



APR 26 2000

Food and Drug Administration
Rockville MD 20857

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

Re: Docket No. 97N-0314/CP3

Dear Drs. Dolch, Spigelman, and Staffa:

This letter responds to the September 25, 1998, citizen petition submitted by Knoll Pharmaceutical Company (Knoll) and supplemented on August 4, 1999, and on November 9, 1999. The citizen petition requests that the Food and Drug Administration (FDA) resolve several scheduling and procedural issues relating to the submission of applications for levothyroxine sodium products. This petition is referred to in this response as the "scheduling petition" to distinguish it from other petitions in this docket. For the reasons discussed fully below, Knoll's scheduling petition is granted in part and denied in part.

In the scheduling petition, Knoll contends that the schedule FDA announced in the August 14, 1997, *Federal Register* notice (62 FR 43535) (1997 notice) is unfair to Knoll because the schedule did not permit enough time for Knoll to receive a response to its citizen petition arguing that Synthroid is generally recognized as safe and effective (GRAS/E petition) before requiring Knoll to submit a new drug application (NDA). Knoll contends that waiting for FDA's answer to its GRAS/E petition made it impossible for Knoll to submit an NDA by August, 1999, the target date by which Knoll suggests an NDA would have to have been submitted in order to be approved by the August 14, 2000, date specified in the 1997 notice.

Knoll also argues that the timing problem was compounded by FDA's alleged failure to provide a timely response to its Freedom of Information Act (FOIA) request, submitted on September 12, 1997. Knoll represents that it cannot complete its GRAS/E petition until it receives all of the documents responsive to its FOIA request. Knoll asks FDA not to rule on the GRAS/E petition until Knoll has the opportunity to supplement it based on the additional documents received in response to its FOIA request.

In addition to the above scheduling issues, Knoll states its belief that FDA intends to review only one application as an NDA while requiring other applications to be submitted, reviewed, and approved through the abbreviated new drug application (ANDA) review process. Knoll suggests that such an approach would depart from the procedure announced in the 1997 notice and would "unfairly and unlawfully" compound the scheduling difficulties that Knoll currently faces.

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To resolve these issues, Knoll asks FDA to modify the schedule in the 1997 notice to state a date by which NDAs must be received by the Agency, not a date by which they must be approved. Knoll requests that the Agency set a date for receipt of applications that is at least 6 months after FDA rules on Knoll's GRAS/E petition and the courts have completed their review of FDA's decision, and at least 6 months after FDA has declared that all applications filed pursuant to the 1997 notice will be filed, reviewed, and approved (if warranted) as NDAs. Knoll further requests that FDA confirm that it will allow Knoll at least 60 days to supplement its GRAS/E petition after Knoll receives a complete response to its FOIA request. Finally, Knoll asks FDA to declare that any and all applications for levothyroxine sodium products submitted under the 1997 notice will be filed, reviewed, and approved (if warranted) as NDAs, not ANDAs.

Knoll supplemented its scheduling petition on August 4, 1999, with an additional argument in support of allowing Knoll more time to submit an NDA. In that supplement, Knoll notes that FDA published a draft guidance for industry entitled *In Vivo Pharmacokinetics and Bioavailability Studies and In Vitro Dissolution Testing for Levothyroxine Sodium Tablets* (bioavailability guidance) on June 10, 1999. Knoll argues that publication of this draft guidance proves that FDA has not determined the methodology to be used for the required bioavailability study; thus applicants may be required to perform additional studies when the methodology is finalized. In Knoll's view, this alleged indecision on the part of the Agency also justifies departing from the announced schedule.

Knoll supplemented its scheduling petition again on November 9, 1999. The second supplement asks that "FDA declare that it will not refuse to file, review, or approve a § 505(b)(2) application for any levothyroxine sodium product on the ground that FDA has previously approved one or more NDAs for a levothyroxine sodium product" (November 9, 1999, supplement at 2). 21 CFR 314.101(d)(9) provides that FDA may refuse to file a 505(b)(2) application for a duplicate of an approved drug that is eligible for approval under section 505(j) of the Federal Food, Drug, and Cosmetic Act (the Act). Citing this regulation, FDA stated in its draft guidance *Levothyroxine Sodium* (August 1999) (enclosed) that it may refuse to file a 505(b)(2) application for a duplicate of an approved levothyroxine sodium product. Knoll asserts that if FDA were to refuse to file a 505(b)(2) application from Knoll, that refusal would be unlawful because section 314.101(d)(9) is not authorized by the Act.

I. Background

A. 1997 Notice

The 1997 notice addressed a serious public health issue. In that notice, the Agency expressed its concern that product recalls, adverse drug experience reports, and inspection reports

documented widespread problems with the potency and stability of levothyroxine sodium products that resulted in a number of observed clinical problems. As the 1997 notice made clear, inadvertent substitution of a levothyroxine sodium product of greater or lesser potency than the dose a patient is accustomed to receiving can result (and has resulted) in a range of adverse events, including hypothyroidism and toxic manifestations of hyperthyroidism such as cardiac pain, palpitations, or cardiac arrhythmia.

After reviewing the Agency's information concerning the potency and stability of currently marketed levothyroxine sodium products, FDA concluded that no currently marketed levothyroxine sodium product has demonstrated consistent potency and stability and that no levothyroxine sodium product is generally recognized as safe and effective. To ensure that the stability and potency problems with levothyroxine sodium products are addressed, FDA issued the 1997 notice requiring manufacturers of these products to submit and obtain approved applications for their products.

Because it concluded that levothyroxine sodium products are medically necessary and should not be withdrawn from the market immediately, the 1997 notice gave manufacturers until August 14, 2000 (3 years from the date of the 1997 notice) to prepare and conduct the required studies, to prepare and submit NDAs, and to obtain approval of those applications. During those 3 years, manufacturers would be permitted to continue marketing orally administered levothyroxine sodium products. The 1997 notice stated that after 3 years, any levothyroxine sodium product that does not have an approved application (or is not found exempt from the new drug requirements) would be subject to enforcement action as an unapproved new drug. The 1997 notice further provided that a manufacturer who contends that its levothyroxine sodium product is not subject to the new drug requirements of the Act should submit its claims in the form of a citizen petition within 60 days of publication of the 1997 notice.

B. September 12, 1997, FOIA Request

In its September 12, 1997, FOIA request, Knoll asked for, with respect to 24 separate items, "any and all documents which, with respect to levothyroxine sodium or any orally administered drug product which contains the drug substance levothyroxine sodium as an active ingredient ('levothyroxine sodium products'), or any other drug products which contain natural or synthetic thyroid hormones as an active ingredient, intended for human use, constitute, identify, discuss or relate or refer to the following or were relied upon, reviewed, or referenced by FDA in connection with the following" Knoll extended the scope of the request in letters dated October 27, 1997, November 3, 1997, February 10, 1998, April 14, 1998, May 12, 1998, December 4, 1998, and December 14, 1998. In sum, Knoll requested every document in the agency's possession that related to levothyroxine sodium or to any other thyroid drug.

By October 30, 1997, 48 days after the request was submitted, FDA had provided more than 900 pages of documents in response to this request. As Knoll elaborated and expanded on its original request, additional documents were provided on January 3, March 12, March 18, and October 16, 1998, and on April 21, 1999. To answer Knoll's request, the Agency conducted an exhaustive search, querying numerous agency components, including several field offices, and retrieving documents going back more than 20 years from FDA's record storage location. On April 28, 1999, FDA informed Knoll that the Agency had given Knoll all of the documents that were disclosable under the FOIA.

On July 29, 1999, Knoll's counsel sent a letter complaining that the Agency's response was deficient because material had been redacted from some documents and because Knoll had not received documents whose existence Knoll posited. On August 4, 1999, Knoll informed FDA that it did not consider the Agency's response to the FOIA request to be complete because the Agency had neither supplied what Knoll regarded as missing documents, nor officially denied Knoll's request for those documents. (August 4, 1999, supplement to the scheduling petition.) On August 19, 1999, the Interim Associate Commissioner for Public Affairs sent a letter to Knoll denying access to documents that are protected from disclosure under 5 U.S.C. 552(b)(4), (5), and (7)(A). Knoll appealed this denial to the Deputy Assistant Secretary for Public Affairs (Media) of the Department of Health and Human Services (HHS) on September 22, 1999. On January 1, 2000, in the United States District Court for the District of Columbia, Knoll brought a complaint for declaratory and injunctive relief against FDA and HHS concerning the September 12, 1997, FOIA request and four additional FOIA requests relating to levothyroxine sodium.

II. Time To Comply with the 1997 Notice

The petition asks that FDA modify the schedule to provide "enough time for all manufacturers, including Knoll, to conduct or locate and include in their applications whatever studies are needed" (Petition at 3-4). On April 26, 2000, FDA published a *Federal Register* notice (65 FR 24488) amending the 1997 notice to permit manufacturers of levothyroxine sodium products to continue marketing these products without FDA approval until August 14, 2001. Assuming that it takes FDA 10 months to review an application, this revised schedule means that manufacturers of levothyroxine sodium products will have had 38 months to consult with FDA about application requirements, plan and conduct a bioavailability study, conduct stability studies, and prepare and submit applications. We believe that is a sufficient amount of time.

FDA denies Knoll's request to set a date by which NDAs must be submitted rather than approved and to have that submission date be determined with reference to Agency and court action on Knoll's two citizen petitions.¹ We believe the additional year the Agency is allowing for all sponsors to obtain NDA approval grants in substantial part Knoll's request for additional time to comply with the 1997 notice.

The 1997 notice stated that a petition claiming exemption from the new drug requirements of the act must be submitted by October 14, 1997. Knoll filed part of its GRAS/E petition on December 15, 1997. When it was submitted, Knoll stated that the GRAS/E petition was not complete; Knoll stated its intention to supplement the petition to address Synthroid's alleged GRAS/E status for thyroid cancer. Knoll submitted the second part of its GRAS/E petition on May 29, 1998. Knoll submitted the third part of its GRAS/E petition on November 17, 1999. This submission made use of the documents Knoll received in response to the FOIA request. Yet Knoll still does not consider its GRAS/E petition complete and ripe for an answer from the Agency.² The Agency can surmise that Knoll does not yet believe that it has sufficient information to establish that Synthroid is GRAS/E, but believes that the GRAS/E status of Synthroid may be revealed in a yet-to-be-disclosed FDA document. However, it is FDA's position that a manufacturer who markets an unapproved drug on the basis that it believes it is exempt from the new drug provisions of the Act (as Knoll has with Synthroid) must be ready to defend that claim at any time. Knoll has marketed Synthroid without an approved application for more than 40 years and is expected to have the information to defend its GRAS/E status already in its possession.

Knoll argues that because the bioavailability guidance was published as a draft, FDA has not determined the methodology to be used for the bioavailability study. Knoll, thus, contends that sponsors may be required to conduct additional studies once the preferred methodology is finalized, and therefore, FDA should allow more time for NDAs to be submitted. This

¹ Knoll asks FDA to set a date by which applications must be submitted, rather than a date by which they must be approved. The 1997 notice declared that levothyroxine sodium products are new drugs and require approved applications. It was only because of the medical necessity of levothyroxine sodium products that FDA gave manufacturers the time it did in which to obtain approvals. FDA's decision to require approval, not merely submission of NDAs, reflects its judgment that mere submission of an application would not address the pressing public health problem.

² Knoll has taken the position that the GRAS/E petition will not be complete until it receives what it regards as a complete response to the September 12, 1997 FOIA request. The August 4, 1999, supplement to the scheduling petition states that FDA's response to the FOIA request is not complete.

reasoning is based on an incorrect assumption. Even if FDA publishes a final guidance that differs from its draft, sponsors who have conducted a bioavailability study using a protocol previously approved by FDA will not be required to conduct additional studies using a different protocol. FDA made this clear in the notice of availability announcing the draft guidance (64 FR 31280; June 10, 1999).

III. Regulatory and Filing Issues

The scheduling petition suggests that all applications for levothyroxine sodium must be accepted for filing as NDAs and that FDA lacks authority to convert subsequent NDAs to ANDAs after the first NDA is approved. Knoll further claims that the statement in the 1997 notice that the Agency was prepared to accept NDAs for levothyroxine sodium products, including 505(b)(2) applications, precludes FDA from requiring applicants to submit ANDAs for levothyroxine sodium products at any time.

The 1997 notice referred only to NDAs because at that time there was no approved levothyroxine sodium product that could serve as a reference listed drug for an ANDA. Once an NDA is approved, that approved application can serve as a reference listed drug. The Act makes the ANDA route available for approval of duplicates of listed drugs, and FDA will accept ANDAs for levothyroxine sodium products. As explained in the enclosed guidance, FDA does not intend to convert filed NDAs to ANDAs. Any NDAs filed before the first NDA is approved will be reviewed under the NDA review process.

IV. 21 CFR 314.101(d)(9)

Knoll's claim that 21 CFR 314.101(d)(9) is unlawful is not relevant to the issues raised in the original scheduling petition.³ Moreover, the potential application of this regulation to Knoll is not ripe for response from the Agency. To date, FDA has not refused to file any 505(b)(2) application for levothyroxine sodium; Knoll has not submitted an application of any kind for its levothyroxine sodium product; and the Agency has not stated that it *will* refuse to file a 505(b)(2) application for a duplicate of a previously approved NDA for levothyroxine sodium eligible for approval under 505(j). The Agency simply pointed out that its authority under section 314.101(d)(9) to refuse to file a 505(b)(2) application could apply to an application for levothyroxine sodium.

³ The original petition only mentioned section 314.101(d)(9) in a footnote, stating that the regulation cannot be invoked against an applicant that does not want its NDA converted to an ANDA.

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V. Conclusion

For the reasons discussed above, the scheduling petition is granted in part and denied in part.

Sincerely yours,



for

Dennis E. Baker
Associate Commissioner
for Regulatory Affairs

Enclosure