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April 28, 2000

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

Re: Docket No. 97N-0314/CP3
Citizen Petition on Scheduling
and Procedure

5603 00 HW -5 P150

Please file the attached letter in the above-referenced docket. Thank you.

Sincerely,



Nancy L. Buc

97N-0314

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Reply to Food and Drug Administration's
Response to Knoll Pharmaceutical Company's
Citizen Petition on Scheduling and Procedure
Docket No. 97N-0314/CP3

and

Supplement to Citizen Petition on
the Regulatory Status of Synthroid®
Orally Administered Levothyroxine
Sodium USP
Docket No. 97N-0314/CP2

Knoll Pharmaceutical Company ("Knoll" or "the Company") has received the Food and Drug Administration's April 26, 2000 response to its Citizen Petition on Scheduling and Procedure, and is writing to correct the record in certain significant respects. FDA's response contains numerous misinterpretations of Knoll's arguments, the applicable law, and the agency's own regulations. Knoll addresses in this letter only the most important of them.¹

Of primary importance, FDA's assertion that Knoll's Citizen Petition requesting a determination that Synthroid® levothyroxine sodium USP is generally recognized as safe and effective for the hypothyroidism indication was incomplete on the day it was filed in December 1997 and is still incomplete is simply incorrect. The GRAS/E Citizen Petition filed on December 15, 1997² demonstrated that Synthroid is generally recognized as safe and effective,

1. Knoll's addressing in this letter only the most important issues does not constitute a waiver of, and Knoll expressly reserves, its right to challenge the response and/or other FDA decisions or actions, including but not limited to FDA's assertion of its authority to refuse to file under Section 314.101(d)(9) of its regulations a 505(b)(2) NDA for Synthroid if an NDA has previously been approved for another levothyroxine sodium product.

2. In its response, FDA states that Citizen Petitions were due on October 14, 1997 and that Knoll filed its Citizen Petition on December 15, 1997. By omitting to state that Knoll had received a letter dated October 9, 1997 from CDER's Associate Director for Policy extending its time for submission to December 15, 1997, FDA creates the misimpression that the Citizen Petition was filed untimely. It was not.

a conclusion that was bolstered by the supplement Knoll filed on November 17, 1999.³ Under FDA's regulations, filing a supplement is permissible at any time until the agency rules on the Citizen Petition. 21 CFR § 10.30(g). That Knoll did file a supplement to its GRAS/E Citizen Petition utilizing, inter alia, documents FDA provided in response to the Company's Freedom of Information Act request, does not mean that the original GRAS/E Citizen Petition was inadequate to support the relief it sought. Also, contrary to footnote 2 in FDA's response, Knoll has not taken the position that the GRAS/E Citizen Petition will not be complete until it receives a complete response to its FOIA request. Knoll merely asked FDA to allow it time to supplement the petition once the response to the FOIA request is complete, a request that FDA has now apparently denied some 19 months after it was made. Asking for time to supplement a petition is not tantamount to a position that the petition was or will be incomplete if the request is not granted.

Let there be no mistake. As demonstrated in the GRAS/E Citizen Petition submitted on December 15, 1997, Synthroid is generally recognized as safe and effective for the hypothyroidism indication. The supplement filed on November 17, 1999, as FDA's regulations permit, further supports the conclusion that Synthroid is generally recognized as safe and effective. Knoll's December 15, 1997 GRAS/E Citizen Petition on the hypothyroidism indication was ready for FDA review on the day it was filed, and as supplemented on November 17, 1999, it has been and continues to be ready for FDA review.⁴

And let there be no mistake, either, about two more points. First, FDA's "surmise" that Knoll "does not yet believe that it has sufficient information to establish that Synthroid is GRAS/E, but believes that the GRAS/E status of Synthroid may be revealed in a yet-to-be-disclosed FDA document" is flat wrong. As stated above, the Citizen Petition amply demonstrated that Synthroid is GRAS/E when it was filed in 1997, and the supplement filed in 1999 confirmed that conclusion. What the supplement does show is that documents in FDA's own files squarely belie FDA's contentions as to Synthroid in its August 14, 1997 Federal Register Notice, and that the Notice was therefore arbitrary and capricious not only because it

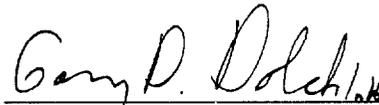
3. FDA's response treats the supplement to the GRAS/E petition filed on May 29, 1998 as if it were relevant to the hypothyroidism indication. It is not. It demonstrates that Synthroid is also generally recognized as safe and effective for the cancer indication.

4. Similarly, the GRAS/E supplement on the cancer indication was ready for FDA review on the day it was filed, and has been and continues to be ready for FDA review.

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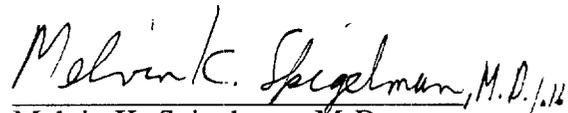
is incorrect, but also because FDA knew it was incorrect.⁵ Second, Knoll has been and is ready to defend at any time its claim that Synthroid is generally recognized as safe and effective, and FDA's insinuations to the contrary are baseless.

Respectfully submitted,



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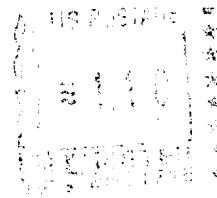
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5. For example, the Notice asserted and the FDA response reasserts that there are "widespread" problems with the potency and stability of levothyroxine sodium products. Knoll's December 15, 1997 GRAS/E Citizen Petition stated that whatever might be the case with other levothyroxine sodium products, "there are ample data in both the published literature and Knoll's and FDA's own files" demonstrating that Synthroid is reliably stable and potent, and provided the data in question. See pages 20-33 and exhibits pertaining thereto. The November 17, 1999 supplement provided additional support on this point, including documents from FDA's files obtained in response to Knoll's FOIA request, e.g.: a 1995 FDA memorandum describing results of an analysis conducted by FDA's Seattle laboratory showing that Synthroid met compendial limits for assay, identification, uniformity of dosage units, and dissolution; a 1993 FDA memorandum stating that "[r]ecent [Synthroid] sample collections do not reveal potency problems"; and a 1998 Establishment Inspection Report stating that stability data for at least 22 randomly selected lots manufactured in 1995-1998 satisfied all USP and firm specifications.

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