

D. CERTIFICATION

The undersigned certify that, to their best knowledge and belief, this petition includes all information and views upon which the petition relies, and that it includes representative data and information known to the petitioner which are unfavorable to the petition.



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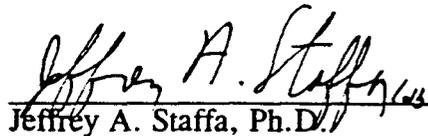
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**SUPPLEMENT TO CITIZEN PETITION**

**REGULATORY STATUS OF SYNTHROID® ORALLY ADMINISTERED  
LEVOTHYROXINE SODIUM USP**

Docket No. 97N-0314/CP2

Knoll Pharmaceutical Company ("Knoll" or "the company") is submitting this supplement to the above-cited citizen petition under sections 201(p) and 505 of the Food, Drug, and Cosmetic Act ("FDCA" or "the Act") and 21 C.F.R. § 10.30(g).<sup>1</sup> That Petition asked the Commissioner of Food and Drugs (the "Commissioner") to issue an order declaring that Synthroid® brand orally administered levothyroxine sodium USP ("Synthroid") is generally recognized as safe and effective ("GRAS/E") within the meaning of section 201(p) of the Act for the treatment of hypothyroidism, and therefore not subject to regulation as a

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1. Citizen Petition 97N-0314, Regulatory Status of Synthroid Orally Administered Levothyroxine Sodium USP, filed December 15, 1997 (hereinafter "Petition"). The Petition is incorporated by reference in this supplement. As stated in the Petition, there is no legal or factual basis to deny GRAS/E status for any Synthroid indication, on grounds of manufacturing quality concerns or otherwise.

"new drug" under the Act.<sup>2</sup> This supplement seeks a like determination for the additional indication specified below.

#### Actions Requested

1. The Commissioner is requested to determine that Synthroid is GRAS/E for use under the conditions prescribed, recommended, or suggested in its labeling. The particular indication for which this supplement seeks a determination that Synthroid is GRAS/E is:

[a]s a pituitary TSH suppressant in conjunction with surgery and/or radioactive iodine therapy in the management of differentiated (papillary or follicular) carcinoma of the thyroid ("the cancer indication").<sup>3</sup>

2. The Commissioner is requested to determine that Synthroid does not require an approved new drug application ("NDA") for the cancer indication as called for by the Food and Drug Administration ("FDA") in its Federal Register Notice entitled "Prescription Drug Products; Levothyroxine Sodium" ("the Notice"), 62 Fed. Reg. 43,535 (Aug. 14, 1997).

3. The Commissioner is requested to waive specific requirements for "adequate and well-controlled studies" pursuant to 21 C.F.R. § 314.126 to the extent necessary to accept as "substantial evidence" of efficacy the published research studies described and relied upon to

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2. The specific indication for which the Petition seeks a GRAS/E determination is for the use of Synthroid

[a]s a replacement or supplemental therapy in patients of any age or state (including pregnancy) with hypothyroidism of any etiology except transient hypothyroidism during the recovery phase of subacute thyroiditis: primary hypothyroidism resulting from thyroid dysfunction, primary atrophy, or partial or total absence of the thyroid gland, or from the effects of surgery, radiation or drugs, with or without the presence of goiter, including subclinical hypothyroidism; secondary (pituitary) hypothyroidism; and tertiary (hypothalamic) hypothyroidism[.]

Knoll's intention to supplement the Petition to demonstrate that other labeled Synthroid indications also are GRAS/E was stated in the Petition at 1 n.2.

3. This indication is included in current Synthroid labeling (with slightly different wording), a copy of which is attached as Exhibit 1.

A third indication that appears on current Synthroid labeling is for use as a pituitary TSH suppressant in the treatment or prevention of various types of euthyroid goiters, including thyroid nodules, subacute or chronic lymphocytic thyroiditis (Hashimoto's), and multinodular goiter. Knoll is not seeking a GRAS/E determination for that indication at this time.

support the cancer indication in this petition supplement and in the attached declarations of experts.

## STATEMENT OF GROUNDS

### I. Thyroid Cancer and its Treatment<sup>4</sup>

Although carcinoma of the thyroid gland is an uncommon cancer, it is the most common cancer of the endocrine system, and occurs as frequently as other well-publicized cancers such as multiple myeloma, cervical, and laryngeal cancers. Approximately 15,000 to 16,000 new cases of thyroid cancer are diagnosed annually. The broad category of thyroid cancer includes a number of different tumor types. This supplement is concerned solely with differentiated (papillary and follicular) thyroid cancers, which together account for approximately 90% of all thyroid carcinomas.<sup>5</sup>

Differentiated thyroid cancer is highly treatable and usually curable with appropriate diagnosis, treatment, and followup.<sup>6</sup> Surgical removal is the primary treatment of choice for

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4. The summary discussion that follows in the text above is drawn primarily from Fraker DL, Skarulis M, Livolsi V. Thyroid tumors. In: DeVita VT, Hellman S, Rosenberg SA, editors. Cancer: principles & practice of oncology. 5<sup>th</sup> ed. Philadelphia: Lippincott-Raven Publishers; 1997. p. 1629-52; see also Carcinoma of follicular epithelium. In: Braverman LE, Utiger RD, editors. Werner & Ingbar's the thyroid a fundamental and clinical text. 7<sup>th</sup> ed. Philadelphia: Lippincott-Raven Publishers; 1996. p.902-45; National Cancer Institute, Physician's Data Query, Health Professional Information - Thyroid Cancer (March 1998); Farwell AP, Braverman LE. Thyroid and antithyroid drugs. In: Hardman JG, Limbird LE, Molinoff PB, Ruddon RW, Gilman AG, editors. Goodman & Gilman's the pharmacological basis of therapeutics. 9<sup>th</sup> ed. New York: McGraw Hill; 1996. p.1383-1409; The merck manual of diagnosis and therapy. 16<sup>th</sup> ed. Rahway, N.J.: Merck Research Laboratories; 1992. Thyroid cancers; p.1085-7.

Copies of all published materials cited in this Supplement and in the expert declarations and reports attached to it are attached as Exhibit 2. Publications in Exhibit 2 are ordered alphabetically by first author.

5. Fraker et al., supra note 4 at 1629. Within this group, papillary cancers are the most prevalent, accounting for 80-85% of differentiated cancers.

6. The death rate from thyroid cancers is 0.16% for men and 0.24% for women. Braverman and Utiger, supra note 4, at 902.

differentiated thyroid tumors, although debate continues concerning the optimal degree of surgical excision in various prognostic circumstances. Most patients are rendered hypothyroid as a result of thyroid cancer surgery, and therefore require lifelong hormone replacement therapy. Although several drugs are available for this purpose, orally administered levothyroxine sodium is the overwhelming drug of choice for thyroid replacement therapy.

The most commonly used postsurgical adjuvant treatment for patients with differentiated thyroid cancer is suppression of pituitary secretion of thyrotropin ("TSH") by levothyroxine sodium, as a means of preventing recurrence of cancer and death from that cause. As the discussion below and the attached expert declarations and exhibits demonstrate, the safety and effectiveness of levothyroxine sodium for this use are well established and generally recognized by medical experts.

## II. When Used for the Cancer Indication, Synthroid is Not a "New Drug"

### A. Synthroid is Generally Recognized among Medical Experts as Safe and Effective for the Cancer Indication

Section 201(p) of the Act provides in pertinent part that the definition of "new drug" does not include any drug which is GRAS/E, i.e., "generally recognized, among experts qualified by scientific training and experience to evaluate the safety and effectiveness of drugs, as safe and effective for use under the conditions prescribed, recommended, or suggested in the labeling thereof." In their declarations attached to this Supplement, three leading thyroid experts, Ernest L. Mazzaferri, M.D., M.A.C.P., Steven I. Sherman, M.D., and Leonard Wartofsky, M.D., M.A.C.P., each states that it is his considered view as well as that of other experts that Synthroid is GRAS/E for the cancer indication on the basis, among other things, of published studies that provide substantial evidence of efficacy.<sup>7</sup> Drs. Mazzaferri, Sherman, and Wartofsky also have reviewed evidence of potential health risks associated with long-term TSH suppression therapy, and have concluded that it is safe for differentiated thyroid cancer patients when dosing is carefully individualized at the minimum level required for adequate suppression.

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7. Declaration of Ernest L. Mazzaferri, M.D., M.A.C.P., Exhibit 3; Declaration of Steven I. Sherman, M.D., Exhibit 4; Declaration of Leonard Wartofsky, M.D., M.A.C.P., Exhibit 5. Their curricula vitae ("CVs"), attached to their declarations, demonstrate that they are unquestionably expert, and that they are extremely well-qualified by scientific training and experience to evaluate the safety and efficacy of thyroid drugs and thyroid cancer therapies.

Published studies relied on by Drs. Mazzaferri, Sherman, and Wartofsky include the following:

Mazzaferri EL, Young RL, Oertel JE, Kemmerer WT, Page CP. Papillary thyroid carcinoma: the impact of therapy in 576 patients. *Medicine* 1977;56:171-96.

Mazzaferri EL, Young RL. Papillary thyroid carcinoma: a 10 year follow-up report of the impact of therapy in 576 patients. *Am J Med* 1981;70:511-18.

Mazzaferri EL, Jhiang SM. Long-term impact of initial surgical and medical therapy on papillary and follicular thyroid cancer [published erratum appears in *Am J Med* 1995;98:215]. *Am J Med* 1994;97:418-28;

Cunningham MP, Duda RB, Recant W, Chmiel JS, Sylvester J, Fremgen A. Survival discriminants for differentiated thyroid cancer. *Am J Surg* 1990;160:344-7;

Staunton MD. Thyroid cancer: a multivariate analysis on influence of treatment on long-term survival. *Eur J Surg Oncol* 1994;20:613-21;

Simpson WJ, Panzarella T, Carruthers JS, Gospodorwicz MK, Sutcliffe SB. Papillary and follicular thyroid cancer: impact of treatment in 1578 patients. *Int J Radiation Oncology Biol Phys* 1988;14:1063-75; and

Pujol P, Daures JP, Nsakala N, Baldet L, Bringer J, Jaffiol C. Degree of thyrotropin suppression as a prognostic determinant in differentiated thyroid cancer. *J Clin Endocrinol Metab* 1996;81:4318-23.

Dr. Marion Finkel, a leading expert in evaluating the quality of clinical trials, states in her report<sup>8</sup> that each of the studies satisfies FDA's standard for "substantial evidence" of efficacy under the FDCA, confirming the views of Drs. Mazzaferri, Sherman, and Wartofsky in that regard. Moreover, as stated in Dr. Sherman's declaration, although the clinical literature on TSH suppression in differentiated thyroid cancer patients reflects the use of several different forms of thyroid hormone over the years, levothyroxine sodium today is the drug of choice. Administration of levothyroxine sodium (such as Synthroid) reliably and reproducibly suppresses TSH, whether the goal is to render the patient euthyroid when treating primary hypothyroidism or to suppress TSH in the medical management of differentiated

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8. Report of Marion Finkel, M.D., Exhibit 6. Her CV, attached to her report, demonstrates that she is unquestionably expert and that she is extremely well qualified by scientific training and experience to evaluate studies of the safety and efficacy of drugs.

thyroid cancer.<sup>9</sup> Thus, evidence that TSH suppression by thyroid hormone in any form is safe and effective in treating thyroid cancer may appropriately be relied upon to conclude that Synthroid is GRAS/E for this use.<sup>10</sup>

B. Synthroid Has Been Used For the Cancer Indication to a Material Extent and for a Material Time.

Sales of Synthroid for the cancer indication clearly satisfy the Act's requirement that a GRAS/E drug must have been used "to a material extent or for a material time." With respect to "material time," the use of levothyroxine sodium to suppress TSH in thyroid cancer patients has been recognized in FDA's own class labeling guidelines since 1982,<sup>11</sup> and the medical literature reflects an even longer history of use for this purpose.<sup>12</sup> As to "material extent," the American Cancer Society has estimated the thyroid cancer population at 200,000 patients, while other estimates range as high as 500,000.<sup>13</sup> Given that many if not most of those patients have been treated with levothyroxine sodium to suppress TSH and that Synthroid accounts for approximately two thirds of the levothyroxine sodium prescriptions in the United States, there can be no doubt that use of Synthroid for the cancer indication has satisfied the "material extent" requirement for GRAS/E status.<sup>14</sup>

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9. Sherman Declaration, Exhibit 4 at ¶ 7. The general recognition of effectiveness of levothyroxine sodium and Synthroid in controlling TSH has already been demonstrated. See Petition at 9-12.

10. This conclusion also is consistent with FDA's expressed intention to accept NDA applications for levothyroxine sodium drug products based on studies in the published literature, as provided in section 505(b)(2) of the Act. 62 Fed. Reg. 43,535, 43,538 (Aug. 14, 1997).

11. Class Labeling Guidelines for Professional Labeling, announced at 47 Fed. Reg. 29,878 (July 9, 1982).

12. For example, the entry for levothyroxine sodium and other thyroid hormones in the 1967 edition of the American Medical Association's New and Nonofficial Remedies stated that "their use seems reasonable for carcinoma that may be thyrotropin dependent." New and nonofficial remedies. 1967 ed. American Medical Association, at 419. For a historical overview, see Clark OH. TSH suppression in the management of thyroid cancer. World J Surg 1981;5:39-47.

13. See Finkel Report, Exhibit 6 at 1.

14. For further discussion of the marketing history of Synthroid and the standard for establishing "material time and extent" of marketing under section 201(p) of the Act, see Petition at 12-13.

III. Conclusion

For all the reasons detailed above and in the attached exhibits, it is evident that Synthroid is generally recognized by leading thyroid experts as safe and effective for the cancer indication. Accordingly, Knoll requests the Commissioner to issue the requested order declaring that Synthroid is generally recognized as safe and effective, and therefore not subject to regulation as a new drug.

Environmental Impact

Petitioner claims a categorical exclusion from the requirement of an environmental impact assessment under 21 C.F.R. § 25.24(a)(1) and, by analogy, §§ 25.24(c)(1) and (6).

Certification

The undersigned certify that, to the best knowledge and belief of the undersigned, this petition supplement includes all information and viewed upon which the petition relies, and that it includes representative data and information known to the petitioner which are unfavorable to the petition. The undersigned further certify that this petition includes all studies and information specified as required for determination of GRAS/E status under section 314.200(d).

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December 15, 1997

CITIZEN PETITION

REGULATORY STATUS OF SYNTHROID ORALLY ADMINISTERED  
LEVOTHYROXINE SODIUM USP

Docket No. 97N-0314

Knoll Pharmaceutical Company ("Knoll" or "the company")<sup>1</sup> submits this Citizen Petition under sections 201(p) and 505 of the Food, Drug, and Cosmetic Act ("FDCA" or "the Act") to request the Commissioner of Food and Drugs (the "Commissioner") to issue an order determining that Synthroid® brand orally administered levothyroxine sodium USP ("Synthroid") is generally recognized as safe and effective ("GRAS/E") within the meaning of section 201(p) of the FDCA, and, therefore, not subject to regulation as a "new drug" under the Act.

Actions Requested

1. The Commissioner is requested to determine that Synthroid is GRAS/E for use under the conditions prescribed, recommended, or suggested in its labeling. The indication for which a determination that Synthroid is GRAS/E is requested is:

[a]s replacement or supplemental therapy in patients of any age or state (including pregnancy) with hypothyroidism of any etiology except transient hypothyroidism during the recovery phase of subacute thyroiditis: primary hypothyroidism resulting from thyroid dysfunction, primary atrophy, or

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1. Knoll is a subsidiary of BASF Corporation. Unless otherwise specified, "Knoll" or "the company" as used in this petition also refers to companies which previously manufactured and/or marketed Synthroid. A more detailed corporate history is provided below at note 23.

partial or total absence of the thyroid gland, or from the effects of surgery, radiation or drugs, with or without the presence of goiter, including subclinical hypothyroidism; secondary (pituitary) hypothyroidism; and tertiary (hypothalamic) hypothyroidism[.]

A copy of the current prescribing information for Synthroid is attached as Exhibit 1.<sup>2</sup>

2. The Commissioner is requested to determine that Synthroid does not require an approved new drug application ("NDA"), as called for in the Food and Drug Administration's ("FDA") Federal Register notice entitled "Prescription Drug Products; Levothyroxine Sodium" ("the Notice"), 62 Fed. Reg. 43,535 (Aug. 14, 1997).<sup>3</sup>

3. The Commissioner is requested to waive specific requirements for "adequate and well-controlled studies" pursuant to 21 C.F.R. § 314.126 to the extent necessary to accept as "substantial evidence" of efficacy the published research studies described and relied upon in this petition and in the attached declarations of experts.

#### STATEMENT OF GROUNDS

##### Introduction

Synthroid is not a new drug. As discussed in this Citizen Petition and the expert statements attached to it, Synthroid is

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2. As FDA recognizes in its August 14, 1997 Federal Register notice, Synthroid and other orally administered levothyroxine sodium drug products also are indicated to suppress the secretion of thyrotropin in the management of simple nonendemic goiter, chronic lymphocytic thyroiditis, and thyroid cancer. 62 Fed. Reg. 43,535, 45,536 (Aug. 14, 1997) [hereinafter the Notice]; see also Synthroid prescribing information, Exhibit 1 (Indication 2). Because the concerns addressed in FDA's notice clearly arise from the products' use as chronic replacement therapy for hypothyroidism, this submission will focus primarily on that indication. Knoll intends to supplement this petition in the near future with additional data and information to demonstrate that other labeled indications and conditions also are GRAS/E.

3. The Notice specified October 14, 1997 as the deadline for Citizen Petitions contending that a drug product is not a new drug. FDA granted Knoll an extension until December 15, 1997. Letter from Jane A. Axelrad, Associate Director for Policy, Center for Drug Evaluation and Research, to Nancy L. Buc (Oct. 9, 1997).

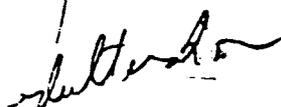
the quintessential "old drug" because it is generally recognized as safe and effective by leading thyroid experts on the basis of adequate and well-controlled studies and more than forty years of safe and effective use in millions of patients. FDA's refusing to declare Synthroid as generally recognized as safe and effective, and therefore not a new drug, would be tantamount to nullifying section 201(p) of the Act.

Yet in its Notice, FDA asserts that although levothyroxine sodium (sometimes referred to herein as NaLT4) is effective in treating hypothyroidism and is safe when carefully and consistently manufactured and stored,

no currently marketed orally administered levothyroxine sodium product has been shown to demonstrate consistent potency and stability and, thus, no currently marketed orally administered levothyroxine sodium product is generally recognized as safe and effective.<sup>4</sup>

① That conclusion misconceives the applicable law and is factually wrong as to Synthroid. When the law is correctly stated, and in light of the product's long history of careful and consistent manufacture, resulting in a reliably stable and potent levothyroxine sodium drug, the only proper conclusion is that Synthroid is generally recognized as safe and effective. ②

As discussed in more detail below, the Notice confuses FDA's sweeping authority to regulate the manufacture of drugs, whether new drugs or not, with the definition of "new drug." In brief, section 201(p) of the FDCA has to do with general recognition of safety and efficacy, as demonstrated in published studies, not with general recognition of manufacturing quality. Although Congress included manufacturing questions in the list of issues to be addressed once an NDA is required,<sup>5</sup> it did not include such issues in the list of questions to be addressed in deciding whether an NDA is required. It did, however, give FDA wide-ranging authority over manufacturing for both new drugs and not new drugs ("old drugs") in provisions of the Act other than section 505. Thus, while FDA has ample authority to deal with stability, potency, and other manufacturing issues under other sections of the Act, including section 501 and regulations issued pursuant thereto, it lacks authority to import these issues into the definition of "new drug."



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4. Notice at 43,538.

5. FDCA § 505(b)(1)(D).

Moreover, whatever may be the case with other levothyroxine sodium products, Synthroid has been carefully, consistently, and reliably manufactured for many years. Thus, even if manufacturing concerns could, in theory, undo GRAS/E status, they do not do so as to Synthroid.

## I. Hypothyroidism and Its Treatment

### A. The Disease of Hypothyroidism<sup>6</sup>

"Hypothyroidism, known as myxedema when severe, is the most common disorder of thyroid function."<sup>7</sup> It is most often caused by disorders of the thyroid gland that result in decreased thyroid hormone production and secretion (primary or thyroidal hypothyroidism), and is accompanied by increased thyrotropin (TSH) secretion. Much less often, hypothyroidism is due to decreased thyroid stimulation by TSH (central, secondary, or hypothyrotropic hypothyroidism).

In the United States, where iodine supply is sufficient, primary hypothyroidism is most frequently caused by either chronic autoimmune or radiation-induced thyroiditis, the latter most frequently caused by radioiodine treatment for thyrotoxicosis or external neck irradiation for lymphoma of the neck or head and neck cancers.

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6. This section is excerpted from Farwell AP, Braverman LE. Thyroid and antithyroid drugs. In: Hardman JG, Limbird LE, Molinoff PB, Ruddon RW, Gilman AG, editors. Goodman and Gilman's the pharmacological basis of therapeutics. 9<sup>th</sup>.ed. New York: McGraw-Hill Press; 1996. p. 1383-1409, which should be consulted for a fuller discussion. See also Singer PA, Cooper DS, Levy EG, Ladenson PW, Braverman LE, Daniels G, et al. Treatment guidelines for patients with hyperthyroidism and hypothyroidism. JAMA 1995;273:808-12. These guidelines were prepared by the Standards of Care Committee of the American Thyroid Association ("ATA") and are referenced below as the "ATA guidelines."

Copies of the ATA Guidelines and other published articles referred to in this Citizen Petition and in the expert declarations and reports attached to it are attached as Exhibit 2. Articles in Exhibit 2 are ordered alphabetically by first author.

7. Farwell and Braverman, supra at 1393.

## B. Diagnosis of Hypothyroidism<sup>8</sup>

The clinical manifestations of hypothyroidism are largely independent of its cause, and affect persons of all ages and both sexes. Clinical manifestations of hypothyroidism include the symptoms of fatigue, lethargy, sleepiness, mental impairment, depression, cold intolerance, hoarseness, dry skin, decreased perspiration, weight gain, decreased appetite, constipation, menstrual disturbances, arthralgia, and paresthesias. Signs include slow movement, slow speech, hoarseness, bradycardia, dry skin, nonpitting edema, hyporeflexia, and delayed relaxation of reflexes.<sup>9</sup>

Ladenson notes that "clinical manifestations usually provide clues to the diagnosis of hypothyroidism, but they are usually too insensitive and nonspecific for definitive diagnosis." Thus, he says; "Accurate diagnosis of hypothyroidism requires awareness of clinical features that define a patient's risk for thyroid hormone deficiency and proper use of the two laboratory tests usually required to confirm the disorder: serum TSH and free NaLT4."<sup>10</sup>

It is now generally agreed that measurement of serum TSH is the cornerstone of the diagnosis of hypothyroidism<sup>11</sup> and that normalization of TSH is the goal of treatment.<sup>12</sup> Signs and

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8. This section is excerpted from Ladenson PW. Diagnosis of hypothyroidism. In: Braverman LE, Utiger RD, editors. Werner and Ingbar's the thyroid. A fundamental and clinical text. 7<sup>th</sup> ed. Philadelphia: Lippincott-Raven Publishers; 1996. p. 878-82, which should be consulted for further discussion.

9. See also American Association of Clinical Endocrinologists. AACE clinical practice guidelines for the evaluation and treatment of hyperthyroidism and hypothyroidism. Endocrine Practice 1995;1:54-62. Also available from: URL: [http://www.aace.com/guidelines/thyroid\\_guide.html](http://www.aace.com/guidelines/thyroid_guide.html) [hereinafter AACE Guidelines]. Exhibit 2.

10. Ladenson, supra note 8, at 878.

11. Declaration of Carole A. Spencer, Ph.D., M.T., Exhibit 3 at ¶ 5 [hereinafter Spencer Declaration]; Farwell and Braverman, supra note 6, at 1395; AACE Guidelines, supra note 9; ATA Guidelines, supra note 6, at 811; FDA, Thyroid Hormone Human Prescription Drugs. Class Labeling Guidelines for Professional Labeling, announced at 47 Fed. Reg. 29,878 (July 9, 1982) [hereinafter Class Labeling].

12. Declaration of Peter A. Singer, M.D., Exhibit 4, at ¶ 9 [hereinafter Singer Declaration]; Declaration of Leonard

symptoms of hypothyroidism will generally improve along with the serum TSH although not necessarily at exactly the same rate.<sup>13</sup>

C. Treatment of Hypothyroidism

Treatment of the hypothyroid patient is straightforward and consists of hormone replacement.<sup>14</sup>

Over the past 100 years several sources of replacement hormone have been used.

In 1891, George Murray showed that an extract from the thyroid gland of sheep reversed the symptoms of myxedema.<sup>15</sup> A year later, Fox and McKenzie showed that oral doses of fresh thyroid were an effective form of replacement.<sup>16</sup> Standardized thyroid preparations (desiccated thyroid) came into use as replacement therapy shortly thereafter.<sup>17</sup>

On Christmas Day in 1914, Kendall isolated the active hormone of the thyroid gland, which he named thyroxin.<sup>18</sup> Harrington and Barger described the structure of levothyroxine sodium, and Lyon first tested it in humans in pure form.<sup>19</sup>

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Wartofsky, M.D., M.A.C.P., Exhibit 5, at ¶ 9 [hereinafter Wartofsky Declaration]; Farwell and Braverman, supra note 6, at 1395; AACE Guidelines, supra note 9; ATA Guidelines, supra note 6, at 811; Surks MI, Chopra IJ, Mariash CN, Nicoloff JT, Solomon DH. American Thyroid Association guidelines for use of laboratory tests in thyroid disorders. JAMA 1990;263:1529-32, at 1531, Exhibit 2.

13. Spencer Declaration, Exhibit 3 at ¶ 7; Sawin CT. Hypothyroidism. Med Clin North Am 1985;69:989-1004, at 993-4.

14. Farwell and Braverman, supra note 6, at 1383.

15. Spencer Declaration, Exhibit 3 at ¶ 2; Bunner DL. Organic medicine-thyroid hormone replacement therapy, 1891-1977. Arch Intern Med 1978;138:978-9, at 978.

16. Bunner, supra at 978.

17. Desiccated thyroid is still sold as Armour Thyroid Tablets, USP. Physician's desk reference. 51st ed. Montvale, (NJ): Medical Economics Company, Inc; 1997. Armour; p. 1008.

18. Clapesattle H. The doctors Mayo. Minneapolis (MN): University of Minnesota Press, 1954, at 305.

19. Bunner, supra note 15, at 978.

Levothyroxine sodium was first synthesized in the laboratory about 1927.<sup>20</sup> Thyroxine, as "Thyroxinum," was first listed in the U.S. Pharmacopeial Convention's compendium ("USP") in 1933.<sup>21</sup> The first successful high yield synthesis of thyroxine occurred in 1949.<sup>22</sup>

Flint introduced the first orally administered levothyroxine sodium product, Synthroid, in 1955.<sup>23</sup> Synthroid was first listed in the USP in 1957. Thereafter, Armour and other companies also began to market levothyroxine sodium tablets.<sup>24</sup>

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20. Sawin CT. The heritage of the thyroid. In: Braverman LE, Utiger RD, editors. Werner and Ingbar's the thyroid, supra note 8, p. 2-5, at 4.

21. The 1936 USP said, "Thyroxine is an active physiological principle obtained from the thyroid gland, or prepared synthetically[.]" The pharmacopoeia of the United States of America, 11th ed. Easton (PA): Mack Printing, Co; 1936. Thyroxinum; p. 389, Exhibit 7.

22. Sawin, supra note 20, at 4.

23. In the late 1950's, Baxter acquired Flint-Eaton Company, Inc., which became a division of Baxter's Travenol unit. From that time until April 1986, Synthroid was manufactured by Travenol and distributed by Flint. In April 1986, Baxter sold its Flint division to Boots Pharmaceuticals, Inc., which continued distribution of Synthroid. In April 1995, Boots Pharmaceuticals, Inc. was sold to BASF, where it was merged with BASF's subsidiary, Knoll.

24. Although combinations of NaLT4 and triiodothyronine ("T3") were reviewed in FDA's Drug Efficacy Study Implementation ("DESI") and have NDAs, no levothyroxine sodium product ever had an NDA or was reviewed in DESI. No records exist to explain why the manufacturer of Synthroid did not seek NDAs, but it seems likely that it viewed the product as containing the same active ingredient as desiccated thyroid, which had been introduced to the market before 1938, or the synthesized NaLT4 mentioned in, e.g., the 1936 USP. See supra note 21. This view is supported by FDA's "Orange Book," which lists Synthroid tablets as an example of a pre-1938 drug. Approved drug products with therapeutic equivalence evaluations. 17th ed. Rockville (MD): U.S. Dept. Of Health and Human Services, Public Health Service, Food and Drug Administration, Center for Drug Evaluation and Research; 1997. See also Transcript of Hearings on Bioequivalence, Sept.-Oct., 1986, Session V, attached to Report by the Bioequivalence Task Force, January 1988 at 713 (Dr. Young: "The Chair also wants to add - as a technical issue - that the drug that you're studying [levothyroxine sodium] is a pre-

By the 1970's, expert clinicians definitely preferred levothyroxine sodium to thyroid USP because of its greater consistency.<sup>25</sup> The preference for NaLT4 as compared to combinations of NaLT4 and T3 grew stronger after Braverman et al. demonstrated that serum concentrations in hypothyroid patients given NaLT4 were much more constant - like those in normal subjects - than those treated with T3 or combinations of NaLT4/T3.<sup>26</sup> Especially after 1982-era advances in NaLT4 assay technology and related reformulations of levothyroxine products resolved FDA's and others' concerns about stability,<sup>27</sup> levothyroxine became a still more popular choice. It is now unquestionably the standard of care for treating hypothyroidism.<sup>28</sup> As Mandel et al. put it:

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1938[.]"), Exhibit 8; and Letter from JoAnne C. Marrone, Consumer Safety Officer, Division of Metabolism and Endocrine Drug Products; to Francine R. Klein (July 12, 1978) ("Levothyroxine sodium was marketed prior to the enactment of the Federal Food, Drug, and Cosmetic Act of 1938[.]"), Exhibit 9.

25. Roti E, Minelli R, Gardini E, Braverman LE. The use and misuse of thyroid hormone. *Endocr Rev* 1993;14:401-23, at 402 (footnote omitted) ("[P]ercent of desiccated thyroid prescriptions in the United States has decreased from approximately 80% of all thyroid prescriptions in 1964 to 26% in 1988."); Bunner, supra note 15, at 979; Jackson IM, Cobb WE. Why does anyone still use desiccated thyroid USP? *Am J Med* 1978;64:284-8, at 284.

26. Braverman LE, Ingbar SH, Sterling K. Conversion of thyroxine (T4) to triiodothyroxine (T3) in athyreotic human subjects. *J Clin Inv* 1970;49:855-64, cited in Stock JM, Surks MI, Oppenheimer JH. Replacement dosage of L-thyroxine in hypothyroidism. *N Engl J Med* 1974;290:529-33. See also Wartofsky Declaration, Exhibit 5, at ¶ 7; Toft AD. Thyroxine therapy. *N Engl J Med* 1994;331:174-80 at 174 ("[C]ombination therapy cannot be recommended."), Exhibit 2.

27. See discussion below at § IV.C.2.

28. See, e.g., Wartofsky Declaration, Exhibit 5 at ¶ 7; AACE Guidelines, supra note 9; ATA Guidelines, supra note 6, at 811 ("Levothyroxine sodium is the treatment of choice for the routine management of hypothyroidism."); Roti E, Braverman LE. Thyroid hormone therapy: when to use it, when to avoid it. *Drug Therapy* 1994;24:28-35, at 28 ("L-thyroxine is currently the thyroid hormone preparation of choice in treating patients with hypothyroidism[.]"), Exhibit 2; Sawin, supra note 13, at 1001 (Effective treatment, unchanged in principle since the 1890's, is best done with oral L-thyroxine."); Bunner, supra note 15, at 979; Jackson and Cobb, supra note 25, at 287; Stock, supra note 26, at 529 ("L-thyroxine appears to be a particularly suitable

With proper patient monitoring, levothyroxine replacement therapy should be effective, inexpensive, and free of complications.<sup>29</sup>

II. Synthroid Is Not a "New Drug" Within the Meaning of Section 201(p) of the Act.

Section 201(p) provides, in pertinent part, that the term "new drug" means:

any drug . . . the composition of which is such that such drug is not generally recognized, among experts qualified by scientific training and experience to evaluate the safety and effectiveness of drugs, as safe and effective for use under the conditions prescribed, recommended, or suggested in the labeling thereof[.]

When tested by the standards laid down by the Supreme Court,<sup>30</sup> lower courts,<sup>31</sup> and FDA itself<sup>32</sup> for interpreting section 201(p), Synthroid is unequivocally GRAS/E. In their declarations attached to this Petition, four leading thyroid experts, Terry F. Davies, M.D., Peter A. Singer, M.D., Carole A. Spencer, Ph.D., M.T., and Leonard Wartofsky, M.D., M.A.C.P., each states it is his or her view and the virtually unanimous view of other experts that Synthroid is GRAS/E on the basis, among other things, of adequate and well-controlled published studies.<sup>33</sup>

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agent in hormonal replacement therapy of patients with hypothyroidism."); see Class Labeling, supra note 11, at 2 ("These facts would seem to advocate levothyroxine as the treatment of choice for the hypothyroid patient[.]").

29. Mandel SJ, Brent GA, Larsen PR. Levothyroxine therapy in patients with thyroid disease. *Ann Intern Med.* 1993;119:492-502, at 492.

30. See Weinberger v. Hynson, Westcott, and Dunning, Inc., 412 U.S. 609 (1973); Weinberger v. Bentex Pharmaceuticals, Inc., 412 U.S. 645 (1973).

31. See, e.g., United States v. Alcon Laboratories, Inc., 745 F.2d 105 (1st Cir. 1984) (retired Supreme Court Justice Stewart, sitting by designation).

32. E.g., 21 C.F.R. § 314.200(d) and (e).

33. Singer Declaration, Exhibit 4 at ¶ 17; Declaration of Terry F. Davies, M.D., Exhibit 6 at ¶¶ 18 and 20 [hereinafter Davies Declaration]; Wartofsky Declaration, Exhibit 5 at ¶ 15; Spencer

They state that the safety and effectiveness of Synthroid have been evaluated in numerous adequate and well-controlled published studies, all of which show that Synthroid in the correct dose normalizes TSH and show that Synthroid is safe.<sup>34</sup> These studies include the following:<sup>35</sup>

*Berg Mayre - 300 mg.*

Ain KB, Pucino F, Csako G, Wesley RA, Drass JA, Clark C, et al. Effects of restricting levothyroxine dosage strength availability. *Pharmacotherapy* 1996;16:1103-10.

Jaeschke R, Guyatt G, Gerstein H, Patterson C, Molloy W, Cook D, et al. Does treatment with L-thyroxine influence health status in middle-aged and older adults with subclinical hypothyroidism? *J Gen Intern Med* 1996; 11:744-9.

Germak JA, Foley TP. Longitudinal assessment of l-thyroxine therapy for congenital hypothyroidism. *J Pediatr* 1990;117:211-9.

Kabadi UM. Optimal daily levothyroxine dose in primary hypothyroidism. Its relation to pretreatment thyroid hormone indexes. *Arch Inter Med* 1989;149:2209-12.

Fish LH, Schwartz HL, Cavanaugh J, Steffes MW, Bantle JP, Oppenheimer JH. Replacement dose, metabolism, and bioavailability of levothyroxine in the treatment of hypothyroidism. *N Engl J Med* 1987;316:764-70.

Hennessey JV, Burman KD, Wartofsky L. The equivalency of two L-thyroxine preparations. *Ann Inter Med* 1985;102:770-3.

Stock JM, Surks MI, Oppenheimer JH.

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Declaration, Exhibit 3 at ¶ 10. Their curricula vitae ("CVs"), attached to their declarations, demonstrate that they are unquestionably expert, and that they are extremely well qualified by scientific training and experience to evaluate the safety and efficacy of thyroid drugs.

34. Davies Declaration, Exhibit 6 at ¶¶ 15, 16, and 17; Singer Declaration, Exhibit 4 at ¶¶ 10-11 and 15; Spencer Declaration, Exhibit 3, at ¶ 10; Wartofsky Declaration, Exhibit 5, at ¶¶ 9-11 and 15.

35. Copies of these studies are included in Exhibit 2.

Replacement dosage of L-thyroxine in  
hypothyroidism. N Engl J Med  
1974;290:529-33.

Dr. Marion Finkel, a leading expert in evaluating the quality of clinical trials, states in her report<sup>36</sup> that each of these studies is adequate and well-controlled under 21 C.F.R. § 314.126,<sup>37</sup> confirming the views of Drs. Davies, Spencer, Singer, and Wartofsky in that regard.<sup>38</sup>

So generally are studies of Synthroid relied on to support the expert consensus that levothyroxine is safe and effective that it can fairly be said that the consensus as to levothyroxine is a consensus as to general recognition of the safety and

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36. Report of Marion J. Finkel, M.D., Exhibit 10. Her CV, attached to her report, demonstrates that she is unquestionably expert and that she is extremely well qualified by scientific training and experience to evaluate studies of the safety and efficacy of drugs.

37. Dr. Finkel's description and analysis of each study provide the factual analysis demonstrating that the studies relied on to support GRAS/E status are adequate and well-controlled, as contemplated by 21 C.F.R. § 314.200(d)(2).

FDA implicitly acknowledges in the Notice that these studies provide sufficient support for a New Drug Application (and must therefore be adequate and well-controlled). FDA states that it is prepared to accept § 505(b)(2) applications for levothyroxine products, and that an applicant may therefore rely on literature supporting the safety and/or the effectiveness of levothyroxine sodium. Notice at 43,538. Because so much of the literature is on Synthroid, and because there are so many levothyroxine products which appear never to have been the subject of a published study, FDA's willingness to accept literature for any product essentially concedes the validity of the Synthroid literature.

38. Other adequate and well-controlled studies relied on by one or more of the thyroid experts are: Kabadi UM, Jackson T. Serum thyrotropin in primary hypothyroidism. A possible predictor of optimal daily levothyroxine dose in primary hypothyroidism. Arch Intern Med 1995;155:1046-8; Kabadi U. Optimal LT4 dosage in primary hypothyroidism. Iowa Med 1994;84:535-7; Sawin CT, Surks MI, London M, Ranganathan C, Larsen, PR. Oral thyroxine: variation in biologic action and tablet content. Ann Intern Med 1984;100:641-5; Bernstein RS, Robbins J. Intermittent therapy with L-thyroxine. N Engl J Med 1969;281:1444-8. Copies of these studies are included in Exhibit 2.

efficacy of Synthroid.<sup>39</sup> The following experts are among those who rely on studies of Synthroid for their published conclusions about the safety and efficacy of levothyroxine:

- Mandel et al.<sup>40</sup> (citing Fish et al.);
- the American Thyroid Association<sup>41</sup> (citing Mandel et al., who cite Fish et al.);
- the American Association of Clinical Endocrinologists<sup>42</sup> (citing Mandel et al., who cite Fish et al., and Surks et al., who cite Fish et al. and Hennessey); and
- Roti et al.<sup>43</sup> (citing Hennessey et al., Fish et al., Kabadi, and Stock et al.).

In sum, Synthroid has been so thoroughly studied for safety and efficacy, so widely prescribed, so often taken by so many millions of patients and, on all these bases, so generally recognized as safe and effective,<sup>44</sup> that there can be no doubt that Synthroid is generally recognized as safe and effective and therefore not a new drug within the meaning of section 201(p) of the Act.

### III. Synthroid Has Been Labeled and Marketed for the Treatment of Hypothyroidism for a Material Time and to a Material Extent.

Sales of Synthroid clearly satisfy the Act's requirement that a GRAS/E drug have been used "to a material extent or for a material time" under the labeled conditions of use.<sup>45</sup> Throughout

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39. Davies Declaration, ¶ 19;

40. Mandel et al., supra note 29, at 500.

41. ATA Guidelines, supra note 6, at 812.

42. AACE Guidelines, supra note 9.

43. Roti et al., supra note 25, at 417.

44. Davies Declaration, Exhibit 6, at ¶ 19; Wartofsky Declaration, Exhibit 5, at ¶¶ 8 and 14; Singer Declaration, Exhibit 4, at ¶ 14.

45. FDCA § 201(p). See Exhibit 1 for current Synthroid prescribing information. Synthroid has been labeled for the treatment of hypothyroidism throughout its marketing history. For example, the 1955 edition of the American Medical

more than forty years of marketing, Synthroid has been used to treat millions of patients for hypothyroidism who have taken literally billions of tablets. Based on IMS data, Knoll estimates that over 500 million Synthroid tablets were sold in 1977, and that annual sales increased to just under 700 million tablets of Synthroid in 1982 and to about 1.6 billion tablets of Synthroid in 1996. The first-marketed strengths (20, 50, and 100 mcg.) have been sold for more than 40 years; the most recently introduced strength (88 mcg.) for seven years.<sup>46</sup> The current Synthroid formulation has been fundamentally unchanged since 1982.<sup>47</sup> It is plain from this history that Synthroid is, indeed, an "old" drug, not just legally<sup>48</sup> but as a matter of plain, indisputable fact.

IV. There Is No Legal or Factual Basis for FDA's Assertion That Synthroid Is a "New Drug" Because It Has Not Been "Shown to Demonstrate Consistent Potency and Stability."

For all the reasons set forth above, the evidence is overwhelming that Synthroid is generally recognized by leading experts to be safe and effective for the treatment of hypothyroidism. Moreover, those experts' conclusions are based on published clinical studies and experience gained over decades of use by millions of patients. If ever there was a quintessential "old drug" according to FDA's well-established legal and evidentiary standards, Synthroid surely is that drug.

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Association's New and Nonofficial Remedies lists "Synthroid Sodium (Travenol)" as "useful in replacement therapy of diminished or absent thyroid function[.]" New and nonofficial Remedies. 1955 ed. American Medical Association, at 466, 486, Exhibit 11.

46. Letter from Barbara A. Buhler, Associate Director, Regulatory Services, Boots Pharmaceuticals, to Frank R. Fazari, Chief, Prescription Drug Compliance Branch, CDER (July 31, 1992), Exhibit 12.

47. Changes in the Synthroid formulation are discussed more fully in Section IV.C.2, below.

48. FDA has elaborated on the "material time" element of the definition as requiring at least five years' marketing history, while "material extent" is to be determined more flexibly based on factors such as total units sold and whether the extent of a condition's use has been sufficient to demonstrate a favorable adverse event profile. See Eligibility Criteria for Considering Additional Conditions in the Over-the-Counter Drug Monograph System; Request for Information and Comments, 61 Fed. Reg. 51,625 (Oct. 3, 1996).

FDA's Notice nevertheless would divest Synthroid of its statutorily conferred GRAS/E status on the grounds that "new information" demonstrates "significant stability and potency problems . . . [having] the potential to cause serious health consequences to the public."<sup>49</sup> Specifically, FDA asserts that "[t]here is evidence . . . that even when a physician consistently prescribes the same brand of orally administered levothyroxine sodium, patients may receive products of variable potency at a given dose. Such variations in product potency present actual safety and effectiveness concerns."<sup>50</sup> For this reason, FDA concludes,

[N]o currently marketed orally administered [NaLT4] product has been shown to demonstrate consistent potency and stability and, thus, no . . . [such] product is generally recognized as safe and effective. Accordingly, any orally administered drug product containing levothyroxine sodium is a new drug . . . subject to the [NDA]

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49. Notice at 43,535; the cited "evidence" is detailed at 43,536-37. As detailed below, what FDA describes as "new information" about Synthroid in fact relates to events that happened from five to fifteen years ago.

50. Notice at 43,538. As described by FDA, "[t]he drug substance levothyroxine sodium is unstable in the presence of light, temperature, air, and humidity. Unless the manufacturing process can be carefully and consistently controlled, orally administered [NaLT4] products may not be fully potent through the labeled expiration date, or be of consistent potency from lot to lot." Id.

The specific medical risks with which the agency is concerned are those associated with inadvertent undertreatment or (rarely) overtreatment of hypothyroidism resulting from manufacturers' asserted failure to manufacture LT4 tablets with consistent potency and stability. See id. ("Variations in the amount of available active drug can affect both safety and effectiveness. Patients who receive superpotent tablets may experience angina, tachycardia, or arrhythmias. There is also evidence that overtreatment can cause osteoporosis. Subpotent tablets will not be effective in controlling hypothyroid symptoms or sequelae."); id. at 43,536 ("Because of the risks associated with overtreatment or undertreatment with levothyroxine sodium, it is critical that patients have available to them products that are consistent in potency and bioavailability. Recent information concerning stability problems . . . shows that this goal is not currently being met.").

requirements of section 505 of the [FD&C  
A]ct.<sup>51</sup>

In effect, FDA is declaring - with no support for its position - that the legal standard for general recognition of safety and effectiveness under the FDCA requires a determination that the processes and controls used to manufacture a drug result in "consistent potency and stability." As the following discussion demonstrates, there simply is no basis in either law or fact for FDA to require any such demonstration as part of the determination whether a drug is GRAS/E. Indeed, imposing such a requirement would nullify the fundamental statutory distinction between "new" and "generally recognized" (old) drugs.

Moreover, as a matter of policy, there is no need to graft manufacturing standards onto the definition of GRAS/E in section 201(p). FDA has ample authority under the other provisions of the Act to deal with whatever manufacturing problems may exist with old drugs.

Equally flawed, at least in the case of Synthroid, is FDA's key factual premise: that a "lack of stability and consistent potency has the potential to cause serious health consequences to the public."<sup>52</sup> Whatever may or may not be the case for other NaLT4 products, the consistent potency and stability of Synthroid have been extensively documented, both in published research and in Knoll's and FDA's records. Indeed, throughout the product's history, Knoll and its corporate predecessors have consistently led the industry (and sometimes FDA itself) in improving methods and processes for assuring the purity, potency, and stability of orally administered NaLT4 products.

A. A Showing of "Consistent Potency and Stability" Is Not Required As a Matter of Law in Order for Synthroid to Be "Generally Recognized As Safe and Effective."

FDA's Federal Register notice offers no legal analysis to explain its bald declaration that, absent a showing of "consistent potency and stability" any currently manufactured oral levothyroxine product simply "is not" GRAS/E, and therefore "is" a new drug. As a matter of law, such a showing is not required.

Certainly nothing in the statute itself would support such a requirement. Section 201(p) of the FDCA provides in relevant part that a product is not a "new drug" if it is "generally recognized, among experts qualified by scientific training and

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51. Id. at 43,538.

52. Notice at 43,535.

experience to evaluate the safety and effectiveness of drugs, as safe and effective for use under the conditions prescribed, recommended, or suggested in the labeling thereof[.]” The specified bases for “general recognition” thus are “safety” and “effectiveness,” not, as FDA now would have it, “safety, effectiveness, potency, stability, or any other aspect of drug manufacture.” Nor does section 201(p) define either safety or effectiveness in terms of manufacturing processes and controls.<sup>53</sup>

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While the Act does not tie manufacturing to general recognition of safety, it does explicitly tie manufacturing to the safety of all drugs, new and not new. In particular, section 501(a)(2)(B) mandates conformity with current good manufacturing practice “to assure that [a] drug meets the requirements of this Act as to safety[.]” The difference between section 201(p) and section 501(a)(2)(B) is critical - manufacturing is not a statutory element of general recognition of safety, though it is a statutory element of drug safety assurance.

FDA’s regulations clearly and appropriately reflect the statutory dichotomy between GRAS/E, on the one hand, and manufacturing controls on the other. Manufacturing controls are addressed in depth in Current Good Manufacturing Practices (“CGMP”) regulations, and apply to all drugs, new and old alike.<sup>54</sup> Detailed regulatory criteria for GRAS/E determinations appear elsewhere and, just like section 201(p) of the Act, are silent with respect to manufacturing quality issues such as potency and stability assurance. In particular, the very regulation that the Notice cites as governing GRAS/E petitions for levothyroxine sodium products contains a comprehensive outline of data requirements pertaining to drug safety and efficacy, and says absolutely nothing about manufacturing issues.<sup>55</sup>

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53. Indeed, “general recognition” of manufacturing processes and controls is a practical impossibility due to the confidential nature of most information about manufacturing. See U.S. v. Premo Pharmaceutical Laboratories, Inc., 511 F. Supp. 958, 1020-21 (D.N.J. 1981) (“The identity and quality of the inactive ingredients . . . and the quality control procedures and manufacturing practices and procedures” used in drug manufacture “are not generally known to the scientific community, as this information is considered proprietary and confidential. The same thing is true for virtually every finished pharmaceutical product produced by any firm in the United States.” (citation omitted)).

54. 21 C.F.R. Parts 210 and 211.

55. See 21 C.F.R. § 314.200(d)(3). While this section on its face concerns GRAS/E showings in the context of disputed NDA

B. There is No Practical Need to Use section 201(p) to Control Manufacturing

That a GRAS/E product does not require an NDA does not mean that it is free of FDA regulation - indeed close scrutiny - of its manufacturing.<sup>56</sup> The Act takes care of that in its adulteration provisions, which apply to all drugs, new and old alike. Under section 501(a), a drug is deemed to be adulterated, and thus may not lawfully be introduced into interstate commerce, if

the methods used in, or the facilities or controls used for, its manufacture, processing, packing, or holding do not conform to or are not operated or administered in conformity with current good manufacturing practice to assure that such drug meets the requirements of this Act as to safety and has the identity and strength, and meets the quality and purity characteristics,

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denials, the Notice describes such proceedings as "similar" to the instant petition process and "[n]otes especially that a contention that a [NaLT4] drug product is [GRAS/E] within the meaning of section 201(p) of the act is to be supported by the same quantity and quality of scientific evidence that is required to obtain approval of an application for the product. (See § 314.200(e)(1).)" The cited regulation goes on to state that GRAS/E submissions "should be in the format and with the analyses required under paragraph (d) of this section" (emphasis added).

56. Nor does the fact that FDA may not approve a new drug without reviewing "a full description of the methods used in, and the facilities and controls used for, the [drug's] manufacture, processing, packing and holding" mean that NDA review is required any time FDA identifies a "concern" about the manufacturing of a product that is not a new drug because it is GRAS/E. See FDCA §§ 505(b)(1)(D) and (d)(3); see also 47 Fed. Reg. 46,622, 46,641 (Oct. 19, 1982) (preamble to proposed "NDA Rewrite" regulation) ("The statute contemplates regulation of all drugs through enforcement actions against drugs that are adulterated or misbranded. Because of the potential for serious dangers from untested products, however, the statute imposes additional requirements on new drugs . . . . [The NDA approval] regulations do not insulate new drugs from the general requirements of the act; instead they impose additional burdens on these drugs." (emphasis added)).

which it purports or is represented to possess[.]<sup>57</sup>

Section 501(b) further provides that a drug is adulterated if it is recognized in an official compendium (as levothyroxine sodium is), and "its strength differs from, or its quality or purity falls below" the compendial standards, as determined by the assay specified in the compendium.<sup>58</sup>

Under these provisions, FDA has ample authority to address every issue it raises as a concern in the Notice. There certainly can be no dispute, for example, that the specific potency and stability concerns raised in the Notice are squarely within the ambit of FDA's CGMP regulations and enforcement authority.<sup>59</sup> Indeed, as reflected in the Notice itself, FDA has for decades regulated the manufacturing of Synthroid and other NaLT4 products under the authority of its GMP regulations and the FDCA's adulteration provisions, without ever suggesting that GMP-related deficiencies caused the products to be "new drugs."<sup>60</sup>

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57. FDCA § 501(a)(2). The statute's express statement that the purpose of the CGMP requirement is "to assure that such drug meets the requirements of this Act as to safety" flatly negates FDA's apparent assumption that the only way to deal with manufacturing issues is to import them into the GRAS/E standard.

58. Id. § 501(b).

59. See 21 C.F.R. §§ 211.100-.115 (production and process controls); id. §§ 211.160 (general requirements for laboratory controls), 211.165 (testing and release for distribution), and 211.166 (stability testing); id. § 211.137 (expiration dating). The CGMP requirements were substantially revised and made more comprehensive and stringent in the late 1970s, in part as a response to recommendations by an Office of Technology Assessment special panel on drug bioequivalence that stronger CGMP controls were needed to ensure drug quality and uniform bioavailability. See 41 Fed. Reg. 6878 (Feb. 13, 1976) (preamble to revised CGMP regulations); id. at 6881 (Revised CGMP requirements "will provide a high probability that lots with unacceptable percentages of defective units in components, in-process materials, or drug products will be rejected.") Also see generally 43 Fed. Reg. 45,014 (Sept. 29, 1978) (preamble to final rule). FDA later described the effect of the revised CGMP regulations (along with the agency's surveillance and enforcement programs) as providing "important assurance of batch-to-batch consistency in drug product quality." 44 Fed. Reg. 2932, 2945-46 (Jan. 12, 1979) ("Orange Book" preamble).

60. See, e.g., Warning Letter SJN 95-04 to Robert E. Cawthorn (Rhone-Poulenc Rorer, Inc.) from Samuel Jones, Nov. 4, 1994

Another regulatory option that FDA has used effectively in the past is that of promulgating regulations requiring manufacturers of "old" drugs to provide FDA with whatever additional information the agency thinks is necessary to ensure, for example, drug safety. That is precisely how FDA handled the problem of obtaining adverse drug effect information for old drugs, not just drugs marketed under approved NDAs.<sup>61</sup> Indeed, FDA has in the past addressed specific concerns about levothyroxine sodium drug products using class-wide regulations<sup>62</sup> and guidelines,<sup>63</sup> rather than by declaring them to be new drugs.<sup>64</sup>

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(addressing stability issues under CGMP/adulteration authority); Warning Letter to Piet M. Bleyendaal (Pharmaceutical Basics, Inc.) from John H. Scharmann, March 1, 1993 (stability concerns addressed as CGMP/adulteration violations); Regulatory Letter CHI-275-81 to Vernon R. Loucks (Travenol Laboratories, Inc.) from William R. Clark, Feb. 13, 1981 (invoking adulteration and CGMP authorities to address concerns about NaLT4 assay validation and product stability issues) (events relating to this letter are discussed in detail at Section IV.C.2, below). Copies of these letters are attached as Exhibit 13.

61. 21 C.F.R. § 310.305. The previous reporting regulation on its face had applied only to drugs marketed under NDAs. FDA amended the regulation to require reports on all marketed drugs, not just those covered by the new drug authority of FDCA § 505, citing as authority FDCA §§ 704(a) (record inspection authority, including GMP records), 701(a) (authority to promulgate regulations for efficient enforcement of the Act), 502 (prohibition against misbranded drugs, including those which are unsafe and/or ineffective for their labeled uses), and 501 (prohibition against adulterated drugs). See 50 Fed. Reg. 11,478, 11,480-81 (Mar. 21, 1985) (preamble to Proposed Rule).

62. See 21 C.F.R. § 201.316 (required warning against use of thyroid hormone drugs for the treatment of obesity).

63. Class Labeling, supra note 11.

64. Indeed, during the very period when FDA was promulgating the regulation referenced in note 62 above, the agency's General Counsel had recommended that thyroid drugs (including NaLT4) should be considered as candidates for "not new drug" monographs. Memo from Mary A. McEniry, (date illegible), Exhibit 14. (FDA at that time was working on an "old drug monograph" program, analogous to the Over-the-Counter Drug Review, to establish and regulate classes of GRAS/E prescription drugs. Although that program was never established, this recommendation provides still further confirmation that FDA recognized both that regulatory questions with old drugs did not convert them into new drugs, and that levothyroxine sodium was thought to be an old drug as early

FDA could, if it wished, apply similar logic to manufacturing issues such as potency, formulation changes, or stability of NaLT4 products, and require reports to FDA.

C. FDA Also Lacks Any Factual Basis for Concluding That Synthroid Lacks Potency or Consistent Stability.

FDA's arguments for regulating Synthroid as a new drug fare no better factually than they do legally. Contrary to FDA's broad assertion that "no currently marketed orally administered levothyroxine sodium product has been shown to demonstrate consistent potency and stability," there are ample data in both the published literature and Knoll's and FDA's own files demonstrating that Synthroid, for one, is manufactured in a state of control which ensures precisely that. The "evidence" cited in FDA's notice fails utterly to undermine these data: the bulk of FDA's purported "evidence" concerns products other than Synthroid,<sup>65</sup> while the few statements that do refer to Synthroid are distorted, outdated, or both.

1. There Is No Significant Evidence of Adverse Health Effects Caused by Variations in Synthroid Potency.

FDA's Notice fails to provide any credible support for the assertion that adverse drug experience reports ("ADRs") related to tablet potency provide evidence of an "actual medical risk" to Synthroid users.<sup>66</sup> As a threshold point, NaLT4 has an excellent safety profile, and adverse reactions are both predictable and

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as the 1970s.)

65. In this regard it is critical to bear in mind that the key question at issue in this petition is whether Synthroid, not some or all other levothyroxine sodium products, is generally recognized as safe and effective. Alleged or potential deficiencies in other products are simply irrelevant to this determination.

66. As recently as 1995, the Acting Chief of FDA's Epidemiology Branch has stated that "[f]or thyroid medications, the most frequently reported adverse events do not appear to be serious in nature (resulting in hospitalization, death, life-threatening illness, or disability)." Memorandum from Diane K. Wysowski, Ph.D., to Director, Division of Drug Marketing, Advertising, and Communications (April 24, 1995), Exhibit 15. The same memorandum also cautioned, "Please recall that the number of reports of a specific adverse event is not equivalent to the number of patients experiencing the event since there are duplicate reports and initial and followup reports for the same patient. Also, usually more than one event is reported per patient."

rare.<sup>67</sup> More specifically, FDA's "evidence" of "adverse events associated with inconsistencies in product potency" is a summary analysis of 58 ADRs received between 1987 and 1994.<sup>68</sup> Of these, by FDA's own description, at least some involved inter-brand switching, not potential intra-brand inconsistencies. Only 30 of the 58 reports were supported by thyroid function blood tests to confirm that the reported symptoms actually resulted from NaLT4 therapy and not some other cause. Nor is it at all clear that all reports relied on by FDA even involved product "potency." In fact, Knoll's analysis suggests that the adverse events could be reasonably ascribed to causes other than potency.<sup>69</sup>

FDA's discussion also is silent as to the breakdown of ADRs by specific products or manufacturers. However, Knoll's analysis of the corresponding ADR data supplied by FDA reveals that fewer

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67. For an overview of adverse events associated with NaLT4, see Class Labeling, supra note 11, at "Adverse Reactions." A number of factors contribute to NaLT4's excellent safety profile. The potential for acute adverse events is minimized by the fact that NaLT4 is a pro-drug with a long half-life, and that the content of triiodothyronine (T3) is limited by USP release specifications. The availability of multiple dosage strengths and sensitive TSH assays enable physicians to monitor thyroid status with sufficient precision and accuracy to permit fine titration of replacement doses while minimizing the potential for thyrotoxicity. Finally, as discussed in detail below, consistent tablet potency and stability are ensured for Synthroid by excellent manufacturing processes and controls, in conformance with USP specifications, FDA's GMP regulations, and Knoll's own stringent internal standards.

68. Notice at 43,536.

69. Knoll's examination of ADR report summaries obtained from FDA under the Freedom of Information Act ("FOIA") and apparently used as the basis for the Notices's conclusions about the incidence of "potency-related" ADRs indicates that virtually every report involving hypothyroid symptoms was automatically ascribed to "subpotent" tablets, while those involving hyperthyroid-like symptoms were classified as "superpotent." See Exhibit 16. As a result, FDA's analysis is almost certainly overinclusive because it does not take into account alternative etiologies such as suboptimal dosing or poor patient compliance. This limitation is quite relevant, given the importance of proper dose titration, and the fact that poor compliance is widely recognized to be a major factor contributing to therapeutic failures in hypothyroid patients. See, e.g., England ML, Hershman JM. Serum TSH concentration as an aid to monitoring compliance with thyroid hormone therapy in hypothyroidism. Am J Med Sci 1986;292:264-6, at 266, Exhibit 2.

than 40% (22 of 58) involved Synthroid, despite the fact that Synthroid is by far the most commonly prescribed NaLT4 tablet. Of the 30 incidents confirmed by blood tests, only eight reports in six years - fewer than two per year - involved Synthroid out of literally billions of tablets marketed during the same period. Far from demonstrating any "actual safety and effectiveness concern," this minuscule number offers persuasive corroboration that Synthroid is both effective and safe.<sup>70</sup>

A more current and comprehensive review of reported safety data by Knoll yields the same conclusion. Specifically, Knoll has obtained through FOIA a copy of adverse drug reaction reports submitted to the FDA for the period 1971-1997. Knoll's analysis of those data reveals a worst-case total of 115 reports potentially related to potency for all products.<sup>71</sup> Of those, an even smaller number (56%) involved Synthroid, and a smaller number yet (20%) involved patients taking Synthroid alone (i.e., without other medications suggesting a concomitant condition). By any analysis, there simply is no credible evidence of any "actual medical risk" based on reported adverse drug events even potentially related to variations in Synthroid potency.

2. Patients Were Significantly Benefitted, Not Placed at Risk, by the 1980-1982 Era Changes in the Synthroid Formulation.

FDA also makes much of the fact that "manufacturers have not sought FDA approval each time they reformulate their products," citing as an example the 1982 reformulation of Synthroid by its

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70. Indeed, the same conclusion would hold true even if the number of Synthroid-related adverse drug experiences were higher by several orders of magnitude and all incidents were assumed to result from subpotent or superpotent tablets. For this reason, FDA's conclusions gain no further support from the agency's suggestion that some unspecified number of NaLT4 potency problems may go unreported because they are not regarded as "serious or unexpected," and therefore are not required to be reported under 21 C.F.R. § 310.305. Moreover, as noted above, if FDA believes that it needs additional information on old drugs such as Synthroid it is free to modify the reporting regulation accordingly.

71. See Exhibit 17. Knoll's analysis used broadly inclusive search terms that (like FDA's approach) would be expected to include and almost certainly overstate, all incidents potentially related to tablet sub- or super-potency. These included: "no drug effect;" "hypothyroidism;" "hyperthyroidism;" and "altered hormone level."

then-manufacturer, Baxter Travenol.<sup>72</sup> As described by FDA, the reformulation involved

removing two inactive ingredients and changing the physical form of coloring agents. The reformulated product increased significantly in potency . . . . This increase in product potency resulted in serious clinical problems.<sup>73</sup>

The clear implication of this description is that patients have been, and continue to be, placed at risk by changes in Synthroid's formulation. Nothing could be farther from the truth. To the contrary, FDA's portrayal egregiously distorts both the actual course of events and the very significant improvements in product potency and stability that resulted from the 1982 formulation change (which also was the last significant change in the Synthroid formulation).

The reformulation at issue was a direct result of Travenol's pioneering efforts - urged on by FDA - to develop an improved NaLT4 assay using high performance liquid chromatography ("HPLC"). Although a USP monograph for oral levothyroxine sodium tablets had been in existence since the late 1950's, by the late 1970's it was recognized that the USP-specified iodometric assay had significant limitations. Most notably, it was nonspecific (i.e., it did not discriminate between NaLT4 and other forms of iodine), and it could not be used to predict product stability.<sup>74</sup> During the late 1970's, scientists at FDA, Travenol, and Armour (then manufacturer of Letter brand NaLT4 tablets, later called Levothroid) developed HPLC assays which more accurately measured the amount of NaLT4 in the product and could also be used to assess tablet stability over time.<sup>75</sup>

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72. Notice at 43,536.

73. Id. (citation omitted).

74. Larsen PR. The present compendial condition of thyroid hormones and thyroid hormone preparations. Gueriguian JL, Bransome ED, Outschoorn AS, workshop organizers. Hormone Drugs. Proceedings of the FDA-USP Workshop on Drug Reference Standards for Insulins, Somatropins, and Thyroid-axis Hormones; 1982 May 19-21; Bethesda, Maryland. Rockville: The United States Pharmacopeial Convention, Inc; 1982 [hereinafter Workshop Proceedings]. p. 405-8, at 407, Exhibit 18.

75. Knoll's records indicate that FDA's Chief Chemist, Dr. D. Kertesz contacted Travenol in May, 1978 to ask for the company's assistance in evaluating HPLC as a possible alternative assay for NaLT4.

In 1982, FDA and USP convened a major conference on hormone drugs, the FDA-USP Workshop on Drug and Reference Standards for Insulins, Somatotropins, and Thyroid-Axis Hormones.<sup>76</sup> Travenol's chief HPLC expert was among the invited speakers, who were chosen, in FDA's own words, from "an abundance of excellence" offered by "the extreme quality of the general participation."<sup>77</sup>

In his opening remarks, Dr. Solomon Sobel, then as now Director of FDA's Division of Endocrine and Metabolism Drugs, observed that, "Everyone probably would agree that the definition of all synthetic and natural thyroid hormone preparations is in need of complete revision."<sup>78</sup> The attendees at the workshop undertook such revision. During the conference, representatives of FDA, NIH, academia, and industry (including Armour and Travenol) were unanimous in their view that the old (iodometric) assay was "antiquated"<sup>79</sup> and "ha[d] gone by the board."<sup>80</sup> Dr. Benson (FDA) said "[t]here seems here to be enough of a consensus that HPLC works",<sup>81</sup> a view with which Dr. Kartinos (Travenol) and Mr. Hill (Armour) agreed.<sup>82</sup> In short, attendees at the workshop were virtually unanimous in recommending that USP adopt HPLC as the assay for NaLT4,<sup>83</sup> and USP soon adopted the

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76. See Workshop Proceedings, supra note 74.

77. See Letter from John L. Gueriguian to (Travenol's) Dr. R. Jacobus, April 30, 1982 (thanking Dr. Jacobus for agreeing to speak at the conference, and praising the "extreme quality" and "excellence" of the program participants), Exhibit 19.

78. Workshop Proceedings, supra note 74, at 16.

79. Dr. Kumkumian of FDA and Dr. Robbins of NIH, quoted in Schaffenburg CA, Gueriguian JL, editors. Report of the consensus-forming session on thyroid-axis hormones. In: Workshop Proceedings, supra note 74, at 565.

80. Dr. Kartinos of Travenol, Id. at 566.

81. Id.

82. Id.

83. It also is evident that conference participants recognized NaLT4 as the treatment of choice for hypothyroid patients, notwithstanding the need for improved assay techniques and USP specifications. See id. at 565-6 (Dr. Jackson: synthetic NaLT4 has replaced desiccated thyroid in patient therapy and "does a very satisfactory job"); id. at 566 (Dr. Larsen: FDA advisory committee "has already made the recommendation that levo-thyroxine is the treatment of choice"). Likewise, although questions of potency, stability, and bioavailability were much

Travenol HPLC method as the official assay for NaLT4.<sup>84</sup> HPLC has remained the USP assay method ever since.

The development of an HPLC assay and USP's adopting it also had important consequences for Synthroid. In the course of Travenol's HPLC research, it became apparent for the first time that NaLT4 tablets which had appeared to be fully potent throughout their shelf life when measured by the existing method actually could contain less than the labeled amount of NaLT4 when assayed using HPLC; and also that NaLT4 content appeared less stable over time than was previously thought. Travenol also determined that the Synthroid formulation would need to be modified to permit routine HPLC assay, due to apparent interference by one or more excipients.<sup>85</sup> After further research, it was discovered that modifying the inactive ingredients and coloring agents to facilitate reliance on the HPLC assay also would significantly improve product stability.

Accordingly, the company developed a modified formulation reflecting those changes, which was phased into the marketplace for all strengths between late 1981 and early 1982; remaining stocks of "old" Synthroid were removed from the company's distribution system in July of 1983. The amount of levothyroxine sodium used in Synthroid tablets did not change as a result of the reformulation.

Contrary to the implication in FDA's Notice that the reformulation was done without agency review, FDA was closely involved in reviewing the company's HPLC research and the ensuing reformulation before, during, and after the formulation change. As part of that review, FDA was provided with extensive data documenting the company's research, validating the HPLC assay,

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discussed throughout the Workshop, and although the FDA participants were surely aware that no orally administered NaLT4 product had an NDA, the published proceedings offer no mention - not even a hint - by any FDA representatives (or anyone else) that any of these questions caused such products to be new drugs.

84. The method was submitted by Travenol for USP review in May, 1982, and was adopted in USP XX, Supplement IV, Addendum a (citing the Travenol method as published in Jacobus R, Rabinow B, Lueck J. Determination of levothyroxine sodium in the drug substance and Synthroid levothyroxine sodium tablets by reverse-phase high-performance liquid chromatography. In: Workshop Proceedings, supra note 74, at 487); it was incorporated in the next full edition, USP XXI, in 1985.

85. I.e., it appeared that several excipients interacted with NaLT4 to form complexes that the extremely specific HPLC assay was unable to quantitate.

describing the formula and process changes, and establishing the potency, bioavailability, and stability of the new product formulation.<sup>86</sup>

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86. These issues were repeatedly addressed in inspections, meetings, letters, and ongoing reports to the agency beginning in late 1980 and continuing into early 1984. See Exhibit 20. These included: Letter from Robert A. Patterson, M.D. (Boots) to Arlyn Baumgarten (FDA), June 9, 1980 (responding to FDA inspector's questions about product stability and assay issues; summarizing work on HPLC research and reformulation action plan, and describing extensive published literature demonstrating consistent clinical performance of Synthroid); Letter from Robert A. Patterson, M.D. to Arlyn Baumgarten, Jan. 22, 1981 (progress report including results of stability and bioavailability testing on modified formulation); Regulatory Letter CHI-275-81, from William R. Clark to Vernon R. Loucks, Jr., Feb. 13, 1981 (invoking CGMP authority to allege that Synthroid was adulterated because (then-experimental) HPLC results indicated some lots of Synthroid were subpotent, and because FDA did not consider HPLC assay adequately validated); Letter from Robert A. Patterson, M.D. to Philip Scheeler, Feb. 24, 1981 (responding to Regulatory Letter, attaching prior correspondence, and explaining that HPLC test remained experimental, and that products were not adulterated when assayed by the official USP test); Letter from Robert A. Patterson, M.D. to Theodore E. Byers, Apr. 8, 1981 (followup from meeting with list of additional data to follow); Letter from R. A. Patterson, M.D., to Daniel L. Michels, July 30, 1981 (update on HPLC validation and reformulation program, with attached data on assay validation, stability testing, and animal and human studies comparing bioavailability of existing and modified formulations); Letter from Daniel Michels to William B. Graham, July 23, 1981 (calling for submission of additional promised data on assay validation and formulation change); Letter from Robert A. Patterson, M.D. to Daniel L. Michels, Oct. 13, 1981 (providing additional details and data concerning stability testing, bioavailability testing, and reformulation schedule); Letter from Daniel L. Michels to Vernon R. Loucks, Jr., Nov. 19, 1981 (itemizing outstanding assay validation and reformulation issues); Letter from Maynard L. Youngs to Thomas Scarlett (attaching letter to Daniel L. Michels), Dec. 3, 1981 (requesting meeting and reasserting Synthroid compliance with FDCA based on current USP test); Letter from Robert A. Patterson, M.D. to Daniel L. Michels, Jan. 27, 1982 (confirming telephone statement by Mr. Michels that "our program is acceptable"; stating that modified formulation is in production scaleup phase; and promising additional stability data); Letter from Thomas H. Schmitz, Ph.D. to Daniel Michels, Feb. 10, 1982 (enclosing HPLC assay procedure and stability data); Letter from Daniel L. Michels to Thomas H. Schmitz, Ph.D., Mar. 31, 1982 (FDA feedback

Perhaps because it had been an enthusiastic proponent of the new assay and was quite aware of what was happening, FDA does not appear to have raised the issue of whether improved stability (which was exactly what HPLC was supposed to measure) somehow converted Synthroid (or any of the other products which likely were also changed in light of the HPLC assay) into new drugs. It also is noteworthy that throughout several years of detailed communications about the formulation and assay changes and their implications for product potency and stability, FDA consistently relied upon its authority to prevent adulteration under § 501 of the FDCA, and not the "new drug" authority of § 505.<sup>87</sup>

The major practical effect of the reformulation was to accomplish precisely what FDA and the company had sought; it now was possible to determine with unprecedented confidence that the actual NaLT4 content of Synthroid tablets consistently and reliably matched that stated in its labeling throughout its labeled shelf life. A transitory effect of the change was that for many patients the nominal dosage of Synthroid required to maintain a euthyroid state was now lower than their previous maintenance dose, requiring a one-time dosage readjustment.<sup>88</sup>

While the Notice purports to view the events of the early 1980's as evidence of a "serious problem" with Synthroid potency,<sup>89</sup> there was no such problem. To the contrary, published studies designed specifically to assess the effects of the

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on data submissions); Letter from Thomas H. Schmitz, Ph.D. to Daniel L. Michels, Apr. 23, 1982 (additional followup on FDA questions); Letter from Daniel L. Michels to Thomas H. Schmitz, Ph.D., May 21, 1982 (noting outstanding data deficiencies); Letter from Robert A. Patterson, M.D. to Daniel L. Michels, June 21, 1982 (providing additional stability data and promising ongoing stability studies on all strengths, with quarterly updates to FDA through 24 months and beyond). Ongoing stability data reports were provided to Daniel L. Michels on Sept. 23, 1982; Jan. 12, 1983; Apr. 7, 1983; Aug. 2, 1983; Sept. 27, 1983; and Jan. 9, 1984.

87. See id.

88. The company provided physicians with an explanation of the Synthroid reformulation, the HPLC assay, and the reformulation's implications for Synthroid users in 1984. Letter from David L. Horwitz, M.D. to Physicians (undated copy), Exhibit 21.

89. Notice at 43,536. FDA's evidence of "serious clinical problems" during this transition rests on three anecdotal reports from physicians. Such information is hardly "evidence" of a significant potency problem at the time of the formulation change - much less "new evidence" of any current problem.

reformulation on product potency and efficacy directly refute such a conclusion.<sup>90</sup> Once it was recognized that the new product was reproducibly potent and more stable than the old, and as clinicians recognized that patients using the new formulation might therefore have to be retitrated once, the fuss died down, never to recur.

Published studies that subsequently used reformulated Synthroid tablets and included potency assays also have demonstrated that Synthroid tablet potency satisfied applicable regulatory limits.<sup>91</sup> Indeed, experts at FDA's own drug testing laboratory published an article in 1984 showing that Synthroid tablets fell within USP standards for individual tablet content. These results provide still further confirmation of Synthroid's

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90. In particular, Fish et al. concluded that: (1) reformulated Synthroid tablets were within USP potency limits when assayed using HPLC; (2) absorption characteristics were not significantly changed as a result of the reformulation; and (3) as one would expect, the earlier Synthroid formulation appeared subpotent when measured using HPLC. Fish et al., supra page 10, at 765-767. The authors further concluded that "if any errors had been made in the past in assessing the [LT4] content of the tablets, they had been corrected during the reformulation." Id. at 765. Other studies reported similar conclusions. See, e.g., Curry SH, Gums JG, Williams LL, Curry RW, Wolfson BB. Levothyroxine sodium tablets: chemical equivalence and bioequivalence. Drug Intell Clin Pharm 1988;22:589-91. Hennessey JV, Evaul JE, Tseng Y, Burman KD, Wartofsky L. L-thyroxine dosage: a reevaluation of therapy with contemporary preparations. Ann Intern Med 1986;105:11-15 at 13-15; and Stoffer SS, Szpunar WE. Potency of Levothyroxine Products. JAMA 1984;251:635-6. Copies of the cited articles are found in Exhibit 2.

91. See, e.g., Berg JA, Mayor GH. A study in normal human volunteers to compare the rate and extent of levothyroxine absorption from Synthroid and Levoxine. J Clin Pharmacol 1993;33:1135-40, at 1136; Blouin RA, Clifton GD, Adams MA, Foster TS, Flueck J. Biopharmaceutical comparison of two levothyroxine sodium products. Clin Pharm 1989;8:588-92, at 588; Stoffer SS, Szpunar WE. Potency of current levothyroxine preparations evaluated by high-performance liquid chromatography. Henry Ford Med J 1988;36:64-5, at 64. Copies of these articles are included in Exhibit 2. Note also that since the immediate post-reformulation period, potency assays have been conducted primarily in connection with bioequivalence studies, and not because of any expressed concern about changed or inconsistent potency. Copies of the cited articles are found in Exhibit 2.

potency and stability.<sup>92</sup> FDA itself appears to have been satisfied by 1985 that any potency/stability related concerns with respect to Synthroid or other NaLT4 products had been addressed by the move to HPLC testing and the associated product reformulations.<sup>93</sup>

In sum, Synthroid's 1982 reformulation provides no support whatsoever for FDA's attempt to impose new drug status on Synthroid. To the contrary, the change in formulation was a timely response to advancing scientific knowledge that resulted in substantially improved potency and stability not only for Synthroid, but also (through the general application of the HPLC assay) for all NaLT4 products. The same Synthroid formulation introduced in 1982 remains in use today for all Synthroid strengths.<sup>94</sup> As a factual matter, therefore, the statement in FDA's notice that "manufacturers continue to make formulation changes to orally administered levothyroxine sodium products"<sup>95</sup> does not apply to Synthroid.<sup>96</sup>

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92. Brower JF, Toler DY, Reepmeyer JC. Determination of sodium levothyroxine in bulk, tablet, and injection formulations by high-performance liquid chromatography. JPharm Sci 1984;73:11315-7, Exhibit 2.

93. In this regard, an FDA "Rx Drug Wrapup Briefing Sheet" on thyroid drug products prepared in 1985 noted that "[t]here has been concern that the potency of . . . oral levothyroxine, may vary from older to newer tablets made by the same manufacturer . . . . A recent change in the U.S.P. assay method apparently has led to modification of the manufacturing process and reformulation of . . . Synthroid. Other manufacturers may have reformulated their products. While newer tablets probably all contain close to 100% of their labeled content, whether they are all alike in bioavailability is unknown." Exhibit 22.

Note also that a 1985 study of NaLT4 tablet potency performed by Hazelton Laboratories and obtained from FDA's files likewise indicates that Synthroid potency was 'within USP specifications. Exhibit 23.

94. The only formulation change made in the intervening years was the temporary replacement in one Synthroid strength of one of the excipients removed as part of the 1982 reformulation; that excipient was again removed in 1991.

95. Notice at 43,536.

96. Based on FDA's discussion later in the Notice, one of the two examples cited to support this statement appears to refer to Pharmaceutical Basics, Inc. ("PBI"), which promised to reformulate its product after receiving a warning letter in

D. Synthroid is reliably potent and stable.

As a final basis for declaring Synthroid to be a new drug, FDA's Notice asserts that there is a "pattern of stability problems" that "rais[es] concerns about the consistent potency of orally administered levothyroxine sodium products[.]""<sup>97</sup> FDA bases this conclusion on "numerous reports indicating problems with the stability of [such] . . . products in the past several years," as evidenced by product recalls, rejected batches, and CGMP deficiencies cited in FDA inspection reports and warning letters."<sup>98</sup>

FDA's evidence of "stability problems" with levothyroxine sodium products amounts to an amalgam of incidents involving a number of different products (none identified by name) and occurrences that took place over many years, none more recently than 1995. Knoll has established that most of the cited examples actually involved products other than Synthroid, and therefore are irrelevant to this petition."<sup>99</sup> The few examples that do relate to Synthroid, are hardly "recent" - in fact, none is later than 1992. Nor do they stand as evidence that Synthroid has "serious stability or potency problems" that pose potential risks to Synthroid users or in any way cause Synthroid to be a "new drug."

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March, 1993. See id. 43,536-37; the PBI warning letter is attached as part of Exhibit 13. FDA's second "reformulation" example is an article by Das Gupta et al., which reports chromatographic variations in one NaLT4 product "suggesting that different excipients" had been used. Notice at 43,536 and Ref. 5. While the authors do not identify that product by name, Synthroid can be ruled out based on the absence of any formulation changes during the relevant period. Note also that the analytical conclusions reported in a preliminary version of that article were challenged at the time by another NaLT4 manufacturer. See Memorandum from Nancy R. Cafmeyer to Bernard B. Wolfson, Ph.D., Sept. 27, 1990. Exhibit 24; this memorandum was prepared by Daniels Pharmaceuticals, Inc. (manufacturer of Levoxine), and was submitted in 1990 to the Massachusetts Department of Public Health in connection with state formulary deliberations.

97. Notice at 43,537.

98. See id. at 43,536-37.

99. FDA obviously is aware of the identity of the products and manufacturers in question, even though it has chosen not to name them in the Notice. Knoll's basis for concluding that incidents not discussed in this Citizen Petition involved products other than Synthroid is attached as Exhibit 25.

For example, FDA asserts that "[f]rom 1990 to 1992, the firm destroyed 46 lots of levothyroxine sodium tablets that failed to meet potency or content uniformity specifications during finished product testing."<sup>100</sup> The fact that out-of-specification batches are rejected before release because they do not meet internal control limits does not mean that product manufacture is not properly controlled.<sup>101</sup> To the contrary, it appropriately reflects the fact that - like all other drugs - Synthroid is subject to FDA's CGMP regulations, which impose manufacturing standards designed to ensure (among other things) the potency and stability of finished drug products.

In accordance with those standards, all lots of Synthroid tablets are tested before release to ensure that they meet all USP compendial standards as well as Knoll's own internal standards or control limits, which are more stringent than the USP's in some regards, particularly with respect to potency. Indeed, virtually every batch that was rejected for failure to meet the company's internal potency standard from 1992 to the present also clearly would have been releasable under the corresponding USP specifications.<sup>102</sup> Rejection of Synthroid tablets that fail to meet internal standards is a routine GMP procedure designed to protect the public health, and not a potential health concern as FDA seems to suggest.

FDA's suggestion that Synthroid cannot be GRAS/E because of rare past recalls is equally unconvincing, for similar reasons. The specific Synthroid recalls cited in FDA's notice all occurred prior to 1992. None was a Class I recall. One was not a recall at all, but a voluntary market withdrawal. The other two were classified by FDA as Class II recalls, i.e., situations in which use of the product may cause temporary or medically reversible adverse health consequences, or where the probability of severe adverse health consequences is remote. None was the subject of subsequent enforcement action by FDA. All were followed by extensive investigation by the company and, as needed,

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100. Notice at 43,537.

101. In recent Human Drug CGMP Notes, CDER's Division of Manufacturing and Product Quality advised that it is not always necessary to note on a Form 483 situations in which a distributed product failed a company's internal release specifications but complied with USP requirements. 5 Human Drug CGMP Notes No. 4 (Dec. 1997), 3, Exhibit 26. A fortiori, a product which fails internal specifications but meets USP standards and is not distributed need not be noted on a Form 483 and does not constitute a violation of CGMP.

102. The sole exception was one batch in which a weighing error resulted in high potency.

implementation of improved manufacturing processes and controls. Far from evidencing ongoing "problems," such changes exemplify the fundamental goal of FDA's CGMP regulation: to establish and encourage the continuing evolution of manufacturing processes and controls that are both "current" and "good."

Voluntary product recalls are an accepted mechanism used by manufacturers of new and old drugs alike to minimize potential health risks from unexpected manufacturing problems that may occur with particular product lots despite the use of good manufacturing practices. Indeed, a major purpose of the CGMP requirements dealing with potency and stability testing is to ensure that manufacturers will have the information needed to recognize and recall products that may not remain potent throughout their labeled shelf life. GRAS/E "old" drugs certainly are not transformed into "new drugs" by virtue of product recalls, any more than an approved NDA guarantees that a product will remain forever recall-free.

In short, the "stability problems" recited in FDA's Notice merely illustrate that levothyroxine sodium tablet potency and stability already are closely scrutinized and regulated by FDA under its existing power to monitor and enforce CGMP compliance. As part of the CGMP process, the company has provided FDA with extensive data to demonstrate that the processes and controls used to manufacture Synthroid are adequate to ensure product potency and stability within compendial standards.<sup>103</sup>

Synthroid potency and stability are clearly demonstrated by Knoll's review of data on 320 lots of Synthroid tablets manufactured and monitored on stability study since 1991, none of which have had any failure to meet specifications.<sup>104</sup> Furthermore, Knoll's review of manufacturing records for more than 2000 lots of Synthroid tablets released to the marketplace from January, 1993 to August, 1997 indicates that all lots exceeded USP requirements at the time of manufacture and released for distribution. In sum, Synthroid has, in fact, been "shown to demonstrate consistent potency and stability." The critical

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103. To name only a few examples, in the period since 1992 (where FDA's "new information" about Synthroid stops) the company has provided FDA with extensive long-term stability studies on all Synthroid strengths, as well as a comprehensive process revalidation study on every stage of Synthroid manufacture.

104. Stability data on product stored at room temperature (25 degrees C) reveal no product failures through the expiration period for product packaged in foil/foil pouches, and for product packaged in 100 or 1000 count bottles. A special stability study on Synthroid tablets stored at 30 degrees C showed all lots stable through 18 months.

factual premise for FDA's call for new drug applications is therefore plainly inapplicable to Synthroid.

#### V. Conclusion

When all is said and done, it is inescapable that Synthroid is, in fact, a prototypic "old drug." It is generally recognized as safe and effective for treatment of hypothyroidism by leading thyroid experts on the basis of numerous adequate and well-controlled studies in the published literature. Experts also generally recognize Synthroid as safe and effective on the basis of long and successful use in millions of patients. Unless the concept of general recognition is to be read out of the statute, Synthroid must be determined to be GRAS/E.

Nothing that FDA has invoked as so-called "stability and potency problems" undercuts that conclusion. As a matter of law, the Food, Drug, and Cosmetic Act does not provide for the regulation of these sorts of issues by making them part of the definition of general recognition. Rather, the Act provides for them to be dealt with under section 501 and other provisions applicable to all drugs, old and new; and FDA has successfully used these provisions to regulate the manufacture of levothyroxine sodium, including Synthroid, and other drugs, new and not new. Finally, Synthroid is both potent and stable. Whatever may be the case with other products, there is no need for FDA to seek additional (and unwarranted) authority to regulate Synthroid.

Accordingly, Knoll requests the Commissioner to issue the requested order declaring that Synthroid is generally recognized as safe and effective, and therefore not subject to regulation as a new drug under the act.

#### VI. Environmental Impact

Petitioner claims a categorical exclusion from the requirement of an environmental impact assessment under 21 C.F.R. § 25.24(a)(1) and, by analogy, §§ 25.24(c)(1) and (6).

VII. Certification

The undersigned certify that, to the best knowledge and belief of the undersigned, this petition includes all information and views upon which the petition relies, and that it includes representative data and information known to the petitioner which are unfavorable to the petition. The undersigned further certify that this petition includes all studies and information specified as required for determination of GRAS/E status under section 314.200(d).

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