granted expedited review.

The Chemistry Review for ANDA 90-097

The Executive Summary

I. Recommendations

A. Recommendation and Conclusion on Approvability

ANDA 90-097 is not ready for approval. A minor amendment is requested.

B. Recommendation on Phase 4 (Post-Marketing) Commitments, Agreements, and/or Risk Management Steps, if Approvable

Coastal has provided a stability commitment.

II. Summary of Chemistry Assessments

A. Description of the Drug Product(s) and Drug Substance(s)

Liothyronine Sodium Tablets, USP contain liothyronine (L-triiodothyronine or LT_3), a synthetic form of a natural thyroid hormone, and is available as the sodium salt.

Each round, white Liothyronine Sodium Tablet, USP contains liothyronine sodium equivalent to liothyronine as follows: 5 mcg debossed 5 and 220; 25 mcg scored and debossed 25 and 222; 50 mcg scored and debossed 50 and 223. Inactive ingredients consist of calcium sulfate, NF, microcrystalline cellulose, NF, hypromellose, USP, talc, USP and colloidal silicon dioxide, NF.

B. Description of How the Drug Product is Intended to be Used

Thyroid hormone drugs are indicated:

1. As replacement or supplemental therapy in patients with hypothyroidism of any etiology, except transient hypothyroidism during the recovery phase of subacute thyroiditis. This category includes cretinism, myxedema and ordinary hypothyroidism in patients of any age (pediatric patients, adults, the elderly), or state (including pregnancy); primary hypothyroidism resulting from functional deficiency, primary atrophy, partial or total absence of thyroid gland, or the effects of surgery, radiation, or drugs, with or without the presence of goiter; and secondary (pituitary) or tertiary (hypothalamic) hypothyroidism.

25 Pages have been Withheld as b4 (CCI/TS) immediately following this page

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/s/

Eugene Schaefer
12/4/2008 10:31:26 AM
CHEMIST

Esther Chuh
12/8/2008 05:05:29 PM
CSO

Michael Smela
12/11/2008 09:49:29 AM
CHEMIST

ANDA 90-097

Liothyronine Sodium Tablets USP, 5 mcg, 25 mcg and 50 mcg

Coastal Pharmaceuticals

Eugene L. Schaefer, Ph.D.
Division of Chemistry I

Review #1

Table of Contents

Chemistry Review Data Sheet

1. ANDA 90-097

2. REVIEW #: 1

3. REVIEW DATE: 31-JUL-2008 REVISED: 08-AUG-2008

4. REVIEWER: Eugene L. Schaefer, Ph.D.

5. PREVIOUS DOCUMENTS:

Previous Documents	Volumes	Document Date
None		

6. SUBMISSION(S) BEING REVIEWED:

Submission(s) Reviewed*	Volumes	Document Date
*Original ANDA	A1.1 to A1.14 (1.6 to 1.14 are Bio only.)	10/31/07
Misc. correspondence	A2.1 (Bio only)	01/29/08

The ANDA is in CTD format. Module 2 (the QOS) is electronic as Document 3177152 at Location \\Fdswa150\nonectd\N90097\N_000\2007-10-31 and Module 3 is paper only.

Chemistry Review Data Sheet

7. NAME & ADDRESS OF APPLICANT:

Name:	Coastal Pharmaceuticals
Address:	1240 Sugg Parkway Greenville, NC 27834
Representative:	William A. Tilghman, Jr. MSc, RAC
Telephone:	252-317-3804
Fax:	252-758-8522

8. DRUG PRODUCT NAME/CODE/TYPE:

a) Proprietary Name: None
b) Non-Proprietary Name (USAN): Liothyronine Sodium, USP
c) Code Name/# (ONDC only):
d) Chem. Type/Submission Priority (ONDC only):

- Chem. Type:
- Submission Priority:

9. LEGAL BASIS FOR SUBMISSION:

The RLD is Cytomel® Tablets 50 mcg, King Pharmaceuticals, Inc., NDA 10379. The NDA also covers the 5 mcg and 25 mcg strengths.

10. PHARMACOLOGIC CATEGORY: Thyroid hormone

11. DOSAGE FORM: Tablet

12. STRENGTH/POTENCY: 5 mcg, 25 mcg and 50 mcg

13. ROUTE OF ADMINISTRATION: Oral

14. Rx/OTC DISPENSED: _X__Rx ___OTC

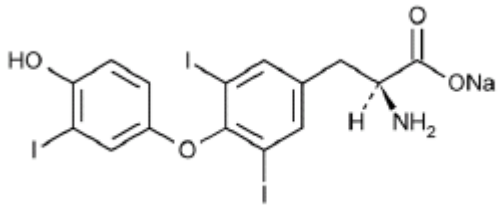
15. SPOTS (SPECIAL PRODUCTS ON-LINE TRACKING SYSTEM):

_____SPOTS product – Form Completed

___X___Not a SPOTS product

16. CHEMICAL NAME, STRUCTURAL FORMULA, MOLECULAR FORMULA, MOLECULAR WEIGHT:

IUPAC name: Sodium (2*S*)-2-amino-3-[4-(4-hydroxy-3-iodophenoxy)-3,5-diiodophenyl]propionate



Molecular formula: $C_{15}H_{11}I_3NNaO_4$

Molecular weight**:** 672.96

17. RELATED/SUPPORTING DOCUMENTS:

A. DMFs:

Chemistry Review Data Sheet

DMF #	TYPE	HOLDER (LoA Date)	ITEM REFERENCED	CODE [1]	STATUS[2]	DATE REVIEW COMPLETED	COMMENTS
(b) (4)	II	(b) (4)		1	Adequate but Info Request	08/05/08	
	III			4	N/A		
	III			4	N/A		
	III			4	N/A		
	III			4	N/A		
	III			4	N/A		
	III			4	N/A		
	III			4	N/A		
	III			4	N/A		
	III			4	N/A		
	III			4	N/A		
	III			4	N/A		

* Ametek has indicated their DMF is inactive but they have provided a CoA letter stating the color concentrate meets the applicable 21 CFR Indirect Food Additives regulations.

[1] Action codes for DMF Table:
1 – DMF Reviewed.
Other codes indicate why the DMF was not reviewed, as follows:
2 –Type 1 DMF

3 – Reviewed previously and no revision since last review
4 – Sufficient information in application
5 – Authority to reference not granted
6 – DMF not available
7 – Other (explain under "Comments")

[2] Adequate, Inadequate, or N/A (There is enough data in the application, therefore the DMF did not need to be reviewed)

B. Other Documents:

DOCUMENT	APPLICATION NUMBER	DESCRIPTION
None		

18. STATUS:

CONSULTS/ CMC RELATED REVIEWS	RECOMMENDATION	DATE	REVIEWER
Microbiology	N/A		
EES	Acceptable	3/19/08	S.Adams
Methods Validation	Not needed	6/30/08	E.L.Schaefer
Labeling	Deficient	8/11/08	A.Payne
Bioequivalence	Pending		
EA	Acceptable	6/30/08	E.L.Schaefer
Radiopharmaceutical	N/A		

19. ORDER OF REVIEW

The application submission(s) covered by this review was taken in the date order of receipt. __X__ Yes ____ No If no, explain reason(s) below:

The Chemistry Review for ANDA 90-097

The Executive Summary

I. Recommendations

A. Recommendation and Conclusion on Approvability

ANDA 90-097 is not ready for approval. A minor amendment is requested.

B. Recommendation on Phase 4 (Post-Marketing) Commitments, Agreements, and/or Risk Management Steps, if Approvable

Coastal has provided a stability commitment.

II. Summary of Chemistry Assessments

A. Description of the Drug Product(s) and Drug Substance(s)

Liothyronine Sodium Tablets, USP contain liothyronine (L-triiodothyronine or LT_3), a synthetic form of a natural thyroid hormone, and is available as the sodium salt.

Each round, white Liothyronine Sodium Tablet, USP contains liothyronine sodium equivalent to liothyronine as follows: 5 mcg debossed 5 and 220; 25 mcg scored and debossed 25 and 222; 50 mcg scored and debossed 50 and 223. Inactive ingredients consist of calcium sulfate, NF, microcrystalline cellulose, NF, hypromellose, USP, talc, USP and colloidal silicon dioxide, NF.

B. Description of How the Drug Product is Intended to be Used

Thyroid hormone drugs are indicated:

1. As replacement or supplemental therapy in patients with hypothyroidism of any etiology, except transient hypothyroidism during the recovery phase of subacute thyroiditis. This category includes cretinism, myxedema and ordinary hypothyroidism in patients of any age (pediatric patients, adults, the elderly), or state (including pregnancy); primary hypothyroidism resulting from functional deficiency, primary atrophy, partial or total absence of thyroid gland, or the effects of surgery, radiation, or drugs, with or without the presence of goiter; and secondary (pituitary) or tertiary (hypothalamic) hypothyroidism.

2. As pituitary thyroid-stimulating hormone (TSH) suppressants, in the treatment or prevention of various types of euthyroid goiters, including thyroid nodules,

subacute or chromic lymphocytic thyroiditis (Hashimoto's) and multinodular goiter.

3. As diagnostic agents in suppression tests to differentiate suspected mild hyperthyroidism or thyroid gland autonomy.

Liothyronine Sodium Tablets, USP can be used in patients allergic to desiccated thyroid or thyroid extract derived from pork or beef.

The MDD is 100 mcg.

C. Basis for Approvability or Not-Approval Recommendation

MV and Micro are not needed. Dissolution and Facilities are acceptable.

There are chemistry and labeling deficiencies. Bioequivalence is pending.

40 Pages have been Withheld as b4 (CCI/TS) immediately following this page

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/s/

Eugene Schaefer
8/25/2008 10:47:52 AM
CHEMIST

Esther Chuh
8/25/2008 02:51:48 PM
CSO

Michael Smela
8/25/2008 03:02:59 PM
CHEMIST

ANDA 90-097

Liothyronine Sodium Tablets USP, 5 mcg, 25 mcg and 50 mcg

Coastal Pharmaceuticals

Eugene L. Schaefer, Ph.D.
Division of Chemistry I

Review #3

Table of Contents

Chemistry Review Data Sheet

1. ANDA 90-097

2. REVIEW #: 3

3. REVIEW DATE: 2/23/2009

4. REVIEWER: Eugene L. Schaefer, Ph.D.

5. PREVIOUS DOCUMENTS:

Previous Documents	Volumes	Document Date
Original ANDA	A1.1 to A1.14 (1.6 to 1.14 are Bio only.)	10/31/07
Misc. correspondence	A2.1 (Bio only)	01/29/08
Minor amendment	A3.1	09/30/08
Gratuitous amendment	Gateway	11/18/08

The ANDA is in CTD format. Module 2 (the QOS) of the original ANDA was electronic as Document 3177152 at Location \\Fdswa150\nonectd\N90097\N_000\2007-10-31 and Module 3 was paper only.

The minor amendment of 9/30/08 was electronic as Document 4022367 at Location \\FDSWA150\NONECTD\N90097\N_000\2008-09-30 .

The gratuitous amendment of 11/18/08 was electronic at Location \\FDSWA150\NONECTD\N90097\N_000\2008-11-18 .

6. SUBMISSION(S) BEING REVIEWED:

Submission(s) Reviewed	Volumes	Document Date
Minor amendment	Gateway	01/15/09

The minor amendment of 1/15/09 is electronic at Location \\FDSWA150\NONECTD\N90097\N_000\2009-01-15 .

7. NAME & ADDRESS OF APPLICANT:

Name:	Coastal Pharmaceuticals
Address:	1240 Sugg Parkway Greenville, NC 27834
Representative:	William A. Tilghman, Jr. MSc, RAC
Telephone:	252-317-3804
Fax:	252-758-8522

8. DRUG PRODUCT NAME/CODE/TYPE:

a) Proprietary Name: None
b) Non-Proprietary Name (USAN): Liothyronine Sodium, USP
c) Code Name/# (ONDC only):
d) Chem. Type/Submission Priority (ONDC only):

- Chem. Type:
- Submission Priority:

9. LEGAL BASIS FOR SUBMISSION:

The RLD is Cytomel® Tablets 50 mcg, King Pharmaceuticals, Inc., NDA 10379. The NDA also covers the 5 mcg and 25 mcg strengths.

10. PHARMACOLOGIC CATEGORY: Thyroid hormone

11. DOSAGE FORM: Tablet

12. STRENGTH/POTENCY: 5 mcg, 25 mcg and 50 mcg

13. ROUTE OF ADMINISTRATION: Oral

14. Rx/OTC DISPENSED: _X__Rx ___OTC

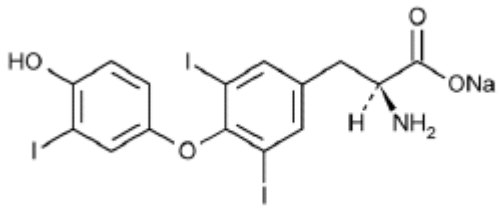
15. SPOTS (SPECIAL PRODUCTS ON-LINE TRACKING SYSTEM):

_____SPOTS product – Form Completed

___X___Not a SPOTS product

16. CHEMICAL NAME, STRUCTURAL FORMULA, MOLECULAR FORMULA, MOLECULAR WEIGHT:

IUPAC name: Sodium (2*S*)-2-amino-3-[4-(4-hydroxy-3-iodophenoxy)-3,5-diiodophenyl]propionate



Molecular formula: $C_{15}H_{11}I_3NNaO_4$

Molecular weight**:** 672.96

17. RELATED/SUPPORTING DOCUMENTS:

A. DMFs:

Chemistry Review Data Sheet

DMF #	TYPE	HOLDER (LoA Date)	ITEM REFERENCED	CODE [1]	STATUS [2]	DATE REVIEW COMPLETED	COMMENTS
(b) (4)	II		(b) (4)	1	Adequate	02/23/09	
	III			4	N/A		
	III			4	N/A		
	III			4	N/A		
	III			4	N/A		
	III			4	N/A		
	III			4	N/A		
	III			4	N/A		
	III			4	N/A		
	III			4	N/A		
	III			4	N/A		
	III			4	N/A		
	III			4	N/A		

* Ametek has indicated their DMF is inactive but they have provided a CoA letter stating the color concentrate meets the applicable 21 CFR Indirect Food Additives regulations.

[1] Action codes for DMF Table:
1 – DMF Reviewed.
Other codes indicate why the DMF was not reviewed, as follows:
2 –Type 1 DMF
3 – Reviewed previously and no revision since last review

4 – Sufficient information in application
5 – Authority to reference not granted
6 – DMF not available
7 – Other (explain under "Comments")

[2] Adequate, Inadequate, or N/A (There is enough data in the application, therefore the DMF did not need to be reviewed)

B. Other Documents:

DOCUMENT	APPLICATION NUMBER	DESCRIPTION
None		

18. STATUS:

CONSULTS/ CMC RELATED REVIEWS	RECOMMENDATION	DATE	REVIEWER
Microbiology	N/A		
EES	Acceptable	3/19/08	S.Adams
Methods Validation	Not needed	6/30/08	E.L.Schaefer
Labeling	Acceptable	1/14/09	A.Payne
Bioequivalence	Acceptable	10/08/08	Nam J. Chun
EA	Acceptable	6/30/08	E.L.Schaefer
Radiopharmaceutical	N/A		

19. ORDER OF REVIEW

The application submission(s) covered by this review was taken in the date order of receipt. ____ Yes __X__ No If no, explain reason(s) below:

The application was granted expedited review.

The Chemistry Review for ANDA 90-097

The Executive Summary

I. Recommendations

A. Recommendation and Conclusion on Approvability

ANDA 90-097 is ready for approval.

B. Recommendation on Phase 4 (Post-Marketing) Commitments, Agreements, and/or Risk Management Steps, if Approvable

Coastal has provided a stability commitment.

II. Summary of Chemistry Assessments

A. Description of the Drug Product(s) and Drug Substance(s)

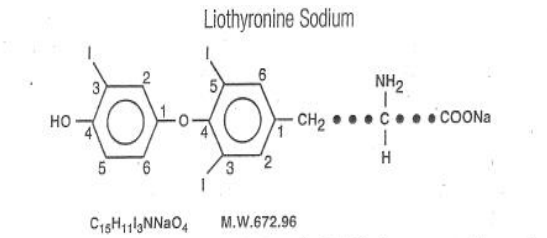
Drug Product:

Liothyronine Sodium Tablets, USP contain liothyronine (L-triiodothyronine or LT_3), a synthetic form of a natural thyroid hormone, and is available as the sodium salt.

Each round, white Liothyronine Sodium Tablet, USP contains liothyronine sodium equivalent to liothyronine as follows: 5 mcg debossed 5 and 220; 25 mcg scored and debossed 25 and 222; 50 mcg scored and debossed 50 and 223. Inactive ingredients consist of calcium sulfate, NF, microcrystalline cellulose, NF, hypromellose, USP, talc, USP and colloidal silicon dioxide, NF.

Drug Substance:

The structural and empirical formulas and molecular weight of liothyronine sodium are given below.



$C_{15}H_{11}I_3NNaO_4$ M.W.672.96

L-Tyrosine, *O*-(4-hydroxy-3-iodophenyl)-3,5-diiodo-, monosodium salt

B. Description of How the Drug Product is Intended to be Used

Thyroid hormone drugs are indicated:

1. As replacement or supplemental therapy in patients with hypothyroidism of any etiology, except transient hypothyroidism during the recovery phase of subacute thyroiditis. This category includes cretinism, myxedema and ordinary hypothyroidism in patients of any age (pediatric patients, adults, the elderly), or state (including pregnancy); primary hypothyroidism resulting from functional deficiency, primary atrophy, partial or total absence of thyroid gland, or the effects of surgery, radiation, or drugs, with or without the presence of goiter; and secondary (pituitary) or tertiary (hypothalamic) hypothyroidism.

2. As pituitary thyroid-stimulating hormone (TSH) suppressants, in the treatment or prevention of various types of euthyroid goiters, including thyroid nodules, subacute or chronic lymphocytic thyroiditis (Hashimoto's) and multinodular goiter.

3. As diagnostic agents in suppression tests to differentiate suspected mild hyperthyroidism or thyroid gland autonomy.

Liothyronine Sodium Tablets, USP can be used in patients allergic to desiccated thyroid or thyroid extract derived from pork or beef.

The MDD is 100 mcg.

C. Basis for Approvability or Not-Approval Recommendation

MV and Micro are not needed. Dissolution, Labeling, Bioequivalence and Facilities are acceptable.

The chemistry deficiencies have been remedied.

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/s/

Eugene Schaefer
3/18/2009 01:36:03 PM
CHEMIST

Esther Chuh
3/18/2009 01:40:58 PM
CHEMIST

Ramnarayan Randad
3/18/2009 02:42:39 PM
CHEMIST

CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

ANDA 90-097

BIOEQUIVALENCE REVIEWS

DIVISION OF BIOEQUIVALENCE ACCEPTABLE DSI INSPECTION REPORT REVIEW

ANDA No.	79-167
Drug Product Name	Rosuvastatin Calcium Tablets
Strength	5 mg, 10 mg, 20 mg and 40 mg
Applicant Name	Cobalt Pharmaceuticals, Inc.
Date of Original Submission	August 13, 2007
Date of Report	October 2, 2008
Reviewer	Nam Chun, Pharm.D.

EXECUTIVE SUMMARY

The Division of Scientific Investigations (DSI) inspection report of (b) (4) was received by the Division of Bioequivalence and found acceptable. The site inspection was requested for ANDA 79-167. The following applications contained studies conducted at these sites. Given the acceptable inspection of the sites, the bioequivalence section of the applications are now acceptable.

ANDA #	Firm	Drug Product
90-097	Coastal Pharmaceuticals	Liothyronine Tablets, USP
90-326	Mylan Pharmaceuticals, Inc.	Liothyronine Tablets, USP

The applications are complete.

COMMENTS:

None

DEFICIENCY COMMENTS:

None

RECOMMENDATIONS:

The Division of Scientific Investigation (DSI) inspection report of clinical and analytical sites was received by the Division of Bioequivalence on October 2, 2008 and found acceptable.

From a bioequivalence point of view, the firm has met the requirements for *in-vivo* bioequivalence and *in-vitro* dissolution testing. The bioequivalence section of the application is acceptable.

I. Completed Assignment for 79167 ID: 6604

Reviewer: Chun, Nam **Date Completed:**
Verifier: , **Date Verified:**
Division: Division of Bioequivalence
Description:

Productivity:

ID	*Letter Date*	*Productivity Category*	*Sub Category*	*Productivity*	*Subtotal*
6604	8/13/2007	Other	DSI Inspection Report	1	1
				Bean Total:	1

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/s/

Nam J Chun
10/6/2008 12:45:31 PM
BIOPHARMACEUTICS

Lizzie Sanchez
10/8/2008 08:46:13 AM
BIOPHARMACEUTICS

DIVISION OF BIOEQUIVALENCE REVIEW

ANDA No.	90-097
Drug Product Name	Liothyronine Sodium Tablets, USP
Strength(s)	5 mcg, 25 mcg & 50 mcg
Applicant Name	Coastal Pharmaceuticals
Address	1240 Sugg Parkway Greenville, NC 27834
Applicant's Point of Contact	William A. Tilghman, Jr.
Contact's Telephone Number	(252) 317-3804
Contact's Fax Number	(252) 758-8522
Original Submission Date(s)	Date of application: October 31, 2007 Acceptable for filing: November 1, 2007
Submission Date(s) of Amendment(s) Under Review	N/A
Reviewer	Santhosh K. Pabba
Study Number (s)	70092
Study Type (s)	A randomized, two-way crossover, single-dose, open-label study under fasted condition in healthy adult subjects
Strength (s)	50 mcg
Clinical Site	Anapharm
Clinical Site Address	5160, boul. Décarie, suite 800 Montréal (Québec), Canada H3X 2H9 Tel.: (514) 485-7500 Fax: (514) 485-7501
Analytical Site	(b) (4)
Analytical Site Address	(b) (4)
OUTCOME DECISION	Incomplete pending the outcome of the analytical site inspection

1 EXECUTIVE SUMMARY

This application contains the results of a fasting bioequivalence (BE) study comparing a test product, Liothyronine Sodium Tablets, USP, 50 mcg, to the corresponding reference product, Cytomel® (Liothyronine Sodium) Tablets, 50 mcg. The fasted BE study was designed as a single-dose, two-way crossover study in healthy male and female subjects. The firm's fasting BE study is acceptable. The results are summarized in the table below.

Liothyronine Sodium Tablets, USP, 50 mcg Dose (2 x 50 mcg) Fasting Bioequivalence Study No. 70092, N=65 (Male=45 and Female=20) Least-Square Geometric Means, Point Estimates and 90% Confidence Intervals					
Parameter (units)	**Test**	**Reference**	**Ratio**	**90% C.I.**	
AUC0-48 (ng·hr/mL)	72.71	75.07	0.97	92.37	101.56
AUC∞ (hr *ng/ml)	80.99	84.01	0.96	91.54	101.52
Cmax (ng/mL)	7.85	8.01	0.98	95.55	100.66

* Based on serum liothyronine sodium levels with baseline-correction by the reviewer.

The firm has conducted acceptable comparative dissolution testing on all strengths of Liothyronine Sodium Tablets, using the USP dissolution method, and the results met the USP specification at S1 level. The dissolution testing is acceptable.

The DBE grants the waiver requests for *in vivo* BE study requirements for the following strengths:

(A) 5 mcg of Liothyronine Sodium tablets, USP (B) 25 mcg of Liothyronine Sodium tablets, USP, based on criteria set forth in 21 CFR § 320.22 (d) (2).

The clinical site was inspected on 3/6/06, outcome NAI (no action indicated). The analytical site was inspected on 8/18/08, no outcome given.

The application is incomplete pending the outcome of the analytical site inspection.

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3 SUBMISSION SUMMARY

3.1 Drug Product Information[1] [2]

Test Product	Liothyronine Sodium Tablets, USP, 50 mcg, 25 mcg and 5 mcg
Reference Product	Cytomel® Tablets, 50 mcg, 25 mcg and 5 mcg
RLD Manufacturer	King Pharmaceuticals, Inc.
NDA No.	10-379
RLD Approval Date	May 8, 1956
Indication	Liothyronine sodium tablets are indicated : 1. As replacement or supplemental therapy in patients with hypothyroidism of any etiology, except transient hypothyroidism during the recovery phase of subacute thyroiditis. This category includes cretinism, myxedema and ordinary hypothyroidism in patients of any age (pediatric patients, adults, the elderly), or state (including pregnancy); primary hypothyroidism resulting from functional deficiency, primary atrophy, partial or total absence of thyroid gland, or the effects of surgery, radiation, or drugs, with or without the presence of goiter; and secondary (pituitary) or tertiary (hypothalamic) hypothyroidism . 2. As pituitary thyroid-stimulating hormone (TSH) suppressants, in the treatment or prevention of various types of euthyroid goiters, including thyroid nodules, subacute or chronic lymphocytic thyroiditis (Hashimoto's) and multinodular goiter. 3. As diagnostic agents in suppression tests to differentiate suspected mild hyperthyroidism or thyroid gland autonomy.

3.2 PK/PD Information

Bioavailability	Orally administered liothyronine sodium is almost totally absorbed, 95% in 4 hours.
Food Effect	Label for RLD does not mention food effect.
Tmax	Tmax is approximately 1-2 hours.[3] Maximum pharmacological response occurs within 2 or 3 days.
Metabolism/Excretion	Liothyronine is primarily metabolized in the liver to deiodinated and conjugate metabolites. The drug is renally excreted as metabolites. The percent of the dose expressed as maximum value in the urine ranges from 76% to 83% depending on the patient's condition and thyroid status or L-thyroxine loading.[4]

[1] Online-Clinical Pharmacology (2008 http://www.clinicalpharmacology-ip.com/Forms/drugoptions.aspx?cpnum=1406&aprid=18785
[2] Online-Orange Book (2008). http://www.accessdata fda.gov/scripts/cder/ob/docs/tempai.cfm
[3] http://csi.micromedex.com/DKS/DATA/DE/DE2597.HTM?Top=Yes#02000000$$00$$
[4] http://dailymed nlm nih.gov/dailymed/drugInfo.cfm?id=2844

Half-life	2.5 days[2]
Drug Specific Issues (if any)	Black Box Warning: 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.

3.3 OGD Recommendations for Drug Product

Number of studies recommended:	1, fasting

1.	**Type of study:**	Fasting
	Design:	Single-dose, two-treatment, two-period crossover *in-vivo*
	Strength:	50 mcg
	Subjects:	Normal healthy males and females in general population
	Additional Comments:	N/A

Analytes to measure (in plasma/serum/blood):	Total Liothyronine (free + bound) in plasma* (please see to the comments below)
Bioequivalence based on:	90% CI of total Liothyronine (free + bound)
Waiver request of *in-vivo* testing:	Liothyronine Tablets 5 mcg and 25 mcg
Source of most recent recommendations*:	Guidance for Industry: Individual Product Bioequivalence Recommendations fo**r Liothyronine** Sodium Tablets

Summary of OGD or DBE History	DBE has received the following ANDA's: ANDA# 76-923 (Gen) ANDA# (b) (4) ANDA# (b) (4) ANDA# 90326 (Mylan)- First Generic ANDA# 90097 (Coastal)-current review ANDA# 85753 (Circa) ANDA# 85755 (Circa) ANDA# (b) (4) ANDA# ANDA# ANDA# DBE has received the following Control correspondence's from industries requesting BE and/or Dissolution requirements: Control # (b) (4) Control # Control # Control # Control # Control # Control # Control # Control # Control # Protocol (b) (4) Guidance for Industry: **Levothyroxine** Sodium Tablets - In Vivo Pharmacokinetic and Bioavailability Studies and In Vitro Dissolution Testing.

*** Reviewer's Comments for the Study Design:**

Guidance for Industry: "Individual Product Bioequivalence Recommendations for Liothyronine Sodium Tablets" recommends to measure total Liothyronine (T3) concentration in **plasma**. In Control #05-0973, it is stated that "*T3 can be measured in plasma so a standard bioequivalence single dose, two-period, two- sequence crossover fasting study in healthy subjects is appropriate. T3 is present in plasma as both free drug and drug reversibly bound to protein. Total T3 can be measured and should be used to determine pharmacokinetic parameters*" (\\cdsogdl\bewg\DrugProductsReview_In Word\Review 10379 BE database- Liothyronine021006.doc). However, the firm measured total Liothyronine (T3) concentration in **serum**. The DBE considers it acceptable for the following three reasons[5]:

1. The firm used a commercially available radioimmunoassay (RIA) kit, Double Antibody Liothyronine (T3-RIA-CT) from Bio Source Europe to determine the concentration of liothyronine in human serum. The Double Antibody

[5] DFS N 090326 N 000 06-Mar-2008

Liothyronine procedure is based on a highly specific anti-T3 monoclonal antibody and ^{125}I tracer. Sample, anti-T3 monoclonal antibody and labeled T3 are incubated where radiolabeled liothyronine competes with liothyronine in the mixture for monoclonal antibody. The antibody-bound fraction of the radiolabeled liothyronine bound to the goat anti- mouse antibodies immobilized to the wall of a polystyrene tube. The amount of liothyronine tracer that binds to the antibody is inversely proportional to the liothyronine concentration in the human serum sample. The radioactivity is measured using a gamma counter. The concentration of liothyronine in the sample is obtained by comparing the sample counts per minute with those obtained for the set of calibrators. This assay is validated and the validation is acceptable.

2. In the past, DBE has received several applications (e.g., ANDA # 76-187 and ANDA # 76-752) for **Levothyroxine (T4)** Sodium Tablets, in which the concentration of T4 was also measured in **serum** by a radioimmunoassay (RIA). T3 and T4 belong to the same category of thyroid hormone drugs. T4 contains four iodine atoms and is formed by the coupling of two molecules of diiodotyrosine (DIT). T3 contains three atoms of iodine and is formed by the coupling of one molecule of DIT with one molecule of monoiodotyrosine (MIT). Both hormones are stored in the thyroid colloid as thyroglobulin.

3. In Guidance for Industry: **Levothyroxine** Sodium Tablets - In Vivo Pharmacokinetic and Bioavailability Studies and In Vitro Dissolution Testing, it is stated that "**plasma/serum**" profiles of T4 are required for a single dose bioavailability study, implying that both plasma or serum are amenable to be used as the vehicle in determining concentration of T4, a similar compound to T3.

3.4 Contents of Submission

Study Types	Yes/No?	How many?
Single-dose fasting	Yes	1
Single-dose fed		
Steady-state		
In vitro dissolution	Yes	3
Waiver requests	Yes	2
BCS Waivers		
Clinical Endpoints		
Failed Studies		
Amendments		

3.5 Pre-Study Bioanalytical Method Validation

Information Requested Fast-Fed	Data
Bioanalytical method validation report location	Annex 1 of bioanalytical report section 14 (Module 5, Volume 14 page 170)
Analyte	**liothyronine**
Internal standard (IS)	None
Method description	This method is for the quantitation of liothyronine from human serum using a validated radioimmunoassay method (RIA) / BioSource T3-RIA-CT kit method. Samples are kept frozen at -80°C prior to analysis and 0.050mL of human serum was used for analysis.
Limit of quantitation (ng/mL)	0.50
Average recovery of drug (%)	None
Average recovery of IS (%)	None
Standard curve concentrations (ng/mL)	0.50 to 20.19
QC concentrations (ng/mL)	QC1:1.52 QC2:6.09 QC3:14.20
QC Intraday precision range (%)	1.59 to 7.06
QC Intraday accuracy range (%)	95.61 to 110.13
QC Interday precision range (%)	2.98 to 3.89
QC Interday accuracy range (%)	93.75 to 98.61
Bench-top stability (hrs)	26 hours at room temperature for T3 free human serum 25 hours at room temperature for T3 normal human serum
Stock stability (days)	None
Recounting Reproducibility (hrs)	72 hours at room temperature
Freeze-thaw stability (cycles)	4 cycles at -20°C and -80ºC
Long-term storage stability (days)	91 days at -80ºC for T3 free human serum and for T3 normal human serum 30 days at -20ºC for T3 free human serum and 47 days at -20ºC for T3 normal human serum
Dilution integrity	QC3 diluted 1/2: CV (%) 2.70 %Nominal (%) 96.81% DQC diluted 1/20: CV (%) 4.08% Nominal (%) 100.97%
Specificity	The specificity data for T3 anti-serum was provided by kit supplier, BioSource. % of Cross-reactivity for L-T3, rT3, L-T4, D-T4, TRIAC and 3,5-diiodo-L-tyrosine are 100, <0.001, 0.17, 0.04, 52 and 2.2, respectively.

SOPs submitted	Yes
Bioanalytical method is acceptable	Acceptable

Comments on the Pre-Study Method Validation:

- The long-term storage data of 91 days exceeds the storage period for the samples of the fasted (90 days) BE study.

- The firm performed partial validation to extend the calibration range from 0.26-10.20 ng/mL to 0.50-20.19 ng/mL. The firm performed partial validation to improve the evaluation of PK parameters. The firm performed partial validation for calibration curves, between-run accuracy and precision, within- run accuracy and precision, dilution integrity.
- The pre-study validation data is **acceptable**.

3.6 In Vivo Studies

Table 1(A). Summary of Bioavailability Studies for Triiodothyronine Baseline Corrected Data

Study Ref. No.	Study Objective	Study Design	Treatments (Dose, Dosage Form, Route) [Product ID]	Subjects (No. (M/F) Type Age: mean (Range)	Mean Parameters (+/-SD)						Study Report Location
					Cmax (ng/mL)	Tmax (hr)	AUC0-t (ng·h/mL)	AUC∞ (ng·h/mL)	T½ (hr)	Kel (hr-1)	
70092	Randomized, Open-Label, 2-Way Crossover, Bioequivalence Study of Liothyronine Sodium 50 µg Tablet and Cytomel® (Reference) Following a 100 µg Dose in Healthy Subjects Under Fasting Conditions	Randomized single-dose crossover	Liothyronine Sodium (2 x 50 µg tablets p.o.) [6J078-P1]	65 completing (45M/20F) Healthy subjects Age (years) = 37 (21-50)	8.02 (1.79)	2.35 (0.58) 2.25 (0.75)*	74.81 (18.02)	84.60** (21.04)	15.19** (6.20)	0.0526** (0.0191)	Section 2, 11.4.2.1, 14.1 and 14.2 (Module 5 Volume 6 Pgs 36-41 and Pgs 48-55)
			Cytomel® (2 x 50 µg tablets p.o.) [29425]	Data set for statistical analysis = 65	8.19 (1.88)	2.32 (0.62) 2.25 (0.75)*	77.53 (19.21)	88.74** (25.44)	16.35** (7.01)	0.0504** (0.0223)	

*Median (interquartile range)
**For these parameters, N=63

Table 1(B). Summary of Bioavailability Studies for Triiodothyronine Baseline Uncorrected Data

Study Ref. No.	Study Objective	Study Design	Treatments (Dose, Dosage Form, Route) [Product ID]	Subjects (No. (M/F) Type Age: mean (Range)	Mean Parameters (+/-SD)						Study Report Location
					Cmax (ng/mL)	Tmax (hr)	AUC0-t (ng·h/mL)	AUC∞ (ng·h/mL)	T½ (hr)	Kel (hr-1)	
70092	Randomized, Open-Label, 2-Way Crossover, Bioequivalence Study of Liothyronine Sodium 50 µg Tablet and Cytomel® (Reference) Following a 100 µg Dose in Healthy Subjects Under Fasting Conditions	Randomized single-dose crossover	Liothyronine Sodium (2 x 50 µg tablets p.o.) [6J078-P1] Cytomel® (2 x 50 µg tablets p.o.) [29425]	65 completing (45M/20F) Healthy subjects Age (years) = 37 (21-50) Data set for statistical analysis = 65	9.79 (2.06) 9.96 (2.13)	2.35 (0.58) 2.25 (0.75)* 2.32 (0.62) 2.25 (0.75)*	159.16 (33.42) 160.40 (22.07)	- -	- -	- -	Section 2, 11.4.2.1, 14.1 and 14.2 (Module 5 Volume 6 Pgs 36-41 and Pgs 48-55)

* Median (interquartile range)

Table 2. Statistical Summary of the Comparative Bioavailability Data Calculated by the Reviewer

Liothyronine Sodium Tablets, USP, 50 mcg Dose (2 x 50 mcg) Fasting Bioequivalence Study No. 70092, N=65(Male=45 and Female=20) Least-Square Geometric Means, Point Estimates and 90% Confidence Intervals					
Parameter (units)	**Test**	**Reference**	**Ratio**	**90% C.I.**	
AUC0-48 (ng·hr/mL)	72.71	75.07	0.97	92.37	101.56
AUC∞ (hr *ng/ml)	81.58	84.62	0.96	91.51	101.55
Cmax (ng/mL)	7.85	8.01	0.98	95.55	100.66

Table 3. Reanalysis of Study Samples

70092OOP Randomized, open-label, 2-way crossover, bioequivalence study of liothyronine sodium 50 µg tablet and Cytomel® (reference) following a 100 µg dose in healthy subjects under fasting conditions								
Reason why assay was repeated	**Number of samples reanalyzed**				**Number of recalculated values used after reanalysis**			
	Actual number		**% of total assays**		**Actual number**		**% of total assays**	
	T	**R**	**T**	**R**	**T**	**R**	**T**	**R**
Pharmacokinetic[1]	0	0	0.00	0.00	0	0	0.00	0.00
Sample concentration above upper limit of quantitation	4	2	0.14	0.07	4	2	0.14	0.07
Sample reanalyzed to obtain confirming value	2	1	0.07	0.04	2	1	0.07	0.04
Sample repeated or reinjected by error	2	1	0.07	0.04	0	0	0.00	0.00
% difference between duplicate concentration >15%, >20% (CS1, LLOQ)	37	51	1.30	1.79	37	51	1.30	1.79
Single value	2	3	0.07	0.11	2	3	0.07	0.11
Total	47	58	1.58	2.03	45	57	1.58	2.00

Treatment T: Liothyronine sodium tablet (equivalent to liothyronine 50µg), Coastal Pharmaceuticals, USA Lot: 6J078-P1
Treatment R: Liothyronine sodium tablet Cytomel® (equivalent to liothyronine 50µg), King Pharmaceuticals Inc., USA Lot: 29425

Did use of recalculated plasma concentration data change study outcome?

Subject 11 has reassays which coded as "Sample reanalyzed to obtain confirming value". Because this subject was excluded from the statistical analysis (Kel for this subject could not be calculated, details please refer to PK section in the appendix [4.1.1.4]), the reassays from this subject did not change the study outcome.

The SOP's provided by the firm for reanalysis are **acceptable**.

Comments from the Reviewer:

The firm's other reassays of the study samples are because of analytical reasons, "Sample concentration above upper limit of quantitation", "sample repeated or reinjected by error" and "error between duplicate >15%, 20% (CS1, LLOQ)", and the SOPs of sample re-analysis were provided and acceptable.

3.7 Formulation

Location in appendix	Refer to Formulation Data in Appendix Section
If a tablet, is the RLD scored?	No
If a tablet, is the test product biobatch scored	No
Is the formulation acceptable?	**FORMULATION ACCEPTABLE**
If not acceptable, why?	N/A

3.8 In Vitro Dissolution

Location of DBE Dissolution Review	N 090097 N 000 31-Oct-2007
Source of Method (USP, FDA or Firm)	USP
Medium	pH 10.0 ± 0.05 alkaline borate buffer
Volume (mL)	250 mL
USP Apparatus type	USP Apparatus 3
Rotation (rpm)	30 dips per minute, using 20-mesh screen on the top and 40-mesh screen on the bottom of the glass reciprocating cylinder.
USP specification	NLT 70% (Q) in 45 minutes
If a modified-release tablet, was testing done on ½ tablets?	N/A
F2 metric calculated?	No
If no, reason why F2 not calculated	(b) (4)
Is method acceptable?	**METHOD ACCEPTABLE**
If not then why?	N/A

3.9 Waiver Request(s)

Strengths for which waivers are requested	5 mcg and 25 mcg
Proportional to strength tested in vivo?	Yes
Is dissolution acceptable?	Yes
Waivers granted?	**WAIVERS GRANTED**
If not then why?	

3.10 Deficiency Comments

The clinical site was inspected on 3/6/06, outcome NAI (no action indicated). The analytical site was inspected on 8/18/08, no outcome given.

3.11 Recommendations

1. The Division of Bioequivalence accepts the fasting BE study 70092 conducted by the Coastal Pharmaceuticals on its Liothyronine Sodium Tablets, USP, 50 mcg, lot # 6J078-P1, comparing it to King Pharmaceuticals Inc.'s Cytomel® (Liothyronine Sodium) Tablets, 50 mcg, lot # 29425.

2. The firm's in vivo dissolution testing, using the USP dissolution method, is acceptable.

   The dissolution testing should be conducted as per current USP method for Liothyronine Sodium Tablets. The test product should meet the USP specification.

3. The Division of Bioequivalence (DBE) agrees that the information submitted by Coastal Pharmaceuticals, demonstrates that Liothyronine Sodium Tablets, USP, 5 mcg and 25 mcg, meet the requirements of Section 21 CFR § 320.22 (d)(2). The DBE recommends that the waiver of in vivo bioequivalence testing be granted for these strengths.

4. The Division of Bioequivalence deems the test product Liothyronine Sodium Tablets, USP, 50 mcg, 25 mcg and 5 mcg, manufactured by Coastal Pharmaceuticals, to be bioequivalent to the reference product, Cytomel® Tablets, 50 mcg, 25 mcg and 5 mcg, manufactured by King Pharmaceuticals Inc., respectively.

The final DBE recommendation on this application is pending the DSI inspection results.

3.12 Comments for Other OGD Disciplines

Discipline	Comment
DSI	The clinical site was inspected on 3/6/06, outcome NAI (no action indicated). The analytical site was inspected on 8/18/08, no outcome given.

4 APPENDIX

4.1 Individual Study Reviews

4.1.1 Single-dose Fasting Bioequivalence Study

4.1.1.1 Study Design

Table 4 Study Information

Study Number	70092
Study Title	Randomized, Open-Label, 2-Way Crossover, Bioequivalence Study of Liothyronine Sodium 50 µg Tablet and Cytomel® (Reference) Following a 100 µg Dose in Healthy Subjects Under Fasting Conditions
Clinical Site (Name, Address, Phone #)	Anapharm 5160, boul. Décarie, suite 800 Montréal (Québec), Canada H3X 2H9 Tel.: (514) 485-7500 Fax: (514) 485-7501
Principal Investigator	Benoît J. Deschamps, M.D.
Dosing Dates	April 19, 2007, and May 26, 2007, for Subjects No. 01 to 36 April 30, 2007, and June 4, 2007, for Subjects No. 37 to 62 and 64 to 68
Analytical Site (Name, Address, Phone #)	(b) (4)
Analysis Dates	
Analytical Director	
Storage Period of Biostudy Samples (no. of days from the first day of sample collection to the last day of sample analysis)	90 days (2007-04-19 to 2007-07-18)

Table 5. Product information

Product	Test	Reference
Treatment ID	A	B
Product Name	liothyronine sodium	liothyronine sodium (Cytomel®)
Manufacturer	Coastal Pharmaceuticals U.S.A.	King Pharmaceuticals Inc., U.S.A.
Batch/Lot No.	6J078-P1	29425
Manufacture Date	September 2006	N/AV
Expiration Date	Sep 2007	Sep 2007
Strength	50 µg	50 µg
Dosage Form	tablet	tablet
Bio-batch Size	(b) (4) tablets	N/AV
Production Batch Size	(b) (4) tablets	N/AV

Potency	(b) (4)%	Whole Tablet (b) (4)%
Content Uniformity (mean, %CV)	100.1%, 2.7%	N/AV
Dose Administered	2 x 50 µg	2 x 50 µg
Route of Administration	oral	oral

Table 6. Study Design, Single-Dose Fasting Bioequivalence Study

Number of Subjects	68* (enrolled), 65 (completed and analyzed)
No. of Sequences	2
No. of Periods	2
No. of Treatments	2
No. of Groups	2
Washout Period	35 days
Randomization Scheme	AB: 04, 05, 06, 07, 09, 12, 14, 15, 16, 21, 22, 23, 25, 26, 28, 31, 34, 36, 38, 39, 42, 43, 45, 47, 49, 50, 52, 55, 58, 60, 61, 64, 65, 67, 68, 69 BA:01, 02, 03, 08, 10, 11, 13, 17, 18, 19, 20, 24, 27, 29, 30, 32, 33, 35, 37, 40, 41, 44, 46, 48, 51, 53, 54, 56, 57, 59, 62, 63, 66
Blood Sampling Times	Pre-dose at -0.5, -0.25, -0.083 hour and post-dose at 0.5, 0.75, 1.00, 1.25, 1.50, 1.75, 2.00, 2.25, 2.50, 2.75, 3.00, 4.00, 6.00, 8.00, 10.00, 12.00, 18.00, 24.00, 48.00
Blood Volume Collected/Sample	3 ml
Blood Sample Processing/Storage	Blood samples were collected by direct venipuncture. Blood samples were kept at RT for a minimum of 30 min and centrifuged at 3,000 rpm for at least 10 min at RT. Two aliquots of atleast 0.5 ml of serum were dispensed into polypropylene tubes. The aliquots were flash frozen at -80^0 C and subsequently transferred to -80^0 C freezer. Upon completion of the study, the serum samples were shipped to the analytical laboratory for analysis.
IRB Approval	March 27, 2007
Informed Consent	Yes
Length of Fasting	Ten hours prior to dosing and additional 4 hours after dosing
Length of Confinement	Ten hours proceeding each study day and 24 hours following each dose
Safety Monitoring	Adverse events were collected and reports were tabulated. The vital signs were measured throughout the study.

* The firm mentioned as Sixty-eight (68) subjects, but the reviewer found the Subject count is 70 instead.

Comments on Study Design:

The firm's samples were collected in 48 hrs rather than 72 hrs as recommended by the general BA/BE guidance. The DBE considers it acceptable for the following reasons[6]:

[6] DFS N 090326 N 000 06-Mar-2008

- At 48 hrs, the mean levothyronine T3 concentrations of test and reference products are already decreased to the levels which are both below the LOQ of analytical method, therefore, further measurement beyond 48 hrs are not expected to give accurate results.

- The DBE has recently reviewed a first generic ANDA for Liothyronine Sodium (ANDA # 90-326). The firms' sampling times were also conducted for up to 48 hrs.

- For a similar compound Levothyroxine T4, the Guidance to Industry: *Levothyroxine Sodium Tablets-In Vivo Pharmacokinetic and Bioavailability Studies and in Vitro Dissolution Testing* suggested blood sampling times are up to 48 hours post-dose. In addition, the DBE has reviewed several ANDA's for levothyroxine T4 sodium (ANDA # 76-187 and ANDA # 76-752). The firms' sampling times were also conducted for up to 48 hrs.

The study design is acceptable.

4.1.1.2 Clinical Results

Table 7. Demographics Profile of Subjects Completing the Bioequivalence Study

Study No. 70092			
		Treatment Groups	
		Test Product N = 65	Reference Product N = 65
Age (years)	Mean ± SD	37 ± 9	37 ± 9
	Range	21 - 50	21 - 50
Age Groups	< 18	0	0
	18 – 40	39 (60.0%)	39 (60.0%)
	41 – 64	26 (40.0%)	26 (40.0%)
	65 – 75	0	0
	> 75	0	0
Sex	Male	45 (69.2%)	45 (69.2%)
	Female	20 (30.8%)	20 (30.8%)
Race	Asian	1 (1.5%)	1 (1.5%)
	Black	3 (4.6%)	3 (4.6%)
	Caucasian	53 (81.5%)	53 (81.5%)
	Hispanic	7 (10.8%)	7 (10.8%)
	Other	1 (1.5%)	1 (1.5%)
BMI	Mean ± SD	25.4 ± 2.7	25.4 ± 2.7
	Range	20.0 - 29.9	20.0 - 29.9
Height	Mean ± SD	169.9 ± 8.4	169.9 ± 8.4
	Range	154.0 - 191.5	154.0 - 191.5
Weight	Mean ± SD	73.7 ± 11.3	73.7 ± 11.3
	Range	52.0 - 109.6	52.0 - 109.6

Table 8. Dropout Information, Fasting Bioequivalence Study

Study No. 70092				
Subject No	**Reason for dropout/replacement**	**Period**	**Replaced?**	**Replaced with**
04	2007-05-25 18:11 / test /elected to withdraw (reason not recorded)	1	No	N/AP
14	2007-04-19 05:44 / pre-dose / elected to withdraw for personal reason	N/AP	Yes	Stand by A
35	2007-04-19 06:28 / pre-dose / was withdrawn due to adverse event (Pulse rate increased)	N/AP	Yes	Stand by B
48	2007-05-03 * / reference / elected to withdraw for personal reason (subject did not show up at check-in of Period 2)	1	No	N/AP
54	2007-05-02 * / reference / was withdrawn due to study history behavior	1	No	N/AP
63	2007-04-30 05:32 / pre-dose / elected to withdraw for personal reason	N/AP	No	N/AP
70	2007-04-30 08:15 / pre-dose / was withdrawn due to adverse events (Headache, Left ear pain, Sore throat, Dizziness, Nausea, Cough and Pressure around the eyes)	N/AP	No	N/AP

* Time of withdrawal not recorded.

Table 9. Study Adverse Events, Fasting Bioequivalence Study

Body System / Adverse Event	Reported Incidence by Treatment Groups	
	Fasted Bioequivalence Study Study No. 70092	
	Test N = 66	Reference N = 67
Blood and lymphatic system disorders		
Lymphadenopathy		1 (1.5%)
Ear and labyrinth disorders		
Ear pain		1 (1.5%)
Eye disorders		
Photophobia	1 (1.5%)	
Gastrointestinal disorders		
Abdominal pain	3 (4.5%)	2 (3.0%)
Constipation	1 (1.5%)	
Diarrhoea	5 (7.6%)	2 (3.0%)
Dry mouth	1 (1.5%)	
Flatulence	1 (1.5%)	
Nausea	2 (3.0%)	
Palatal disorder	1 (1.5%)	
Stomach discomfort		1 (1.5%)
Vomiting		**1 (1.5%)**
General disorders and administration site conditions		
Asthenia		3 (4.5%)
Catheter site erythema	1 (1.5%)	1 (1.5%)
Catheter site haematoma	1 (1.5%)	
Catheter site pain	2 (3.0%)	1 (1.5%)
Catheter site related reaction	1 (1.5%)	
Feeling abnormal		1 (1.5%)
Feeling cold		2 (3.0%)
Feeling hot		1 (1.5%)
Peripheral coldness	1 (1.5%)	

Body System / Adverse Event	Reported Incidence by Treatment Groups	
	Fasted Bioequivalence Study Study No. 70092	
	Test N = 66	Reference N = 67
Injury, poisoning and procedural complications		
Post procedural swelling	1 (1.5%)	
Procedural complication		1 (1.5%)
Scratch	1 (1.5%)	
Investigations		
Alanine aminotransferase increased		1 (1.5%)
Blood chloride decreased	1 (1.5%)	
Blood potassium increased		1 (1.5%)
Blood pressure decreased		1 (1.5%)
Blood pressure increased	2 (3.0%)	1 (1.5%)
Blood sodium increased	1 (1.5%)	
Blood urine present	1 (1.5%)	1 (1.5%)
Heart rate decreased		5 (7.5%)
Nitrite urine present		2 (3.0%)
Protein urine present	2 (3.0%)	3 (4.5%)
Red blood cells urine positive		1 (1.5%)
White blood cells urine positive		2 (3.0%)
Musculoskeletal and connective tissue disorders		
Back pain		1 (1.5%)
Pain in extremity		1 (1.5%)
Nervous system disorders		
Dizziness		1 (1.5%)
Dysgeusia	1 (1.5%)	
Headache	5 (7.6%)	7 (10.4%)
Hypoaesthesia	1 (1.5%)	
Somnolence		2 (3.0%)

Body System / Adverse Event	Reported Incidence by Treatment Groups	
	Fasted Bioequivalence Study Study No. 70092	
	Test N = 66	Reference N = 67
Respiratory, thoracic and mediastinal disorders		
Cough	1 (1.5%)	1 (1.5%)
Increased upper airway secretion		1 (1.5%)
Nasal congestion	2 (3.0%)	1 (1.5%)
Nasal dryness		1 (1.5%)
Pharyngolaryngeal pain		1 (1.5%)
Skin and subcutaneous tissue disorders		
Eczema	1 (1.5%)	
Vascular disorders		
Hot flush	1 (1.5%)	1 (1.5%)
Total	21 (31.8%)	24 (35.8%)

Table 10. Protocol Deviations, Fasting Bioequivalence Study

Study No. 70092		
Type	**Subject #s (Test)**	**Subject #s (Ref.)**
A total of 68 subjects were dosed instead 72 subjects as required by the protocol.	01-62, 64-69 (pre-dose)	01-62, 64-69 (pre-dose)
During the medication storage, the humidity of the storage facility fell beneath the accepted range, to as low as 22.79 %RH, between April 25, 2007, to May 3, 2007.	01-03, 08, 10, 11, 13, 17-20, 24, 27, 29, 30, 32, 33, 35, 37-47, 49-53, 55-62, 64-69	05-07, 09, 12, 14-16, 21-23, 25, 26, 28, 31, 34, 36-62, 64-69
All these subjects' serum samples collected in Period 1 were stored correctly at -80°C for 4 days, but were retrieved for bagging on dry ice and then transferred into a -20°C freezer for 31 days. However, there is no impact on samples integrity since triiodothyronine is found to be stable in human serum for 47 days at -20°C and for 91 days at -80°C.	38, 39, 42, 43, 45, 47, 49, 50, 52, 55, 58, 60, 61, 64, 65, 67-69	37, 40, 41, 44, 46, 48, 51, 53, 54, 56, 57, 59, 62, 66
No post-study procedures (including laboratory tests, vital signs measurements and ECG) were performed for this subject since he could not return to the clinical facility. However, screening laboratory results and vital signs measurements and ECG performed in Period 1 were normal or considered not clinically significant by a Medical Sub-Investigator, and no adverse event was reported for this subject during the study. This subject is healthy, therefore his safety was not compromised. A letter was sent referring the subject to his family physician.	04 (post-study)	

Study No. 70092		
Type	**Subject #s (Test)**	**Subject #s (Ref.)**
This subject consumed 250 mL of coffee 1 day 22 hours 46 minutes prior to dosing of Period 1.	09	
These subjects' 48.0 hour post-dose Period 1 ECG was not performed since subjects did not show up for the 48.0-hour post-dose return visit. All adverse events reported for theses subjects during the study were resolved. These subjects are healthy persons; therefore it is unlikely to have abnormal ECG tracings after taking two doses of study medication. Subjects' safety was unlikely compromised.	52, 69	08, 11
No post-study hematology test was performed for this subject since sample was rejected, and she could not return to the clinical facility. However, this subject is healthy; therefore it is unlikely to have abnormal laboratory tests results after taking two doses of study medication. Moreover, all adverse events reported for this subject during the study were resolved. The subject's safety was unlikely compromised. A letter was sent referring the subject to her family physician.	41 (post-study)	
Post-study procedures (including laboratory tests, vital signs measurements and ECG) were performed 35 days after the last participation of the subject in the study. However, all results were within normal ranges or judged not clinically significant by the Qualified Investigator.		48 (post-study)
No post-study procedures (including laboratory tests, vital signs measurements, ECG, and serum pregnancy test) were performed for this subject since she could not return to the clinical facility. However, screening laboratory results and vital signs measurements and ECG performed in Period 1 were normal or considered not clinically significant by a Medical Sub-Investigator, and no adverse event was reported for this subject during the study. Furthermore, the urine pregnancy test performed at check-in of Period 1 was negative, and the subject is post-menopausal since 2000. This subject is healthy, therefore his safety was not compromised. A letter was sent referring the subject to his family physician.		54 (post-study)
Although this subject's Period 1 pre-dose blood pressure was out of the ranges specified in protocol, no repeat was performed due to technical error. However, blood pressure measurements and repeat blood pressure measurements were performed at 1.00, 2.00 hours post-dose, and were considered not clinically significant, and blood pressure measurement performed 4.00 hours post-dose was normal. The subject's safety was not compromised since he was under constant supervision and remained asymptomatic.		59 (pre-dose)
No post-study hematology test was performed for this subject since sample was rejected. However, this subject is healthy; therefore it is unlikely to have abnormal laboratory tests results after taking two doses of study medication. Moreover, all adverse events reported for this subject during the study were resolved. The subject's safety was unlikely compromised. A letter was sent referring the subject to her family physician.	62 (post-study)	

Comments on Dropouts/Adverse Events/Protocol Deviations:

- A total of 70 healthy, adult subjects were enrolled and dosed in the study; 65 of these enrolled subjects completed the study.

- Total No. of Subjects discontinued (Nos. 04, 14, 35, 48, 54, 63 and 70) from the Fasting study (Study No. 70092**)** were seven. Out of the seven (7) Subjects, five (5) subjects withdrew from the study on their own accord. The remaining two (2) subjects were withdrawn from the study for medical reasons (Subject No. 35 for increased pulse rate and Subject No. 70 for [Headache, Left ear pain, Sore throat, Dizziness, Nausea, Cough and Pressure around the eyes]). Only two (2) subjects (No. 35 and 14) were replaced in the study. The firm did not account for one of the subject. The replacement of these subject in the study is in accordance with the firm's protocol to compensate for any dropout prior to the dosing of period-I. (Section 8.12 of Subject withdrawal and replacement, Module 5, Volume 7, pp. 294).

- The severity of the adverse effects ranged from mild to moderate. There were no serious adverse effects. A total of 21 subjects (31.8%) in the test treatment and 24 subjects (35.8%) in the reference treatment. Vomiting was experienced by Subject 66 during Period-I (30 April 07 at 14:35) approximately 7 hrs after administering the reference product. However, this effect was observed after 2X median of Tmax, so these subject was not excluded from the study.

- There are some other protocol deviations (medication storage, sample storage, post-study procedures) which did not affect the integrity of the study.

- There were some blood sampling deviations during the fasting BE study. However, these sampling time deviations were minor deviations (less than 5% of the nominal time point). So, the sampling time deviations were considered to be insignificant. The sample time deviations did not compromise the outcome of the BE study.

4.1.1.3 Bioanalytical Results

Table 11. Assay Validation – Within the Fasting Bioequivalence Study

Bioequivalence Study No. 70092OOP Liothyronine								
Parameter	**Standard Curve Samples**							
Concentration (ng/mL)	0.52	1.04	2.07	4.14	8.29	12.43	16.58	20.72
Inter day Precision (%CV)	2.47	2.99	1.73	1.23	1.88	1.77	2.85	3.17
Inter day Bias (%)	8.85	-6.25	0.43	3.24	-2.28	-3.27	-1.33	6.99
Linearity	0.9934 to 0.9997							
Linearity Range (ng/mL)	0.52 to 20.72							
Sensitivity/LOQ (ng/mL)	0.52							

Bioequivalence Study No. 70092OOP Liothyronine				
Parameter	**Quality Control Samples**			
Concentration (ng/mL)	1.53	6.11	14.26	3.06
Inter day Precision (%CV)	6.93	3.85	4.58	5.40
Inter day Bias (%)	-5.47	-3.31	-6.94	-2.52

Comments on Study Assay Validation:

Acceptable.

Any interfering peaks in chromatograms?	N/A
Were 20% of chromatograms included?	N/A
Were chromatograms serially or randomly selected?	N/A

Comments on Chromatograms:

Not applicable.

Table 12. SOP's Dealing with Bioanalytical Repeats of Study Samples

SOP No.	Effective Date of SOP	SOP Title
ANI 156.09	2005-09-23	Sample Reassays and Reporting of Final Concentrations

A copy of this SOP is provided in Module 5, Volume 14 beginning on page 220

Table 13. Additional Comments on Repeat Assays

Were all SOPs followed?	Yes
Did recalculation of PK parameters change the study outcome?	No. Sample reanalyzed to obtain confirming value" is considered as PK repeat. [Refer to comments under

	Section 3.6 (In Vivo studies)]
Does the reviewer agree with the outcome of the repeat assays?	Yes
If no, reason for disagreement	

Summary/Conclusions, Study Assays:

Acceptable.

4.1.1.4 Pharmacokinetic Results

Table 14. Arithmetic Mean Pharmacokinetic Parameters

Mean plasma concentrations are presented in Table 18 and Figure 1

Fasting Bioequivalence Study, Study No. 70092									
Parameter (units)	**Test**				**Reference**				**T/R**
	Mean	**%CV**	**Min**	**Max**	**Mean**	**% CV**	**Min**	**Max**	
AUC0-t (hr *ng/ml)	74.751	24.09	41.42	129.26	77.465	24.73	29.04	119.60	0.96
AUC∞ (hr *ng/ml)	82.914	23.03	42.61	142.08	87.032	26.93	33.89	152.87	0.95
Cmax (ng/ml)	8.022	22.29	4.93	15.29	8.192	22.91	5.55	14.64	0.98
Tmax* (hr)	2.500	.	1.50	4.00	2.250	.	1.25	4.00	1.11
Kel (hr^{-1})	0.051	22.44	0.03	0.08	0.052	33.08	0.02	0.10	0.99
T1/2 (hr)	14.252	23.10	9.01	24.02	14.901	36.55	6.70	36.87	0.96

* Tmax values are presented as median, range

Table 15. Geometric Means and 90% Confidence Intervals - Firm Calculated

Liothyronine Sodium Tablets, USP, 50 mcg Dose (2 x 50 mcg) Least Squares Geometric Means, Ratio of Means, and 90% Confidence Intervals				
Fasting Bioequivalence Study, Study No. 70092				
Parameter (units)	**Test**	**Reference**	**Ratio(%)**	**90% C.I.**
AUC0-t (hr *ng/ml)	72.75	75.38	96.52	92.12-101.13
AUC∞ (hr *ng/ml)#	82.15	85.56	96.02	90.81-101.52
Cmax (ng/ml)	7.86	8.03	97.85	95.34-100.43

n = 63

Table 16. Geometric Means and 90% Confidence Intervals - Reviewer Calculated

Liothyronine Sodium Tablets, USP, 50 mcg Dose (2 x 50 mcg) Least Squares Geometric Means, Ratio of Means, and 90% Confidence Intervals

Fasting Bioequivalence Study, Study No. 70092					
Parameter (units)	**Test**	**Reference**	**Ratio**	**90% C.I.**	
AUC0-t (hr *ng/ml)	72.71	75.07	0.97	92.37	101.56
AUC∞ (hr *ng/ml)	80.99	84.01	0.96	91.54	101.52
Cmax (ng/ml)	7.85	8.01	0.98	95.55	100.66

Table 17. Additional Study Information, Fasting Study No. 70092

Root mean square error, AUC0-t	0.1588	
Root mean square error, AUC∞	0.1721	
Root mean square error, Cmax	0.0872	
	Test	**Reference**
Kel and AUC∞ determined for how many subjects?	64	64
Do you agree or disagree with firm's decision?	Disagree	Disagree
Indicate the number of subjects with the following:		
measurable drug concentrations at 0 hr	0	0
first measurable drug concentration as Cmax	0	0
Were the subjects dosed as more than one group?	Yes	Yes

Ratio of AUC0-t/AUC∞				
Treatment	**n**	**Mean**	**Minimum**	**Maximum**
Test	64	0.89	0.58	0.99
Reference	64	0.89	0.64	1.00

Comments on Pharmacokinetic and Statistical Analysis:

- Serum concentration baseline corrections were obtained by subtracting the serum concentrations from the mean of the first three predose serum measurements (e.g., -0.5, -0.25 and -0.083 hour) for each subject per period.

- The mean half-life of Liothyronine is 1.5 to 2.5 days under fasted condition. For long half-life drugs, DBE recommends only Cmax and suitably truncated AUC to characterize peak and total drug exposure. So that the reviewer considers only AUC 0-48 and Cmax values to evaluate the CIs.

- The Subjects in the Fasting BE study were dosed in two groups. The reviewer used the model GRP SEQ SEQ*GRP SUB (SEQ*GRP) PER(GRP) TRT TRT*GRP for statistical analysis. There was no significant TRT*GRP effect (p>0.1) for AUCs and Cmax. Therefore, this term was dropped from subsequent analysis.

- The firm calculated Kel and AUCi using 63 subjects (excluded Subject 11 and 34). The reviewer does not agree with the firm for excluding subject 34 from both test and reference treatment and subject 11 for test treatment. The reviewer calculated Kel and AUCi using 64 subjects (excluding subject 11 only).

- In summary, the 90% confidence intervals for LAUC0-t, LAUC∞ and LCmax, from both firm's calculation and reviewer's calculation, are within the acceptable limits of 80-125%.

- The fasting study is acceptable.

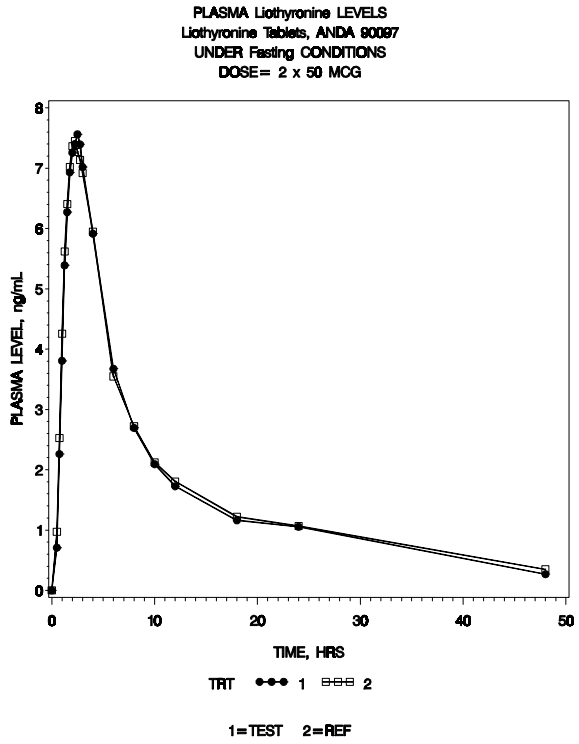
Summary and Conclusions, Single-Dose Fasting Bioequivalence Study:

The firm's *in vivo* BE study under fasted condition is acceptable.

Table 18. Mean Plasma Concentrations, Single-Dose Fasting Bioequivalence Study

	Test (n=65)		Reference (n=65)		Ratio
Time (hr)	Mean (ng/mL)	CV%	Mean (ng/mL)	CV%	(T/R)
0.00	0.00	.	0.00	.	.
0.50	0.71	80.64	0.97	95.16	0.73
0.75	2.26	60.06	2.53	62.83	0.90
1.00	3.81	44.38	4.25	50.31	0.89
1.25	5.39	38.61	5.62	43.18	0.96
1.50	6.27	32.22	6.41	39.04	0.98
1.75	6.93	31.75	7.02	37.33	0.99
2.00	7.26	25.36	7.36	31.33	0.99
2.25	7.40	25.28	7.45	27.79	0.99
2.50	7.56	23.98	7.27	22.48	1.04
2.75	7.40	22.65	7.14	19.30	1.04
3.00	7.02	21.21	6.92	21.02	1.01
4.00	5.91	21.49	5.95	22.81	0.99
6.00	3.67	22.25	3.55	22.62	1.04
8.00	2.69	23.88	2.72	23.10	0.99
10.00	2.09	25.45	2.13	26.84	0.99
12.00	1.73	28.28	1.81	34.67	0.96
18.00	1.16	31.87	1.22	33.12	0.95
24.00	1.06	31.28	1.07	32.62	0.99
48.00	0.27	76.49	0.35	73.73	0.77

Figure 1. Mean Plasma Concentrations, Single-Dose Fasting Bioequivalence Study



4.2 Formulation Data

Ingredient	Amount (mg) / Tablet			Amount (%) / Tablet		
	5 mcg Tablet	25 mcg Tablet	50 mcg Tablet	5 mcg Tablet	25 mcg Tablet	50 mcg Tablet
Cores						
Liothyronine Sodium, USP[1],						
Calcium Sulfate, (b) (4), NF						
Microcrystalline Cellulose, NF (b) (4)						
Microcrystalline Cellulose, NF (b) (4)						
Hypromellose, USP (b) (4)						
Talc, USP						
Colloidal Silicon Dioxide, NF (b)						
(b) (4)						
Coating						
There is no coating on the tablets.	N/A	N/A	N/A	N/A	N/A	N/A
Total						

(b) (4)

Is there an overage of the active pharmaceutical ingredient (API)?	NO
If the answer is yes, has the appropriate chemistry division been notified?	N/A
If it is necessary to reformulate to reduce the overage, will bioequivalence be impacted?	N/A
Comments on the drug product formulation:	1. The amounts of all inactive ingredients in the tablets are below those used in the approved drug products based on CDER's Inactive Ingredient Guide (IIG) for Approved Drug Products. 2. The formulations of the 5 mcg and 25 mcg tablets are proportionally similar to the one of the 50 mcg tablets. 2. The formulation is acceptable.

4.3 Dissolution Data

Dissolution Review Path	N 090097 N 000 31-Oct-2007

Dissolution Conditions	**Apparatus:**	USP Apparatus III
	Speed of Rotation:	30 dips per minute, using 20-mesh screen on the top and 40-mesh screen on the bottom of the glass-reciprocating cylinder
	Medium:	Alkaline Borate Buffer, pH 10.0±0.05
	Volume:	250 mL
	Temperature:	37°C
Firm's Proposed Specifications	Not less than 70% (Q) of the labeled amount of liothyronine ($C_{15}H_{12}I_3NO_4$) is dissolved in 45 minutes	
Dissolution Testing Site (Name, Address)	Metrics, Inc. 1240 Sugg Parkway Greenville, NC 27834	

Study Ref No.	Testing Date	Product ID \ Batch No. (Test - Manufacture Date) (Reference – Expiration Date)	Dosage Strength & Form	No. of Dosage Units		Collection Times (minutes or hours) 5 mins.	10 mins.	15 mins.	30 mins.	45 mins.	Study Report Location
Study Report #: 70092	3/15/07	**Test Product:** Liothyronine Sodium Tablets, USP Batch 6J078 Manufacture Date: 09/28/2006	50 mcg Tablet	12	Mean	88	100	100	100	98	Module 5 (Volume 6) Section 5.3.1.3
					Range	94-76	107-96	103-97	102-97	102-96	
					%CV	6.0	3.0	2.1	1.9	2.0	
Study Report #: 70092	3/20/07	**Reference Product:** Cytomel® (liothyronine sodium) Tablets, LOT: 29425 Expiration Date: 09/2007 Manufacture Date: Unknown	50 mcg Tablet	12	Mean	62	90	91	91	91	Module 5 (Volume 6) Section 5.3.1.3
					Range	64-56	93-89	93-89	92-89	94-91	
					%CV	3.6	1.3	1.3	1.2	1.0	

Dissolution Conditions	**Apparatus:**	USP Apparatus III
	Speed of Rotation:	30 dips per minute, using 20-mesh screen on the top and 40-mesh screen on the bottom of the glass-reciprocating cylinder
	Medium:	Alkaline Borate Buffer, pH 10.0±0.05
	Volume:	250 mL
	Temperature:	37°C
Firm's Proposed Specifications	Not less than 70% (Q) of the labeled amount of liothyronine ($C_{15}H_{12}I_3NO_4$) is dissolved in 45 minutes	
Dissolution Testing Site (Name, Address)	Metrics, Inc. 1240 Sugg Parkway Greenville, NC 27834	

Study Ref No.	Testing Date	Product ID \ Batch No. (Test - Manufacture Date) (Reference – Expiration Date)	Dosage Strength & Form	No. of Dosage Units		Collection Times (minutes or hours)					Study Report Location
						5 mins.	10 mins.	15 mins.	30 mins.	45 mins.	
Study Report #: 70092	4/27/07	**Test Product:** Liothyronine Sodium Tablets, USP Batch 7C032 Manufacture Date: 04/05/2007	25 mcg Tablet	12	Mean	95	97	97	96	96	Module 5 (Volume 6) Section 5.3.1.3
					Range	97-93	99-96	99-94	98-94	100-94	
					%CV	1.4	0.9	1.5	1.3	1.7	
Study Report #: 70092	4/30/07	**Reference Product:** Cytomel® (liothyronine sodium) Tablets, LOT: 36425 Expiration Date: 03/2008 Manufacturing Date: Unknown	25 mcg Tablet	12	Mean	73	104	104	105	104	Module 5 (Volume 6) Section 5.3.1.3
					Range	79-66	107-100	108-100	108-100	108-99	
					%CV	5.1	2.5	2.7	2.7	3.0	

Dissolution Conditions	**Apparatus:**	USP Apparatus III
	Speed of Rotation:	30 dips per minute, using 20-mesh screen on the top and 40-mesh screen on the bottom of the glass-reciprocating cylinder
	Medium:	Alkaline Borate Buffer, pH 10.0±0.05
	Volume:	250 mL
	Temperature:	37°C
Firm's Proposed Specifications	Not less than 70% (Q) of the labeled amount of liothyronine ($C_{15}H_{12}I_3NO_4$) is dissolved in 45 minutes	
Dissolution Testing Site (Name, Address)	Metrics, Inc. 1240 Sugg Parkway Greenville, NC 27834	

Study Ref No.	Testing Date	Product ID \ Batch No. (Test - Manufacture Date) (Reference – Expiration Date)	Dosage Strength & Form	No. of Dosage Units		Collection Times (minutes or hours)					Study Report Location
						5 mins.	10 mins.	15 mins.	30 mins.	45 mins.	
Study Report #: 70092	6/19/07	**Test Product:** Liothyronine Sodium Tablets, USP Batch 6J076 Manufacture Date: 09/22/2006	5 mcg Tablet	12	Mean	85	89	92	91	93	Module 5 (Volume 6) Section 5.3.1.3
					Range	96-76	94-85	95-82	93-89	98-85	
					%CV	6.7	2.9	3.9	1.7	4.3	
Study Report #: 70092	6/6/07 and 6/14/07	**Reference Product:** Cytomel® (liothyronine sodium) Tablets, LOT: 38312 Expiration Date: 04/2008 Manufacture Date: Unknown	5 mcg Tablet	12	Mean	59	67	71	71	72	Module 5 (Volume 6) Section 5.3.1.3
					Range	65-51	71-62	73-66	74-63	75-68	
					%CV	8.5	4.2	2.9	4.1	2.8	

Comments:

The dissolution testing was already reviewed (N 090097 N 000 31-Oct-2007). Per the dissolution review:

The firm's dissolution testing results on its Liothyronine Sodium Tablets, USP, 5 mcg, 25 mcg and 50 mcg, comparing them to the reference product, Cytomel® Tablets, 5 mcg, 25 mcg and 50 mcg, respectively, using the USP dissolution method, met the USP specification at S1 level. The dissolution testing is acceptable.

4.4 Detailed Regulatory History (If Applicable)

Draft Guidance on Liothyronine Sodium

This draft guidance, once finalized, will represent the Food and Drug Administration's (FDA's) current thinking on this topic. It does not create or confer any rights for or on any person and does not operate to bind FDA or the public. You can use an alternative approach if the approach satisfies the requirements of the applicable statutes and regulations. If you want to discuss an alternative approach, contact the Office of Generic Drugs.

Active ingredient: Liothyronine Sodium
Form/Route: Tablets/Oral
Recommended studies: 1 study

1. Type of study: Fasting

Design: Single-dose, two-way crossover *in-vivo*
Dose and Strength: 100 mcg (2 x 50 mcg)
Subjects: Normal healthy males and females, general population

Additional comments: Baseline levels of liothyronine should be measured at 3 pre-dose time points (-30 min, -15 min, 0 min). The mean of the three pre-dose samples should be subtracted from each measured post-dose concentration.

Analytes to measure (in appropriate biological fluid): Total (free+bound) liothyronine in plasma.
Bioequivalence based on (90% CI): Total (free +bound) liothyronine in plasma after baseline correction.
Waiver request of in-vivo testing: 25 mcg and 5 mcg based on (i) acceptable bioequivalence studies on the 50 mcg strength, (ii) proportional similarity of the formulations across all strengths, and (iii) acceptable in vitro dissolution testing of all strengths.
Dissolution test method and sampling times:
Please conduct comparative dissolution testing on 12 dosage units of all strengths of the test and reference products using the following USP method.

Guidance for Industry
Levothyroxine Sodium Tablets - In Vivo Pharmacokinetic and Bioavailability Studies and In Vitro Dissolution Testing[7]

This guidance represents the Food and Drug Administration's (FDA's) current thinking on this topic. It does not create or confer any rights for or on any person and does not operate to bind FDA or the public. An alternative approach may be used if such approach satisfies the requirements of the applicable statutes and regulations.

I. INTRODUCTION

This guidance is intended to assist sponsors of new drug applications (NDAs) for levothyroxine sodium tablets who wish to conduct in vivo pharmacokinetic and bioavailability studies and in vitro dissolution testing for their products. Information from these studies would generally be submitted in section 6 of an NDA. Sponsors who wish to use approaches other than those recommended in this guidance should discuss their plans with the FDA prior to preparing an NDA.

II. BACKGROUND

Levothyroxine sodium is the sodium salt of the levo isomer of the thyroid hormone thyroxine. Thyroid hormones affect protein, lipid, and carbohydrate metabolism, growth, and development. They stimulate the oxygen consumption of most cells of the body, resulting in increased energy expenditure and heat production, and possess a cardiostimulatory effect that may be the result of a direct action on the heart.

The production of levothyroxine hormone is regulated by the hypothalamus-pituitary axis through a negative feedback system. When hormone levels are inadequate, the hypothalamus secretes thyroid stimulating hormone-releasing hormone (TSH-RH), which stimulates the anterior pituitary to produce thyroid stimulating-hormone (TSH). TSH then stimulates the thyroid gland to produce levothyroxine (T_4) and triiodothyronine (T_3). T_4 is subsequently converted to the highly active T_3 in the peripheral tissues. High levels of T_4 inhibit the production of TSH and (to a lesser degree) TSH-RH. This effect in turn decreases the further production of T_4 (Farwell 1996).

Orally administered levothyroxine sodium is used as replacement therapy in conditions characterized by diminished or absent thyroid function such as cretinism, myxedema, nontoxic goiter, or hypothyroidism. The diminished or absent thyroid function may result from functional deficiency, primary atrophy, partial or complete absence of the thyroid gland, or the effects of surgery, radiation, or antithyroid agents. Levothyroxine sodium may also be used for replacement or supplemental therapy in patients with secondary (pituitary) or tertiary (hypothalamic) hypothyroidism.

[7] DFS N 090326 N 000 06-Mar-2008

Levothyroxine sodium is a compound with a narrow therapeutic range. If a drug product of lesser potency or bioavailability is substituted in the regimen of a patient who has been controlled on another product, a suboptimal response and hypothyroidism could result. Conversely, substitution of a drug product of greater potency or bioavailability could result in toxic manifestation of hyperthyroidism such as cardiac pain, palpitation, or cardiac arrhythmia. In patients with coronary heart disease, even a small increase in the dose of levothyroxine sodium may be hazardous. Hyperthyroidism is a known risk factor for osteoporosis (Paul et al. 1988). To minimize the risk of osteoporosis, it is advisable that levothyroxine sodium be titrated to the lowest effective dose. Because of the risks associated with over- or under-treatment with levothyroxine sodium, it is critical that patients have available to them products that are consistent in potency and bioavailability.

It is a challenge to determine the bioavailability of levothyroxine sodium products because levothyroxine is naturally present in minute quantities in the blood, with the total levels reaching 5.0-12.0 _g/dl and free (or unbound) levels reaching 0.8-2.7 ng/dl in a healthy adult. To assess the bioavailability of levothyroxine sodium after a single dose, several times the normal dose should be given to raise the levels of the drug significantly above baseline to allow measurement. Furthermore, levothyroxine has a long half-life of 6 to 9 days, and therefore, a long washout period is necessary between treatments.

III. PHARMACOKINETIC AND BIOAVAILABILITY STUDIES IN VIVO

Information on the pharmacokinetics (absorption, distribution, metabolism, and excretion) of levothyroxine sodium can be obtained from the literature and/or from original studies. If the studies cited have used levothyroxine sodium formulations other than the formulation intended for marketing, the submission should contain information identifying how those formulations differ from the to-be-marketed formulation.

For sponsors who have a product on the market, we recommend that in vivo bioavailability studies be conducted using the formulation(s) already on the market, assuming that the sponsor intends to keep marketing the formulation(s). The tablets used in the study should be made from a full-scale production batch and should meet all compendial requirements. The formulations used should demonstrate sufficient stability for the length of the study. Stability evaluations should be made for the bio-batch prior to and after the study. All dissolution, potency, and content uniformity data should be submitted to the NDA for review.

For sponsors who do not have a levothyroxine sodium formulation on the market, the usual approaches to developing pilot-scale batches for bioavailability studies apply.[2]

A. Inclusion Criteria

For each pharmacokinetic and bioavailability study outlined below, at least 24 volunteers should complete the trial. The subjects should be healthy volunteers, 18 to 50 years of age and within 15 percent of ideal body weight for their height and build. Sponsors should attempt to enroll an

equal number of men and women, if possible. Volunteers recruited for the study should have an acceptable medical history, physical examination, and clinical laboratory tests. All thyroid function tests should be within normal limits. Volunteers with any current or past medical condition that might significantly affect their pharmacokinetic or pharmacodynamic response to levothyroxine sodium should be excluded. Female volunteers should be given a pregnancy test prior to beginning the study. Pregnant women should be excluded from the study. Written informed consent should be obtained from all volunteers before they are accepted into the study.

B. Single-Dose Bioavailability Study

Objective: To determine the bioavailability of the to-be-marketed formulation of levothyroxine relative to a reference (oral solution) under fasting conditions.

Design: The study is a single-dose, two-treatment, two-sequence crossover design. An equal number of volunteers should be randomly assigned to each sequence. The washout period between treatments should be at least 35 days.

Tablet Strength and Dose: A multiple of the highest tablet strength to achieve a total dose of 600 _g should be given to detect T_4 above baseline levels.

Procedure: Following a 10-hour overnight fast, volunteers should be administered a single dose of levothyroxine sodium orally with 240-mL water. The treatments should be as follows:

Treatment 1: Multiples of the highest strength of levothyroxine sodium tablets to be marketed.

Treatment 2: Levothyroxine sodium as an oral solution at an equivalent dose with treatment 1. The intravenous formulation can be used as a convenient source of an oral levothyroxine solution.

Volunteers should remain fasted for 4 hours after dosing, with water only allowed after the first hour. Volunteers should be served standardized meals according to the schedule throughout the study.

Blood Sampling: Blood samples should be drawn at -0.5, -0.25, 0, 0.5, 1, 1.5, 2, 2.5, 3, 4, 6, 8, 10, 12, 18, 24, and 48 hours post dose.

Data Analysis: Individual and mean plasma/serum concentration-time profiles of total (bound + free) T_4 and T_3 should be included in the report. The plasma/serum profiles and pharmacokinetic measures should be presented without the adjustment of baseline levels since endogenous levothyroxine concentrations are unpredictable during the course of the study. The following pharmacokinetic measures should be computed:

· Area under the plasma/serum concentration-time curve from time 0 to the last measurable time point (AUC_{0-t})

· Peak concentration (C_{max})

· Time to peak concentration (T_{max})

Analysis of variance (ANOVA) should be performed for both log-transformed AUC_{0-t} and C_{max} using the SAS General Linear Models (GLM) procedure. The oral solution should be used as the reference formulation. The geometric means and 90 percent confidence intervals of the geometric mean ratio (test/reference) in AUC_{0-t} and C_{max} should be presented as evidence of bioavailability.

C. Dosage-Form Proportionality Study

Objective: To determine the dosage-form proportionality among the to-be-marketed tablet strengths of levothyroxine sodium.[3]

Design: The recommended study is a single-dose, three-treatment, six-sequence crossover design. An equal number of volunteers should be randomly assigned to each sequence. The washout period between treatments should be at least 35 days.

Tablet Strengths and Dose: Three strengths of tablets should be studied that represent the low, middle, and high strength of the formulations to be marketed. Generally, the middle strength studied is the 100-_g tablet. A multiple of each tablet strength should be given to detect T_4 above baseline levels. The total dose given for each treatment in the study will usually be 600 _g and should be the same dose for each treatment.

Procedure: Following a 10-hour overnight fast, volunteers should be given a single dose of levothyroxine sodium orally with 240-mL water. The treatments consisting of equal doses of levothyroxine should be as follows:

Treatment 1: Multiples of the representative low strength tablets (usually 50 _g).

Treatment 2: Multiples of the representative mid-strength tablets. This is normally the 100-_g tablet, and should be considered as the reference for this study.

Treatment 3: Multiples of the representative high strength tablets (usually 300 _g).

Volunteers should fast for an additional 4 hours after dosing, with only water allowed after the first hour. Volunteers should be served standardized meals throughout the study according to the schedule.

Blood Sampling: The blood sampling schedule for this study should be identical to that recommended for the bioavailability study.

Data Analysis: Individual and mean plasma/serum concentration-time profiles of total (bound + free) T_4 and T_3 should be included in the report. The plasma/serum profiles and pharmacokinetic

measures should be presented without adjustment of baseline levels since endogenous levothyroxine concentrations are unpredictable during the course of the study.

The pharmacokinetic measures, including AUC_{0-t}, C_{max} and T_{max}, should be computed for both total T_4 and T_3. For the assessment of proportionality between strengths, both log-transformed AUC_{0-t} and C_{max} should be analyzed with ANOVA using the SAS GLM procedure. The geometric means and 90 percent confidence intervals of the geometric mean ratio of AUC_{0-t} and C_{max} should be presented for each pairwise comparison. Dosage-form proportionality is demonstrated if the 90 percent confidence intervals fall within the 80-125 percent range.

For both single-dose bioavailability and dosage-form proportionality studies, the assessment of bioavailability should be based on the measurement of total (bound + free) T_4 and total T_3 levels. The determination of free T_4 and T_3 is not necessary. However, if sufficiently precise and accurate assays are available for free T_4 and T_3, these moieties can be measured as well. Statistical analyses of free T_4 and T_3 should then be performed, with the results used as supportive data. If free T_4 and T_3 are measured, the assays used should be based on the immuno-extraction (two-step) method, rather than the labeled analog (one-step) method. Levels of TSH should be measured as part of the volunteer-screening process as well as post-study examination. These TSH data should be reported in the NDA.

IV. DISSOLUTION TESTING IN VITRO

Dissolution studies can be performed using an appropriate method developed by a sponsor[4] or the current USP method. For each tablet strength to be marketed, multi-point dissolution studies should be performed on three production-sized batches using 12 tablets per batch. The time points used should be 10, 20, 30, 45, 60, 80, 100, and 120 minutes, or until 80 percent of the labeled claim is dissolved, so that a complete profile may be obtained. Dissolution testing should include lots used in the bioavailability studies.

V. FORMULATION

The composition of the formulation for each tablet strength of levothyroxine sodium to be marketed should be provided in the NDA.

VI. BIOWAIVER

For tablet strengths not studied in the dosage-form proportionality study (see section III. C), the sponsor should request biowaivers and provide appropriate formulation information as well as in vitro dissolution data as covered under 21 CFR 320.22(d)(2). Specifically, all of the following conditions should be met:

1. The dosage-form proportionality study among the to-be-marketed tablet strengths of levothyroxine sodium (low, medium, and high strengths) has been found acceptable, and proportionality has been shown among the strengths included in the study (also see section III. C. *Data Analysis).*

2. For tablet strengths to be covered under the waiver request, they should differ only in the amount of levothyroxine sodium and filler needed to maintain the tablet weights.

3. Multi-point dissolution profiles are similar across tablet strengths using an f2 test. If both test and reference products dissolve 85 percent or more of the label amount of the drug in ↗15 minutes, the f2 test is not necessary.[4] The dissolution method as well as dissolution data have been found acceptable by the Agency.

Sponsors whose products do not meet the above conditions should contact the Division of Pharmaceutical Evaluation II for further guidance.

VII. ASSAY VALIDATION

Assays used for both in vivo and in vitro studies should be fully validated, reproducible, precise, accurate, specific, stable, and linear. If commercial kits are used, they should be validated in-house at the analytical site where the assay for the study is performed. Please note that the validation data from the kit manufacturer alone is insufficient.

REFERENCES

Farwell A. P., and L. E. Braverma, 1996, "Thyroid and Antithyroid Drugs," *Goodman & Gilman's The Pharmacologic Basis of Therapeutics*, 9th ed. pp. 1383-1409, McGraw-Hill.

Paul T. L., J. Kerrigan, A. M. Kelly et al., 1988, "Long-term Thyroxine Therapy Is Associated with Decreased Hip Bone Density in Premenopausal Women," *JAMA*, vol. 259, pp. 3137-3141.

[1] This guidance has been prepared by the Division of Pharmaceutical Evaluation II, Office of Clinical Pharmacology and Biopharmaceutics, which operates under the direction of the Office of Pharmaceutical Science in the Center for Drug Evaluation and Research (CDER) at the Food and Drug Administration (FDA). The guidance has also been reviewed by the Guidance's Technical Committee of the Biopharmaceutics Coordinating Committee, as well as the Division of Metabolic and Endocrine Drug Products in CDER.

[2] See *Q1A Stability Testing of New Drug Substances and Products* (59 FR 48754, September 1994).

[3] Available strengths of levothyroxine sodium tablets from many manufacturers include 25, 50, 75, 88, 100, 112, 125, 137, 150, 200 and 300 _g.

[4] See FDA's guidance for industry on *Dissolution Testing of Immediate Release Solid Oral Dosage Forms* (August 1997).

4.5 SAS Output

4.5.1 Fasting Study Data

FASTING CONCENTRATION DATASET

Obs	SUB	SEQU	PER	TREAT	GRP	c1	c2	c3	c4	c5	c6	c7	c8	c9	c10	c11	c12	c13	c14	c15	c16	c17	c18	c19	c20	SEQ	TRT
1	1																										(b) (4)
2	1																										
3	2																										
4	2																										
5	3																										
6	3																										
7	5																										
8	5																										
9	6																										
10	6																										
11	7																										
12	7																										
13	8																										
14	8																										
15	9																										
16	9																										
17	10																										
18	10																										
19	11																										
20	11																										
21	12																										

15 Pages have been Withheld in Full as b4 (CCI/TS) immediately following this page

Note to the Project Manager:

Please do not send this letter until the outcome of the DSI inspection for the analytical site is received and reviewed.

BIOEQUIVALENCE COMMENTS TO BE PROVIDED TO THE APPLICANT

ANDA: 90-097

APPLICANT: Coastal Pharmaceuticals

DRUG PRODUCT: Liothyronine Sodium Tablets, USP
5 mcg, 25 mcg and 50 mcg

The Division of Bioequivalence has completed its review and has no further questions at this time.

Please note that the bioequivalence comments provided in this communication are preliminary. These comments are subject to revision after review of the entire application, upon consideration of the chemistry, manufacturing and controls, microbiology, labeling, or other scientific or regulatory issues. Please be advised that these reviews may result in the need for additional bioequivalence information and/or studies, or may result in a conclusion that the proposed formulation is not approvable.

Sincerely yours,

{See appended electronic signature page}

Dale P. Conner, Pharm.D.
Director, Division of Bioequivalence I
Office of Generic Drugs
Center for Drug Evaluation and Research

4.6 Outcome Page

ANDA: 90-097

Reviewer: Pabba, Santhosh **Date Completed:**
Verifier: **Date Verified:**
Division: Division of Bioequivalence
Description:

Productivity:

ID	*Letter Date*	*Productivity Category*	*Sub Category*	*Productivity*	*Subtotal*
6400	10/31/2007	Bioequivalence Study	Fasting Study	1	1
6400	10/31/2007	Other	Dissolution Waiver	1	1
6400	10/31/2007	Other	Dissolution Waiver	1	1
				Bean Total:	3

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

/s/

Santosh Pabba
9/22/2008 09:20:20 AM
BIOPHARMACEUTICS

Bing Li
9/22/2008 10:42:51 AM
BIOPHARMACEUTICS

Dale Conner
9/22/2008 03:26:52 PM
BIOPHARMACEUTICS

DIVISION OF BIOEQUIVALENCE DISSOLUTION REVIEW

ANDA No.	90097
Drug Product Name	Liothyronine SodiumTablets, USP
Strength(s)	5 mcg, 25 mcg and 50 mcg
Applicant Name	Coastal Pharmaceuticals
Address	1240 Sugg Parkway Greenville, NC 27834
Applicant's Point of Contact	William A. Tilghman, Jr.
Contact's Telephone Number	(252) 317-3804
Contact's Fax Number	(252) 758-8522
Original Submission Date(s)	October 31, 2007
Submission Date(s) of Amendment(s) Under Review	N/A
Reviewer	Glendolynn S. Johnson, Pharm.D.
Study Number (s)	70092
Study Type (s)	Fasting
Strength (s)	50 µg
Clinical Site	Anapharm
Clinical Site Address	5160, boul. Décarie, suite 800 Montréal (Québec), Canada H3X 2H9
Analytical Site	(b) (4)
Analytical Site Address	
OUTCOME DECISION	**Acceptable**

I. EXECUTIVE SUMMARY

This is a review of the dissolution testing data only.

There is a USP method for this product. The firm's dissolution testing data with the USP method are acceptable (meeting the specification at S1 level). The DBE acknowledges that the firm will follow the USP method and specification.

The DBE will review the fasted BE studies and waiver requests at a later date.

The clinical site was inspected on 5/23/06, outcome NAI. The analytical site is pending a DSI inspection for 79-167.

Table 1: SUBMISSION CONTENT CHECKLIST

Information			YES	NO	N/A
Did the firm use the FDA-recommended dissolution method			☐	☒	☐
Did the firm use the USP dissolution method			☒	☐	☐
Did the firm use 12 units of both test and reference in dissolution testing			☒	☐	☐
Did the firm provide complete dissolution data (all raw data, range, mean, % CV, dates of dissolution testing)			☒	☐	☐
Did the firm conduct dissolution testing with its own proposed method			☐	☒	☐
Is FDA method in the public dissolution database (on the web)			☐	☐	☒
SAS datasets submitted to the electronic document room (edr)	Fasting BE study	PK parameters	☒	☐	☐
		Plasma concentrations	☒	☐	☐
	Fed BE study	PK parameters	☐	☐	☒
		Plasma concentrations	☐	☐	☒
	Other study	PK parameters	☐	☐	☒
		Plasma concentrations	☐	☐	☒
Are the DBE Summary Tables present an in either PDF and/or MS Word Format?			☒	☐	☐
If any of the tables are missing or incomplete please indicate that in the comments and request the firm to provide the complete DBE Summary Tables 1-16.					
Is the Long Term Storage Stability (LTSS) sufficient to cover the maximum storage time of the study samples?			☒	☐	☐
If the LTSS is NOT sufficient please request the firm to provide the necessary data.					

Table 2: SUMMARY OF IN VITRO DISSOLUTION DATA

Dissolution Conditions	**Apparatus:**	USP Apparatus III
	Speed of Rotation:	30 dips per minute, using 20-mesh screen on the top and 40-mesh screen on the bottom of the glass-reciprocating cylinder
	Medium:	Alkaline Borate Buffer, pH 10.0±0.05
	Volume:	250 mL
	Temperature:	37ºC
Firm's Proposed Specifications	Not less than 70% (Q) of the labeled amount of liothyronine ($C_{15}H_{12}I_3NO_4$) is dissolved in 45 minutes	
Dissolution Testing Site (Name, Address)	Metrics, Inc. 1240 Sugg Parkway Greenville, NC 27834	

Study Ref No.	**Testing Date**	**Product ID \ Batch No. (Test - Manufacture Date) (Reference – Expiration Date)**	**Dosage Strength & Form**	**No. of Dosage Units**		**Collection Times (minutes or hours)**					**Study Report Location**
						5 mins.	**10 mins.**	**15 mins.**	**30 mins.**	**45 mins.**	
Study Report #: 70092	3/15/07	**Test Product:** Liothyronine Sodium Tablets, USP Batch 6J078 Manufacture Date: 09/28/2006	50 mcg Tablet	12	Mean	88	100	100	100	98	Module 5 (Volume 6) Section 5.3.1.3
					Range	94-76	107-96	103-97	102-97	102-96	
					%CV	6.0	3.0	2.1	1.9	2.0	
Study Report #: 70092	3/20/07	**Reference Product:** Cytomel® (liothyronine sodium) Tablets, LOT: 29425 Expiration Date: 09/2007 Manufacture Date: Unknown	50 mcg Tablet	12	Mean	62	90	91	91	91	Module 5 (Volume 6) Section 5.3.1.3
					Range	64-56	93-89	93-89	92-89	94-91	
					%CV	3.6	1.3	1.3	1.2	1.0	

Dissolution Conditions	**Apparatus:**	USP Apparatus III
	Speed of Rotation:	30 dips per minute, using 20-mesh screen on the top and 40-mesh screen on the bottom of the glass-reciprocating cylinder
	Medium:	Alkaline Borate Buffer, pH 10.0±0.05
	Volume:	250 mL
	Temperature:	37ºC
Firm's Proposed Specifications	Not less than 70% (Q) of the labeled amount of liothyronine ($C_{15}H_{12}I_3NO_4$) is dissolved in 45 minutes	
Dissolution Testing Site (Name, Address)	Metrics, Inc. 1240 Sugg Parkway Greenville, NC 27834	

Study Ref No.	**Testing Date**	**Product ID \ Batch No. (Test - Manufacture Date) (Reference – Expiration Date)**	**Dosage Strength & Form**	**No. of Dosage Units**		**Collection Times (minutes or hours)**					**Study Report Location**
						5 mins.	**10 mins.**	**15 mins.**	**30 mins.**	**45 mins.**	
Study Report #: 70092	4/27/07	**Test Product:** Liothyronine Sodium Tablets, USP Batch 7C032 Manufacture Date: 04/05/2007	25 mcg Tablet	12	Mean	95	97	97	96	96	Module 5 (Volume 6) Section 5.3.1.3
					Range	97-93	99-96	99-94	98-94	100-94	
					%CV	1.4	0.9	1.5	1.3	1.7	
Study Report #: 70092	4/30/07	**Reference Product:** Cytomel® (liothyronine sodium) Tablets, LOT: 36425 Expiration Date: 03/2008 Manufacturing Date: Unknown	25 mcg Tablet	12	Mean	73	104	104	105	104	Module 5 (Volume 6) Section 5.3.1.3
					Range	79-66	107-100	108-100	108-100	108-99	
					%CV	5.1	2.5	2.7	2.7	3.0	

Dissolution Conditions	**Apparatus:**	USP Apparatus III
	Speed of Rotation:	30 dips per minute, using 20-mesh screen on the top and 40-mesh screen on the bottom of the glass-reciprocating cylinder
	Medium:	Alkaline Borate Buffer, pH 10.0±0.05
	Volume:	250 mL
	Temperature:	37ºC
Firm's Proposed Specifications	Not less than 70% (Q) of the labeled amount of liothyronine ($C_{15}H_{12}I_3NO_4$) is dissolved in 45 minutes	
Dissolution Testing Site (Name, Address)	Metrics, Inc. 1240 Sugg Parkway Greenville, NC 27834	

Study Ref No.	**Testing Date**	**Product ID \ Batch No. (Test - Manufacture Date) (Reference – Expiration Date)**	**Dosage Strength & Form**	**No. of Dosage Units**		**Collection Times (minutes or hours)**					**Study Report Location**
						5 mins.	**10 mins.**	**15 mins.**	**30 mins.**	**45 mins.**	
Study Report #: 70092	6/19/07	**Test Product:** Liothyronine Sodium Tablets, USP Batch 6J076 Manufacture Date: 09/22/2006	5 mcg Tablet	12	Mean	85	89	92	91	93	Module 5 (Volume 6) Section 5.3.1.3
					Range	96-76	94-85	95-82	93-89	98-85	
					%CV	6.7	2.9	3.9	1.7	4.3	
Study Report #: 70092	6/6/07 and 6/14/07	**Reference Product:** Cytomel® (liothyronine sodium) Tablets, LOT: 38312 Expiration Date: 04/2008 Manufacture Date: Unknown	5 mcg Tablet	12	Mean	59	67	71	71	72	Module 5 (Volume 6) Section 5.3.1.3
					Range	65-51	71-62	73-66	74-63	75-68	
					%CV	8.5	4.2	2.9	4.1	2.8	

COMMENTS:
The firm's dissolution testing data with the USP method are acceptable. The DBE acknowledges that the firm will follow the USP method and specification.

II. DEFICIENCY COMMENTS:

None

III. RECOMMENDATIONS:

The *in vitro* dissolution testing conducted by Coastal Pharmaceuticals on its test product, Liothyronine Sodium Tablets USP, 5 mcg, 25 mcg and 50 mcg, comparing it to King Pharmaceuticals' Cytomel® Tablets, 5 mcg, 25 mcg and 50 mcg, respectively, is acceptable. The DBE acknowledges that the firm will follow the USP method and specification.

BIOEQUIVALENCE COMMENTS TO BE PROVIDED TO THE APPLICANT

ANDA: 90-097

APPLICANT: Coastal Pharmaceuticals

DRUG PRODUCT: Liothyronine Sodium Tablets USP, 5 mcg, 25 mcg and 50 mcg

The Division of Bioequivalence (DBE) has completed its review of the dissolution testing portion of your submission acknowledged on the cover sheet. The review of the bioequivalence study and waiver requests will be conducted later.

Your dissolution testing using the USP method is acceptable. We acknowledge that you will conduct dissolution testing for the test product using the USP method and specification.

Sincerely yours,

{See appended electronic signature page}

Dale P. Conner, Pharm.D.
Director, Division of Bioequivalence
Office of Generic Drugs
Center for Drug Evaluation and Research

IV. OUTCOME

ANDA: 90-097

Enter Review Productivity and Generate Report

http://cdsogd1/bioprod

V. *Completed Assignment for 90097 ID: 5034*

Reviewer: Johnson, Glendolynn **Date Completed:**
Verifier: , **Date Verified:**
Division: Division of Bioequivalence
Description: Liothyronine Sodium Tablets

Productivity:

ID	*Letter Date*	*Productivity Category*	*Sub Category*	*Productivity*	*Subtotal*
5034	10/31/2007	Dissolution Data	Dissolution Review	1	1
				Bean Total:	1

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/s/

Glendolynn S Johnson
3/14/2008 03:26:19 PM
BIOPHARMACEUTICS

Yih Chain Huang
3/14/2008 03:28:27 PM
BIOPHARMACEUTICS

Barbara Davit
3/18/2008 06:25:04 PM
BIOPHARMACEUTICS

BIOEQUIVALENCE CHECKLIST FOR FIRST GENERIC ANDA FOR APPLICATION COMPLETENESS

ANDA# 090097 **FIRM NAME** Coastal Pharmaceuticals

DRUG NAME Liothyronine Sodium Tablets USP, 5 mcg, 25 mcg, and 50 mcg

DOSAGE FORM Tablets

SUBJ: Request for examination of:

Requested by: _____ Date: _____
Chief, Regulatory Support Team, (HFD-615)

	Summary of Findings by Division of Bioequivalence
☒	**Study meets statutory requirements**
☐	**Study does NOT meet statutory requirements**
	Reason:
☒	**Waivers meet statutory requirements**
☐	**Waivers do NOT meet statutory requirements**
	Reason:

RECOMMENDATION: ☒ **COMPLETE** ☐ **INCOMPLETE**

Reviewed by:

Farahnaz Nouravarsani, Ph.D. 12/14/2007
_____ Date: _____
Reviewer

Chandra Chaurasia, Ph.D. 12/17/2007
_____ Date: _____
Team Leader

Fasting Study:

Item Verified:	YES	NO	Required Amount	Amount Sent	Comments
Protocol	☒	☐			Vol. C1.2
Assay Methodology	☒	☐			Vol. C1.9
Procedure SOP	☒	☐			Vol. C1.9
Methods Validation	☒	☐			Vol. C1.9
Study Results Ln/Lin	☒	☐			Vol. C1.1, Anapharm BE Clinical Study Report
Adverse Events	☒	☐			Vol. C1.1, Anapharm BE Clinical Study Report
IRB Approval	☒	☐			Vol. C1.2
Dissolution Data	☒	☐			Vol. C1.1, 5.3.1.3
Pre-screening of Patients	☒	☐			Volumes C1.6, C1.7, C1.8
Chromatograms	☐	☒			Not Applicable. Radioimmunoassay (RIA) method.
Consent Forms	☒	☐			Vol. C1.2
Composition	☒	☐			Vol. C1.1, 5.3.1.3
Summary of Study	☒	☐			Vol. C1.1, Anapharm BE Clinical Study Report
Individual Data & Graphs, Linear & Ln	☒	☐			Vol. C1.1, Anapharm BE Clinical Study Report
PK/PD Data Disk Submitted)	☒	☐			EDR
Randomization Schedule	☒	☐			Vol. C1.1, Anapharm BE Clinical Study Report
Protocol Deviations	☒	☐			Vol. C1.1, Anapharm BE Clinical Study Report
Clinical Site	☒	☐			Vol. C1.1, Anapharm BE Clinical Study Report

Analytical Site	☒	☐			Vol. C1.1, Anapharm BE Clinical Study Report
Study Investigators	☒	☐			Vol. C1.1, Anapharm BE Clinical Study Report
Medical Records	☒	☐			Volumes C1.6, C1.7, C1.8
Clinical Raw Data	☒	☐			Volumes C1.2, C1.3, C1.4, C1.5
Test Article Inventory	☒	☐			Vol. C1.2
BIO Batch Size	☒	☐			Electronic BE Summary Data
Assay of Active Content Drug	☒	☐			Vol. C1.1, Anapharm BE Clinical Study Report
Content Uniformity	☒	☐			Vol. C1.1, Anapharm BE Clinical Study Report
Date of Manufacture	☒	☐			Vol. C1.1, Anapharm BE Clinical Study Report
Exp. Date of RLD	☒	☐			Vol. C1.1, Anapharm BE Clinical Study Report
BioStudy Lot Numbers	☒	☐			Vol. C1.1, Anapharm BE Clinical Study Report
Statistics	☒	☐			Vol. C1.1, Anapharm BE Clinical Study Report
Summary results provided by the firm indicate study pass BE criteria	☒	☐			Vol. C1.1, Anapharm BE Clinical Study Report
Waiver requests for other strengths / supporting data	☒	☐			Vol. C1.1

Additional Comment regarding the ANDA:

The DBE recommends a Single-dose, Fasting Bioequivalence Study.

Outcome Page:

ANDA 090097

Completed Assignment for 090097 ID: 4306

Productivity:

ID	Letter Date	Productivity Category	Sub Category	Productivity	Subtotal		
4306	10/31/2007	Paragraph 4	Paragraph 4 Checklist	1	1	Edit	Delete
				Bean Total:	1		

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/s/

Chandra S. Chaurasia
12/17/2007 01:50:50 PM

CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

ANDA 90-097

ADMINISTRATIVE and CORRESPONDENCE DOCUMENTS

OGD APPROVAL ROUTING SUMMARY

ANDA # 90-097 Applicant Coastal Pharmaceuticals
Drug Liothyronine Sodium Tablets USP Strength(s) 5 mcg, 25 mcg and 50 mcg

APPROVAL ☒ **TENTATIVE APPROVAL** ☐ **SUPPLEMENTAL APPROVAL (NEW STRENGTH)** ☐ **OTHER** ☐

REVIEWER: **DRAFT Package** **FINAL Package**

1. **Martin Shimer** Date 3 March 2009 Date _____
Chief, Reg. Support Branch Initials MHS Initials _____
Contains GDEA certification: Yes ☒ No ☐ Determ. of Involvement? Yes ☐ No ☐
(required if sub after 6/1/92) Pediatric Exclusivity System
RLD = _____ NDA# _____
Patent/Exclusivity Certification: Yes ☒ No ☐ Date Checked _____
If Para. IV Certification- did applicant Nothing Submitted ☐
Notify patent holder/NDA holder Yes ☐ No ☐ Written request issued ☐
Was applicant sued w/in 45 days: Yes ☐ No ☐ Study Submitted ☐
Has case been settled: Yes ☐ No ☐ Date settled:
Is applicant eligible for 180 day
Generic Drugs Exclusivity for each strength: Yes ☐ No ☒
Date of latest Labeling Review/Approval Summary _____
Any filing status changes requiring addition Labeling Review Yes ☐ No ☒
Type of Letter: Full Approval.
Comments: ANDA submitted on 11/1/2007, BOS=Cytomel NDA 10-379, no relevant patents certification provided. ANDA ack for filing on 11/1/2007(LO dated 2/6/2008). There are no remaining patents or exclusivities which preclude approval of this ANDA. ANDA is eligible for Full Approval.

2. Project Manager, Esther Chuh Team 2 Date 3/3/2009 Date _____
Review Support Branch Initials EC Initials _____

Original Rec'd date 11/1/2007 EER Status Pending ☐ Acceptable ☒ OAI ☐
Date Acceptable for Filing 11/1/2007 Date of EER Status 3/19/2008
Patent Certification (type) PI Date of Office Bio Review 10/8/2008
Date Patent/Exclus.expires n/a Date of Labeling Approv. Sum 1/14/2009
Citizens' Petition/Legal Case Yes ☐ No ☒ Date of Sterility Assur. App. n/a
(If YES, attach email from PM to CP coord) Methods Val. Samples Pending Yes ☐ No ☒
First Generic Yes ☒ No ☐ MV Commitment Rcd. from Firm Yes ☐ No ☐
Priority Approval Yes ☐ No ☒ Modified-release dosage form: Yes ☐ No ☒
(If yes, prepare Draft Press Release, Email it to Cecelia Parise) Interim Dissol. Specs in AP Ltr: Yes ☐
Acceptable Bio reviews tabbed Yes ☐ No ☒
Bio Review Filed in DFS: Yes ☒ No ☐
Suitability Petition/Pediatric Waiver
Pediatric Waiver Request Accepted ☐ Rejected ☐ Pending ☐
Previously reviewed and tentatively approved ☐ Date _____
Previously reviewed and CGMP def. /NA Minor issued ☐ Date _____
Comments:

3. Labeling Endorsement
Reviewer: Labeling Team Leader:
Date 3/5/2009 Date 3/5/2009
Name/Initials Angela Payne Name/Initials John Grace

Comments:

From: Grace, John F
Sent: Thursday, March 05, 2009 9:24 AM
To: Payne, Angela; Chuh, Esther
Subject: RE: ANDA 90-097 Coastal Pharm/Liothyronine Sodium Tablets

concur

From: Payne, Angela
Sent: Tuesday, March 03, 2009 3:21 PM

To: Chuh, Esther; Grace, John F
Subject: RE: ANDA 90-097 Coastal Pharm/Liothyronine Sodium Tablets

John/Esther,

The Labeling AP1 summary in DFS signed 1.24.09 by John and Angela remains acceptable. There are not new changes in USP/NF, OB or Comis for the rld.

Angela

4. David Read **(PP IVs Only)** Pre-MMA Language included ☐ Date _____
OGD Regulatory Counsel, Post-MMA Language Included ☐ Initials_____
Comments:

5. Div. Dir./Deputy Dir. Date3/5/09
Chemistry Div. I Initials PS

Comments:CMC OK

6. Frank Holcombe **First Generics Only** Date3/17/09
Assoc. Dir. For Chemistry Initials RR
Comments: (First generic drug review)
CMC ok, For Frank,

7. Vacant Date_____
Deputy Dir., DLPS Initials_____

8. Peter Rickman Date3/18/2009
Director, DLPS Initials wpr
Para.IV Patent Cert: Yes☐ No☒;Pending Legal Action: Yes ☐ No ☒; Petition: Yes☐ No☒
Comments:no patents or exclusivity issues; labeling acceptable 1/14/2009 per AP Summary; bio acceptable 10/8/2008; EER acceptable 3/19/2008

1st generic okay for full approval

OR

8. Robert L. West Date _____
Deputy Director, OGD Initials _____
Para.IV Patent Cert: Yes☐ No☐; Pending Legal Action: Yes☐ No☐; Petition: Yes☐ No☐
Press Release Acceptable ☐
Comments:

9. Gary Buehler Date _____
Director, OGD Initials _____
Comments:
First Generic Approval ☐ PD or Clinical for BE ☐ Special Scientific or Reg.Issue ☐
Press Release Acceptable ☐

10. Project Manager, Esther Chuh Team 2 Date3/23/2009

Review Support Branch Initials EC
_____Date PETS checked for first generic drug (just prior to notification to firm)

Applicant notification:
8:00 AM Time notified of approval by phone
8:57 AM Time approval letter faxed

FDA Notification:
3/23/2009 Date e-mail message sent to "CDER-OGDAPPROVALS" distribution list.

3/23/2009 Date Approval letter copied to \\CDS014\DRUGAPP\ directory.

EER DATA:

COMIS TABLE:

ORANGE BOOK PRINT OFF:

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

/s/

Esther Chuh

3/24/2009 09:29:57 AM

COMPLETE RESPONSE -- MINOR

ANDA 90-097

OFFICE OF GENERIC DRUGS, CDER, FDA
Document Control Room, Metro Park North II
7500 Standish Place, Room 150
Rockville, MD 20855-2773 (240-276-9327)

APPLICANT: Coastal Pharmaceuticals TEL: (252) 317-3804

ATTN: William A Tilghman FAX: (252) 758-8522

FROM: Esther Chuh FDA CONTACT PHONE: (240) 276-8530

Dear Sir:

This facsimile is in reference to your abbreviated new drug application dated October 31, 2007, submitted pursuant to Section 505(j) of the Federal Food, Drug, and Cosmetic Act for Liothyronine Tablets, 5 mcg, 25 mcg and 50 mcg.

Reference is also made to your amendments dated September 30, and November 18, 2008.

SPECIAL INSTRUCTIONS:

Please submit your response in electronic format. This will improve document availability to review staff.

We have completed the review of your ANDA and have determined that we cannot approve this application in its present form. We have described below our reasons for this action and, where possible, our recommendations to address these issues in the following attachments (__2__ pages). This facsimile is to be regarded as an official FDA communication and unless requested, a hard copy will not be mailed.

The file on this application is now closed. You are required to take an action described under 21 CFR 314.120 which will either amend or withdraw the application. Your amendment should respond to all of the deficiencies listed. Facsimiles or partial replies will not be considered for review, nor will the review clock be reactivated until all deficiencies have been addressed. The response to this facsimile will be considered to represent a MINOR AMENDMENT and will be reviewed according to current OGD policies and procedures. The designation as a MINOR AMENDMENT should appear prominently in your cover letter. Upon OGD's acceptance for filing of your ANDA, it was determined that an adequate amount of information was submitted to allow for review of your Bioequivalence and Microbiology data. You will be notified in a separate communication of any further deficiencies identified during our review of your Bioequivalence and Microbiology data If you have substantial disagreement with our reasons for not approving this application, you may request an opportunity for a hearing.

THIS DOCUMENT IS INTENDED ONLY FOR THE USE OF THE PARTY TO WHOM IT IS ADDRESSED AND MAY CONTAIN INFORMATION THAT IS PRIVILEGED, CONFIDENTIAL, OR PROTECTED FROM DISCLOSURE UNDER APPLICABLE LAW.
If received by someone other than the addressee or a person authorized to deliver this document to the addressee, you are hereby notified that any disclosure, dissemination, copying, or other action to the content of this communication is not authorized If you have received this document in error, please immediately notify us by telephone and return it to us by mail at the above address

CHEMISTRY COMMENTS TO BE PROVIDED TO THE APPLICANT

ANDA: 90-097 APPLICANT: Coastal Pharmaceuticals

DRUG PRODUCT: Liothyronine Sodium Tablets USP, 5 mcg, 25 mcg and 50 mcg

The deficiencies presented below represent MINOR deficiencies.

A. Deficiencies:

(b) (4)

B. In addition to responding to the deficiencies presented above, please note and acknowledge the following comments in your response:

(b) (4)

2. Please respond to the labeling deficiencies that were communicated to you on August 11, 2008.

Sincerely yours,

{See appended electronic signature page}

Rashmikant M. Patel, Ph.D.
Director
Division of Chemistry I
Office of Generic Drugs
Center for Drug Evaluation and Research

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/s/

Michael Smela
12/11/2008 09:50:19 AM
For Rashmikant M. Patel, Ph.D.

COMPLETE RESPONSE -- MINOR

ANDA 90-097

OFFICE OF GENERIC DRUGS, CDER, FDA
Document Control Room, Metro Park North II
7500 Standish Place, Room 150
Rockville, MD 20855-2773 (240-276-9327)

APPLICANT: Coastal Pharmaceuticals TEL: (252) 317-3804

ATTN: William A Tilghman FAX: (252) 758-8522

FROM: Esther Chuh FDA CONTACT PHONE: (240) 276-8530

Dear Sir:

This facsimile is in reference to your abbreviated new drug application dated October 31, 2007, submitted pursuant to Section 505(j) of the Federal Food, Drug, and Cosmetic Act for Liothyronine Tablets, 5 mcg, 25 mcg and 50 mcg.

SPECIAL INSTRUCTIONS:

Please submit your response in electronic format. This will improve document availability to review staff.

We have completed the review of your ANDA and have determined that we cannot approve this application in its present form. We have described below our reasons for this action and, where possible, our recommendations to address these issues in the following attachments (3 pages). This facsimile is to be regarded as an official FDA communication and unless requested, a hard copy will not be mailed.

The file on this application is now closed. You are required to take an action described under 21 CFR 314.120 which will either amend or withdraw the application. Your amendment should respond to all of the deficiencies listed. Facsimiles or partial replies will not be considered for review, nor will the review clock be reactivated until all deficiencies have been addressed. The response to this facsimile will be considered to represent a MINOR AMENDMENT and will be reviewed according to current OGD policies and procedures. The designation as a MINOR AMENDMENT should appear prominently in your cover letter. Upon OGD's acceptance for filing of your ANDA, it was determined that an adequate amount of information was submitted to allow for review of your Bioequivalence and Microbiology data. You will be notified in a separate communication of any further deficiencies identified during our review of your Bioequivalence and Microbiology data If you have substantial disagreement with our reasons for not approving this application, you may request an opportunity for a hearing.

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If received by someone other than the addressee or a person authorized to deliver this document to the addressee, you are hereby notified that any disclosure, dissemination, copying, or other action to the content of this communication is not authorized If you have received this document in error, please immediately notify us by telephone and return it to us by mail at the above address

CHEMISTRY COMMENTS TO BE PROVIDED TO THE APPLICANT

ANDA: 90-097 APPLICANT: Coastal Pharmaceuticals

DRUG PRODUCT: Liothyronine Sodium Tablets USP, 5 mcg, 25 mcg and 50 mcg

The deficiencies presented below represent MINOR deficiencies.

A. Deficiencies:

(b) (4)

1.

2.

3.

4.

5.

6.

7.

B. In addition to responding to the deficiencies presented above, please note and acknowledge the following comments in your response:

1. Your bioequivalence information is pending review. Deficiencies, if any, will be communicated separately.

2. Please respond to the labeling deficiencies that were communicated to you on August 11, 2008.

Sincerely yours,

{See appended electronic signature page}

Rashmikant M. Patel, Ph.D.
Director
Division of Chemistry I
Office of Generic Drugs
Center for Drug Evaluation and Research

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/s/

Michael Smela
8/25/2008 03:04:24 PM
For Rashmikant M. Patel, Ph.D.

Memo

Expedited Review Status Granted:

Application Number:	ANDA 90-097
Drug Name:	Liothyronine Sodium Tablets, 0.005MG, 0.025MG, 0.050MG
Applicant:	Coastal Pharmaceuticals

From: Shimer, Martin
Sent: Friday, August 22, 2008 9:04 AM
To: Chuh, Esther
Cc: Shimer, Martin
Subject: RE: ANDA 90-097 Costal Pharm's Liothyronine Tablets

Esther,

Yes we can go ahead and expedite the ANDA from Coastal Pharmaceuticals since we already know that another application for the same drug product has been expedited.

Tx,

Marty

From: Chuh, Esther
Sent: Thursday, August 21, 2008 2:55 PM
To: Shimer, Martin
Subject: ANDA 90-097 Costal Pharm's Liothyronine Tablets

Dear Marty,

It looks that ANDA 90-097 is eligible for Expedited Review (no unexpired patent nor generic in the market)
Same drug under ANDA 90-326 (Mylan) is under Expedited Review.

Please let me know if the firm should formally request for a Expedited Review.

Thank you,
Esther

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

/s/

Esther Chuh

8/22/2008 10:58:06 AM

Telephone Fax

ANDA 90-097

OFFICE OF GENERIC DRUGS, CDER, FDA
Document Control Room, Metro Park North I
7520 Standish Place
Rockville, MD 20855-2773
Angela.payne@fda.hhs.gov

TO: Coastal Pharmaceuticals

TEL: 252-752-3800

ATTN: William A. Tilghman, Jr.

FAX: 252-758-8522

FROM: Mrs. Angela Payne

This facsimile is in reference to your abbreviated new drug application submitted pursuant to Section 505(j) of the Federal Food, Drug, and Cosmetic Act for Liothyronine Sodium Tablets, USP.

Pages (including cover): 3

SPECIAL INSTRUCTIONS:

See attached labeling comments.

THIS DOCUMENT IS INTENDED ONLY FOR THE USE OF THE PARTY TO WHOM IT IS ADDRESSED AND MAY CONTAIN INFORMATION THAT IS PRIVILEGED, CONFIDENTIAL, OR PROTECTED FROM DISCLOSURE UNDER APPLICABLE LAW.
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REVIEW OF PROFESSIONAL LABELING #1
DIVISION OF LABELING AND PROGRAM SUPPORT
LABELING REVIEW

ANDA Number: 90-097 Date of Submission: 31 OCT 2007

Applicant's Name: Coastal Pharmaceuticals

Established Name: Liothyronine Sodium Tablet USP 5 mcg*, 25 mcg*, and 50 mcg * (as the base)

Labeling Deficiencies:

1. CONTAINER - 100s - Please submit for our review. Ensure that the RX only statement appears on the label.

2. INSERT - HOW SUPPLIED- Please include the description and distinguishing markings in this section as well as the "RX only" statement.

Please revise your labels and labeling, as instructed above, and submit electronic final printed labels and labeling according to the guidance for industry titled Providing Regulatory Submissions in Electronic Format – ANDA.

Prior to approval, it may be necessary to revise your labeling subsequent to approved changes for the reference listed drug. In order to keep ANDA labeling current, we suggest that you subscribe to the daily or weekly updates of new documents posted on the CDER web site at the following address -
http://www.fda.gov/cder/cdernew/listserv.html

To facilitate review of your next submission, and in accordance with 21 CFR 314.94(a)(8)(iv), please provide a side-by-side comparison of your proposed labeling with the reference listed drug (or your last submission) with all differences annotated and explained.

{See appended electronic signature page}

_____

Wm Peter Rickman
Director
Division of Labeling and Program Support
Office of Generic Drugs
Center for Drug Evaluation and Research

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/s/

John Grace
8/11/2008 10:28:45 AM
for Wm Peter Rickman

ANDA CHECKLIST FOR CTD or eCTD FORMAT
FOR COMPLETENESS and ACCEPTABILITY of an APPLICATION FOR FILING

For More Information on Submission of an ANDA in Electronic Common Technical Document (eCTD) Format please go to: http://www fda.gov/cder/regulatory/ersr/ectd.htm
***For a Comprehensive Table of Contents Headings and Hierarchy please go to:**
http://www fda.gov/cder/regulatory/ersr/5640CTOC-v1.2.pdf
**** For more** CTD and eCTD informational links **see the final page of the ANDA Checklist**
*** **A model Quality Overall Summary for an immediate release tablet and an extended release capsule can be found on the OGD webpage** http://www.fda.gov/cder/ogd/ ***

ANDA #: 90-097 **FIRM NAME**: COASTAL PHARMACEUTICALS

PIV: NO **Electronic or Paper Submission:** PAPER (CTD FORMAT)

RELATED APPLICATION(S): NA

First Generic Product Received? YES

(PER MARTY 12/12/07)

Bio Assignments:		**Micro Review (No)**
☒ **BPH**	☐ **BCE**	☐
☐ **BST**	☒ **BDI**	

DRUG NAME: LIOTHYRONINE SODIUM

DOSAGE FORM: TABLETS USP, 5 MCG, 25 MCG AND 50 MCG

Random Queue: 2

Chem Team Leader: Smela, Michael PM: Esther Chuh Labeling Reviewer: Angela Payne

Letter Date: OCTOBER 31, 2007 **Received Date**: NOVEMBER 1, 2007

Comments: EC - 3 YES **On Cards:** YES

Therapeutic Code: 3032300 THYROID

Archival copy: PAPER (CTD FORMAT) **Sections** I

Review copy: YES E-Media Disposition: YES SENT TO EDR

Not applicable to electronic sections

PART 3 Combination Product Category N Not a Part3 Combo Product

(Must be completed for ALL Original Applications) Refer to the Part 3 Combination Algorithm

Reviewing CSO/CST Rebekah Granger	**Recommendation:**
Date 1/23/2008	☒ **FILE** ☐ **REFUSE to RECEIVE**

Supervisory Concurrence/Date: _____ **Date:** _____

ADDITIONAL COMMENTS REGARDING THE ANDA:

1/28/2008- William A Tilghman (252-317-3804). The firm was contacted and the following was requested:
Submit FDA Form 3454, box should be checked and list names of investigators
Revise LOA for Type II DMF
Spectra and chromatograms for reference standards and test samples

Per correspondence submitted by sponsor dated 1/29 the above is adequate for filing

MODULE 1
ADMINISTRATIVE

ACCEPTABLE

1.1	**1.1.2** **Signed and Completed Application Form (356h) (original signature)** YES (Check Rx/OTC Status) RX YES	☒
1.2	**Cover Letter** Dated: OCTOBER 31, 2007 YES	☒
*	**Table of Contents (paper submission only)** YES	☒
1.3.2	**Field Copy Certification (original signature)** YES **(N/A for E-Submissions)**	☒
1.3.3	**Debarment Certification-GDEA (Generic Drug Enforcement Act)/Other:** 1. Debarment Certification (original signature) YES 2. List of Convictions statement (original signature) YES	☒
1.3.4	**Financial Certifications** Bioavailability/Bioequivalence Financial Certification (Form FDA 3454) or Disclosure Statement (Form FDA 3455) YES	☐
1.3.5	**1.3.5.1** **Patent Information** Patents listed for the RLD in the Electronic Orange Book Approved Drug Products with Therapeutic Equivalence Evaluations **1.3.5.2** **Patent Certification** 1. Patent number(s) 2. Paragraph: (Check all certifications that apply) MOU ☐ PI ☒ PII ☐ PIII ☐ PIV ☐ No Relevant Patents ☐ 3. Expiration of Patent(s): NA a. Pediatric exclusivity submitted? b. Expiration of Pediatric Exclusivity? 4. Exclusivity Statement: YES **Patent and Exclusivity Search Results from query on Appl No 010379 Product 003 in the OB_Rx list.** --- ## Patent Data **There are no unexpired patents for this product in the Orange Book Database.** [Note: Title I of the 1984 Amendments does not apply to drug products submitted or approved under the former Section 507 of the Federal Food, Drug and Cosmetic Act (antibiotic products). Drug products of this category will not have patents listed.] ## Exclusivity Data **There is no unexpired exclusivity for this product.**	☒

1.4.1	**References** Letters of Authorization 1. DMF letters of authorization a. Type II DMF authorization letter(s) or synthesis for Active Pharmaceutical Ingredient b. Type III DMF authorization letter(s) for container closure YES 2. US Agent Letter of Authorization (U.S. Agent [if needed, countersignature on 356h])	☐
1.12.11	**Basis for Submission** NDA# : 10-379 Ref Listed Drug: CYTOMEL Firm: KING PHARMACEUTICALS, INC. ANDA suitability petition required? NA If Yes, then is change subject to PREA (change in dosage form, route or active ingredient) see section 1.9.1	☒

MODULE 1 (Continued)
ADMINISTRATIVE

ACCEPTABLE

1.12.12	**Comparison between Generic Drug and RLD-505(j)(2)(A)** 1. Conditions of use SAME 2. Active ingredients SAME 3. Inactive ingredients JUSTIFIED 4. Route of administration SAME 5. Dosage Form SAME 6. Strength SAME	☒
1.12.14	**Environmental Impact Analysis Statement** YES	☒
1.12.15	**Request for Waiver** Request for Waiver of In-Vivo BA/BE Study(ies): Paper, YES ON 5 MCG AND 25 MCG - See attached OGD Correspondence (OGD #05-0334)	☒
1.14.1	**Draft Labeling (Mult Copies N/A for E-Submissions)** **1.14.1.1** 4 copies of draft (each strength and container) YES **1.14.1.2** 1 side by side labeling comparison of containers and carton with all differences annotated and explained YES **1.14.1.3** 1 package insert (content of labeling) submitted electronically YES ***Was a proprietary name request submitted? NO (If yes, send email to Labeling Reviewer indicating such.) **HOW SUPPLIED** 5 mcg: Bottles of 100 NDC 0574-0220-01 25 mcg: Bottles of 100 NDC 0574-0222-01 50 mcg: Bottles of 100 NDC 0574-0223-01	☒
1.14.3	**Listed Drug Labeling** **1.14.3.1** 1 side by side labeling (package and patient insert) comparison with all differences annotated and explained YES **1.14.3.3** 1 RLD label and 1 RLD container label YES	☒

ACCEPTABLE

2.3	**Quality Overall Summary** **E-Submission: __x__PDF (archive) __x_ Word Processed e.g., MS Word** A model Quality Overall Summary for an immediate release table and an extended release capsule can be found on the OGD webpage http://www.fda.gov/cder/ogd/ **Question based Review (QbR) __x__ YES _____ NO** **2.3.S** **Drug Substance (Active Pharmaceutical Ingredient)** YES **2.3.S.1** **General Information** **2.3.S.2** **Manufacture** **2.3.S.3** **Characterization** **2.3.S.4** **Control of Drug Substance** **2.3.S.5** **Reference Standards or Materials** **2.3.S.6** **Container Closure System** **2.3.S.7** **Stability** **2.3.P** **Drug Product** YES **2.3.P.1** **Description and Composition of the Drug Product** **2.3.P.2** **Pharmaceutical Development** **2.3.P.2.1** **Components of the Drug Product** **2.3.P.2.1.1** **Drug Substance** **2.3.P.2.1.2** **Excipients** **2.3.P.2.2** **Drug Product** **2.3.P.2.3** **Manufacturing Process Development** **2.3.P.2.4** **Container Closure System** **2.3.P.3** **Manufacture** **2.3.P.4** **Control of Excipients** **2.3.P.5** **Control of Drug Product** **2.3.P.6** **Reference Standards or Materials** **2.3.P.7** **Container Closure System** **2.3.P.8** **Stability**	☒

2.7	**Clinical Summary (Bioequivalence)** **E-Submission: __x__PDF (archive) __x_ Word Processed e.g., MS Word** **2.7.1** **Summary of Biopharmaceutic Studies and Associated Analytical Methods** **2.7.1.1** **Background and Overview** YES **2.7.1.2** **Summary of Results of Individual Studies** YES **2.7.1.3** **Comparison and Analyses of Results Across Studies** 1. Summary Bioequivalence tables: Table 1. Summary of Comparative Bioavailability (BA) Studies YES Table 2. Statistical Summary of the Comparative BA Data YES Table 4. Summary of In Vitro Dissolution Studies YES **2.7.1.4** **Appendix**	☒

MODULE 3

3.2.S DRUG SUBSTANCE

ACCEPTABLE

3.2.S.1	**General Information** **3.2.S.1.1** **Nomenclature** YES **3.2.S.1.2** **Structure** YES **3.2.S.1.3** **General Properties** YES	☒
3.2.S.2	**Manufacturer** **3.2.S.2.1** **Manufacturer(s) (This section includes contract manufacturers and testing labs)** **Drug Substance (Active Pharmaceutical Ingredient)** 1. Addresses of bulk manufacturers YES 2. Manufacturing Responsibilities YES 3. Type II DMF number for API YES – DMF # (b) (4) 4. CFN or FEI numbers (b) (4)	☒
3.2.S.3	**Characterization** Refer to DMF # (b) (4)	☒

3.2.S.4	**Control of Drug Substance (Active Pharmaceutical Ingredient)** **3.2.S.4.1** **Specification** Testing specifications and data from drug substance manufacturer(s) YES **3.2.S.4.2** **Analytical Procedures** YES **3.2.S.4.3** **Validation of Analytical Procedures** **1.** Spectra and chromatograms for reference standards and test samples 2. Samples-Statement of Availability and Identification of: a. Drug Substance YES b. Same lot number(s) YES **3.2.S.4.4** **Batch Analysis** 1. COA(s) specifications and test results from drug substance mfgr(s) YES 2. Applicant certificate of analysis YES **3.2.S.4.5** **Justification of Specification** YES	☐
3.2.S.5	**Reference Standards or Materials**	☐
3.2.S.6	**Container Closure Systems** Refer to DMF # (b) (4)	☒
3.2.S.7	**Stability** Refer to DMF # (b) (4)	☒

MODULE 3

3.2.P DRUG PRODUCT ACCEPTABLE

3.2.P.1	**Description and Composition of the Drug Product** 1) Unit composition YES 2) Inactive ingredients are appropriate per IIG YES	☒
3.2.P.2	**Pharmaceutical Development** Pharmaceutical Development Report YES	☒
3.2.P.3	**Manufacture** **3.2.P.3.1** **Manufacture(s)** (Finished Dosage Manufacturer and Outside Contract Testing Laboratories) 1. Name and Full Address(es)of the Facility(ies) YES 2. CGMP Certification: YES 3. Function or Responsibility YES 4. CFN or FEI numbers **3.2.P.3.2** **Batch Formula** Batch Formulation YES **3.2.P.3.3** **Description of Manufacturing Process and Process Controls** 1. Description of the Manufacturing Process YES 2. Master Production Batch Record(s) for largest intended production runs (no more than 10x pilot batch) with equipment specified YES 3. If sterile product: Aseptic fill / Terminal sterilization 4. Reprocessing Statement YES **3.2.P.3.4** **Controls of Critical Steps and Intermediates** YES **3.2.P.3.5** **Process Validation and/or Evaluation** N/A 1. Microbiological sterilization validation 2. Filter validation (if aseptic fill) **PROPOSED COMMERCIAL BATCH SIZE** 5 mcg: (b) (4) Tablets 25 mcg (b) (4) Tablets 50 mcg: (b) (4) Tablets	☒
3.2.P.4	**Controls of Excipients (Inactive Ingredients)** Source of inactive ingredients identified YES **3.2.P.4.1** **Specifications** 1. Testing specifications (including identification and characterization) YES 2. Suppliers' COA (specifications and test results) YES **3.2.P.4.2** **Analytical Procedures** USP/NF Testing **3.2.P.4.3** **Validation of Analytical Procedures** USP/NF Testing **3.2.P.4.4** **Justification of Specifications** Applicant COA YES	☒

MODULE 3

3.2.P DRUG PRODUCT

ACCEPTABLE

3.2.P.5	**Controls of Drug Product** **3.2.P.5.1** **Specification(s)** YES **3.2.P.5.2** **Analytical Procedures** YES **3.2.P.5.3** **Validation of Analytical Procedures** Samples - Statement of Availability and Identification of: 1. Finished Dosage Form YES 2. Same lot numbers YES **3.2.P.5.4** **Batch Analysis** Certificate of Analysis for Finished Dosage Form YES **3.2.P.5.5** **Characterization of Impurities** YES **3.2.P.5.6** **Justification of Specifications** YES	☒
3.2.P.7	**Container Closure System** 1. Summary of Container/Closure System (if new resin, provide data) YES 2. Components Specification and Test Data YES 3. Packaging Configuration and Sizes YES 4. Container/Closure Testing YES 5. Source of supply and suppliers address YES	☒
3.2.P.8	**3.2.P.8.1** **Stability (Finished Dosage Form)** 1. Stability Protocol submitted YES 2. Expiration Dating Period YES – 18 MONTHS **3.2.P.8.2** **Post-approval Stability and Conclusion** Post Approval Stability Protocol and Commitments YES **3.2.P.8.3** **Stability Data** 1. 3 month accelerated stability data YES 2. Batch numbers on stability records the same as the test batch YES – 5 mcg: LOT #6J076 25 mcg: LOT #7C032 50 mcg: LOT #6J078	☒

MODULE 3

3.2.R Regional Information

ACCEPTABLE

3.2.R (Drug Substance)	**3.2.R.1.S** **Executed Batch Records for drug substance (if available)** **3.2.R.2.S** **Comparability Protocols** **3.2.R.3.S** **Methods Validation Package** NO Methods Validation Package (3 copies) (Mult Copies N/A for E-Submissions) (Required for Non-USP drugs)	☐

MODULE 3
3.2.R Regional Information

ACCEPTABLE

3.2.R (Drug Product)	**3.2.R.1.P.1** **Executed Batch Records** Copy of Executed Batch Record with Equipment Specified, including Packaging Records (Packaging and Labeling Procedures), Batch Reconciliation and Label Reconciliation YES 5 mcg: LOT #6J076 Theoretical Yield (b) (4) Tablets Actual Yield (b) (4) Tablets Packaged Yield (b) (4) Tablets 25 mcg: LOT #7C032 Theoretical Yield (b) (4) Tablets Actual Yield (b) (4) Tablets Packaged Yield (b) (4) Tablets 50 mcg: LOT #6J078 Theoretical Yield (b) (4) Tablets Actual Yield (b) (4) Tablets Packaged Yield (b) (4) Tablets **3.2.R.1.P.2** **Information on Components** YES **3.2.R.2.P** **Comparability Protocols** N/A **3.2.R.3.P** **Methods Validation Package** NO Methods Validation Package (3 copies) (Mult Copies N/A for E-Submissions) (Required for Non-USP drugs)	☒

MODULE 5
CLINICAL STUDY REPORTS

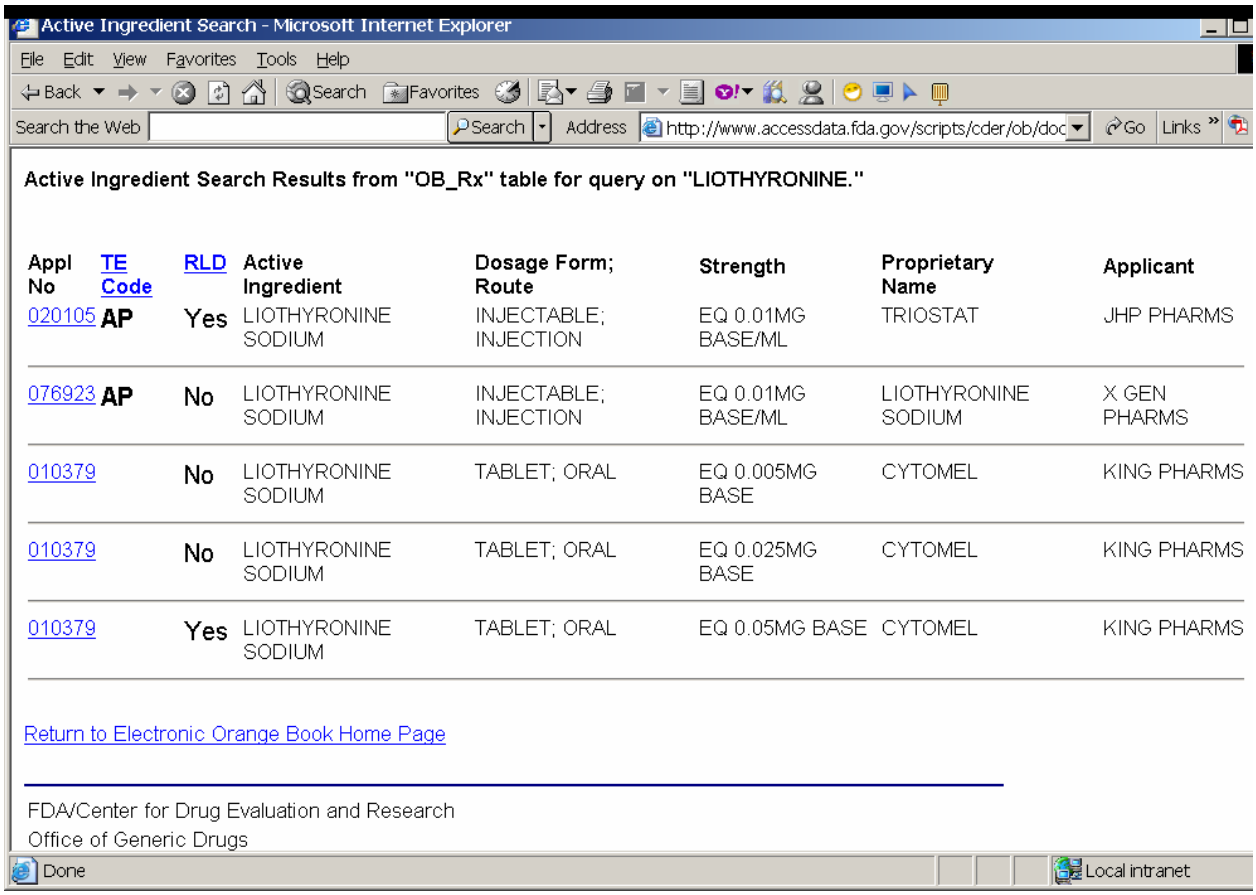
ACCEPTABLE

5.2	**Tabular Listing of Clinical Studies** YES	☒
5.3.1 (complete study data)	**Bioavailability/Bioequivalence** **1. Formulation data same?** a. Comparison of all Strengths (check proportionality of multiple strengths) YES b. Parenterals, Ophthalmics, Otics and Topicals per 21 CFR 314.94 (a)(9)(iii)-(v) **2. Lot Numbers of Products used in BE Study(ies):** RLD: 29425 ANDA: 6J078 **3. Study Type: IN-VIVO PK STUDY(IES)** (Continue with the appropriate study type box below)	☒

	5.3.1.2 **Comparative BA/BE Study Reports** 1. Study(ies) meets BE criteria (90% CI of 80-125, C max, AUC) YES 2. Summary Bioequivalence tables: Table 6. Demographic Profile of Subjects Completing the Comparative BA Study YES Table 7. Incidence of Adverse Events in Individual Studies YES Table 8. Reanalysis of Study Samples YES **5.3.1.3** **In Vitro-In-Vivo Correlation Study Reports** 1. Summary Bioequivalence tables: Table 4. Summary of In Vitro Dissolution Studies YES Table 5. Formulation Data YES **5.3.1.4** **Reports of Bioanalytical and Analytical Methods for Human Studies** 1. Summary Bioequivalence table: Table 3. Bioanalytical Method Validation YES **5.3.7** **Case Report Forms and Individual Patient Listing** YES	☒
5.4	**Literature References**	
	Possible Study Types:	
Study Type	**IN-VIVO PK STUDY(IES) (**i.e., fasting/fed/sprinkle) FASTING ON 50 MCG 1. Study(ies) meets BE criteria (90% CI of 80-125, C max, AUC) YES 2. EDR Email: Data Files Submitted: YES SENT TO EDR 3. In-Vitro Dissolution: YES	☒
Study Type	**IN-VIVO BE STUDY with CLINICAL ENDPOINTS** NO 1. Properly defined BE endpoints (eval. by Clinical Team) 2. Summary results meet BE criteria: 90% CI of the proportional difference in success rate between test and reference must be within (-0.20, +0.20) for a binary/dichotomous endpoint. For a continuous endpoint, the test/reference ratio of the mean result must be within (0.80, 1.25). 3. Summary results indicate superiority of active treatments (test & reference) over vehicle/placebo ($p<0.05$) (eval. by Clinical Team) 4. EDR Email: Data Files Submitted	☐
Study Type	**IN-VITRO BE STUDY(IES) (**i.e., in vitro binding assays) NO 1. Study(ies) meets BE criteria (90% CI of 80-125) 2. EDR Email: Data Files Submitted: 3. In-Vitro Dissolution:	☐

Study Type	**NASALLY ADMINISTERED DRUG PRODUCTS** NO 1. Solutions (Q1/Q2 sameness): a. In-Vitro Studies (Dose/Spray Content Uniformity, Droplet/Drug Particle Size Distrib., Spray Pattern, Plume Geometry, Priming & Repriming, Tail Off Profile) 2. Suspensions (Q1/Q2 sameness): a. In-Vivo PK Study 1. Study(ies) meets BE Criteria (90% CI of 80-125, C max, AUC) 2. EDR Email: Data Files Submitted b. In-Vivo BE Study with Clinical End Points 1. Properly defined BE endpoints (eval. by Clinical Team) 2. Summary results meet BE criteria (90% CI within +/- 20% or 80-125) 3. Summary results indicate superiority of active treatments (test & reference) over vehicle/placebo ($p<0.05$) (eval. by Clinical Team) 4. EDR Email: Data Files Submitted c. In-Vitro Studies (Dose/Spray Content Uniformity, Droplet/Drug Particle Size Distrib., Spray Pattern, Plume Geometry, Priming & Repriming, Tail Off Profile)	☐
Study Type	**TOPICAL CORTICOSTEROIDS (VASOCONSTRICTOR STUDIES)** NO 1. Pilot Study (determination of ED50) 2. Pivotal Study (study meets BE criteria 90%CI of 80-125)	☐
Study Type	**TRANSDERMAL DELIVERY SYSTEMS** NO 1. In-Vivo PK Study 1. Study(ies) meet BE Criteria (90% CI of 80-125, C max, AUC) 2. In-Vitro Dissolution 3. EDR Email: Data Files Submitted 2. Adhesion Study 3. Skin Irritation/Sensitization Study	☐

Updated 10/10/2006 C. Bina



Active Ingredient Search Results from "OB_Rx" table for query on "LIOTHYRONINE."

Appl No	TE Code	RLD	Active Ingredient	Dosage Form; Route	Strength	Proprietary Name	Applicant
020105	AP	Yes	LIOTHYRONINE SODIUM	INJECTABLE; INJECTION	EQ 0.01MG BASE/ML	TRIOSTAT	JHP PHARMS
076923	AP	No	LIOTHYRONINE SODIUM	INJECTABLE; INJECTION	EQ 0.01MG BASE/ML	LIOTHYRONINE SODIUM	X GEN PHARMS
010379		No	LIOTHYRONINE SODIUM	TABLET; ORAL	EQ 0.005MG BASE	CYTOMEL	KING PHARMS
010379		No	LIOTHYRONINE SODIUM	TABLET; ORAL	EQ 0.025MG BASE	CYTOMEL	KING PHARMS
010379		Yes	LIOTHYRONINE SODIUM	TABLET; ORAL	EQ 0.05MG BASE	CYTOMEL	KING PHARMS

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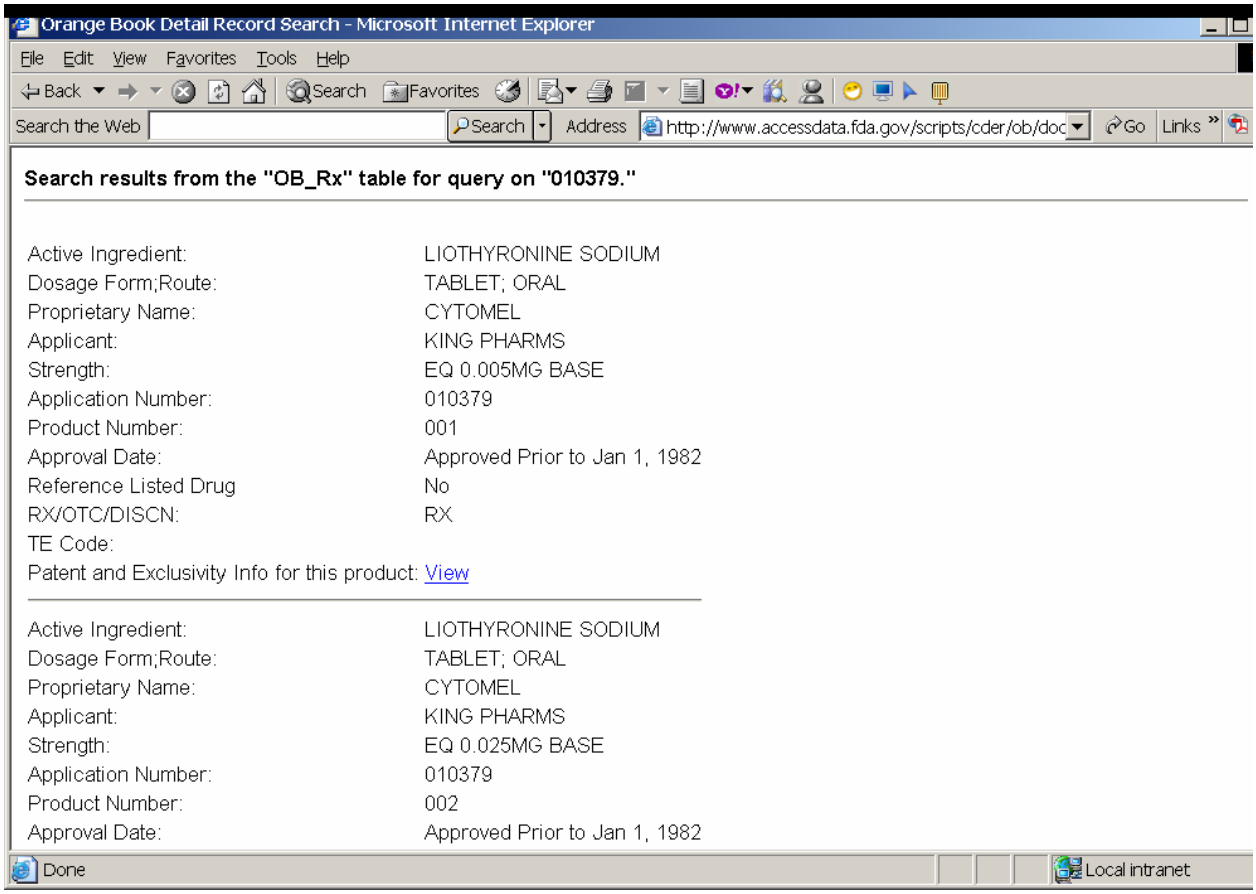
Orange Book Detail Record Search - Microsoft Internet Explorer
File Edit View Favorites Tools Help
Back Search Favorites
Search the Web Search Address http://www.accessdata.fda.gov/scripts/cder/ob/doc Go Links
Search results from the "OB_Rx" table for query on "010379."
Active Ingredient: LIOTHYRONINE SODIUM
Dosage Form;Route: TABLET; ORAL
Proprietary Name: CYTOMEL
Applicant: KING PHARMS
Strength: EQ 0.005MG BASE
Application Number: 010379
Product Number: 001
Approval Date: Approved Prior to Jan 1, 1982
Reference Listed Drug No
RX/OTC/DISCN: RX
TE Code:
Patent and Exclusivity Info for this product: View
Active Ingredient: LIOTHYRONINE SODIUM
Dosage Form;Route: TABLET; ORAL
Proprietary Name: CYTOMEL
Applicant: KING PHARMS
Strength: EQ 0.025MG BASE
Application Number: 010379
Product Number: 002
Approval Date: Approved Prior to Jan 1, 1982
Done
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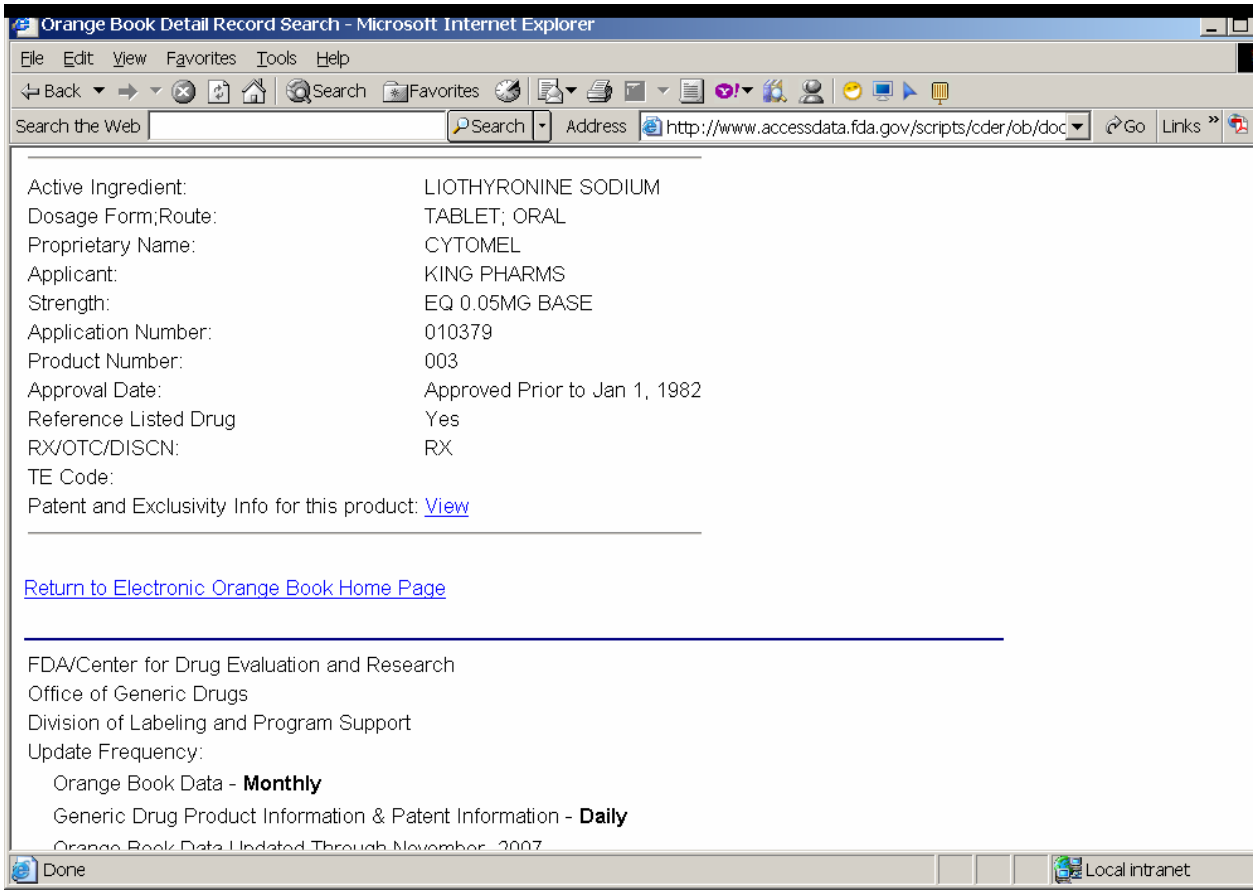
Orange Book Detail Record Search - Microsoft Internet Explorer
File Edit View Favorites Tools Help
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Search the Web Search Address http://www.accessdata.fda.gov/scripts/cder/ob/doc Go Links
Active Ingredient: LIOTHYRONINE SODIUM
Dosage Form;Route: TABLET; ORAL
Proprietary Name: CYTOMEL
Applicant: KING PHARMS
Strength: EQ 0.05MG BASE
Application Number: 010379
Product Number: 003
Approval Date: Approved Prior to Jan 1, 1982
Reference Listed Drug Yes
RX/OTC/DISCN: RX
TE Code:
Patent and Exclusivity Info for this product: View
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Orange Book Data - Monthly
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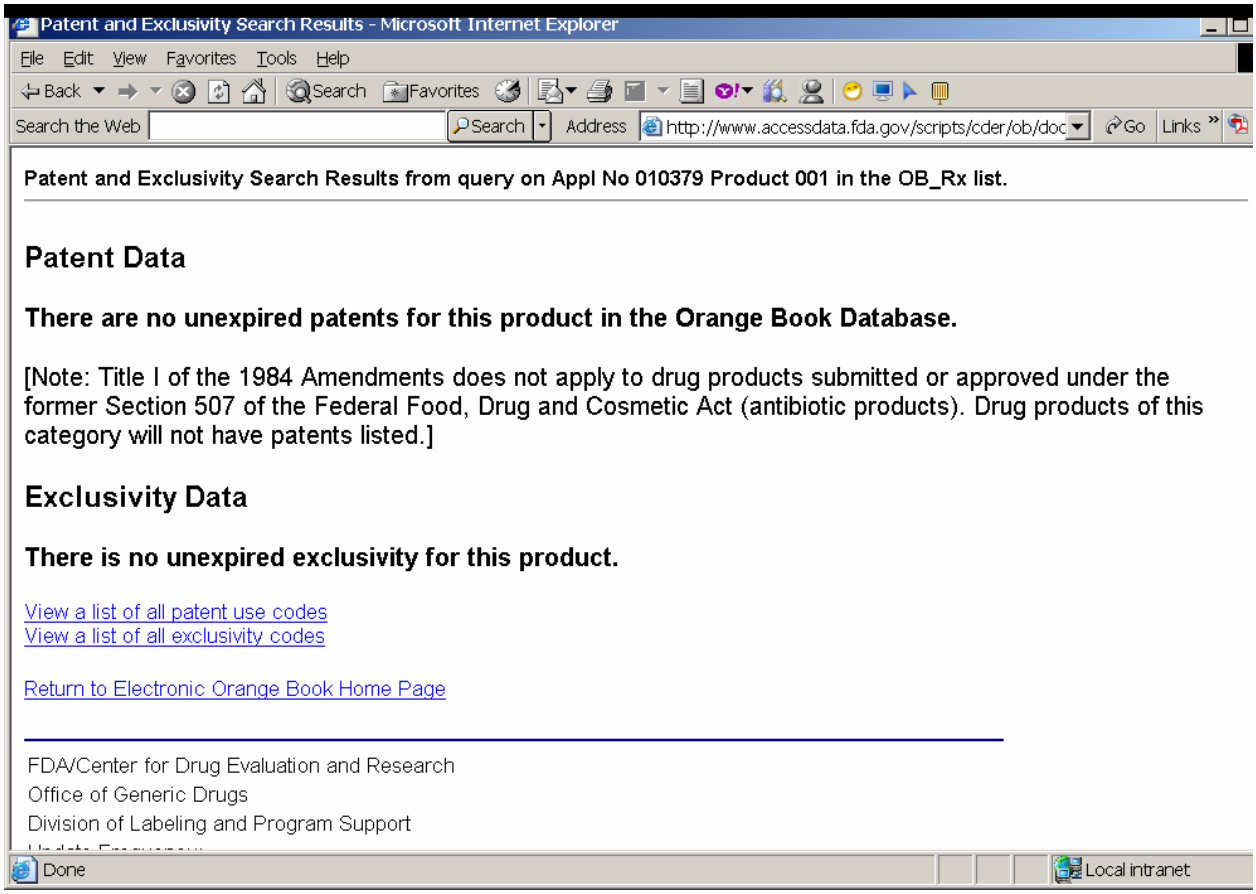
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Search the Web Search Address http://www.accessdata.fda.gov/scripts/cder/ob/doc Go Links
Patent and Exclusivity Search Results from query on Appl No 010379 Product 001 in the OB_Rx list.
Patent Data
There are no unexpired patents for this product in the Orange Book Database.
[Note: Title I of the 1984 Amendments does not apply to drug products submitted or approved under the former Section 507 of the Federal Food, Drug and Cosmetic Act (antibiotic products). Drug products of this category will not have patents listed.]
Exclusivity Data
There is no unexpired exclusivity for this product.
View a list of all patent use codes
View a list of all exclusivity codes
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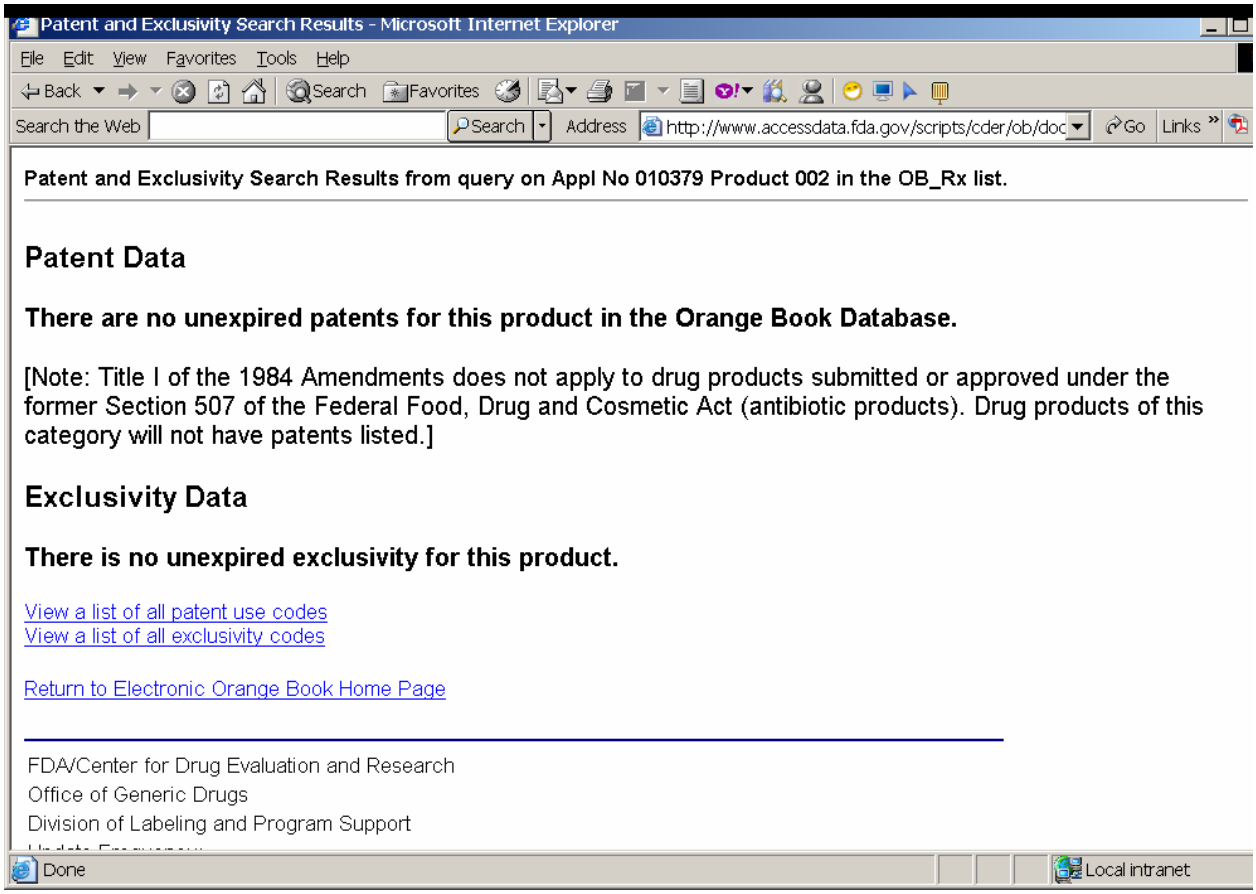
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Search the Web Search Address http://www.accessdata.fda.gov/scripts/cder/ob/doc Go Links
Patent and Exclusivity Search Results from query on Appl No 010379 Product 002 in the OB_Rx list.
Patent Data
There are no unexpired patents for this product in the Orange Book Database.
[Note: Title I of the 1984 Amendments does not apply to drug products submitted or approved under the former Section 507 of the Federal Food, Drug and Cosmetic Act (antibiotic products). Drug products of this category will not have patents listed.]
Exclusivity Data
There is no unexpired exclusivity for this product.
View a list of all patent use codes
View a list of all exclusivity codes
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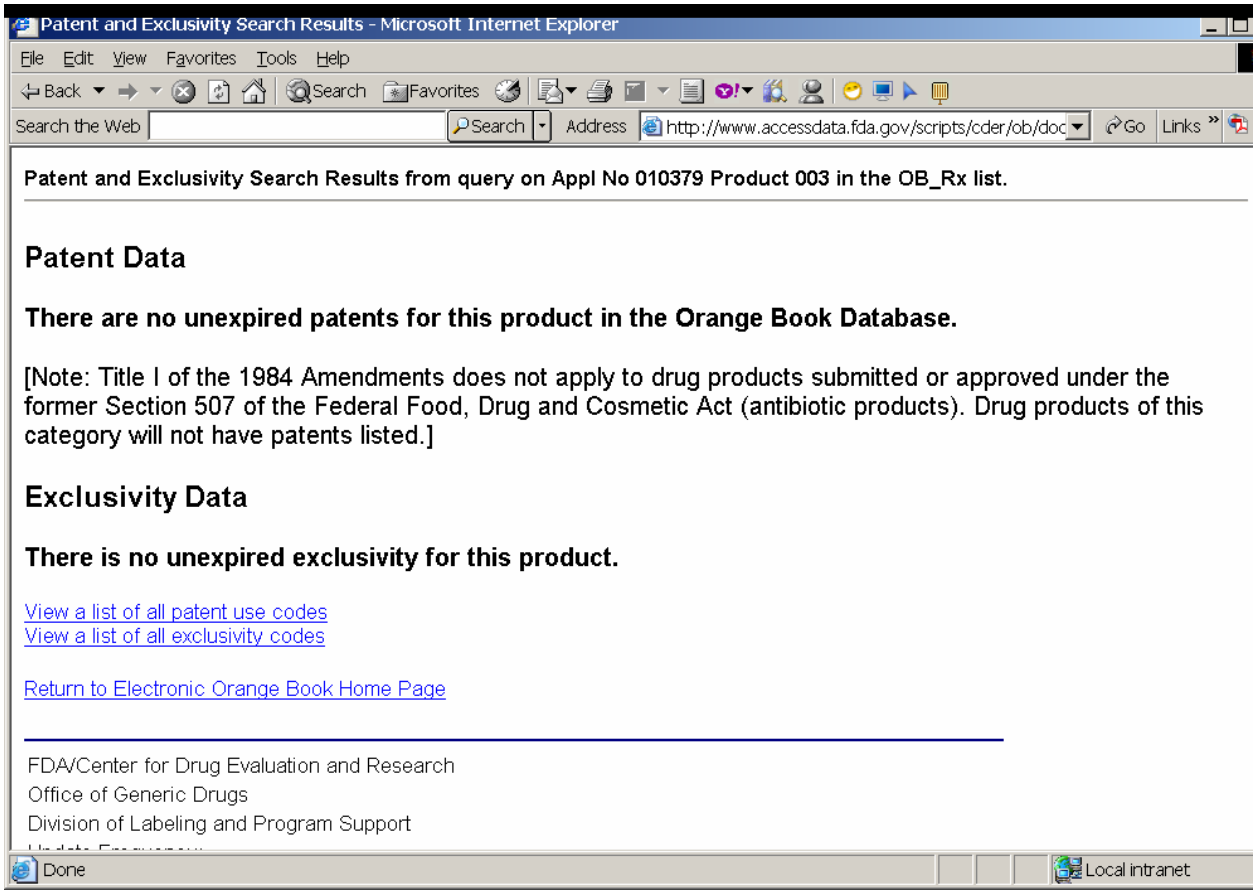
Patent and Exclusivity Search Results - Microsoft Internet Explorer
File Edit View Favorites Tools Help
Back Search Favorites
Search the Web Search Address http://www.accessdata.fda.gov/scripts/cder/ob/doc Go Links
Patent and Exclusivity Search Results from query on Appl No 010379 Product 003 in the OB_Rx list.
Patent Data
There are no unexpired patents for this product in the Orange Book Database.
[Note: Title I of the 1984 Amendments does not apply to drug products submitted or approved under the former Section 507 of the Federal Food, Drug and Cosmetic Act (antibiotic products). Drug products of this category will not have patents listed.]
Exclusivity Data
There is no unexpired exclusivity for this product.
View a list of all patent use codes
View a list of all exclusivity codes
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Coastal Pharmaceuticals, Inc.
Attention: William A. Tilghman, Jr.
1240 Sugg Parkway
Greenville, NC 27834

MAR 0 9 2006

Reference Number: OGD #05-0334

Dear Mr. Tilghman:

This letter is in response to your correspondence dated March 8, 2005. You request that the Office of Generic Drugs (OGD) provide bioequivalence recommendations regarding Liothyronine Sodium Tablets, 5 mcg, 25 mcg and 50 mcg. OGD provides the following comments:

1. The following study is recommended to establish bioequivalence of liothyronine tablets:

   A single-dose fasting *in-vivo* bioequivalence study comparing Liothyronine Sodium Tablets, 50 mcg (using a 100 mcg dose, 2 x 50 mcg), to the reference listed drug (RLD), Cytomel® (Liothyronine Sodium) Tablets, 50 mcg.

2. Please measure total (free + unbound) liothyronine in plasma. Baseline levels of liothyronine should be measured at 3 pre-dose time points (-30 min, -15 min and 0 min). The mean of the three pre-dose samples should be subtracted from each measured post-dose concentration.

3. Liothyronine Sodium Tablets, 5 mcg and 25 mcg, may be considered for a waiver *of in-vivo* bioequivalence testing based on (1) acceptable bioequivalence studies on the 50 mcg strength, (2) acceptable dissolution testing of the 5 mcg, 25 mcg, and 50 mcg strengths, and (3) proportional similarity in the formulations of the 5 mcg, 25 mcg, and 50 mcg strengths.

4. Please conduct comparative dissolution testing on 12 dosage units of all strengths of the test and reference products using the following FDA method:

Apparatus:	USP apparatus 3
Speed:	30 dips per minute, using 20-mesh screen on the top and 40-mesh screen on the bottom of the glass reciprocating cylinder

Medium: Alkaline Borate Buffer, pH 10.0 ± 0.05 at 37°C
Volume: 250 mL
Sampling times: 5, 10, 15, 30, and 45 minutes

5. Please provide a table that identifies every missing sample in the study. Also, for every reassayed sample, please provide a table identifying the reason(s) for reassay, as well as the original and reassayed values of the sample. Please identify which value was selected for the PK analysis. Please provide the Standard Operating Procedures (SOPs) for all types of reassays including those that describe criteria for identifying and reassaying pharmacokinetically anomalous samples. The SOP(s) should clearly state objective criteria for defining pharmacokinetic anomalies, the method of reassay, and acceptance criteria for selecting which value to report for the reassayed sample. This SOP should be in place prior to the start of the study; otherwise, the Division of Bioequivalence may not accept reassayed values of samples. Finally, please conduct all pharmacokinetic and statistical analyses using both the original as well as reassayed values.

6. The bioequivalence data to be submitted in an ANDA should be provided in a diskette or CD in SAS Transport format in two separate files as described below:

   a. SUBJ SEQ PER TRT AUCT AUCI CMAX TMAX KE Thalf
   b. SUBJ SEQ PER TRT C1 C2 C3 ..... . Cn

   Please separate each field with a blank space and indicate missing values with a period (.).

   Please refer to the Guidance for Industry: "Providing Regulatory Submissions in Electronic Format-ANDAs" for information regarding the proper format at: www.fda.gov/cder/guidance/index.htm (under electronic submissions).

If you have any questions, please call Keri Suh, Pharm.D., Project Manager, Division of Bioequivalence at (301) 827-5847In future correspondence regarding this issue, please include a copy of this letter.

Sincerely yours,

Dale P. Conner, Pharm.D.
Director
Division of Bioequivalence
Office of Generic Drugs
Center for Drug Evaluation and Research

OGD # 05-0334

BIOEQUIVALENCE CHECKLIST FOR FIRST GENERIC ANDA FOR APPLICATION COMPLETENESS

ANDA# 090097 **FIRM NAME** Coastal Pharmaceuticals

DRUG NAME Liothyronine Sodium Tablets USP, 5 mcg, 25 mcg, and 50 mcg

DOSAGE FORM Tablets

SUBJ: Request for examination of:

Requested by: _____ Date: _____
Chief, Regulatory Support Team, (HFD-615)

	Summary of Findings by Division of Bioequivalence
☒	**Study meets statutory requirements**
☐	**Study does NOT meet statutory requirements**
	Reason:
☒	**Waivers meet statutory requirements**
☐	**Waivers do NOT meet statutory requirements**
	Reason:

RECOMMENDATION: ☒ **COMPLETE** ☐ **INCOMPLETE**

Reviewed by:

Farahnaz Nouravarsani, Ph.D. 12/14/2007
_____ Date: _____
Reviewer

Chandra Chaurasia, Ph.D. 12/17/2007
_____ Date: _____
Team Leader

Table 3 Statistical Summary of the Comparative Bioavailability Data for Triiodothyronine Baseline Corrected Data

Triiodothyronine Dose (2 x 50 µg) Least Squares Geometric Means, Ratio of Means, and 90% Confidence Intervals Fasted Bioequivalence Study (70092)				
Parameter	**Test**	**Reference**	**Ratio**	**90% C.I.**
AUC0-t	72.75 ng·h/mL	75.38 ng·h/mL	96.52%	92.12% to 101.13%
AUC∞*	82.15 ng·h/mL	85.56 ng·h/mL	96.02%	90.81% to 101.52%
Cmax	7.86 ng/mL	8.03 ng/mL	97.85%	95.34% to 100.43%

*For this parameter, N=63

Table 3 Statistical Summary of the Comparative Bioavailability Data for Triiodothyronine Baseline Uncorrected Data

Triiodothyronine Dose (2 x 50 µg) Least Squares Geometric Means, Ratio of Means, and 90% Confidence Intervals Fasted Bioequivalence Study (70092)				
Parameter	**Test**	**Reference**	**Ratio**	**90% C.I.**
AUC0-t	156.69 ng·h/mL	159.08 ng·h/mL	98.49%	95.57% to 101.51%
AUC∞	-	-	-	-
Cmax	9.63 ng/mL	9.79 ng/mL	98.34%	96.18% to 100.54%

Table 6 Formulation Data

Ingredient	Amount (mg) / Tablet			Amount (%) / Tablet		
	5 mcg Tablet	25 mcg Tablet	50 mcg Tablet	5 mcg Tablet	25 mcg Tablet	50 mcg Tablet
Cores						
Liothyronine Sodium, USP[1],	(b) (4)					
Calcium Sulfate, (b) (4) NF						
Microcrystalline Cellulose, NF (b) (4) (b) (4)						
Microcrystalline Cellulose, NF (b) (4) (b) (4)						
Hypromellose, USP (b) (4)						
Talc, USP						
Colloidal Silicon Dioxide, NF (b) (4) (b) (4)						
Coating						
There is no coating on the tablets.	N/A	N/A	N/A	N/A	N/A	N/A
Total	(b) (4)					

(b) (4)

INACTIVE INGREDIENTS SEARACH FOR ANDA 90097

COASTAL PHARMACEUTICALS – LIOTHYRONINE SODIUM TABLETS USP, 5 mcg, 25 mcg AND 50 mcg

CALCIUM SULFATE (b) (4)	ORAL; TABLET	(b) (4)
CELLULOSE, MICROCRYSTALLINE	ORAL; TABLET	
HYDROXYPROPYL METHYLCELLULOSE (b) (4)	ORAL; TABLET	
TALC	ORAL; TABLET	
SILICON DIOXIDE, COLLOIDAL	ORAL; TABLET	

DEPARTMENT OF HEALTH AND HUMAN SERVICES
Food and Drug Administration

CERTIFICATION: FINANCIAL INTERESTS AND ARRANGEMENTS OF CLINICAL INVESTIGATORS

Form Approved: OMB No. 0910-0396
Expiration Date: April 30, 2009.

TO BE COMPLETED BY APPLICANT

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

Please mark the applicable checkbox.

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

Clinical Investigators		
	Please see attached list to this form.	

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

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

NAME	TITLE
Gerald D. Sakowski	Chief Operating Officer
FIRM / ORGANIZATION: Coastal Pharmaceuticals	
SIGNATURE	DATE: 01/28/2008

Paperwork Reduction Act Statement

An agency may not conduct or sponsor, and a person is not required to respond to, a collection of information unless it displays a currently valid OMB control number. Public reporting burden for this collection of information is estimated to average 1 hour per response, including time for reviewing instructions, searching existing data sources, gathering and maintaining the necessary data, and completing and reviewing the collection of information. Send comments regarding this burden estimate or any other aspect of this collection of information to the address to the right:

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

FORM FDA 3454 (4/08)

PSC Graphics (301) 443-1090 EF

Attachment to Form FDA 3454

The following is a list of the clinical investigators for Anapharm that were involved in conducting the bioequivalence study 70092 for Liothyronine Sodium Tablets, USP 5 mcg, 25 mcg and 50 mcg for Coastal Pharmaceuticals.

Denis Audet
Jean-Jacques Barbeau
Pierre Bélanger
Eric Bicrell
Caroline Champagne
Benoit J. Deschamps
Martine Gobeil
Marie-Christine Godin
Richard Larouche
Geneviève Ostiguy
Mario Tanguay
Luc Tremblay

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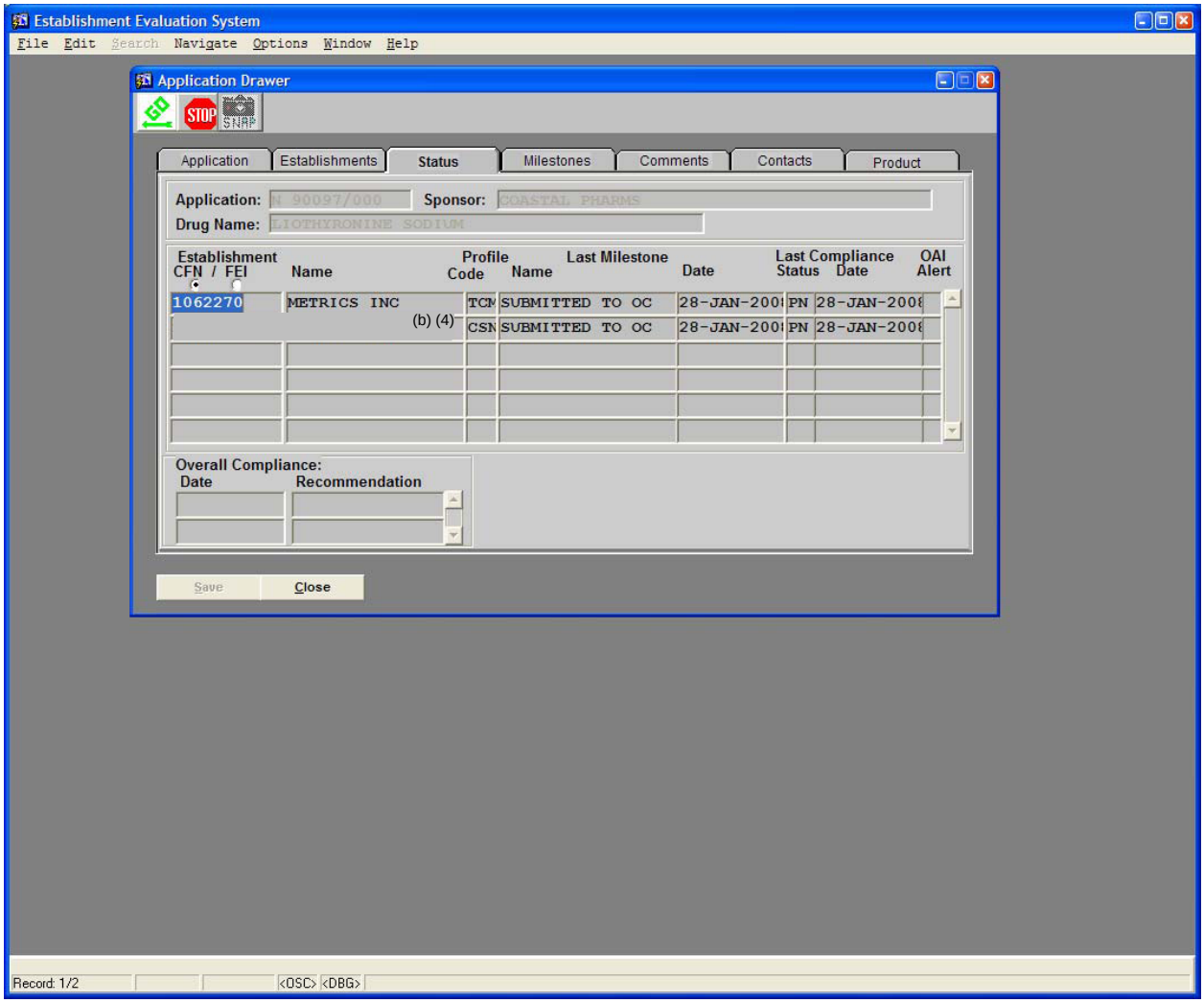
Establishment Evaluation System
File Edit Search Navigate Options Window Help
Application Drawer
GO
STOP
SNAP
Application Establishments Status Milestones Comments Contacts Product
Application: N 90097/000 Sponsor: COASTAL PHARMS
Drug Name: LIOTHYRONINE SODIUM
Establishment CFN / FEI
Name
Profile Code
Last Milestone Name
Date
Last Compliance Status
Compliance Date
OAI Alert
1062270
METRICS INC
(b) (4)
TCM
SUBMITTED TO OC
28-JAN-200
PN
28-JAN-200
CSN
SUBMITTED TO OC
28-JAN-200
PN
28-JAN-200
Overall Compliance:
Date
Recommendation
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/s/

Martin Shimer

2/6/2008 08:22:23 AM

DEPARTMENT OF HEALTH & HUMAN SERVICES

Food and Drug Administration
Rockville, MD 20857

ANDA 90-097

Coastal Pharmaceuticals
Attention: William A. Tilghman, Jr.
1240 Sugg Parkway
Greenville, NC 27834

Dear Sir:

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

Reference is also made to the telephone conversation dated January 28, 2008 and your correspondence dated January 29, 2008.

NAME OF DRUG: Liothyronine Sodium Tablets USP, .005 mg, .025 mg and .050 mg

DATE OF APPLICATION: October 31, 2007

DATE (RECEIVED) ACCEPTABLE FOR FILING: November 1, 2007

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 ANDA number shown above.

Should you have questions concerning this application, contact:

Esther Chuh
Project Manager
240-276-8530

Sincerely yours,

{See appended electronic signature page}

Wm Peter Rickman
Director
Division of Labeling and Program Support
Office of Generic Drugs
Center for Drug Evaluation and Research

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

/s/

Martin Shimer
2/6/2008 08:22:03 AM
Signing for Wm Peter Rickman

M E M O R A N D U M

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

DATE : December 12, 2007

TO : Director
Division of Bioequivalence (HFD-650)

FROM : Chief, Regulatory Support Branch
Office of Generic Drugs (HFD-615)

SUBJECT: Examination of the bioequivalence study submitted with an ANDA 90-097 for Liothyronine Sodium Tablets USP, 5 mcg, 25 mcg and 50 mcg to determine if the application is substantially complete for filing.

Coastal Pharmaceuticals has submitted ANDA 90-097 for Liothyronine Sodium Tablets USP, 5 mcg, 25 mcg and 50 mcg. It is a first generic. In order to accept an ANDA that contains a first generic, the Agency must formally review and make a determination that the application is substantially complete. Included in this review is a determination that the bioequivalence study is complete, and could establish that the product is bioequivalent.

Please evaluate whether the request for study submitted by Coastal Pharmaceuticals on October 31, 2007 for its Liothyronine Sodium product satisfies the statutory requirements of "completeness" so that the ANDA may be filed.

A "complete" bioavailability or bioequivalence study is defined as one that conforms with an appropriate FDA guidance or is reasonable in design and purports to demonstrate that the proposed drug is bioequivalent to the "listed drug".

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/s/

Eda Howard
12/13/2007 08:02:03 AM
APPLICATIONS EXA