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Dockets Management Branch
Food and Drug Administration
5630 Fishers Lane
Room 1061
Rockville, MD 20852

CITIZEN PETITION

SCHEDULING AND PROCEDURE

Docket No. 97N-0314

Knoll Pharmaceutical Company ("Knoll" or "the Company") submits this Citizen Petition under sections 201 and 505 of the Food, Drug, and Cosmetic Act ("FDCA" or "the Act") to request the Commissioner of Food and Drugs ("the Commissioner") to resolve certain scheduling and procedural issues in connection with the Food and Drug Administration's ("FDA" or "the Agency") August 14, 1997 Federal Register notice entitled "Prescription Drug Products; Levothyroxine Sodium," 62 Fed. Reg. 43,535 ("the Notice"). The Notice announced FDA's tentative view that orally administered levothyroxine sodium drug products are new drugs under the Act, and declared that it will be unlawful to market such products on or after August 14, 2000 without an approved new drug application ("NDA").[1] At the same time, recognizing that no NDA is required for a product that is not subject to the Act's new drug provisions, the agency invited any manufacturer to submit a Citizen Petition demonstrating that its product is not a new drug. Knoll submitted such a petition, which asserts that Synthroid® brand levothyroxine sodium USP ("Synthroid") is generally recognized as safe and effective ("GRAS/E") and therefore is not a new drug (the "GRAS/E Petition").[2] Knoll now submits this petition to address certain scheduling and procedural issues in connection with FDA's review of Knoll's GRAS/E petition and any applications submitted under the Notice.

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1. Notice at 43,538.

2. The GRAS/E petition was submitted in two segments: one filed on December 15, 1997 which addressed the product's indication for primary hypothyroidism (97N-0314/CP2), and a supplement filed on May 29, 1998 which addressed the indication for treatment of thyroid cancer (97N-0314/SUP1). The December 15, 1997 petition was submitted on the date agreed to by FDA, see Petition note 3. Knoll reserved in that petition the right to supplement it as to other indications, id. note 2, and FDA was aware that the supplement would be submitted at the time it was. Additionally, both Knoll and FDA contemplate that Knoll will file at least one additional supplement following receipt and review of FDA's complete response to outstanding document requests under the Freedom of Information Act. See discussion infra at 3-4.

97N-0314 CP3

Background

With respect to scheduling, FDA's 1997 Notice stated only that NDAs (if required) must be approved by August 14, 2000 in order for products to remain on the market after that date. While the Notice did not specify a date by which NDAs must be submitted to be assured of receiving timely review and, if warranted, approval, Knoll believes it is reasonable to assume that in general NDA review takes approximately one year.[3] As a practical matter, therefore, an NDA would have to be submitted by August, 1999 in order to meet the specified approval deadline. But, the Notice did not provide a means for integrating the timing of a decision on the Citizen Petition it invited with the timing of an NDA should one be required.[4] Specifically, it did not build in time for a review and decision on any Citizen Petition as solicited by the Notice in advance of the August, 1999 target date for NDA submissions.[5] So Knoll is now confronted with the distinct possibility that in order to ensure continued marketing after August 14, 2000, it must submit an NDA before FDA (and perhaps the courts) have ruled on its GRAS/E Petition, even though no NDA may ultimately be required. For the reasons detailed below, such an outcome would be neither fair nor lawful.

The timing problem already inherent in the Notice has been seriously compounded by FDA's failure to provide a timely complete response to the Freedom of Information Act ("FOIA") request which Knoll submitted on September 12, 1997.[6] In correspondence and discussions with FDA staff beginning shortly thereafter, counsel for Knoll emphasized that the requested documents would be used in preparing Knoll's GRAS/E Petition, and were assured that the company would be given sufficient time to supplement its Citizen Petition after FDA provided a complete response. Knoll believes that FDA does intend to allow it such time, but is becoming increasingly concerned that not enough time has been provided in the overall scheme for FDA to complete its FOIA response, allow Knoll time to review the documents

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3. This estimate reflects FDA's commitments under recent amendments to the Act. Letter from Donna E. Shalala, Secretary of Health and Human Services, to Hon. James M. Jeffords, Committee on Labor and Human Resources, United States Senate (Nov. 12, 1997).

4. Any statements in this petition about the necessity or procedure for future NDA/ANDA submissions do not constitute agreement by Knoll that it is required to submit any such application for Synthroid. To the contrary, Knoll reasserts its contention that Synthroid is generally recognized as safe and effective and therefore not a new drug.

5. The Notice says the agency will respond to Citizen Petitions within 180 days of receipt of the petition as required by § 10.30 (e)(2) of its regulations, Notice at 43,538, but as FDA well knows, that regulation allows the 180 day response to indicate that the agency has not been able to reach a decision. Thus a "response" need not be - and often is not - dispositive.

6. Letter from Nancy L. Buc and Edward J. Parr, Jr. to Ms. Betty Dorsey, Director, Freedom of Information Staff (September 12, 1997) [hereinafter FOIA Request Cover Letter], attaching Letter from Nancy L. Buc and Edward J. Parr, Jr. to Freedom of Information Staff (Sept. 12, 1997) (FOI No. 97-031022) [hereinafter FOIA Request].

and submit a supplement, and then give the supplemented Citizen Petition full and fair consideration - all before Knoll must submit its NDA, if necessary, and still have time for FDA to review and approve it before August 14, 2000.

Knoll and presumably other manufacturers as well have recently learned of a serious additional issue, one that clearly will affect the content and timing of any application submitted in response to the Notice. That issue is the possibility that FDA may be planning to use some new drug approval procedure other than the one specified in the Notice. The Notice specifically requires applicants who wish to market affected products after August, 2000 to submit New Drug Applications. The Notice makes no reference to Abbreviated New Drug Applications ("ANDAs"). However, subsequent communications have indicated that FDA may intend to review and approve only one application as an NDA, while requiring other applications to be submitted and/or reviewed and approved as ANDAs.[7] As discussed below, any such departure from FDA's announced procedure would unfairly and unlawfully compound the scheduling problem Knoll already faces, for it would have significant consequences in terms of Knoll's (and indeed other companies') ability to know what kind of application (NDA or ANDA) will be needed and what kinds of supporting studies it therefore will or will not have to conduct. Moreover, any departure from the announced procedure could place Knoll at a further practical disadvantage by effectively forcing the company to choose between waiving either its right to obtain a final ruling on its GRAS/E petition before seeking any new drug approval, or its right to submit an NDA and not an ANDA if Synthroid is found to be a new drug.

The scheduling issues and the procedural issue are intertwined from the legal and practical standpoints. In addition to the scheduling issues, all manufacturers of levothyroxine sodium - including Knoll - have a right to know exactly what procedure will be used. If the procedure is not what the Notice has led them to expect, they will need time to respond.

A. ACTION REQUESTED

Knoll asks the Commissioner to resolve the concerns outlined above. As to scheduling matters, Knoll asks the Commissioner to modify the schedule contemplated by the Notice to provide enough time for Knoll to supplement its GRAS/E Petition after FDA has provided a complete FOIA response; enough time for FDA to give Knoll's GRAS/E Petition full and fair consideration; enough time for judicial review of FDA's GRAS/E determination, if necessary; and enough time for all manufacturers, including Knoll, to conduct or locate and include in

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7. Specifically, the Notice docket contains a letter from Jones Medical Industries ("JMI") to FDA, stating JMI's understanding that FDA does not plan to accept NDAs for additional levothyroxine sodium products after the first NDA has been approved. Letter from Jess H. Stribling to Dr. Solomon Sobel, Director, Division of Metabolic & Endocrine Drug Products (May 18, 1998) at 2 ("JMI understands that CDER will refuse to accept § 505(b)(2) applications after approval of the first § 505(b)(2) application. As a result of this policy, manufacturers of levothyroxine are in a race[.]") (emphasis in original). An FDA staff member also has advised Knoll's counsel that the agency would approve only one NDA and would then convert any pending NDAs into ANDAs.

their applications whatever studies are needed. As to procedural matters, Knoll asks FDA to confirm that it will use the Notice procedure and no other.

To these ends, Knoll asks the Commissioner to:

1. Modify the schedule set forth in the Notice so that, instead of stating a date by which NDAs must be approved, the Notice specifies a date by which NDAs must be received by the agency. Further, Knoll requests that FDA set the date by which NDAs must be received so that it is:

   A. At least 6 months after FDA rules on Knoll's GRAS/E Petition and the courts (if their jurisdiction is invoked) have completed their review of FDA's decision; and

   B. At least 6 months after FDA rules on the request in this Citizen Petition with respect to the procedure it will use pursuant to the Notice (see Action Requested 3, infra).

2. Confirm that FDA will allow Knoll at least 60 days to submit a supplement to its GRAS/E Petition after Knoll has received a complete response to its September 12, 1997 Freedom of Information request.

3. Declare that the procedure set forth in the Notice is the procedure FDA will follow, viz., that any and all applications for levothyroxine sodium products submitted pursuant to the Notice must be NDAs and will be reviewed and, if warranted, approved as NDAs; and declare that FDA will not follow any other procedure such as approving only one or a few NDAs and treating other submissions as ANDAs.

B. STATEMENT OF GROUNDS

1. Scheduling

Under the FDCA, an NDA is required only for a new drug. Thus, if Synthroid is not a new drug, no NDA (or ANDA) can be required. This critical threshold question remains to be determined, as the Notice itself makes plain. Although FDA purported to announce that all levothyroxine products are new drugs, it also invited Citizen Petitions demonstrating that particular products are not new drugs. That invitation - which Knoll accepted - was the

beginning of a process not yet complete. Until the process is completed, there is no final decision as to the new drug status of Synthroid, and until then, Synthroid is not a new drug.[8]

For these reasons, a final decision (and, if need be, judicial review) on Knoll's GRAS/E Petition must precede the requirement that an NDA be submitted for Synthroid. Putting the NDA process and the Citizen Petition process onto parallel rather than sequential tracks, as the Notice does, would effectively force Knoll to submit an NDA for Synthroid by approximately August 1999, even if Synthroid has not been determined by that time to be a new drug and may never be determined to be a new drug. This FDA cannot do.

Knoll also is concerned that if it is forced as a practical matter to submit an NDA while FDA is still considering its GRAS/E petition, FDA will be sorely tempted to give the GRAS/E petition shorter shrift than it would otherwise receive. Knoll believes it is entitled to full and fair consideration of its GRAS/E petition free of the gravitational pull that may be exerted by an NDA, assuming, as seems evident, that FDA does want an NDA rather than GRAS/E status for Synthroid. Technically, an NDA submitted for Synthroid would not be part of the GRAS/E petition, and FDA would have no right to consider the NDA as part of its GRAS/E deliberations. At the same time, if the same staff are conducting both reviews, it would not be surprising for one review process to influence the other in ways that are only human but outside Knoll's ability ever to know or challenge.

FDA's slowness in providing a complete response to Knoll's FOIA request, although it has had more than a year to do so, has further compounded the timing problems inherent in the Notice by delaying Knoll's ability to muster all available evidence in support of its GRAS/E petition. Knoll submitted its FOIA request on September 12, 1997, less than 30 days after publication of the Notice.[9] The FOIA request stated that "[t]his request is time sensitive, as the documents are relevant to the FDA's [Notice]." To facilitate a prompt response, the request was as specific as possible, and included extensive information to help FDA staff

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8. See, e.g., Rutherford v. United States, 542 F. 2d 1137, 1143 (10th Cir. 1976):

> We are unable, however, to see how the FDA can escape the obligation of producing an administrative record to support its determination of the first and more fundamental issue that [a drug product] is a new drug, for it is not a new drug merely because they say it is. Moreover, such a conclusory ruling precludes effective review under 5 U.S.C. Section 706(2).

9. FOIA Request, supra note 6.

identify and locate responsive documents.[10] Knoll also has provided ongoing updates to the agency as to the adequacy of FDA's response, and has continued to press, via letters and telephone calls, for a full answer.[11] In these phone calls, FDA staff has acknowledged that Knoll should and will have an opportunity to supplement its Citizen Petition with pertinent information from FDA's complete response (when it arrives).[12]

Knoll has welcomed that acknowledgment, but has grown concerned that the timing currently contemplated by the Notice may render it illusory. The longer it takes for FDA to provide a full response to Knoll's FOIA request, the longer Knoll will be delayed in assembling all the available evidence to support its GRAS/E petition, and the less time will be available for FDA to make a GRAS/E determination and then review an NDA (should one be required) by August, 2000. If Knoll is effectively forced to submit an NDA before it can fully supplement its GRAS/E petition using the materials included in a complete FOIA response, the timing problem would be even more unfair, for Knoll's NDA would be there, full and complete and available for review, while the GRAS/E petition would not. FDA might well decide to go ahead and review the NDA, and if that process were well under way - or, worse,

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10. FOIA Request Cover Letter, supra note 6; FOIA Request at 8. This included copies of numerous documents used by Knoll to identify additional relevant documents, and a list of offices within the agency where counsel for Knoll expected responsive documents would likely be located. Id. at 7-8. In addition to sending the request to FDA's central FOIA office, as required by FDA's regulations, copies also were sent to the FOIA officer in the Center primarily responsible for Synthroid as well as to FDA staff known to be working on aspects of the Notice. FOIA Request Cover Letter, supra note 6.

11. See Letter from Edward J. Parr, Jr. to Carolann W. Hooton, Director, Freedom of Information Staff (Oct. 21, 1997); Letter from Edward J. Parr, Jr., to Freedom of Information Staff (Oct. 27, 1997); Letter from Edward J. Parr, Jr., to Freedom of Information Staff (Oct. 31, 1997); Letter from Nancy L. Buc and Edward J. Parr, Jr., to Carolann W. Hooton (Nov. 3, 1997); Letter from Nancy L. Buc and Jane E. Baluss, to Carolann W. Hooton (February 10, 1998); Letter from Nancy L. Buc, to Carolann W. Hooton (April 14, 1998); Letter from Nancy L. Buc and Jane E. Baluss, to Carolann W. Hooton (May 12, 1998); Letter from Nancy L. Buc, to Carolann W. Hooton (June 12, 1998).

12. To give just one example of documents Knoll is eagerly awaiting, it has not yet received documents related to FDA's Government Wide Quality Assurance Program. Under that program, FDA conducts product quality evaluations on drugs and devices purchased on contract by various other federal agencies. See, Federal Cooperative Agreements Manual, FDA, Office of Regulatory Affairs, Office of Enforcement, Division of Compliance Policy, at 6 (August 1, 1996); 1996 FDA Investigations Operations Manual, section 512.3; FDA Compliance Policy Guides, 100.700 (September 1, 1987). If FDA has regularly issued favorable quality evaluations of Synthroid (and perhaps other oral levothyroxine products as well), that would contradict FDA's assertion in the Notice that stability and potency problems with the products are either serious or new.

virtually complete - by the time the GRAS/E petition were ready for review, it is hard to imagine FDA would still be willing and able to open its mind to the possibility that the NDA review had been unnecessary because Synthroid is not a new drug.

In light of these factors, Knoll believes it is both legally necessary and only fair to revise the schedule contemplated by the Notice so that, rather than specifying an end date by which NDAs must be approved, it specifies sequential milestones. Specifically, the Notice should be revised to state that FDA will not begin its review of Knoll's GRAS/E Petition until the company has had sixty days from the completion of FDA's FOIA production to submit its supplement, and that Knoll's NDA will not be due until six months after the date on which FDA (and the courts, if their jurisdiction is invoked) has ruled on Knoll's Citizen Petition.[13] Additionally, in order to reduce uncertainty and confusion and put Knoll and other manufacturers on a level playing field, the revised Notice should state that no NDAs (or other applications) will be due until six months after FDA has confirmed that it intends to follow the procedure specified in the Notice, or whatever other procedure it intends to utilize, as discussed below.

2. Procedure

The Notice plainly stated that FDA is seeking New Drug Applications (NDAs): that term is used throughout the Notice, and the term Abbreviated New Drug Application or ANDA is nowhere mentioned. FDA presumably chose its words by reference to the FDCA and FDA's regulations, both of which clearly distinguish between the two.[14] Also, the Notice calls for the submission of bioavailability data, a standard requirement for NDAs, and not for bioequivalence data, which is required for ANDAs.[15] Yet despite the clarity of the Notice

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13. Knoll has no objection to applying the same due date for NDA submissions to all manufacturers. This may be particularly desirable because, if FDA agrees with Knoll that GRAS/E status for levothyroxine products is independent of manufacturing issues, see GRAS/E petition at 13-20, it could well conclude that all levothyroxine products are GRAS/E and that NDAs are therefore not required for any of them.

14. Section 505(a) of the Act provides that a new drug may not be introduced or delivered for introduction into interstate commerce unless it is the subject of an approved application under either subsection (b) (i.e., an NDA) or subsection (j) (i.e., an ANDA). The fundamental distinction between the two types of applications is further reflected and elaborated in FDA's new drug approval regulations. See, e.g., 21 C.F.R. § 314.3(b) (separately defining "application" and "abbreviated application"); and compare id. §§ 314.50 (content and format of NDA) and 314.94 (content and format of ANDA).

15. Compare 21 C.F.R. § 320.21(a) (NDA applicant must submit bioavailability data or request for bioavailability waiver) with § 320.21(b) (ANDA applicant must submit bioequivalence data or a request for bioequivalence waiver).

itself, there are ominous hints that FDA may be planning not to follow the procedure stated in the Notice.[16]

Having specified the procedure it intends to use, an agency must adhere to it.[17] There can be no doubt what FDA said in the Notice, nor what its words mean in light of the statutory scheme and the agency's own regulations. Thus, it must do what it said it would.

By using some combination of NDAs and ANDAs instead of all NDAs as specified in the Notice, FDA in effect would be doing indirectly what it cannot lawfully do directly. First, section 505(b)(2) and section 505(b)(1) of the Act both provide that "any person" may submit an NDA, and go on to say that FDA "shall approve" it if the applicable conditions are met. Nothing in the statute limits the right of "any person" to submit an NDA should it choose to do so in preference to an ANDA,[18] and FDA cannot limit that right, either directly or indirectly.

Second, having decided that all levothyroxine sodium products are new drugs, FDA would not have been free to pick/compel just one of them to submit an NDA while leaving the others on the market until the NDA was approved and listed in FDA's "Approved Drug Products with Therapeutic Evaluations" ("the Orange Book"), and only then requiring ANDAs of the others.[19] Neither can FDA accomplish that goal by indirection.

Third, the FDCA and FDA's implementing regulations plainly permit the submission and receipt of an ANDA only when there is a reference drug in the Orange Book prior to submission and receipt.[20] Until one NDA is approved and listed for levothyroxine sodium, therefore, no applicant can submit and FDA cannot receive any ANDAs for a drug containing

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16. See supra note 7.

17. See, e.g., Vitarelli v. Seaton, 359 U.S. 535, 547 (1959); Service v. Dulles, 354 U.S. 363, 372 (1957); Accardi v. Shaughnessy, 347 U.S. 260, 267 (1954); Denny Klepper Oil Company v. United States Department of Energy, 598 F. Supp. 522, 528 (D.D.C. 1984).

18. Section 314.101(d)(9) of FDA's regulations purports to give FDA the discretion to refuse to file an NDA submitted under § 505(b)(2) of the act (the type of application contemplated in the Notice) for a drug "that is a duplicate of a listed drug and is eligible for approval [as an ANDA] under section 505(j) of the act." For the reasons stated in the text, Knoll believes this provision cannot be invoked against an applicant that does not want its NDA converted to an ANDA. In any case, that regulation is inapplicable here, for there is no listed (i.e., NDA-approved) orally administered levothyroxine sodium product.

19. Hoffmann-LaRoche v. Weinberger, 425 F. Supp. 890 (D.D.C. 1975); see also Cutler v. Kennedy, 475 F. Supp. 838 (D.D.C. 1979).

20. FDCA § 505(j)(2)(i); 21 C.F.R. §§ 314.92 and 314.94(a)(3).

that active ingredient. Modifying the Notice procedure to convert an NDA into an ANDA which could not lawfully have been submitted or received as an ANDA is impermissible.

Equally important, there is no workload advantage to FDA in departing from the Notice procedure. The Notice itself announces that levothyroxine sodium is safe and effective, and says the agency "is prepared to accept" applications under 505(b)(2). FDA's willingness to accept 505(b)(2) applications suggests the agency's awareness of a core set of studies applicable to all levothyroxine sodium products. Thus, the agency may well be able to make one decision applicable to all applicants based on these studies - that the products are safe and effective. Likewise, the review of chemistry, manufacturing and controls information to decide whether the applicant has met the good manufacturing practices requirement of the statute and regulations is the same whether the application is an NDA or an ANDA. By contrast, deciding also whether a particular product has been shown to be bioequivalent to another, as must be shown for an ANDA under § 505(j) of the Act, will require more work, not less, on FDA's part.[21] Indeed, proceeding directly to ANDAs for most products makes even less sense in light of the fact that FDA's announced reason for requiring NDAs for levothyroxine sodium products in the first place was specifically to address concerns about product manufacturing quality.[22]

Departing from the Notice procedure by converting one or more NDAs into ANDAs also is likely to create considerable confusion and uncertainty. In the usual situation in which an approved NDA is followed by one or more ANDAs, all parties know in advance whether their application is going to be an NDA or an ANDA, and therefore know what studies to conduct and submit in their applications. But if FDA departs from the procedure announced in the Notice, a manufacturer will not know in advance whether its application will be reviewed as an NDA or an ANDA, and so will not know whether to submit studies demonstrating safety, efficacy, and bioavailability, as required for an NDA, or a study demonstrating

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21. Although bioequivalence issues are beyond the scope of the Notice and this Citizen Petition, Knoll notes that they are sufficiently difficult that FDA is unlikely to be able to conduct routine bioequivalence reviews of any ANDAs for levothyroxine products, whether they are submitted pursuant to the Notice or thereafter. Allowing ANDAs rather than NDAs may therefore significantly increase rather than reduce FDA's workload and review time with respect to levothyroxine products.

22. Not only would the review period be shorter for NDAs, but it would seem logical to address bioequivalence issues only after FDA has reviewed bioavailablity and manufacturing data for all products and satisfied itself that any manufacturing concerns have been appropriately addressed.

Knoll's disagreement with FDA's position on the prevalence and legal significance of manufacturing quality problems with levothyroxine sodium drug products in general and Synthroid in particular is discussed at length in Knoll's December 15, 1997 GRAS/E Petition. Knoll continues to contend that FDA's conclusions in the Notice are both legally unsupported and factually wrong as to Synthroid.

bioequivalence to another drug, as required for an ANDA. Moreover, no one, not even FDA, will necessarily know in advance which manufacturer's product will be the NDA, which the ANDAs. Thus, a manufacturer which is willing to submit an ANDA rather than an NDA will not know which product is the reference product, and cannot know, therefore, to which product its product must be shown to be bioequivalent.

3. Conclusion

Knoll has worked diligently over the past year to provide FDA with evidence that Synthroid is GRAS/E, as invited in the Notice. The Company stands prepared to further supplement its GRAS/E Petition with additional pertinent materials from FDA's FOIA response, when it is completed. The requested actions will ensure that Knoll's efforts will receive the full and fair consideration they deserve, while also ensuring fair and orderly review of any other submissions required by the Notice. Accordingly, Knoll requests the Commissioner to take the actions requested in this Petition.

C. ENVIRONMENTAL IMPACT

Petitioner claims a categorical exclusion from the requirement of an environmental impact assessment under 21 C.F.R. § 23.30(a) and by analogy to §§ 25.30(h) and 25.31(a). To Petitioner's knowledge, no extraordinary circumstances exist which would indicate that the requested action may significantly affect the human environment.

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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