



APR 26 2001

Mr. Gary D. Dolch
Dr. Melvin K. Spigelman
Mr. Jeffrey A. Staffa
Knoll Pharmaceutical Company
3000 Continental Drive North
Mt. Olive, NJ 07828-1234

Re: Docket No. 97N-0314/CP2

Dear Messrs. Dolch and Staffa and Dr. Spigelman:

This responds to your citizen petition concerning Synthroid dated December 15, 1997, and supplemented on May 29, 1998, November 17, 1999, and December 18, 2000. The agency has relied on trade secret and confidential commercial information belonging to Knoll in preparing its response. This information has been placed in a confidential appendix that will not be placed in the public docket with this letter.

On August 14, 1997, the Food and Drug Administration (FDA) published a *Federal Register* notice announcing that orally administered levothyroxine sodium drug products are new drugs and require approved applications as a condition of marketing (62 FR 43535) (1997 notice).¹ While that notice announced FDA's conclusions about the currently marketed levothyroxine sodium products as a class, it provided that if the manufacturer of a particular orally administered drug product containing levothyroxine sodium contends that the drug product is not subject to the new drug requirements of the Federal Food, Drug, and Cosmetic Act (the Act), this claim should be submitted in the form of a citizen petition under 21 CFR 10.30.

Your petition requests that FDA issue an order determining that Synthroid brand orally administered levothyroxine sodium USP is generally recognized as safe and effective (GRAS/E) for the treatment of hypothyroidism² and for thyroid cancer³ within the meaning of section 201(p) of the Act (21 U.S.C. section 321(p)) and, therefore, not subject to regulation as

¹ The 1997 notice provided that manufacturers who were marketing levothyroxine sodium products on or before August 14, 1997, could continue to market their products without approved applications until August 14, 2000. A subsequent *Federal Register* notice extended this date to August 14, 2001 (65 FR 24488; April 26, 2000).

² Specifically, the petition requests GRAS/E status for Synthroid as "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" (Petition at 1-2).

³ A supplement to the petition dated May 29, 1998, asked FDA to rule that Synthroid is GRAS/E "[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" (Supplement at 2).

a new drug. You ask FDA to rule that Synthroid may legally be marketed without an approved application. You also ask that FDA waive the requirements of 21 CFR 314.126 for adequate and well-controlled studies to the extent necessary to accept the studies submitted with the petition as substantial evidence of effectiveness. The 1997 notice stated that "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" (62 FR 43535 at 43538). You argue that this conclusion "misconceives the applicable law and is factually wrong as to Synthroid" (Petition at 3).

For the reasons discussed below, your petition is denied.

I FDA Has the Authority To Declare Synthroid a New Drug

Under section 201(p) of the Act, a drug product is classified as a new drug unless its manufacturer can show that (1) its composition is such that the drug product is "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" and (2) it has "been used to a material extent" and "for a material time under such conditions." Based on our review of available evidence, you have not satisfied FDA that both of these conditions have been met for Synthroid.

You argue that "section 201(p) of the FDCA [the Act] has to do with general recognition of safety and efficacy, as demonstrated in published studies, not with general recognition of manufacturing quality" (Petition at 3). However, the definition of "new drug" refers to drug products, not active ingredients. Only drug products, not active ingredients, can be evaluated under "the conditions of use . . . suggested in the labeling" as the statute requires. Moreover, there is nothing in the statutory definition of "new drug" at section 201(p) of the Act that limits FDA's legitimate areas of inquiry to only certain kinds of information about a drug product's safety or effectiveness. Rather, as the Supreme Court held in *Weinberger v. Bentex Pharmaceuticals, Inc.*, 412 U.S. 645, 652 (1973), "the reach of scientific inquiry under both § 505(d) and § 201(p) is precisely the same." Just as § 505(d)(3) requires FDA to refuse to approve an application where "the methods used in, and the facilities and controls used for, the manufacture, processing, and packing of such drug are inadequate to preserve its identity, strength, quality, and purity," so too can inadequate manufacturing and controls defeat a drug's GRAS/E status. Even if an active ingredient has been previously approved as safe and effective in another drug product, a drug product is considered a "new drug" if the particular formulation of active and inactive ingredients has not previously been approved or has not been found to be GRAS/E. See *United States v. Generix Drug Corp.*, 460 U.S. 453 (1983) (holding that "new drug" refers to a finished drug product, not an active ingredient). Your suggestion

that FDA is limited in determining if a drug product is a “new drug” to consulting published studies for evidence of safety or effectiveness has no basis in law and is contrary to the broad remedial purposes of the Act. The definition of “new drug” must be liberally construed in order to effectuate the policy of the statute, which is the protection of public health and safety (*United States v. An Article of Drug . . . Bacto-Unidisk*, 394 U.S. 784, 798 (1969)). Furthermore, “Congress’ exclusion of ‘generally recognized’ drug products from the definition of a ‘new drug’ is a very narrow one” (*Premo Pharmaceutical Laboratories v. United States*, 629 F.2d 795, 802-803 (2d Cir. 1980)). See also “Positron Emission Tomography Drug Products; Safety and Effectiveness of Certain PET Drugs for Specific Indications” (65 FR 12999, 13002; March 10, 2000) (Congress recognized that PET drugs are new drugs because variations in manufacturing procedures can significantly affect identity, strength, quality, and purity).

You argue that “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’” (Petition at 3). This argument implies that because the FDA could bring an action under the adulteration provision of the Act, and has in the past dealt with deficiencies in current good manufacturing practice for levothyroxine sodium products as a compliance matter, it is precluded from bringing an action under the Act’s new drug provisions. To the contrary, FDA is not required to choose between finding current good manufacturing practice violations and finding that a drug is a “new drug” that requires an approved application to be legally marketed. As the court in *United States v. Baxter Healthcare Corp.*, 901 F.2d 1401 (1990) stated:

Much of Baxter’s argument appears to rest on the inaccurate view that the courts may not allow federal agencies to use more rigorous methods of enforcement of a statutory scheme when less rigorous methods would also be allowable under the statute. The fact that some of FDA’s goals could be accomplished through the enforcement of “good manufacturing practices” standards does not mean that the FDA may not use its authority under Section 507(a) [now section 505] (901 F.2d at 1409)

See also *United States v. Premo Pharmaceutical Labs, Inc.*, 511 F. Supp. 958, 976 (D.N.J. 1981) (holding that postmarketing enforcement tools are not an adequate substitute for the drug application review process in protecting public health).

Moreover, FDA’s regulations make clear that a contention that a drug product is GRAS/E under section 201(p) must be “supported by submission of the same quantity and quality of scientific evidence that is required to obtain approval of an application” (21 CFR 314.200(e)(1)). Given this provision, just as a drug product application must be supported by

data showing consistency, potency, and stability, so must a contention that a drug product is GRAS/E. See 21 U.S.C. 505(d)(3); 21 CFR 314.125(b)(1) (authorizing FDA to refuse to approve an application where methods of manufacture, facilities and controls are inadequate to preserve identity, strength, quality and purity).

The fact that the Agency issued its notice on a class-wide basis does not change the fact that it is a particular formulation, not an active ingredient, for which an approved application or a GRAS/E showing is required. FDA's notice stated the Agency's willingness to rely on published literature in place of clinical studies performed by the sponsor to support one requirement for approval, but did not indicate that published literature alone would be sufficient to support a finding that any particular product is safe and effective under the conditions of use prescribed in its labeling. To the contrary, because the potency and stability problem with levothyroxine sodium was found to be class-wide, the Agency adopted a procedure that addresses the problem on a class basis by declaring that all oral levothyroxine sodium drug products are new drugs that require approved applications to be legally marketed. FDA's class-wide approach, however, does not give companies license to establish the safety and effectiveness of their drug products by showing the safety and effectiveness of the active ingredient alone. Applications are approved for drug products, not for drug ingredients. A company seeking to show that a drug product is GRAS/E cannot rely solely on literature establishing the safety or effectiveness of its active ingredient. It must show that its *product* as currently formulated is GRAS/E for the labeled indication. Given the documented history of potency and stability problems, and the dangers of under- and over-dosing, a GRAS/E showing for a levothyroxine sodium product would necessarily include a showing of consistent potency and stability. As discussed above, FDA has ample authority under the Act to take this approach.

II. Synthroid Cannot Be Generally Recognized as Safe and Effective Because It Is of No Fixed Composition

Although FDA has documented potency and stability problems for marketed levothyroxine sodium products as a class, the difficulties in finding Synthroid to be GRAS/E are compounded by the fact that its formula has been changed numerous times throughout its marketing history. A new drug is defined as a 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 . . ." or which, if so recognized "has not . . . been used to a material extent or for a material time" (21 U.S.C. 321(p) (*Emphasis added*)). To be generally recognized as safe and effective, there must be some consistent drug product for experts to recognize. In the case of Synthroid, there is no such consistent product because the composition of Synthroid has been changed repeatedly.

Synthroid tablets have been manufactured using an overage⁴ of the active ingredient that has ranged in size over the last 35 years. In addition to overage changes, FDA is aware of several other changes made to the composition of Synthroid since 1981.⁵

- Synthroid was reformulated in 1981.
- In 1983, an excipient was added to the 50 microgram (mcg) tablet.
- In February 1989, the dye for the 112 mcg tablet was changed.
- In August 1989, dyes for the 100 mcg tablet and the 300 mcg tablet were changed.
- In 1991, an excipient was removed from the 50 mcg tablet.

In support of its characterization of Synthroid as the "quintessential 'old drug,'" the petition states that "the current Synthroid formulation has been *fundamentally* unchanged since 1982"⁶ (Petition at 13, *emphasis added*). However, two formulations that are only basically the same are not the same drug product. "[T]he composition of the drug *is* relevant to the determination of new drug status. It is the particular composition of the drug which must be generally recognized as safe and effective in order to take the drug out of the statute" (*United States v. An Article of Drug . . . Atropine Sulfate*, No. CA3-85-1662-R (N.D. Texas, 1987), *aff'd*, 843 F.2d 860 (5th Cir. 1988)). Studies conducted on an old formulation have been held to be "an inadequate basis for drawing conclusions" about a subsequent formulation (*United States v. 225 Cartons . . . Fiorinal*, 871 F.2d 409, 414 (3rd Cir. 1989)). For this reason, FDA regulations specify: "For an investigation to be considered adequate for approval of a new drug, it is required that the test drug be standardized as to identity, strength, quality, purity, and dosage form to give significance to the results of the investigations" (21 CFR 314.126(d)). Because the formulation of Synthroid has been repeatedly changed, the published literature

⁴ An overage is the amount of active ingredient above 100% of the product's labeled potency at the time the finished product is tested for release. Such an overage is intended to compensate for potential loss of active ingredient by degradation while the product is stored and thus permit an extended shelf life for a product with a poor stability profile.

⁵ These are the changes the Agency is aware of through inspections and from documents submitted by the manufacturer. Because manufacturers of products marketed without approved applications are not required to seek permission to make formulation changes, there may be additional changes which have not been disclosed to the Agency.

⁶ The petition also states that "[t]he only formulation change made [between 1982 and December 15, 1997] 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" (Petition footnote 94).

submitted in support of Knoll's petition is an inadequate basis to draw conclusions about the potency and stability of its existing formulation. It should also be noted that had Knoll been marketing Synthroid under an NDA, it would have been required to obtain preapproval from FDA before making formulation changes (see 21 U.S.C. § 356a as implemented in the guidance for industry on *Changes to an Approved NDA or ANDA* (November 1999)). FDA has cited manufacturers of approved products for marketing an unapproved new drug when they make changes that require FDA preapproval without having obtained such preapproval.⁷ If an approved product becomes an unapproved new drug under these circumstances, then certainly the changes that have been made to Synthroid reinforce its "new drug" status. Only a drug product of a precise composition is approved in an NDA. Similarly, it can only be a drug product of a precise composition about which there might be general recognition of safety and effectiveness. See generally *United States v. Generix Drug Corp.*, 460 U.S. 453 (1983) (differences in excipients may affect the safety and effectiveness of drug products; a product (not merely its active ingredient) is a new drug until the product no longer meets the definition of new drug).

III. Synthroid Has a History of Problems

You assert that Synthroid has a "long history of careful and consistent manufacture, resulting in a reliably stable and potent levothyroxine sodium drug" (Petition at 3). In fact, Synthroid has a long history of manufacturing problems as discussed below. In August 1989, Knoll⁸ initiated a recall of 21 lots of Synthroid tablets in unit dose packaging because of a decrease in potency during stability studies.

In February 1991, 26 lots of Synthroid tablets packaged in hospital unit dose blister packs in strengths of 50, 75, 100, 112, 125, 150, 200, and 300 mcg were recalled because of subpotency. In an April 1991 inspection of the Synthroid manufacturing facility, FDA cited the firm for two deviations from current good manufacturing practices: inadequate validation of a blender and failure to monitor adequately the humidity and temperature in the manufacturing area. The inspector recorded the following observation on the FDA Form 483 issued to the firm:

"The humidity and temperature in the firm's manufacturing area are not monitored at a continuous basis. A drum with a subplot product . . . waiting to be mixed in the [name] mixer was observed uncovered and the product exposed to the ambient. Also the [described] blender with various sublots products, but not all the sublots required for

⁷ See, e.g., Warning Letter to Elder Pharmaceuticals from FDA's Cincinnati District, August 21, 1991.

⁸ Knoll acquired Synthroid from Boots Company PLC in 1995. Petition at 7. To avoid confusion, we refer to Knoll as the manufacturer of Synthroid regardless of the time period being discussed.

the blending step, was observed opened causing long exposure of the product to the ambient."

This inspection also revealed consumer complaints that Synthroid tablets lacked therapeutic effect. Synthroid tablets were recalled again in June 1991. Fifteen lots of Synthroid tablets in 100 and 1,000 tablet bottles in strengths of 25, 50, and 75 mcg were recalled because the lots were found to be subpotent during stability studies or their potency could not be assured through the expiration date.

FDA inspected the Synthroid facility again from October through December, 1992, because the Agency had observed an increase in the frequency of complaints concerning Synthroid. Knoll received 27 complaints in 1991 and 33 complaints in 1992 questioning the potency of Synthroid tablets. FDA's inspection recorded nine observations of failure to follow current good manufacturing practices, briefly summarized below. Knoll lacked adequate production and process control procedures to ensure batch-to-batch uniformity and homogeneity of Synthroid 25, 50, 75, and 100 mcg tablets. FDA also found that the firm had continued to manufacture and distribute low dosage Synthroid tablets during 1990, 1991, and 1992. The firm had failed to identify the causes for the stability failures that resulted in the recall of 21 lots of Synthroid tablets in August 1989, 26 lots in February 1991, and 15 lots in June 1991. The firm had failed to identify the causes for the potency or content uniformity failure of 46 lots of Synthroid tablets manufactured from 1990 through 1992 that it destroyed. The firm had failed to properly investigate in-process failures. The firm had failed to conduct adequate stability studies. The firm had not validated a variety of changes to the formulation and manufacturing processes for Synthroid.

In January 1994, FDA inspected the Shreveport, Louisiana, facility where stability testing of Synthroid was conducted and found that Knoll failed to assay some lots of Synthroid for stability at the interval required by the firm's protocol. In November 1998, Knoll recalled 18 lots of Synthroid tablets in 88, 100, 150, 175 mcg strengths because potency could not be assured through the expiration date.

The history of potency failures discussed above indicates that Synthroid has not been reliably potent and stable. Furthermore, Knoll's use of an overage that has not remained consistent over the years suggests that Synthroid has stability, potency, and consistency problems. Although you claim that Synthroid has been carefully manufactured, the violations of current good manufacturing practices discussed above indicate that Knoll has not always manufactured Synthroid in accordance with current standards for pharmaceutical manufacturing.

IV. Patients Need a Precise Dose of Levothyroxine Sodium

The effect of changes to Synthroid's formulation and Knoll's distribution of low potency

tablets is that patients taking Synthroid have experienced significant, unintended variations in their doses of levothyroxine sodium. As discussed below, these variations are not conducive to proper control of hypothyroidism.

Levothyroxine sodium is used as replacement therapy when endogenous thyroid hormone production is deficient or absent. The goal of thyroid replacement therapy is to replace the same amount of thyroid hormone that would have been present naturally. This amount differs from patient to patient. When a patient is newly diagnosed as needing replacement hormone, he or she is given an initial estimated dosage. In most patients, the response to treatment is assessed by the measurement of serum levels of thyroid stimulating hormone (TSH). The dosage of replacement therapy is increased in gradual increments until the TSH test indicates the correct maintenance dosage has been achieved. In order to allow for fine adjustments of dose, which are necessary due to levothyroxine sodium's narrow therapeutic range, levothyroxine sodium products are marketed in an unusually large number of dosage strengths. Synthroid, for example, comes in 25, 50, 75, 88, 100, 112, 125, 150, 175, 200, and 300 mcg strengths.

Superpotent tablets of levothyroxine sodium pose safety risks. Patients who inadvertently receive more levothyroxine than is necessary to control their condition may experience angina, tachycardia, or arrhythmias. There is also evidence that overtreatment can contribute to osteoporosis. Subpotent tablets of levothyroxine sodium are not adequately effective and, therefore, also pose safety risks. Patients inadvertently receiving less than their proper dose may experience such symptoms as fatigue, lethargy, sleepiness, mental impairment, depression, cold intolerance, hair loss, hoarseness, weight gain, constipation, decreased appetite, dry skin, increased perspiration, arthralgia, menstrual disturbances, and paresthesias. Because of the serious consequences of too much or too little circulating thyroxine, it is very important that patients receive the dose of levothyroxine sodium determined by their physicians to be optimal to replace the amount of hormone that would have been present naturally.⁹

The physician's reliance on the results of a TSH test to establish the optimal amount of replacement therapy is undercut when patients do not get the correct dose when filling and refilling their carefully calculated prescriptions. When patients receive tablets that are filled with a product of unpredictable potency, therapy with levothyroxine sodium is neither safe nor effective. Hypothyroidism is a chronic condition, and therefore patients may take Synthroid for many years. If Synthroid continues to be marketed without an approved application, patients may be subject to future formulation changes that could affect the bioavailability of the product without notice or prior FDA approval.

⁹ The December 15, 1997, Petition itself states: "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" (Petition at 21, footnote 67).

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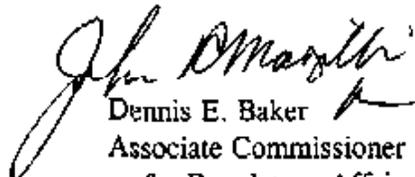
V. **The Evidence Submitted with the Petition Does Not Demonstrate that Synthroid Is Generally Recognized as Safe and Effective**

You present published studies and testimony from experts to demonstrate that Synthroid is generally recognized on the basis of these studies as safe and effective for the treatment of hypothyroidism and thyroid cancer. This evidence fails to address the potency and stability problems that impair the safety and effectiveness of Synthroid and does not address how changes in Synthroid's formulation undercut a finding that the marketed drug product (as currently formulated) has been marketed to a material extent and for a material time. Therefore, it does not establish that Synthroid is generally recognized as safe and effective. Given that manufacturing issues preclude a finding that Synthroid is generally recognized as safe and effective, FDA does not need to rule on your request to waive the requirements for adequate and well-controlled studies in making a GRAS/E finding.

VI. **Conclusion**

For the reasons discussed above, your request that FDA issue an order determining that Synthroid is generally recognized as safe and effective for the treatment of hypothyroidism and thyroid cancer is denied. FDA concludes that Synthroid is a new drug within the meaning of section 201(p) of the Act. It is, therefore, subject to section 505 of the Act and must comply with the provisions of the August 14, 1997, *Federal Register* notice, as amended in the *Federal Register* of April 26, 2000 (65 FR 24488).

Sincerely yours,


Dennis E. Baker
Associate Commissioner
for Regulatory Affairs



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1141 Central Parkway
Cincinnati, OH 45202

August 20, 1991

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WARNING LETTER
CIN-WL-91-678

Adam Jerney, President
Elder Pharmaceuticals, and S.P.I. Pharmaceuticals, Inc.
ICN Plaza
3300 Hyland Avenue
Costa Mesa, California 92626

Dear Mr. Jerney:

The Food and Drug Administration has completed the review of the inspectional findings from the inspections of April 4, 8 and May 6, 1991 and on June 28 through July 23, 1991. We have additionally evaluated the August 6, 1991 response to our inspections, provided by Stephen J. Goldner, Acting Vice-President, Regulatory Affairs.

Mr. Goldner stated that the following information will be submitted to the FDA:

1. Data from historical finished product batch demonstrating product integrity (Benoquin Cream), in the absence of
2. A current bill of material specifying the amount of added to account for manufacturing process losses.
3. Documentation for improved manufacturing instructions for providing increased specificity in the stepwise process.
4. A copy of the manufacturing instructions that specify mixer type, the size and number of propellers and the speed range setting.
5. A bill-of-material specifying quantities of components, manufacturing instructions specifying equipment, and validation data to justify the

proper identity, strength, quality and purity of the product manufactured according to the current lot size.

6. Documentation that the equipment used to manufacture Benoquin is capable of producing the batch size.

7. Documentation to describe the action steps to be taken if stability test results fail out of specifications.

8. A copy of the revised Standard Operating Procedure for stability testing to include tolerance providing for scheduling conflicts and Sampling periods.

It is our view that the failure to address these issues in a supplement to your new drug application in conformance with 21 CFR 314.70 causes the product to be an unapproved new drug. Your failure to promptly make the corrections as pointed out in your August 6, 1991 response to our issuance of the FD-483, may result in regulatory action.

Your current pending supplement to include as a supplier of the active ingredient will not be further processed until the agency receives and evaluates the supplemental data as outlined in your 8-6-91 response.

It should also be understood that if after your submission to the Agency, as outlined in your August 6, 1991 response, all questions have not been answered, the Food and Drug Administration may request additional information to verify conformance to the requirements in the NDA.

The information requested should be provided within fifteen (15) working days of receipt of this letter. If the submission cannot be provided within fifteen (15) working days state the reason for the delay and the time within which it will be provided.

Sincerely,

James C. Simmons
District Director
Cincinnati District

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