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VIA FACSIMILE (301) 594-6197
AND FEDERAL EXPRESS

Ms. Jane A. Axelrad
Associate Director for Policy
Center for Drug Evaluation and Research
Food and Drug Administration
Room 6027, HFD 001, WOCII
1451 Rockville Pike
Rockville, MD 20852

Dear Ms. Axelrad:

On behalf of our client, Jerome Stevens Pharmaceuticals, Inc. ("JSP")[1], we are writing to request that the Food and Drug Administration immediately withdraw Synthroid® from the market due to significant public health concerns identified by the agency. In addition, we are also requesting written confirmation that, at a minimum, the agency will comply with the legally binding approval deadline established by the agency for levothyroxine sodium drug products. Finally, we also urge the agency to issue immediately a press release or other form of public communication addressing these issues.

We believe public health concerns identified by the agency and legal criteria imposed by the courts mandate the immediate removal (e.g. within a couple of months and certainly prior to August 14, 2001) from the market of all levothyroxine sodium drug products not already approved by the agency via the NDA process, and in particular the immediate removal from the market of Synthroid® - which the agency recently determined poses significant health risks to consumers and is not "generally recognized as safe and effective" ("GRAS/E").

As you are aware, on August 14, 1997 the agency published a Federal Register notice announcing that manufacturers who were marketing levothyroxine sodium drug products on or before

[1] JSP currently has the only approved NDA for a levothyroxine drug product, which is known as Unithroid®.

August 14, 1997 could continue to market their products without approved applications until August 14, 2000 (62 Fed.Reg. 43535). A subsequent Federal Register notice, issued on April 26, 2000, extended this date to August 14, 2001 (65 Fed.Reg. 24488). Both Federal Register notices clearly and unambiguously established a deadline for requiring marketing applications to be approved by the agency as of the established dates, or else they would be removed from the market. Statements in Federal Register notices have the force of law and, unlike guidance documents[2], the agency is obligated to comply with legal standards enunciated in such notices.[3]

FDA regulations, however, provide that in situations involving an immediate and significant danger to health, the agency may amend or revoke legal standards enunciated in formal agency Federal Register notices in order to protect public health.[4] In the instant case, the agency recently identified significant public health risks posed by continued marketing of Synthroid® - and possibly other levothyroxine sodium drug products that have not obtained NDA approval. Specifically, in the agency's April 26, 2001 letter to Knoll Pharmaceutical Company, rejecting Knoll's Citizen Petition, the agency concluded that Synthroid® is not GRAS/E. In reaching this conclusion, the agency indicated the following:

- "Synthroid cannot be generally recognized as safe and effective because it is of no fixed composition."
- "Synthroid tablets have been manufactured using an overage of the active ingredient that has ranged in size over the last 35 years."
- "Synthroid has a history of problems" [documenting repeated recalls, consumer complaints, significant stability problems, potency problems, and general manufacturing problems associated with Synthroid].
- "The history of potency failures discussed above indicates that Synthroid has not been reliably potent and stable."
- "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....these variations are not conducive to proper control of hypothyroidism."

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[2] Guidance documents do not create or confer any rights for or on any person and do not operate to bind FDA or the public. To the extent a guidance document may be interpreted (rightly or wrongly) as being inconsistent with official agency policy as established in a Federal Register notice, the Federal Register notice would clearly establish the agency's official and legally binding opinion. Moreover, it would be incumbent upon a company to clarify with the agency an alleged inconsistency between a guidance document and established legal standards enunciated in a Federal Register notice.

[3] 21 C.F.R. § 10.85(e).

[4] 21 C.F.R. § 10.85 (f).

- "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."

Based upon the above conclusions, we believe public health is jeopardized by permitting the continued marketing of Synthroid® until the August 14, 2001 NDA approval date established by the agency. We therefore urge the agency to immediately withdraw Synthroid® from the market. Such withdrawal would protect the public health and would avoid the perpetuation of the type of poor thyroid treatment documented by the agency that unfortunately has become commonplace throughout the country due to Synthroid's® significant market share.

Immediate withdrawal of Synthroid® is also supported by the ten month standard review period that it expected for the agency to review a Synthroid® NDA, as in essence this means that NDA approval by the August 14, 2001 deadline would not be achievable (assuming public reports are accurate and Knoll had not submitted an NDA prior to the agency's April 26, 2001 rejection of its Citizen Petition). Accordingly, because Synthroid® will be legally required to come off the market as of August 14, 2001, there is no reason to jeopardize public health and permit the sale of the product for the additional period of time prior to that date. At a later date, of course, if Knoll can demonstrate to the agency, via the submission and approval of an NDA submitted under Section 505(b)(1) of the Federal, Food, Drug, and Cosmetic Act[5], that Synthroid® is safe and effective and no longer poses potency and stability problems, we would encourage the agency to permit the immediate reintroduction of Synthroid® to the market.[6]

We acknowledge that due to practical considerations it would not be feasible to withdraw Synthroid® from the market tomorrow as our client would need to scale-up its manufacturing facility. By acknowledging and announcing that Synthroid® will be taken off the market imminently, however, our client would be able to initiate scale-up operations to ensure its ability

[5] The agency has indicated that 505(b)(2) applications for levothyroxine sodium will not be accepted after August 14, 2001.

[6] In the alternative, the agency has indicated that an ANDA could be filed demonstrating bioequivalence to the reference listed drug - Unithroid®.

to meet market demand as of August 14, 2001 at the latest (and possibly by as early as July 14, 2001 if notice of Synthroid® withdrawal is provided immediately by the agency).

Importantly, despite the safety concerns identified by the agency, and despite the legal standards established by the agency, Knoll has publicly contended that it only is required to submit an NDA application to the agency prior to August 14, 2001 in order to remain on the market. Specifically, according to the May 7, 2001 "Pink Sheet," Knoll's position is that if an NDA for Synthroid is filed by August 14, 2001, the NDA would be subject to a standard ten-month review and that there is "no chance that the product would have to come off the market in August."

This contention by Knoll is not only entirely inconsistent with the law and FDA's obligation to protect the public health, but also conflicts with the agency's response to the Citizen Petition filed by our client[7]. Specifically, on February 2, 2001, the agency responded to our client's Citizen Petition and indicated that "[a]t present, the August 14, 2001, deadline remains in place, and FDA has no plans to extend the date by which levothyroxine sodium products must have approved applications." Certainly no unforeseen circumstances have arisen that would compel the agency to extend the deadline and only require NDA filing prior to August 14, 2001; as noted above, recent factual developments could only compel the agency to accelerate the withdrawal process in order to protect the public health consistent with the agency's statutory obligations.

We believe it is imperative that Knoll's public contentions be repudiated immediately as failure to do so would continue to mislead the public and health care professionals, encourage continued use of a drug product that has never been approved by the agency, and impede the process of switching patients from Synthroid® to other levothyroxine sodium drug products that have been approved by the agency via the NDA process. We therefore believe an immediate written response from the agency to the issues identified in this letter, including a public statement, are necessary.

In conclusion, failure to immediately remove Synthroid® and all other levothyroxine sodium drug products from the market that have not received NDA approval, and certainly failure to comply with the legally binding August 14, 2001 NDA approval date (and therefore failure to withdraw Synthroid® from the market on August 14, 2001 if an NDA for the product has not been approved by the agency), would jeopardize public health, violate FDA statutory and regulatory obligations, and expose the agency to immediate judicial review and public scrutiny.

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[7] Knoll's contention also conflicts with your verbal assurance to one of my colleagues that the agency intends to comply with the legal standards enunciated in Federal Register notices, and will withdraw from the market any levothyroxine sodium drug product that has not obtained NDA approval as of August 14, 2001.

Thank you for your consideration of these issues. If you have any questions, please feel free to call me at 202-457-5240.

Very truly yours,

Stuart M. Pape (PQR)

Stuart M. Pape

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