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December 22, 1999

Dr. Solomon Sobel, Director
Center for Drugs Evaluation and Research
Division of Metabolic and Endocrine Drug Products (HFD-510)
Document Control Room 14B-19
Food and Drug Administration
5600 Fishers Lane
Rockville, MD 20857

RE: Levothyroxine Sodium: Request for a Pre-NDA Meeting Under FDAMA

Dear Dr. Sobel:

On November 22, 1999 we submitted a letter requesting a Pre-NDA meeting with you and your staff regarding the Center for Drug Evaluation and Research's (CDER) current positions regarding the submission of New Drug Applications (NDA) for levothyroxine sodium tablets. After a discussion with Mr. Steve McCort regarding our request he suggested that we resubmit our request including the specific issues that we want to discuss with the Agency.

Specifically we would like to discuss the two draft guidances: "In Vivo Pharmacokinetics and Bioavailability Studies and In Vitro Dissolution Testing for Levothyroxine Sodium Tablets" (hereby referred to as the June 1999 draft guidance) and "Draft Guidance – Procedural Levothyroxine Sodium Questions and Answers" (hereby referred to as the August 1999 draft guidance).

On the attached pages we are submitting a proposed agenda covering the specific points that need clarification. Following these specific points we are including relevant background information including comments submitted to the Agency on the draft guidance policies by Jones and other levothyroxine manufacturers.

We feel this meeting is imperative in view of the time and resources Jones is dedicating to this project. We are at a point in our development where it is essential for Jones to ascertain the Agency's plans to evaluate the industry comments to the above referenced draft guidances and to discuss with the Agency the dramatic effects that any changes to the published draft guidance documents will have on the companies involved in the NDA preparation process.

In order to commit the necessary time and resources to complete this project, we feel that all the issues presented in the meeting agenda require clarification and closure. Finally, the rationale and justification for extending the August 14, 2000 deadline for NDA approval must be discussed.

We would like to have this meeting in early January 2000 and are requesting an approximate ninety minute meeting. We feel it is relevant to have at this meeting personnel from the agency who are responsible for determining FDA policy. This would include Jane Axelrad, Esq., Director, CDER's Office of Policy as well as the pertinent CDER personnel. We would anticipate that the undersigned, Nancy Cafmeyer, of our Regulatory Affairs office, Elaine Strauss, of our Quality Assurance/Quality Control department and David F. Weeda, our outside FDA counsel, will attend this meeting from Jones.

Please call me at your earliest convenience, so that we can quickly agree on the date for this meeting. We appreciate you time, consideration and understanding.

Sincerely,

G. Andrew Franz
Chief Operating Officer

cc: Jane Axelrad, Esq.
Steve McCort

Attachments

APPEARS THIS WAY
ON ORIGINAL

Point 1:
In the June 1999 draft guidance the protocol for the required bioavailability studies was presented. Since this was a draft guidance there was a comment period during which companies could submit their concerns regarding the protocol. Due to criticism in the design of the studies, we are concerned that the requirements for the bioavailability studies could be modified and therefore jeopardize the validity of our study results. See Attachment 1 and Attachment 2 which are letters sent to the Agency by Knoll Pharmaceutical Company and Elliot G. Levy, M.D. respectively, commenting on the June 1999 draft guidance.

Is the Agency considering modifying the requirements for the bioavailability studies for levothyroxine sodium and what assurances could the agency give to Jones that the data generated from studies conducted with the current protocol will not be rendered invalid in the future?

For the remainder of the Agenda Points, please refer to comments to the August 1999 draft guidance submitted by Jones (Attachment 3); Forest Laboratories (Attachment 4) and Knoll Pharmaceutical Company (Attachment 5).

Point 2:
In the August 1999 draft guidance the agency stated, "Any levothyroxine sodium product marketed on or after August 14, 2000, without an approved NDA will continue to be considered an unapproved new drug and will be subject to enforcement action."

Official policy regarding requirements for conducting the necessary biostudies and for preparation of the NDA was not disseminated by the Agency for at least two years from the date of the original Federal Register Notice in August 1997. Even then the policies were published as draft guidances, subject to public comment and possible revision, and not final policy.

Since the guidances were published as draft documents by very nature their content could be changed as a result of comments and further evaluation by the Agency. Until the draft guidance documents become final there does not exist accurate, consistent policy for all manufacturers of levothyroxine sodium products to equally follow.

Because of the Agency's failure to finalize accurate, timely guidance to all interested parties, it must reevaluate the feasibility and reality that any company can comply with the August 14, 2000 deadline.

We propose that a new deadline be established for NDA approval. This deadline should be at least three years from the date the levothyroxine guidance document becomes final. If the August 1999 draft guidance becomes final in November 1999 then the deadline for submission should be November 2002 at the earliest. (Also refer to Points 3 and 8.)

Point 3:
On December 15, 1997 Knoll Pharmaceutical Company filed a Citizen's Petition with FDA to issue an order declaring that Synthroid is generally recognized as safe and effective for the treatment of hypothyroidism and therefore not subject to regulation as a "new drug". To date the Agency has not ruled on Knoll's Citizen's Petition. When the Agency does announce its ruling, the decision set forth will have major implications that relate to all other levothyroxine sodium tablet manufacturers.

Due to the magnitude and importance of that decision, the current August 14, 2000 timetable for NDA approval is not justified. The Agency must delay the NDA deadline until the later of the following: (1) FDA rules on the Knoll Citizen's Petition; or (2) three years after the date of a final guidance document. (See Point 8.)

Point 4:
In the August 1999 draft guidance the Agency stated, "FDA will review all 505(b)(2) applications for levothyroxine sodium products filed before the first NDA for levothyroxine sodium products is approved. After the first NDA for levothyroxine sodium is approved, FDA may refuse to file any 505(b)(2) application for a drug product that is a duplicate of the product approved in the first NDA. If an application is refused for filing, it may be resubmitted as an ANDA, provided it meets the requirements of section 505(j) of the Act."

The first comment on this tentative policy is that the Agency has created a "race" among pharmaceutical companies to be the first filer and if not the first filer quickly submit an application so not to be disadvantaged by the artificial "race". This position would have the effect of penalizing those levothyroxine manufactures that took a longer time to formulate a high quality, stable drug product with no stability overage and to conduct the testing needed to support a 505(b)(2) NDA approval. The need for a high quality, stable product is FDA's justification for requiring a NDA for levothyroxine sodium products. FDA's position on NDA approvals is in conflict with the intent of the original August 14, 1997 notice. The August 14, 1997 notice made no provisions for the above referenced FDA interpretation. It only states an August 2000 deadline.

The current FDA position represents a major change from its 1997 position. Coming so late in relation to the original timeline, FDA's position is basically unfair to all interested manufacturers of levothyroxine sodium products. If FDA is intent in going forward with the approval process as set forth in the August 18, 1999 Draft Guidance, it should publish it as a proposed rule and conduct notice-and-comment rulemaking.

The second comment on this policy is that the statements presented by the Agency are confusing. The word "duplicate" is not defined in the Federal Food, Drug and Cosmetic Act or FDA's regulations and, as such, sponsors are unaware of the scientific parameters or legal standards by which the Agency will classify and judge an application for a duplicate product. The implication is that if a sponsor's 505(b)(2) application is not identical to a 505(b)(2) application that has been approved the Agency will file that 505(b)(2) application and ultimately approve it if warranted. The Agency must clarify and define the phrase "duplicate of the product" before going forward with its regulatory program for levothyroxine sodium products or delete the section from the policy and review all NDA submissions for levothyroxine sodium products.

Point 5:
In the August 1999 draft guidance the Agency stated "Three year exclusivity is available for applications that contain reports of new clinical investigations (other than bioavailability studies) essential to the approval of the application and conducted or sponsored by the applicant."

Levothyroxine sodium tablets have been on the market and prescribed by physicians for many years. The literature is replete with studies covering almost every aspect of the drug and its effects. It is highly unlikely that any new clinical studies would be "essential to the approval" of levothyroxine sodium tablets for any currently recognized uses; therefore, three year exclusivity is not warranted.

Point 6:
In the August 1999 draft guidance the Agency stated, "An NDA applicant may submit a bioequivalence study comparing its levothyroxine sodium product to one previously approved."

The important issue of bioequivalence can best be addressed only after a reasonable time-frame is established and all interested parties have submitted their NDA applications. FDA should then communicate with companies that have a NDA pending and issue guidelines for those companies on how to conduct and submit bioequivalence data to supplement their NDA submissions if they are interested. These guidelines could also be used in the future by other companies interested in submitting ANDAs.

Point 7:
In the August 1999 draft guidance the Agency stated, "The proposed new dissolution test has not been adopted. Applicants should use the current official USP test. If the USP changes the official test after an NDA is submitted, an applicant can submit new data using that test as a phase-4 study."

The standards for approved applications and pending applications are different. The Agency's position stated in the August 1999 draft guidance document is unusual and not consistent with the regulation for the submission of compendial method's changes to an approved NDA/ANDA. According to 21CFR 314.70(d)(1) changes made to comply with an official compendium are to be submitted in an annual report. Since the new dissolution test becomes effective January 2000, Agency should only require sponsors of INDs and NDA applicants to submit a CMC amendment.

Point 8:
In the August 1999 draft guidance the Agency stated, "A stability overage is not permissible."

Synthroid (levothyroxine sodium tablets, USP), manufactured by Knoll Pharmaceutical Company, as with all other currently available levothyroxine sodium tablets, is manufactured with a stability overage. Companies may mask their overages by stating that they are manufacturing overages. In reality, if a product is released for distribution at a potency which is significantly and consistently over 100% of label claim the overage is not a manufacturing overage but is a stability overage. If FDA accepts the Knoll Citizen's Petition and allows

Synthroid to continue to be marketed without a NDA it would be setting up a dual standard, one which states that a stability overage for a NDA levothyroxine product is not allowed while saying that a stability overage is acceptable for a non-NDA levothyroxine product. The purpose of the August 14, 1997 notice requiring a NDA for this product was, in part, to bring consistency to all the levothyroxine products available. How can a dual standard accomplish this objective? The mandate that a stability overage is unacceptable in the manufacture of levothyroxine sodium tablets is premature.

Since the formulation and stability characteristics are a crucial issue in the preparation of any NDA submissions for levothyroxine sodium tablets, the deadline of August 14, 2000 must be delayed until the later of the following: (1) FDA rules on the Knoll Citizen's Petition; or (2) three years after the date of a final guidance document.

ATTACHMENT 1

knoll

Dockets Management Branch (HFA-305)
Food and Drug Administration
5630 Fishers Lane
Room 1061
Rockville, MD 20852

1105 ... 98-3 ...

BASF Pharma

Re: Docket No. 99D-1149
Draft Guidance for Industry
on In Vivo Pharmacokinetics and
Bioavailability Studies and In
Vitro Dissolution Testing for
Levothyroxine Sodium Tablets

Knoll Pharmaceutical Company ("KPC" or "Knoll") has the following comments on the above-referenced draft guidance. These comments focus on two sets of issues. First, we provide comments on the draft guidance as it will be used in the context of bioavailability for new drug applications.[1] Second, we point out that the study design proposed in the draft guidance for conducting bioavailability studies is unsuitable for conducting bioequivalence studies and that FDA is required by law and its own good guidance policies to provide a full and separate opportunity for public comment on any draft guidance discussing assessment of bioequivalence of levothyroxine sodium tablets.

A. Bioavailability, Dosage Form Equivalence, and Dissolution Studies in the NDA Context

The draft guidance is modeled after the bioavailability study design developed by KPC (formerly Boots Pharmaceuticals, Inc.) and published by Drs. Berg and Mayor.[2] The Berg-Mayor model employs the administration of a single supraphamacologic dose of levothyroxine sodium (600 mcg) to healthy volunteers in order to produce increases over background endogenous T_4 concentrations large enough to measure. Having developed the Berg-Mayor model, Knoll is familiar with both its advantages and with certain limitations.

1. Potential Inapplicability of the Supraphamacologic Dose. Fish et al reported that while the metabolic clearance rate of levothyroxine was constant up to 2.0mcg/kg, it increased sharply at doses above that.[3] The administered dose in the Berg-Mayor model would be approximately 8.6mcg/kg in a 70kg individual. Thus, the kinetics of the 600 mcg dose may not be directly applicable to the therapeutic range of levothyroxine.

Also, the 600 mcg dose will suppress TSH below the sensitivity of current assays. Measurement of TSH is an important and relevant determination because it reflects the concentration of metabolically available thyroid hormone at sites of cellular activity. Knoll therefore questions the desirability of using a bioavailability model that makes impossible the measurement of TSH.

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1. On December 15, 1997, KPC submitted a Citizen Petition, 97N-0314/CP2, stating that its Synthroid® levothyroxine sodium tablets are generally recognized as safe and effective and are therefore not new drugs.
2. Jeffrey A. Berg and Gilbert H. Mayor, Study in Normal Human Volunteers to Compare the Rate and Extent of Levothyroxine Absorption from Synthroid® and Levoxine®, J. Clin. Pharmacol. 1993; 33:1135-1140 (copy attached).
3. Lisa H. Fish, Harold L. Schwartz, John Cavanaugh, Michael W. Steffes, John P. Bantle, and Jack H. Oppenheimer, Replacement Doses, Metabolism and Bioavailability of Levothyroxine in the Treatment of Hypothyroidism, New England J. Med 1987; 316:764-770 (copy attached)

99D-1149

C2

2. Problematic Foods. The guidance should specify that meals not include goitrogenic foods that may affect the synthesis of thyroid hormone, including turnips, cabbage, rutabaga, Brussels sprouts, mustard greens and kale.

3. Possible Need to Measure Absolute Bioavailability. Because levothyroxine sodium is available in IV dosage form, it is possible to conduct studies of absolute bioavailability, as well as the relative bioavailability study contemplated by the draft guidance. Maxon et al have published a model for doing so.[4] For patients with severe hypothyroidism accompanied by gastrointestinal hypomotility and those requiring rapid restoration of thyroid function, IV treatment may be the preferred starting form of levothyroxine. Conversion of such patients from IV to oral dosing is currently done empirically. Knowledge of absolute bioavailability of tablets will make it significantly easier for physicians to select appropriate strengths of tablets after discontinuation of IV administration.

4. Use of Baseline-Corrected Data. The draft guidance proposes to measure total T_4 and total T_3 following a single 600 mcg dose of LT_4. Under these conditions, the concentration of T_4 derived from exogenously administered LT_4 cannot be distinguished from endogenous T_4 by conventional immmoassays, and what is therefore reported is a summation effect, which is at variance from the basic premise of bioavailability as the rate and extent of absorption of exogenously administered drug. In order to measure concentrations of exogenous hormone, and in order to adjust for intersubject differences in baseline endogenous T_4 levels, the Berg-Mayor model reports only baseline-corrected data. Knoll recommends that this approach be incorporated into the draft guidance.

5. Dosage Form Equivalence Study. FDA ordinarily suggests conducting such studies using dosage strengths within the labeled dosage range. In the draft guidance, however, FDA is proposing to assess those strengths by comparing multiples of them totaling 600 mcg, an amount double the highest marketed strength and nearly five times the highest commonly prescribed strength (125 mcg). As noted above, kinetics of levothyroxine may not be linear, and so there is a real question whether these measurements are meaningful. FDA should consider instead use of the Maxon model, supra, note 4, for measuring bioavailability at therapeutic doses, which would also facilitate conducting dosage form equivalence studies at therapeutic strengths.

6. Dissolution. No direct correlation between dissolution rates and bioavailability has been established. Accordingly, there is no need to conduct dissolution studies as part of the demonstration of bioavailability in the NDA context. Until there is definitive information on the dissolution conditions that yields information on bioavailability, this section of the draft guidance should be omitted.

B. The Methodology Proposed for Bioavailability Studies is Unsuitable for Bioequivalence Studies. In any Event, FDA Must Provide a Separate Opportunity for the Public to Comment on Any Draft Guidance on Bioequivalence.

Although the Berg-Mayor model may be suitable for determination of levothyroxine bioavailability in the NDA context, it is not suitable for assessing bioequivalence. As FDA has recognized, levothyroxine sodium is a narrow therapeutic index drug,[5] which makes the issue of how best to determine bioequivalence an important one. How to demonstrate bioequivalence of levothyroxine products has also been the subject of considerable debate about the proper design and execution of such studies.

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4. H.R. Maxon, W.A. Ritschel, C.P. Volle, M.A. Eldon, I.W. Chen, M.F. Fernandez, J. Cline, and G. Mayfield, Pilot Study on the Absolute and Relative Bioavailability of Synthroid and Levothroid, Two Brands of Sodium Levothyroxine, Int. J. Clin. Pharmacol. Ther. Toxicol. 1983; 21: 379-382 (copy attached).
5. Prescription Drug Products, Levothyroxine Sodium, 62 Fed.Reg. 43535 (August 14, 1997).

With all the debate, however, no one has ever suggested that the Berg-Mayor model is appropriate to determine bioequivalence.[6] Indeed, as noted in KPC's earlier comments on this draft guidance, FDA has previously taken the position that the Berg-Mayor model is unsuitable for either bioavailability or bioequivalence.

Under Section 701(h)(1)(C) of the Food, Drug and Cosmetic Act, FDA must "ensure public participation prior to implementation of guidance documents dealing with complex scientific issues and highly controversial issues." Any guidance dealing with bioequivalence of levothyroxine products for oral administration certainly fits both categories. It would also be a Level 1 guidance under FDA's Good Guidance Practices,[7] and FDA must therefore solicit public input and provide for public participation.[8]

FDA cannot satisfy these obligations with respect to any proposed bioequivalence guidance by treating this draft guidance on bioavailability as mooting the need for a separate notice and a separate process as to bioequivalence. Bioavailability and bioequivalence have some commonalities, but many of the issues they implicate are quite different from a scientific or clinical standpoint, especially for narrow therapeutic index drugs, and, in particular, one which is endogenously produced and subject to feedback regulation. Also, many clinicians, scientists, and other members of the public who are greatly interested in the design and conduct of bioequivalence studies of levothyroxine products are indifferent to bioavailability of such products in the NDA context. They would not see any reason to comment on a draft bioavailability guidance, but would participate fully in a process designed to consider bioequivalence issues. That is another reason why a separate process is needed for bioequivalence.

Knoll appreciates the opportunity to comment on this draft guidance.

Sincerely,

Robert W. Ashworth, Ph.D.
Director, Regulatory Affairs

6. It has been and remains Knoll's view that although the Berg-Mayor model is appropriate for demonstration of bioinequivalence, it is unsuited to efforts to demonstrate bioequivalence.
7. 62 Fed. Reg. 8961 (Feb. 1997).
8. Id. at 8968.

ATTACHMENT 2

METAB

Endocrinology and Metabolism

October 8, 1999

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

Re: Levothyroxine Sodium - Docket 99D-2636

I have been a clinician in practice for 24 years as an endocrinologist whose special interest is treating patients with thyroid disorders. I have had extensive experience in the use of levothyroxine sodium (l-T4) products, including both branded name products and generics, and would like to offer my thoughts. I use this drug for the treatment of patients with hypothyroidism, thyroid cancer, and thyroid nodules.

Most of my colleagues and I feel that a physician has to be careful with handling patients who take l-T4 because often they do not feel well until their dose has been adjusted to become the true physiologic replacement dose (in the case of hypothyroidism) or the suppressive dose (in the cases of nodules and cancer). As scientific knowledge has advanced, the laboratory tests have improved, making it very easy to measure the concentration of TSH in a patient's serum and judge the state of replacement or suppression based on that scientific information. The TSH is the pituitary gland's response to circulating levels of thyroid hormone and is the most sensitive way to judge thyroid status that we have.

Most thyroidologists in the United States belong to an organization called the American Thyroid Association, headquartered in New York City. There are approximately 500 members . In 1994 a committee of that organization was formed called "Standards of Care Committee" whose charge was to provide clinical guidelines for physicians to follow who deal with thyroid patients. This panel of experts, of which I was a member, wrote a position paper, which was reviewed by the entire

99D-2636 C 44

membership. It was eventually published in 1995. In that paper (JAMA, 273:808, 1995, a copy of which in enclosed), we recommended that when a patient's brand of l-T4 is changed, the patient should have her or his blood tested in eight to twelve weeks for the TSH concentration, and the patient be reevaluated, if necessary. We felt that even though most l-T4 products were good, they were different from each other, and, in order for our patients to be sure that their dose was correct, they needed to have a repeat TSH test after the drug has come into equilibrium in their bodies. Hence, our recommendation was formed.

I understand that the FDA is considering various steps which, taken together, could result in the agency's designating one or more l-T4 products which, in FDA's view, could be substituted for another such product without retitrating and reevaluation.

While this step may ultimately be appropriate, I do not believe that it should be taken before the FDA takes into account the view of experts, including practicing thyroidologists like myself, on the factors which FDA should consider in deciding whether one product can fairly be said to be equivalent to another. Based on the way the issue is dealt with in this draft guidance, I have a real concern that the FDA may just accept whatever study is put before it, without considering the complexities that are involved, including, especially, whether TSH levels, not just T4 levels, are equivalent.

I therefore request that the FDA make the process of settling on the design of one or more protocols intended to demonstrate comparability of any two l-T4 products an open and public process. If a consensus can be reached on how to do the studies, then FDA's recommendation of substitutability will carry far greater weight than if decisions are made "in the dark."

Sincerely,

Elliot G. Levy, M.D.

APPEARS THIS WAY
ON ORIGINAL

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October 12, 1999

HAND DELIVERED

Dockets Management Branch (HFA-305)
Food and Drug Administration
5630 Fishers Lane
Room 1061
Rockville, Maryland 20852

Re: Docket No. 99D-2636: Comments Of JONES PHARMA INCORPORATED On "Draft Guidance For Industry - Levothyroxine Sodium"

Dear Sir or Madam:

This letter is submitted on behalf of JONES PHARMA INCORPORATED (Jones) and transmits the enclosed comments of Jones in response to the Food and Drug Administration's (FDA) August 18, 1999 Federal Register notice (64 Fed. Reg. 44,935) regarding the Agency's "Draft Guidance for Industry - Levothyroxine Sodium" (Draft Guidance). Jones manufactures and distributes the prescription drug product Levoxyl®, containing the active ingredient levothyroxine sodium, and has a keen and vested interest in this matter.

Jones' enclosed comment speaks for itself. This letter is intended only to point out the legal and equitable problems permeating the Agency's tentative process regarding the development and approval of safe, effective, and stable levothyroxine sodium finished dosage form products. As the Agency is aware, regulatory programs for products and firms subject to FDA's jurisdiction are subject to a reasonableness standard under the Administrative Procedure Act, 5 U.S.C. § 551, et seq. The Agency's actions must not be arbitrary, capricious, or otherwise in violation of the law. 5 U.S.C. § 706. More particularly, FDA has an affirmative obligation to apprise industry of the scientific and legal standards by which applications will be judged, and the courts have recognized that the Agency should not change the rules for product approval in mid-stream of the regulatory process. See Serono Laboratories, Inc. v. Shalala, 158 F.3d 1313, 1323 (D.C. Cir. 1998).

As discussed below, the product development standards as established by FDA's Center for Drug Evaluation and Research (CDER) have not, in our view, been fair to any manufacturer of levothyroxine products and, thus, represent unreasonable Agency action. Moreover, CDER's

unprecedented new drug application (NDA) approval process, as explained in Draft Guidance, has not been justified or reasonably explained, and is arbitrary, capricious, and otherwise in violation of the due process rights of regulated industry, including Jones. Accordingly, Jones requests that the policies underlying the levothyroxine regulatory program be re-evaluated and published as a proposed rule. At a minimum, the current August 14, 2000 deadline for the submission of NDAs for the lawful marketing of levothyroxine sodium drug products must be extended until at least three years after the publication of a final rule. The basis for Jones' requested relief follows.

1. The August 14, 1997 FDA Federal Register notice required interested firms to submit NDAs for levothyroxine drug products by August 14, 2000. We assume the August 14, 2000 NDA filing date was selected by FDA based on the assumption that a bioavailability testing guidance would soon be made available and that product development and testing, based on that guidance, could quickly proceed. However, it became clear following the August 14, 1997 notice that CDER's view as to appropriate bioavailability testing was not established. It was not until June 10, 1999, twenty-two months later, that the Agency issued its Guidance entitled "In Vivo Pharmacokinetics and Bioavailability Studies and In Vitro Dissolution Testing for Levothyroxine Sodium Tablets." CDER's inability to come to closure on the appropriate bioavailability protocol has delayed the development process for levothyroxine sodium drugs by almost two years. In addition, the Draft Guidance concerning the NDA process was only issued in August 1999, a full two years after the August 1997 notice. Since the Draft Guidance is subject to comment before finalization, the Agency's regulatory standards for levothyroxine sodium products are still in a state of flux. Because the August 14, 2000 filing date was somewhat arbitrarily set in August 1997, the significant delays in finalization of the bioavailability protocol and the yet-to-be-finalized August 1999 Draft Guidance require an extension of the August 14, 2000 deadline by at least three years following the finalization of the policies that will govern the development and approval of levothyroxine sodium products. Under these circumstances, the Agency's refusal to extend the August 14, 2000 deadline would be unreasonable, arbitrary, and capricious Agency action.

2. The Agency has not developed clear, consistent, and timely advice to companies that need to prepare 505(b)(2) NDAs for levothyroxine sodium tablets. The initial August 14, 1997 Federal Register notice directed that NDAs be filed within three years. Nowhere in the 1997 Federal Register notice is there any mention -- or even implication -- that once the first NDA is approved by CDER, subsequently filed applications must either be a 505(b)(1) NDA or a 505(j) abbreviated new drug application (ANDA). This new approval scenario appeared for the first time

in the August 18, 1999 Draft Guidance. Not insignificantly, there is no explanation in the Draft Guidance as to why the Agency is establishing such an unusual and arbitrary approval process for this important product. In absence of a reasoned explanation, FDA's implementation of the Draft Guidance, as written, would be arbitrary and capricious.

3. Because the Agency's recently announced position represents such a major change from that set forth in its 1997 Federal Register notice, and considering how late in the process the new position was made public, all interested manufacturers of levothyroxine sodium products have been significantly disadvantaged. We believe that if FDA is intent in going forward with the approval process as set forth in the August 18, 1999 Draft Guidance, it should publish it as a proposed rule and conduct notice-and-comment rulemaking to satisfy the requirements of the Administrative Procedure Act.

4. As pointed out in the enclosed Jones comment, the Agency has not yet addressed the December 15, 1997 Knoll Pharmaceutical Company (Knoll) citizen petition that requests a ruling that its levothyroxine sodium product, Synthroid®, is not a "new drug." If the Agency grants the Knoll petition and determines that Synthroid® is not a new drug, other similarly formulated and labeled products should also be exempt from the FDA preapproval processes. In our view, FDA must rule on the Knoll petition before taking any further action with respect to the regulation of levothyroxine sodium products as new drugs.

* * *

We appreciate this opportunity to present our views.

Sincerely,

David F. Weeda
Counsel to JONES PHARMA INCORPORATED

DFW:mhh
Enclosure (JONES PHARMA INCORPORATED comment)

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Comments to the Draft Guidance Document entitled,
"Guidance for Industry – Levothyroxine Sodium" Published August 1999

Comment 1:
"Any levothyroxine sodium product marketed on or after August 14, 2000, without an approved NDA will continue to be considered an unapproved new drug and will be subject to enforcement action."

On August 14, 1997 a notice was published in the Federal Register requiring a NDA for levothyroxine sodium products to be filed by August 14, 2000. On August 22, 1997, FDA began communicating policy and guidance to pharmaceutical companies on NDA preparation with the release of bioavailability protocols needed for NDA submission. On April 21, 1999, in verbal communication with FDA, Jones learned that FDA had revised the study protocol without notifying the interested parties. The official guidance document for the In Vivo Pharmacokinetics and Bioavailability Studies and In Vitro Dissolution Testing for levothyroxine sodium tablets was not published until June 10, 1999. From August 22, 1997 until June 10, 1999 companies had been operating under the erroneous assumption that the original study protocols were correct.

On February 25, 1998 a telephone conference was held between FDA and Jones to discuss FDA policy and guidance for NDA preparation and submission. On April 20, 1999 a letter was received from Jane A. Axelrad (Associate Director for Policy, CDER) stating that the minutes to the February, 1999 meeting may not reflect current CDER policy. After several attempts were made by Jones to get clarification from FDA, a draft guidance document was finally published in August 1999. This represents a 24 month delay by FDA in disseminating official FDA policy regarding the necessary testing protocol and clearance procedures for levothyroxine sodium products.

To demand pharmaceutical companies comply with the August 14, 2000 deadline for NDA filing is both unreasonable and unfair under these circumstances. A new time-line for submission should be established for the submission of NDAs for levothyroxine sodium tablets which takes in to account FDA's failure to communicate accurate, timely guidance to all interested parties. Since the August 1997 notice gave manufacturers three years to submit a NDA, the new deadline should be at least three years from the date the levothyroxine guidance document becomes final. If the August 1999 draft guidance becomes final in November 1999 then the deadline for submission should be November 2002 at the earliest (see comment 7 regarding a related, pending Citizen's Petition).

Comment 2:
"FDA will review all 505(b)(2) applications for levothyroxine sodium products filed before the first NDA for levothyroxine sodium products is approved. After the first NDA for levothyroxine sodium is approved, FDA may refuse to file any 505(b)(2) application for a drug product that is a duplicate of the product approved in the first NDA. If an application is refused for filing, it may be resubmitted as an ANDA, provided it meets the requirements of section 505(j) of the Act."

The August 14, 1997 Federal Register notice states that FDA will permit orally administered levothyroxine products to be marketed without approved NDAs until August 14, 2000. During the time interval between August 14, 1997 and August 14, 2000 firms are to develop high quality, safe and effective formulations for levothyroxine products, perform bioavailability studies, conduct appropriate testing and submit 505(b)(2) NDAs to the agency for review. Based on the August 1999 draft guidance document 505(b)(2) applications pending at the time the first 505(b)(2) NDA is approved will continue to be reviewed and later submissions would have to be filed as ANDAs. This position is both unusual and unfair.

The Agency has not developed clear, consistent, timely advice to companies in preparing such 505(b)(2) applications and has not communicated this information to everyone involved until August 1999. Moreover the required bioavailability protocols have been changed during this time frame and the official bioavailability guidance document was not released for publication until June 1999. Thus, official FDA bioavailability policy was not disseminated until almost 2 years after the initial announcement and the start of the deadline clock.

FDA's tentative policy (as set forth in the August 1999 draft guidance) on the NDA approval process for levothyroxine has created a "race" among pharmaceutical companies to be the first filer and if not the first filer quickly submit an application so not to be disadvantaged by the artificial "race". This position would have the effect of penalizing those levothyroxine manufactures that took a longer time to formulate a high quality, stable drug product with no stability overage and to conduct the testing needed to support a 505(b)(2) NDA approval. The need for a high quality, stable product is FDA's justification for requiring a NDA for levothyroxine sodium products. FDA's position on NDA approvals is in conflict with the intent of the original August 14, 1997 notice. The August 14, 1997 notice made no provisions for the above referenced FDA interpretation. It only states an August 2000 deadline.

FDAs has demonstrated a failure to disseminate accurate, timely, consistent advice equally to all interested parties. The August 1999 draft guidance document states that an NDA applicant may submit a bioequivalence study comparing its levothyroxine product to one previously approved. This statement suggests that a NDA can be submitted after the first one is approved. If that is not the case how can a company submit bioequivalence data in their NDA submission comparing their product to an approved product if that company's NDA is not allowed to be submitted after the first NDA is approved? This statement demonstrates the inconsistency in this document.

Given this fact and the need for high quality, stable levothyroxine sodium products to be available to the public, the Agency must extend the August 14, 2000 deadline until at least three years after it has established final policy which we would hope would be derived from consideration of comments such as these. Once a final policy has been established, the Agency must allow <u>all</u> NDAs submitted within this revised date to be filed and reviewed.

Comment 2 (Continued):
The current FDA position represents a major change from its 1997 position. Coming so late in relation to the original timeline, FDA's position is basically unfair to all interested manufacturers of levothyroxine sodium products. If FDA is intent in going forward with the approval process as set forth in the August 18, 1999 Draft Guidance, it should publish it as a proposed rule and conduct notice-and-comment rulemaking.

Comment 3:
"FDA will review all NDAs, including 505(b)(2) applications for duplicates, that have been filed even if an NDA is approved before review of an application has been completed. After the first NDA for levothyroxine sodium is approved, FDA may refuse to file any 505(b)(2) application for a drug product that is a duplicate of the product approved in the first NDA."

These statements are confusing. The word "duplicate" is not defined in the Federal Food, Drug and Cosmetic Act or FDA's regulations and, as such, sponsors are unaware of the scientific parameters or legal standards by which the Agency will classify and judge an application for a duplicate product. The implication is that if a sponsor's 505(b)(2) application is not identical to a 505(b)(2) application that has been approved the Agency will file that 505(b)(2) application and ultimately approve it if warranted. The Agency must clarify and define the phrase "duplicate of the product" before going forward with its regulatory program for levothyroxine sodium products.

Comment 4:
"Three year exclusivity is available for applications that contain reports of new clinical investigations (other than bioavailability studies) essential to the approval of the application and conducted or sponsored by the applicant."

Levothyroxine sodium tablets have been on the market and prescribed by physicians for many years. The literature is replete with studies covering almost every aspect of the drug and its effects. It is highly unlikely that any new clinical studies would be "essential to the approval" of levothyroxine sodium tablets for any currently recognized uses; therefore, three year exclusivity is not warranted.

Comment 5:
"An NDA applicant may submit a bioequivalence study comparing its levothyroxine sodium product to one previously approved."

The important issue of bioequivalence can best be addressed only after a reasonable time-frame is established and all interested parties have submitted their NDA applications. FDA should then communicate with companies that have a NDA pending and issue guidelines for those companies on how to conduct and submit bioequivalence data to supplement their NDA submissions if they are interested. These guidelines could also be used in the future by other companies interested in submitting ANDAs.

Comment 6:
"The proposed new dissolution test has not been adopted. Applicants should use the current official USP test. If the USP changes the official test after an NDA is submitted, an applicant can submit new data using that test as a phase-4 study."

The standards for approved applications and pending applications are different. The Agency's position stated in the August 1999 draft guidance document is unusual and not consistent with the regulation for the submission of compendial method's changes to an approved NDA/ANDA. According to 21CFR 314.70(d)(1) changes made to comply with an official compendium are to be submitted in an annual report. If a NDA is pending it seems inappropriate for the Agency to expect that the applicant conduct a phase-4 study when only a CMC amendment is normally required.

Comment 7:
"A stability overage is not permissible."

On December 15, 1997 Knoll Pharmaceutical Company filed a Citizen's Petition with FDA to issue an order declaring that Synthroid is generally recognized as safe and effective for the treatment of hypothyroidism and therefore not subject to regulation as a "new drug". Synthroid, as with all other currently available levothyroxine sodium tablets, is manufactured with a stability overage. Companies may mask their overages by stating that they are manufacturing overages. In reality, if a product is released for distribution at a potency which is significantly and consistently over 100% of label claim the overage is not a manufacturing overage but is a stability overage. If FDA accepts the Knoll Citizen's Petition and allows Synthroid to continue to be marketed without a NDA it would be setting up a dual standard, one which states that a stability overage for a NDA levothyroxine product is not allowed while saying that a stability overage is acceptable for a non-NDA levothyroxine product. The purpose of the August 14, 1997 notice requiring a NDA for this product was, in part, to bring consistency to all the levothyroxine products available. How can a dual standard accomplish this objective? The mandate that a stability overage is unacceptable in the manufacture of levothyroxine sodium tablets is premature.

Since the formulation and stability characteristics are a crucial issue in the preparation of any NDA submissions for levothyroxine sodium tablets, the deadline of August 14, 2000 must be delayed until the later of the following: (1) FDA rules on the Knoll Citizen's Petition; or (2) three years after the date of a final guidance document (see comments 1 and 2).

FAX: 201-524-9711
DIRECT LINE: 201-386-2000

October 14, 1999

Documents Management Branch
HFD-305
Food and Drug Administration
5630 Fishers Lane
Room 1061
Rockville, MD 20852

Ref: Docket No. 99D-2636

Re: Comments provided to Draft Guidance for Industry on Levothyroxine Sodium

Dear Sir or Madam:

Forest Laboratories, Inc. wishes to provide comments to the above referenced Draft Guidance. Please find attached two copies.

Respectfully submitted,

FOREST LABORATORIES, INC.

Gilbert W. Adelstein, Ph.D.
Director of Regulatory Affairs

99D-2636

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II. REGULATORY QUESTIONS AND ANSWERS

A. Status of Marketed Products

Q: After August 14, 1997, is it permissible to begin marketing an unapproved levothyroxine sodium product that has never before been marketed?

A: No. As stated in the *Federal Register* notice, any levothyroxine sodium product marketed *for the first time* after August 14, 1997, must have an approved new drug application. Any product marketed without an approved application is an unapproved new drug and subject to enforcement action.

Q: On August 14, 2000, what will be the status of a marketed product if an application for that product was submitted prior to August 14, 2000, but is not yet approved as of that date?

A: *Any* levothyroxine sodium product marketed on or after August 14, 2000, without an approved NDA will continue to be considered an unapproved new drug and will be subject to enforcement action (62 FR 43535, August 14, 1997). This will be the case even if an application for the product is undergoing review. Whether FDA will initiate enforcement action to remove an unapproved product from the market will depend upon its enforcement priorities and resources.

Comment:

Until July 27, 1999 the agency did not address the standards to be applied in the design and conduct of CMC stability studies for L-thyroxine. On that date, almost 2 years after the August 14, 1997 *Federal Register* Notice it issued a six paragraph statement, without prior notice or providing an opportunity for comment, that significantly restricted, without explanation, previously utilized stability study practices which had not been considered to be outside of cGMP. The July 27 statement did not explain why FDA considered its specifications as essential to be followed. In any event, it is clear that the one-year time period between July 27, 1999 and August 14, 2000, is insufficient to allow data generation and compilation which would be adequate to support an expiration date with a minimum of 24 months of a newly formulated product. It is critical that the August 14, 2000 date be extended to August 14, 2002.

B. Cutoff Date for 505(b)(2) Applications

Q: Will FDA approve only one NDA and convert other 505(b)(2) applications to ANDAs?

A: No. It is possible that more than one NDA will be approved. FDA will not convert any filed NDA to an ANDA.

Q: Will there be a cutoff date after which FDA will no longer accept and review 505(b)(2) applications?

A. FDA will review all 505(b)(2) applications for levothyroxine sodium products filed before the first NDA for levothyroxine sodium products is approved. After the first NDA for levothyroxine sodium is approved, FDA may refuse to file any 505(b)(2) application for a drug product that is a duplicate of the product approved in the first NDA. If an application is refused for filing, it may be resubmitted as an ANDA, provided it meets the requirements of section 505(j) of the Act.

Comment:

As stated above, the August 14, 2000 filing date does not provide sufficient time for reformulation of an old product, if required, generation of stability and bioequivalence data, and submission of the NDA. This date should be extended to August 14, 2002.

Q: What will happen to a 505(b)(2) application that has been filed, but not yet approved, when the first NDA for levothyroxine sodium is approved? What if the application was submitted, but not filed, when the first NDA is approved?

A: FDA will review all NDAs, including 505(b)(2) applications for duplicates, that have been filed even if an NDA is approved before review of an application has been completed. The FDA may refuse to file and review a 505(b)(2) application that was submitted, but not filed, before the first NDA for levothyroxine sodium is approved.

C. Requirements for 505(b)(2) Applications

Q: Should a 505(b)(2) application contain a patent certification?

A: All 505(b)(2) applications are subject to the patent certification requirements at 21CFR 314.50(i). However, if there is no listed drug for levothyroxine sodium at the time the application is filed, the applicant need not make a patent certification.

After an NDA is approved and there is a listed drug, applications that have been submitted or filed, but not yet approved, must be amended to contain a patent certification for each patent listed for the approved product (21 CFR 314.50(i)). If there are no patents listed for the approved product, the applicant should submit a statement, as described at 314.50(i)(1)(ii), that there are no relevant patents.

Q: Will a 505(b)(2) application for levothyroxine sodium be assessed a user fee? If so, is it a full fee or half fee?

A: Yes, a user fee will be assessed. The Act provides that a 505(b)(2) application is subject to an application fee if it requests approval of either (1) a molecular entity that is an active ingredient (including any salt or ester of an active ingredient) that has not been approved under section 505(b) of the Act, or (2) an indication for a use that has not been approved under section 505(b) of the Act (sections 735(1)(B) and 736(a)(1)(A)(i) of the Act). Levothyroxine sodium has been approved previously as an active ingredient in two NDAs (NDA 16-807, Thyrolar, and NDA 16-680, Euthroid). However, levothyroxine sodium as a single-agent therapy has not been approved for any indication. Therefore, the FDA believes that single-agent therapy for thyroid-related disorders is a new indication for use. Therefore, applicants submitting 505(b)(2) applications for levothyroxine sodium must pay a user fee. But once an application has been approved, another 505(b)(2) application for levothyroxine sodium would not be subject to a fee unless the applicant seeks approval of an indication different from that approved in earlier applications. A full fee would be assessed because clinical data (other than bioavailability or bioequivalence studies) with respect to safety or effectiveness are required for approval (section 736(a)(1)(A)(i) of the Act). These clinical data are expected to be in the form of literature reports, but are still considered to be clinical data for purposes of assessing user fees.

An applicant submitting a 505(b)(2) application for levothyroxine sodium may be eligible for a waiver or reduction of user fees under section 736(d) of the Act. For information on how to apply for a waiver, you may contact the Regulatory Policy Staff, CDER, HFD-7, 5600 Fishers Lane, Rockville, Maryland 20857, 301-594-2041.

Comment:

Section 505(b)(2) applications for levothyroxine sodium for the treatment of hypothyroidism, as called for in the *Federal Register* of August 14, 1997 are, by statute, not subject to user fees. Prior to adoption of the "human drug application" definition in the Prescription Drug User Fee Act of 1992 (in which the definition is the same as in FDAMA) the question of the status of § 505(b)(2) applications under that definition was addressed on the House Floor in the "Statement of Floor

Manager Explaining Changes Made After Committee Consideration of HR 5952." (page H9099. Sept. 22. 1992). A copy of the most directly pertinent paragraph is set out below:

> The change, made after the bill was reported by the committee but which is in the bill, would limit the § 505(b)(2) applications included within the definition of "human drug application" – § 735(1)(B), as added by section 3 – to applications that request approval of first, [a] molecular entity which is an active ingredient or second, an indication for a use that had not been approved under § 505(b). The Committee intends that the term "indication" be given the meaning that it is given in the FDA's regulations. 21 C.F.R. § 201.57(c), 1992. This term would include an Rx to OTC switch. User fees would not be required for any other new drug approved under § 505(b)(2).

The context of FDA's regulation at 21 C.F.R. § 201.57(c)(1)(i) through (iv) reveals that no substantive distinction was drawn between "indication" as used in the cited regulation and "indication for a use" as used in § 735(1)(B)(ii). If "an active ingredient" had been approved in a §505(b) application before September 1, 1992, with "an indication for use" of that ingredient , a §505(b)(2) applicant for a drug product containing that same ingredient and the previously approved indication for use would not come within the definition of "human drug application" and therefore would not be subject to a user fee. This User Fee exclusion provision clearly applies to §505(b)(2) applications addressed to the use of levothyroxine sodium in the treatment of hypothyroidism. The "indication" in this situation is the "treatment of hypothyroidism," and the active ingredient is levothyroxine sodium. Both the indication and the ingredient have been previously approved for Thyrolar and Euthroid. "Single-agent" therapy is not a statutory element or a practical requirement since the August 14, 1997 Notice recognizes the efficacy of levothyroxine as a single entity.

Q: Are pediatric studies necessary?

A: As of April 1, 1999, all applications for new active ingredients, new indications, new dosage forms, new dosing regimens, and new routes of administration must contain a pediatric assessment, unless such studies are waived or deferred. Studies that are deferred are not required to be submitted until at least December 2, 2000.[3]

Applications for levothyroxine sodium are subject to the pediatric rule. Applicants should discuss with the division the need for a pediatric assessment for the levothyroxine product proposed in an NDA. It is possible that adequate data to support safety and effectiveness for pediatric use may be available in the scientific literature.

D. Exclusivity

Q: Will there be exclusivity for the first levothyroxine sodium product to be approved?

A: Exclusivity determinations are made at the time a drug product is approved. Although FDA cannot at this time be specific as to which, if any, applications may receive exclusivity, sponsors should consider some issues regarding the requirements for exclusivity. Five-year exclusivity is available for new chemical entities, which are drugs that contain no previously approved active moiety.

Levothyroxine sodium has previously been approved as an active ingredient in two NDAs (NDA 16-807, Thyrolar, and NDA 16-680, Euthroid). Three-year exclusivity is available for applications that contain reports of new clinical investigations (other than bioavailability studies) essential to the approval of the application and conducted or sponsored by the applicant.

Comment:

If the determination is made by the FDA that clinical studies are essential to the approval of NDAs that meet the criteria of the August 14, 1997 Notice, each such NDA should be awarded an exclusivity period.

E. Therapeutic Equivalence Ratings for Levothyroxine Sodium Products

Q: If the Agency approves multiple 505(b)(2) applications, how will they be rated in the Orange Book?

A: They will be listed as BX **C** drug products for which the data are insufficient to determine therapeutic equivalence. To obtain a therapeutic equivalence rating other than BX for levothyroxine sodium tablets, an applicant must submit data comparing its product to a listed drug (*Approved Drug Products with Therapeutic Equivalence Evaluations* – The Orange Book).

Q: Will FDA review a bioequivalence study submitted with an NDA that compares the product to an approved levothyroxine sodium product?

A: Yes. An NDA applicant may submit a bioequivalence study comparing its levothyroxine sodium product to one previously approved. If the products are bioequivalent, they will be AB-rated to each other.

F. ANDAs for Levothyroxine Sodium Products

Q: When will FDA choose a reference listed drug?

A: FDA chooses a reference listed drug when a manufacturer makes a request to submit an ANDA for a product that is eligible for approval under section 505(j) of the Act.

Q: How will FDA choose a reference listed drug for levothyroxine sodium tablets?

A: If there is only one approved product, that product will become the reference listed drug. If more than one product has been approved before FDA receives a request to submit an ANDA, the market leader among the approved products will be designated as the reference listed drug. FDA may also designate an additional reference listed drug if requested to do so by an ANDA sponsor.

Q: Will there be more than one reference listed drug?

A: It is possible.

Comments:

We believe that each currently marketed product should be given the opportunity to submit an NDA. FDA should review all studies submitted in the NDA including a bioequivalence study and approve the bioequivalence study, whether or not another levothyroxine product has been previously approved. Once the other product is approved, at that time an AB-rating for the two products should be granted and included in the Orange Book.

III. SCIENTIFIC QUESTIONS AND ANSWERS

A. Stability Data

Q: How much stability data is required for an application to be acceptable for filing?

A: ICH and FDA stability guidances recommend 12 months' long-term data and 6 months' accelerated data at the time of NDA submission if a 24-month expiration date is requested. However, for levothyroxine sodium products to meet the compliance date specified in the August 14, 1997, *Federal Register* notice, 6 months' long-term data and 3 months' accelerated data will be sufficient. Additional stability data may be submitted as an amendment during the review process, and an expiration date will be granted based on the data submitted.

Comment:

On July 27, 1999, the FDA Division of Metabolic and Endocrine Drug Products issued a document entitled "Guidelines for Submission of CMC Stability Studies For NDA for L-thyroxine." This was almost two years following the Federal Register notice of August 14, 1997. Previously, no official notice of ICH stability requirements had been issued. If the sponsor of a NDA began stability studies under ICH conditions on July 27, 1999, and successfully collected the 3 months' accelerated and 6 months' long-term data, the NDA submission could not take place until well after January 27, 2000. Assuming an additional 6 months of stability data were to be submitted as an amendment to the pending NDA on July 27, 2000, the FDA would have to review and approve the NDA before August 14, 2000, barely 18 days following the latest amendment. This scenario can not realistically be accomplished and illustrates the need for an appropriate time extension for submission and approval of an application.

The imposition of ICH stability storage conditions was intended "only for new molecular entities and associated drug products" (ref: Draft Guidance for Industry: Stability Testing of Drug Substances and Drug Products, May 1998). Although FDA considers L-thyroxine products subject to new drug classification, they have been available and used in medical practice for years. While specified as a new molecular entity for purposes of the NDA, this product has existed in medical practice for years and recognized as essential in the August 14, 1999 Federal Register notice. Manufacturers may still be using adequate and appropriate formulations for products that were never meant to support stability storage temperatures and humidity levels required by contemporary standards. The authors of the Draft Guidance for Industry recognized this and stated that for products already approved, or in this case marketed, "applicants may wish to voluntarily switch to the ICH-recommended storage conditions as defined in ICH Q1A and Sections II.A.4. and II.B.5. of this guidance."

The instability of L-thyroxine formulations under conditions of moisture and heat is well-documented, as has been pointed out in the Federal Register Notice of August 14, 1997. Therefore, applying ICH stability requirements to a product with known sensitivities to ICH conditions will likely result in stability failures. For products that have not been reformulated, the stability storage conditions should remain unchanged from the pre-NDA condition.

Since levothyroxine sodium belongs to a class of products marketed prior to the promulgation of the ICH stability conditions, real time stability data from the marketed product should be sufficient. Stability data compiled from data of marketed lots stored under 25– -2 degrees and

ambient humidity conditions should be accepted. Submission of accelerated storage data should be waived for this product due to the availability of real time data and the known detrimental effect of high temperature and humidity on the active ingredient.

FDA has recognized that "levothyroxine sodium is unstable in the presence of light, temperature, air, and humidity." [62 FR 43537]. As a consequence, manufacturing methods have been developed to compensate for such circumstances. These include manufacturing a batch in conformity with the standards of cGMPs with a fixed overage of active ingredient. For a defined period after manufacture, the batch is "aged" for a specified time. During the aging period a reduction in the level of active ingredient takes place which will decelerate after the passage of a known time period. At the time of release, the batch will be within USP specifications and remain so throughout its expiry period. Whether the described practice involves a "stability overage" or a "manufacturing overage" is a question of semantics. So long as it can be shown that all of the manufacturing practices followed are defined and validated and the product remains within specification throughout the period from its release to expiration, the described course of manufacture should be recognized as acceptable.

As stated above, it has been established that levothyroxine sodium drug substance is unstable in the presence of light, temperature, air and humidity. The fact that a formulation and/or packaging configuration may or may not compromise stability in response to extreme environmental factors does not necessarily relate to the long-term stability of these products. A compilation of all relevant historical stability data for levothyroxine sodium products should suffice to show that the packaging and storage requirements of these products and their expiration dating have been suitably established. Moreover, re-examination of the stability of these products under the ICH accelerated or controlled-room temperature has no relevance to concerns raised regarding the inadequacy of stability test procedures or of the ability to prevent occasional instances of superpotency.

B. Dissolution Test

Q: The USP proposed a new dissolution test for levothyroxine sodium in the January-February 1999 *Pharmacopeial Forum*. Should NDA applicants use that proposed test or continue to use the current official method?

A: The proposed new dissolution test has not been adopted. Applicants should use the current official USP test. If the USP changes the official test after an NDA is submitted, an applicant can submit new data using that test as a phase-4 study.

Comment:

According to the guidance "*In Vivo* Pharmacokinetics and Bioavailability Studies and *In Vitro* Dissolution Testing for Levothyroxine Sodium Tablets", dissolution studies can be performed using the current USP method or others provided that justification for the choice of the method is given. Therefore, the applicant's procedure, if different from the current compendium method, should also be considered acceptable when given with the appropriate justification.

C. Overage

Q: May a stability overage be used?

A: No.

Comment:

A stability overage may be required for selected products. A more valid concern raised by FDA relates to the issue of sub- or super- potency. Based on FDA's own research, a stability overage is necessary otherwise subpotent products will result. If the manufacturer can show that there are no instances of superpotency in products released to the marketplace, then the formulation manufactured with stability overages should be allowed. The dosage should be formulated with the intent to provide 100 percent of the quantity of the active ingredient declared. Where historical data establishing the content of the active to decrease with time, an amount in excess of the declared on the label may be introduced into the dosage form at the time of manufacture to assure compliance with the content requirements of the label throughout the expiration period. This will assure that a super-potent product will not be released to the marketplace. Thus stability overage should be allowed when justified and where the product meets compendial requirements for content uniformity and potency at the time of release.

Q: May a manufacturing overage be used?

A. Yes. The FDA permits the use of a manufacturing overage only in the unusual case when the product is manufactured to be 100 percent potent at the time of release and when the manufacturer can specifically document where in the manufacturing process the loss of potency occurs.

Comment:

A manufacturing overage is sometimes required. There should be no need to specifically document where in the manufacturing process a loss of potency occurs. The fact that a loss occurs combined with product release data demonstrating that the product is neither subpotent nor superpotent should suffice. The FDA and USP both permit the use of a manufacturing overage where there is data supporting potency loss during the manufacturing process.

BASF Pharma

October 18, 1999

Dockets Management Branch
HFD-305
Food and Drug Administration
5630 Fishers Lane
Room 1061
Rockville, MD 20852

Re: Docket No. 99D-2636
Draft Guidance for Industry on
Levothyroxine Sodium

Knoll Pharmaceutical Company ("KPC" or "Knoll") submits herewith its comments on this draft guidance.

The draft guidance begins with the premise that orally administered levothyroxine sodium drug products are "new drugs," and proceeds to answer questions that have arisen about the new drug applications that are to be submitted pursuant to the Food and Drug Administration's August 14, 1997 Federal Register notice (the "Notice"). As discussed in more detail below, however, FDA's initial premise is incorrect, at least as to Knoll's Synthroid® levothyroxine sodium tablets. Knoll also believes that FDA's answers to many of the questions are wrong. Any final guidance must correct these errors. In addition, FDA must recognize that it cannot by issuing a guidance avoid its obligation to respond to Knoll's Citizen Petition on Scheduling and Procedure, which raised many of the issues addressed in the draft guidance.[1]

"New Drug" Issues

Throughout the draft guidance, especially in the Introduction and the section on Regulatory Questions and Answers, FDA states that all levothyroxine sodium drug products are "new drugs" and assumes that the agency's "announcement" in the Notice disposes of the matter. In fact, the Notice itself recognized that some levothyroxine sodium drug products may not be new drugs, and invited the submission of Citizen Petitions to that effect. Knoll submitted such a Citizen Petition on December 15, 1997, demonstrating that Synthroid is

1. Citizen Petition on Scheduling and Procedure, Docket No. 97N-0314/CP3, filed September 25, 1998 and supplemented August 4, 1999 (hereinafter "Scheduling and Procedure Petition"). A copy of the Scheduling and Procedure Petition, without attachments, is attached.

99D-2636 C3

generally recognized as safe and effective and therefore not a new drug.[2] The agency's conspicuous omission from the draft guidance of its own invitation to submit Citizen Petitions and the fact that KPC (and one other manufacturer as well) have done so suggests once again that the agency is refusing to give Knoll's GRAS/E Petition the full and fair consideration it deserves.[3]

Cutoff Date for Section 505(b)(2) Applications

Taken together, the questions and answers in this section of the draft guidance amount to a declaration that once the first NDA or set of NDAs is approved for levothyroxine sodium, FDA may refuse to file and refuse to review and will not approve any further § 505(b)(2) NDAs. Such a declaration is contrary to the Food, Drug, and Cosmetic Act ("FDCA" or "Act") and to the clear intent of the Congress in adopting the relevant statutory provisions.

As applied to Synthroid, such a policy would also be both unfair and peculiar. Because Knoll responded to FDA's invitation in the Notice to submit its GRAS/E Petition, an NDA is not required for Synthroid unless FDA denies Knoll's GRAS/E Petition and the courts uphold it. Thus, if an NDA is ever submitted for Synthroid,[4] it may not be submitted until after one or more of the other NDAs is approved, and, under this draft guidance, FDA would be free to refuse to file, review, and approve it. In so doing, FDA would, in effect, be punishing Knoll for doing what it has every right to do: accepting FDA's published invitation to submit a Citizen Petition and waiting until FDA and the courts reach a decision on whether Synthroid is a new drug before submitting an NDA. Importantly, because the published literature on which levothyroxine NDAs will be based consists entirely or nearly entirely of studies of Synthroid, it seems peculiar indeed to say that every company but Knoll will be allowed to rely on the published literature.

Both the words and the structure of § 505 of the Act compel the conclusion that (except for issues of exclusivity, which are not relevant here) FDA lacks authority to refuse to file, review, and approve a new drug application merely because it has previously approved another

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2. Citizen Petition on Regulatory Status of Synthroid Orally Administered Levothyroxine Sodium USP, Docket No. 97N-0314/CP2, filed December 15, 1997 and supplemented May 29, 1998 (hereinafter "GRAS/E Petition"). A copy of the GRAS/E Petition, without attachments, is attached.

3. See Scheduling and Procedure Petition at 4-7.

4. As noted above and in its GRAS/E Petition, Knoll believes that Synthroid is not a new drug and that no NDA is required for Synthroid. If, however, FDA and the courts disagree, then an NDA will have to be submitted. Knoll's discussing that possibility in these comments is not a waiver of its position that Synthroid is not a new drug.

new drug application for the same active ingredient under § 505(b)(2). Section 505(a) provides that a new drug may not be lawfully marketed unless it is the subject of either an approved New Drug Application under § 505(b) or an approved Abbreviated New Drug Application under § 505(j). Either an NDA or an ANDA is permissible; the statute expresses no preference.

That the choice of an NDA or an ANDA is the applicant's is reinforced by the wording of §§ 505(b) and 505(j). "Any person" may submit an NDA under § 505(b), and "any person" may submit an ANDA under § 505(j).[5] The statute imposes no duty on "any person" to refrain from submitting an NDA if an ANDA is also a possibility; the choice is left up to the applicant.

Certainly the Act does not make FDA's approval of a previous NDA a ground for denial of a later NDA submitted under § 505(b). If an NDA is submitted under § 505(b), FDA must (after a specified time period) approve it unless it finds that one or more of the grounds specified in § 505(d) is applicable. FDCA § 505(c). None of the grounds in § 505(d) has anything to do with whether one or more applications for the same drug were previously approved under § 505(b)(2), an omission which is fatal to FDA's claim of authority to deny an NDA on the ground that it had previously approved another NDA for the product containing the same active ingredient.[6]

There is no doubt that these provisions of § 505 apply to § 505(b)(2) applications as well as § 505(b)(1) applications. FDA has recognized as much. In the preamble to the ANDA/505(b)(2) regulations, for example, FDA stated that in all respects relevant to this issue, § 505(b)(2) applications are "subject to the same statutory provisions as full NDAs." 57 Fed. Reg. 17950, 17952 (April 28, 1992).

The legislative history confirms that the ANDA provisions were intended to supplement - not supplant - the NDA provisions of the Act. As explained in the House Report, "Title I of the bill [the ANDA provisions] allows drug manufacturers to use an abbreviated new drug application (ANDA) when seeking approval to make generic copies of drugs that were approved by the FDA after 1962." H. R. Rep. No. 98-857, pt. 2, at 11 (1984) (emphasis

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5. The Act speaks of any person's "filing" an NDA. These comments follow common usage in using the phrase "submitting" an NDA so as to avoid confusion with the actions FDA may take in "refusing to file" or "filing" a submitted NDA.

6. Nor can FDA avoid its lack of authority to deny an NDA on this ground by calling it a "refusal to file," notwithstanding FDA's regulation claiming such authority. 21 C.F.R. § 314.101(d)(9). Like the draft guidance, this regulation flies in the face of the statute, and is therefore unlawful. The agency's refusal to file certain § 505(b)(2) applications is unlawful for other reasons as well, as set forth in the Scheduling and Procedure Petition at 7-9.

added) (copy attached). The ANDA procedure did not replace the NDA procedure: it "graft[ed] on the NDA procedure . . . authority for an abbreviated new drug application (ANDA) procedure. . . ." Id. Two commentators have confirmed this view:

> The statute continues the availability of paper [505(b)(2)] NDAs for post-1962 drug approval, although it is expected that most applications will take advantage of the new ANDA procedures.

Allan M. Fox and Alan R. Bennett, The Legislative History of the Drug Price Competition and Patent Term Restoration Act of 1984, at 95 (1987) (copy attached).

> The 1984 Waxman-Hatch Act amendments to the FDCA left intact one option for FDA approval of generic drugs that had existed previously. Approval of a generic drug can still be obtained by submitting a new drug application to the agency pursuant to FDCA Section 505(b).

Donald O. Beers, Generic and Innovator Drugs: A Guide to FDA Approval Requirements, at 2-2 (5th ed. 1999) (footnote omitted) (copy attached).

From a policy standpoint, FDA's attempt to remit some applicants to ANDAs once NDA(s) are approved will not save the agency any work, and could be unfair to Knoll and other applicants. In the case of levothyroxine, FDA has twice recognized, once in the Notice and once in the draft guidance, that applicants will be able to rely on published literature for proof of safety and effectiveness. Thus, each § 505(b)(2) application for levothyroxine sodium will likely contain most or all of the same published studies. Once FDA reviews those published data, it can apply its judgments on safety and efficacy to all levothyroxine products, and need not repeat the review. By contrast, it would have to review de novo each bioequivalence study in an ANDA, making more work, not less.[7] Equally important, the published studies are on Knoll's Synthroid.[8] It would be both unfair and peculiar for FDA to allow studies of Synthroid to be utilized in § 505(b)(2) applications for other products but not for Synthroid itself.

The draft guidance's approach to cutoff dates for § 505(b)(2) applications is also mischievous in giving FDA far too great an opportunity to pick and choose among applicants for any reason or no reason. Because of FDA's confidentiality rules, no applicant can be sure of knowing when or whether any other applicant has submitted an NDA, when or whether FDA has filed it or refused to file it, or whether review of a particular application is

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7. See Scheduling and Procedure Petition at 9.

8. See GRAS/E Petition at 10-11.

progressing well toward approval or not. Thus, no applicant can gauge or even guess at when a § 505(b)(2) application needs to get submitted to avoid preclusion of its § 505(b)(2) application. But FDA can easily manipulate the process by holding up approval of one application for a day or so (or a week or a month) to allow it to file one or more other § 505(b)(2) applications, all while not filing one or more other applications before the approval. Such unbridled discretion is a recipe for unfairness, whether intentional or accidental.

User Fees

The Act authorizes user fees for applications submitted under § 505(b)(2) only if the active ingredient "had not been approved under an application submitted under section 505(b)" or, having been so approved, is now being submitted for a new indication. FDCA § 735(1)(B). FDA acknowledges that levothyroxine sodium has been previously approved for hypothyroidism under § 505(b) in combination with triiodothyronine as Euthroid and Thyrolar. It argues, however, that because LT4 has never been approved as a single ingredient for hypothyroidism, applications will be for a new indication and a user fee will therefore be due. But nothing in the statute distinguishes between approval for a particular indication as a single ingredient or in combination. Either way, the active ingredient has previously been approved for that indication, and no user fee can be required.

FDA's interpretation of the statute is not only incorrect, it also creates considerable potential for confusion and unfairness. As FDA itself recognizes, it can collect at most one user fee in this situation, because once the first NDA is approved, no one else owes a user fee. But how will this work in practice? User fees are payable at the time NDAs are submitted, and because most applications for NDAs for levothyroxine will be submitted before the first one is approved, almost every applicant will have to send a check. Then what will FDA do? How will it decide which application to approve first, knowing that only that one applicant will have to pay? Will the unlucky loser have any right to object to having lost? Does FDA plan to cash all the checks and deprive applicants of the use of their money (a considerable sum - $272,282 in FY1999) while review is pending? Or will it put the checks in escrow pending a decision on who owes and who doesn't? How long will it take to make refunds?

Exclusivity

The section on exclusivity is correct in noting that five year exclusivity is not available to levothyroxine products because the active moiety has been previously approved as an active ingredient in two NDAs. The section errs, however, in leaving open the possibility that three year exclusivity may be available for applications that contain reports of "new clinical investigations" that are "essential" to the approval of the application. As the Notice stated,

and as the draft guidance reiterates, published literature supports the safety and efficacy of levothyroxine sodium. Accordingly, new clinical studies are not essential, and no three year exclusivity can attach. FDA should say so.

Therapeutic Equivalence Issues

In suggesting that an applicant can submit as part of its NDA a bioequivalence study comparing its levothyroxine product to one previously approved, FDA seems to be creating an unlawful procedure for ANDAs. As Knoll has explained in its Citizen Petition on Scheduling and Procedure, a copy of which is attached hereto and incorporated herein by reference, the Act and FDA's implementing regulations do not permit the submission and receipt of an ANDA until there is a reference drug listed in the Orange Book, a step which can occur only after approval of an NDA for the drug. Any procedure that allows or results in simultaneous submission of an NDA and an ANDA before FDA approval of the first NDA for levothyroxine sodium contravenes these explicit statutory and regulatory requirements. FDA cannot fix this illegality by pretending that the ANDA does not exist until the time it approves the first NDA.

Perhaps this section is not intended to provide for the submission of ANDAs as such, but rather for the submission in an NDA of bioequivalence data which could result in an AB rating for two NDA-ed products. No such procedure is specified anywhere in the Act, FDA's regulations, or the Preface to the Orange Book (to which FDA generally but vaguely alludes). If Section 1.10 of the Orange Book does imply any means of making two NDA-ed drugs AB to each other (and it does not really seem to), it seems to suggest that before that can happen, both must be approved and listed in the Orange Book (as BX); only then can one of them seek an "upgrade" by submission of a bioequivalence study to the other listed drug. In any event, announcing important changes to FDA's past practice, changes which will have significant effects on the regulated industry as well as consumers, must be done by notice and comment rulemaking, not by casual assertions of authority in a guidance.

In addition, although Section 1.10 contemplates that changes in ratings of a single product from BX to AB will not ordinarily be the subject of notice and comment, the questions of bioequivalence or bioinequivalence of levothyroxine products have been so vexed for so long[9] that notice and comment is surely not only appropriate but necessary in this area. As FDA is aware, numerous studies have purported to show that one or more LT4 products are or are not bioequivalent or bioinequivalent. These studies are not of uniform design, and there is little or no agreement on the appropriate or desirable design of such studies. Indeed, FDA itself has been of two different minds on the subject of whether one design, the Berg-Mayor

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9. See, e.g., Leonard Wartofsky, Bioequivalence of Levothyroxine Preparations: Shortcomings and Implications of a Recently Published Study, The Endocrinologist 1997: 7:322-333 (copy attached).

model. is appropriate for bioinequivalence and bioavailability studies.[10] Many other issues have also evoked considerable debate, for example. whether it is better to study LT4 bioequivalence in athyreotic subjects or in subjects with functioning thyroids, and, if the latter, how to make sure that changes in thyroid output during the study are not confounding. And because, as FDA has recognized, levothyroxine sodium is a narrow therapeutic index drug, Notice at 43538, relatively small differences between two products that might be acceptable in other drugs could have health consequences for patients with thyroid disease. Still another important issue is the desirability of assessing individual bioequivalence using replicate designs. See FDA Draft Guidance for Industry on Average, Population, and Individual Approaches to Establishing Bioequivalence, 64 Fed. Reg. 48842 (Sept. 8, 1999), and FDA Draft Guidance for Industry on BA and BE Studies for Orally Administered Drug Products - General Considerations, 64 Fed. Reg. 48409 (Sept. 3. 1999).

Knoll believes, therefore, that FDA should not consider bioequivalence studies of levothyroxine products until some sort of iterative public process, preferably beginning with the issuance of a draft guidance for public comment. allows the medical, pharmacy, consumer, and manufacturing communities the opportunity to work with FDA to reach consensus on the considerations which should govern LT4 bioequivalence determinations and the kinds of studies which best satisfy the consensus.

Stability

This section seems to suggest that the NDA must include 6 months' accelerated data if 24 month expiration dating is requested. or. at a minimum. 3 months' accelerated data. For products such as Synthroid which have been marketed for many years, real time stability data at 25°C. collected pursuant to FDA's GMP requirements, are available to support expiration, and FDA has in fact reviewed and accepted such data as part of its inspections, including the most recent inspection. Furthermore, accelerated stability data have not been a good predictor of room temperature stability for levothyroxine formulations because potency loss at elevated temperatures has not translated to potency loss under room temperature conditions. Knoll therefore asks FDA to confirm that real time data are acceptable, and that accelerated data are not required if real time data are available.

Overage

In this section. FDA declares point blank that stability overages are impermissible, but cites no references and gives no reasons. Knoll does not believe that a stability overage is prohibited by the USP monograph for levothyroxine sodium, FDA's regulations on Good

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10. See Knoll's comments on FDA Draft Guidance for Industry on In Vivo Pharmacokinetics and Bioavailability Studies and In Vitro Dissolution Testing for Levothyroxine Sodium Tablets. Docket No. 99D-1149. Letter from Nancy L. Buc to Dockets Management Branch. August 2. 1999. at 3-4. A copy of this letter. without attachments. is attached.

Manufacturing Practices, or any other published source. USP, in fact, clearly permits overages, both as a general matter and in connection with levothyroxine in particular. Thus, in the General Notices and Requirements section, USP advises that:

> Where the content of an ingredient is known to decrease with time, an amount in excess of that declared on the label may be introduced into the dosage form at the time of manufacture to assure compliance with the content requirements of the monograph throughout the expiration period.[11]

Likewise, the USP monograph for levothyroxine sodium tablets provides that the tablets must contain "not less than 90.0 percent and not more than 110.0 percent of the labeled amount" of LT4. FDA's own GMP regulations are not to the contrary. They provide that batches shall be formulated with "the intent to provide not less than 100 percent of the labeled or established amount of active ingredient,"[12] but are silent on providing over 100 percent. Knoll therefore questions the procedural permissibility of FDA's purporting to create a GMP or NDA requirement without explaining its reasons for wanting to do so and allowing an opportunity for comment. Nor does Knoll believe that the presence of a stability overage necessarily creates any problems, and it therefore questions the need for such a pronouncement.

Relationship of Draft Guidance to Knoll's Citizen Petition on Scheduling and Procedure

Many of the issues discussed in the draft guidance were raised in Knoll's Citizen Petition on Scheduling and Procedure. Knoll reminds FDA that the agency is obligated to respond to its Citizen Petition, and that even final guidances, much less draft guidances, do not obviate this requirement.

Sincerely,

Robert W. Ashworth /s/

Robert W. Ashworth, Ph.D.
Director, Regulatory Affairs

APPEARS THIS WAY
ON ORIGINAL

Steven J. Goldberg /s/

Steven J. Goldberg
Associate General Counsel
Product and Trade Regulation

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11. United States Pharmacopeial Convention, Inc., United States Pharmacopeia 23 - National Formulary 18, at 3 (1995).

12. 21 C.F.R. § 211.101(a).