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February 25, 2000

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

Re: Citizen Petitions; Actions That Can
Be Requested by Petitions; Denials,
Withdrawals, and Other Referrals
for Administrative Action
Docket No. 99N-2497

Knoll Pharmaceutical Company ("Knoll") submits herewith its comments on the above-referenced proposal (the "proposal"). In addition, Knoll supports the comments of the Pharmaceutical Research and Manufacturers of America.

Introduction

This proposal represents a significant departure from FDA's past practice. For more than 20 years, FDA's regulations have authorized submission of Citizen Petitions "to issue, amend, or revoke a regulation or order, or to take or refrain from taking any other form of administrative action". 21CFR 10.25. FDA was one of the first agencies to invite such a wide array of Citizen Petitions, and its policy of being willing to respond to considered submissions by those with an interest in the agency's work, including regulated corporations, not-for-profit entities, consumers, health care professionals, and associations, has been widely and approvingly viewed as a keystone of its willingness to engage constructively and openly with those who seek to engage with it. FDA's Citizen Petition regulations are also consistent with, indeed essential to, its long-standing determination to resolve in the first instance as a matter of primary jurisdiction issues which the courts might otherwise feel free to resolve without FDA's first having done so. The Citizen Petition system has also served as an early warning system for senior FDA management, because Citizen Petitions often alert senior officials to the existence of issues, disputes, and problems which for whatever reason have not been recognized, acknowledged, or effectively disposed of by others in the agency.

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To be sure, as the proposal notes, there are some problems. Some Citizen Petitions lack appropriate support, some seek actions not within FDA's authority, some are repetitive or duplicative, and some fit better elsewhere, such as in the rule-making records. Some doubtless require more work to respond to than their inherent merit warrants. But all of these problems can be resolved by relatively minor modifications to the regulations. None warrants the wholesale revisions which FDA contemplates.

Knoll urges FDA not to sacrifice the existing system merely because it has flaws. The existing system is important not only to companies like Knoll but also to FDA itself and to the public and the public interest.

Discussion

Knoll manufactures and markets prescription pharmaceuticals.¹ Like other such companies, it routinely deals with FDA in correspondence, faxes, phone calls, e-mails, and/or meetings. Most of the time those means of communicating with FDA are satisfactory, from Knoll's standpoint and, we believe, from FDA's. Occasionally, however, those means are not sufficient. Either because an issue is unusually important, or because it involves so-called "cross-cutting issues" at the intersection of science, law, and policy and in which numerous FDA offices, divisions, and branches must be involved, or because important aspects of the issue have not been and seem unlikely to be addressed by routine means of communication, or because senior management must be involved for proper resolution, Knoll sometimes files Citizen Petitions. Currently, Knoll has three pending Citizen Petitions, one (invited by FDA itself) seeking a determination that Synthroid levothyroxine sodium USP is generally recognized as safe and effective for treatment of hypothyroidism and as a primary TSH suppressant in certain patients who have been treated for thyroid cancer (the "GRAS/E Citizen Petition"), one asking FDA to resolve scheduling and procedure issues in connection with the GRAS/E Citizen Petition (the "Scheduling and Procedure Citizen Petition"), and one requesting FDA to adopt bioequivalency requirements for propafenone (the "propafenone Citizen Petition"). All three Citizen Petitions would have been impermissible had the proposed regulation been made final before their submission.

In the case of the GRAS/E Citizen Petition, FDA's proposed change to its Citizen Petition regulations would have created a conflict with FDA's August 14, 1997 Federal Register notice on levothyroxine sodium (the "notice").² The notice specifically invited manufacturers who believe their levothyroxine sodium products to be not new drugs to submit Citizen Petitions, but had the proposed regulation been in effect, such petitions would not have been permissible. Perhaps the agency believes it can create case-by-case exceptions to a regulation barring such petitions without in each case amending the regulation, but that belief is not necessarily correct. Even if it is, the likelihood that the agency will want to let some people submit Citizen Petitions outside the regulation,

¹ Knoll's parent company, BASF Corporation, also manufactures and markets numerous products subject to FDA jurisdiction, including food contact substances, dietary supplements and cosmetic chemicals.

² 62 Fed. Reg. 43535.

but perhaps not others, creates an obvious unfairness and if anything underscores the need to leave open this route of approach to FDA.

The GRAS/E Citizen Petition is also an excellent example of the kind of Citizen Petition which FDA ought to want to see, rather than having in the first instance to confront the issues it raises in court. Knoll's argument that Synthroid is GRAS/E and that the notice rests on errors of both law and fact is based on, inter alia, published studies, detailed clinical and manufacturing information, detailed information on FDA's own past practices with respect to levothyroxine sodium and other drugs, the applicable law, and considerations of regulatory policy. Before submitting the Citizen Petition, Knoll corresponded with FDA, met with FDA, telephoned FDA, and otherwise sought to present its views on how the agency could and should regulate levothyroxine drug products. Had the alternative of a Citizen Petition been unavailable, Knoll would have had to consider raising the issue by seeking a declaratory judgment that Synthroid is GRAS/E and not a new drug. In that circumstance, FDA might have asked the court to stay its hand while FDA exercised its primary jurisdiction to decide the issue. But if the agency's regulations specifically denied the right to submit the Citizen Petition and supporting documentation allowing FDA to exercise its primary jurisdiction, the court would likely be less receptive to the argument and far more likely to proceed on its own, leaving FDA to make its case in court. Surely it is preferable for FDA - and indeed for companies such as Knoll - to have the opportunity to proceed to a decision in the first instance, and at a time and in a manner of its own choosing, than to force such matters into court because FDA declines to entertain them early enough, or at a high enough level, or with the participation of all the necessary agency disciplines, including clinical, manufacturing, legal, and policy.

It is also important that Citizen Petitions are public. Knoll's GRAS/E Citizen Petition, like the associated Scheduling and Procedure Citizen Petition, is public, and indeed has attracted comment from another industry member, and has also been discussed in comments to other levothyroxine dockets.³ Whatever the desirability of letters, faxes, e-mails, phone calls, and meetings for certain matters that are essentially the business only of FDA and the other party, issues pertaining to an entire industry and a related Federal Register notice and the variety of questions it comprehends are surely better dealt with in the more open and public forum of the Citizen Petition docket.⁴

Although FDA's proposal complains about petitions which are duplicative or repetitive, it fails to recognize that Citizen Petitions also allow the integration into one docket of several related issues. As its name suggests, Knoll's Scheduling and Procedure Citizen Petition, for example, raised questions about the timing of FDA's decision-making process and also about the legality of, e.g., positions taken by FDA staff at meetings with other parties involved in the levothyroxine industry. Like the GRAS/E Citizen Petition, the Scheduling and Procedure petition has served to call the

³ See Jones and Forrest Letters to LT4 procedure docket, etc.

⁴ Although it is true that documents related to mail, fax, e-mail, telephone, and meeting exchanges may ultimately be available under FOIA, they are unlikely to be available in real time under FDA's current FOIA response times, which often take a year or two or more.

attention of both FDA and other manufacturers of LT4 to certain issues which FDA is going to have to resolve. Some of these questions are policy issues for which Knoll may not be able to obtain judicial review, but we would think that unless FDA truly believes that wisdom on policy inheres only in the agency itself, it would nevertheless want to have a clear statement of what the issues are and suggestions for their resolution. Some of these issues could be resolved by declaratory judgment actions in the courts, but it seems preferable - again, for FDA as well as companies like Knoll - for FDA to have a full opportunity to resolve them in an open forum in the first instance.

Knoll's propafenone Citizen Petition raises important questions of how to assess the bioequivalence of these drugs. Knoll is aware, of course, that, although the proposal is silent on the point, FDA considers many bioequivalence Citizen Petitions to be particularly troubling. Why that is so is unclear, for if two products are not, in fact, bioequivalent and therefore not, in fact, therapeutically interchangeable, FDA, the physicians who prescribe the drugs, the pharmacists who dispense them, and the patients who take them, all need to know. If, on the other hand, FDA decides on the basis of the kind of analysis and data typically provided in a Citizen Petition and comments on it, that two products are, in fact, bioequivalent and therefore, in fact, therapeutically interchangeable, then everyone has the assurance that FDA's decision is considered and fair. The Citizen Petition process thus provides the underpinning for FDA to communicate about and be persuasive as to its conclusions, whether the agency comes down on the side of bioequivalence or bioinequivalence.

In short, Citizen Petitions have many important virtues, and eliminating them for situations such as the GRAS/E Citizen Petition the Scheduling and Procedure Citizen Petition, and the propafenone Citizen Petition seems unwise. It would be very easy for FDA to solve the specific problems it mentions in the proposed rule and still maintain the current system, with all its virtues. For example, FDA could alter its rules for laser variances and allow them to be handled outside the Citizen Petition process, thereby eliminating a very substantial number of petitions which do not seem to need the openness and full panoply of process that many other issues do. It could set up a procedure analogous to the "refusal to file" program used successfully in CDER, CBER, and CDRH, and decline to review Citizen Petitions which are facially defective. It could set up an internal procedure by which Citizen Petitions seeking action outside FDA's authority to grant are promptly and briefly denied on that ground.

Finally, there is the desirability, transcending any particular Citizen Petition, of having a procedural mechanism by which anyone can call FDA's attention at the highest levels to an issue he, she, or it believes to be important. History teaches that agencies function best when they expand rather than restrict opportunities to engage with them, when matters of importance are open to comment and discussion by as many as possible, not just by a few, and when the agency appears to be and is genuinely willing to consider positions, ideas, and suggestions it may at first be unreceptive or even hostile to. FDA's willingness to do all these things with its Citizen Petition system has been a matter of public record and one central underpinning to the high regard in which it is held by the public generally, including those subject to its regulation. For it now to

eviscerate the system which has been so important to it and the communities which watch it, are regulated by it, and participate with it, would be an unfortunate rebuke to FDA's own history.

Respectfully submitted,

A handwritten signature in black ink that reads "Steven J. Goldberg". The signature is written in a cursive style with a large, sweeping initial "S".

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