BUC & BEARDSLEY
919 EIGHTEENTH STREET, N.W.
SUITE 600
WASHINGTON, D.C. 20006-5503

WRITER'S TELEPHONE
(202) 736-3610

TELEPHONE
202-736-3600
FACSIMILE
202-736-3608

October 18, 1999

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

Re: Docket No. 98N-0046
Update of Guidance Documents at the Food and Drug Administration

This update of guidance documents, dated August 4, 1999 is said to cover "all guidance documents issued and withdrawn since the compilation of the previous quarterly list that published on January 6, 1999, and the annual comprehensive list that published on June 10, 1999."

However, this update, like the January 6 and June 10, 1999 lists, omits the Draft Guidance for Industry on In Vivo Pharmacokinetics and Bioavailability Studies and In Vitro Dissolution Testing for Levothyroxine Sodium Tablets, Docket No. 99D-1149, a Level I guidance which was announced in the Federal Register on June 10, 1999. Because the levothyroxine draft guidance has already had an "on again-off again" history,[1] it is important for my client to know if its omission was inadvertent or deliberate. I would appreciate a prompt answer.

Thank you.

Sincerely,

Nancy L. Buc

98N-0046

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1. See my August 2, 1999 letter on behalf of my client, Knoll Pharmaceutical Company, to Docket 99D-1149, a copy of which is attached.

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August 2, 1999

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

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Draft Guidance for Industry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

I am writing on behalf of my client, Knoll Pharmaceutical Company ("Knoll" or "KPC") to protest violations of the Food, Drug, and Cosmetic Act, FDA's regulations, and FDA's Good Guidance Practices in connection with this draft guidance.[1]

FDA is bound by law and its own guidance policies to let the public know when it is considering issuance of important guidances and to allow the public a full and fair opportunity to participate in the process. It is also bound by law, its own guidance policies, and fundamental principles of fairness to deal evenhandedly with all members of the public, especially including companies which compete with each other. The agency's conduct with respect to the proposed guidance on bioavailability of levothyroxine products failed to honor these important precepts. Instead, the agency provided one company which FDA knew to be one of several major competitors with an earlier but quite similar version of the proposed guidance ("the earlier version") at least 17 months and perhaps as many as 22 months before it published the notice of the draft guidance's availability in the Federal Register. During that time, FDA affirmatively told Knoll there would be no guidance on levothyroxine bioavailability and failed to correct that advice for months. During that time, the agency also failed to provide documents responsive to a FOIA request which, when finally delivered, contained the very document FDA had provided to Knoll's competitor more than one to nearly two years earlier.

1. Knoll may separately submit comments on the draft guidance itself.

The problems created by this course of conduct are not just problems of timing. Equally important, the draft guidance adopts an approach to bioavailability studies that was developed by KPC but which FDA had previously described as "flawed" and had for that reason directly and specifically objected to when Knoll used it in a promotional context. Thus, FDA's failure to announce its about face to Knoll for some 21 months during which Knoll's major competitor knew FDA had literally reversed direction had substantive significance as well.

Also, the draft guidance contains references which appear to serve no substantive purpose in the document, and should therefore be deleted.

Statutory and Regulatory Background

Section 701(h)(1) of the Food, Drug, and Cosmetic Act ("FDCA") provides that FDA must develop guidance documents "with public participation" and must "insure that information identifying the existence of such documents and the documents themselves are made available to the public." In addition, for guidance documents that set forth "changes in interpretation or policy that are of more than a minor nature, complex scientific issues, or highly controversial issues," FDA must ordinarily "ensure public participation prior to implementation." Even for guidance documents that state "existing practices or minor changes," FDA must "provide for public comment upon implementation."

Added to the FDCA by the Food and Drug Modernization Act, Section 701(h) underscores Congress' determination that FDA more closely follow the policies the agency adopted in its 1997 Good Guidance Practices, 62 Fed. Reg. 8961 (Feb. 1997) ("GGP"). That document, and the preamble to its announcement, repeatedly assert FDA's willingness and determination to ensure "adequate public participation" in development of guidance documents and make guidance documents "readily available to the public." E.g., id. at 8967.

Neither the FDCA nor FDA's Good Guidance Practices define the word "public," but it plainly comprehends those outside FDA, including members of the affected industry, academics, and consumers, who are interested in a particular topic such as a guidance. The word "public" equally obviously comprehends all those who might be interested, not just one set of consumers, or those academics who have published views taking one rather than another view of an issue, or one among a group of competitors.

FDA's regulations likewise require that the agency not choose just one or some among those similarly situated to get an early look at its intentions. Thus, 21 CFR § 10.80 permits furnishing a draft of a notice to "an interested person," but "only if it is made available to all interested persons by a notice published in the Federal Register."

These provisions of law and FDA declarations of policy all mandate simple fairness: giving those similarly situated an equal and fair shot at knowing what FDA's policies are or may be and giving them an equal and fair shot at participating in the process of shaping those

policies. As discussed below, FDA missed numerous opportunities to give Knoll such a full and fair shot, and in one case affirmatively deflected Knoll from having such an opportunity.

Factual Background

In August, 1994, FDA's Division of Drug Marketing, Advertising, and Communications sent Boots Pharmaceuticals, Inc., Knoll's predecessor as marketer of Synthroid, a letter challenging Boots' distribution of an article by Berg and Mayor[2] demonstrating the bioinequivalence of Synthroid to Daniels' (now Jones) Levoxine (now Levoxyl). FDA objected to the Berg-Mayor methodology on the grounds, for example, that sampling time in bioavailability studies should span at least 3 times the half-life of the active drug ingredient, whereas Berg and Mayor had used only 48 hours of sampling. The FDA letter also challenged the 600 mcg dose used in the study because it is "much higher than the average dose used to treat hypothyroidism." FDA said that, "for [those] reasons, this study is an inadequate bioavailability or bioequivalence study."[3]

Boots vigorously defended the Berg-Mayor methodology as appropriate for demonstrations of bioinequivalence. (It was and remains Knoll's view that the Berg-Mayor model is unsuited to efforts to demonstrate the bioequivalence of two drugs.) But FDA never deviated from its position that Berg-Mayor was inappropriate for reasons including too-short sampling time and too high a dose. Internal FDA documents obtained through FOIA demonstrate that numerous FDA staff members shared these views; one memorandum written by the contact person for the draft guidance describes the Berg-Mayor methodology as "flawed."[4] As late as December 1996, Knoll knew that FDA was still concerned about its promotional use of Berg-Mayor, and had absolutely no reason to think that FDA had changed its view that Berg-Mayor was methodologically unsound.

Unbeknownst to Knoll, however, FDA had changed its views as early as August 1997. In that month, FDA had completed the draft of an earlier version of the guidance. A copy of the earlier version bears the phrase "Cleared for Faxing" and is signed by S. Sobel and dated

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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. Letter from Anne M. Reb, MS, RN, C, Regulatory Review Officer, FDA, to Kenneth F. King, Ph.D., Vice President, Scientific Affairs, Boots Pharmaceuticals, Inc. (copy attached).

4. Michael J. Fossler, Pharm.D., Ph.D., Biopharmaceutics Review, March 13, 1995 (copy attached).

by him August 22, 1997.[5] Whether Jones Medical Industries (JMI or Jones) received a copy of the earlier version in August 1997 is unclear. Jones certainly had a copy by January 22, 1998 because Jones' Nancy Cafmeyer attached a copy to her letter of that date to Dr. Sobel.[6] The earlier version; like the draft guidance itself, essentially adopts the Berg-Mayor methodology as the preferred FDA method for assessing the bioavailability of levothyroxine sodium products. Though FDA surely knew it was adopting the very Berg-Mayor methodology it had challenged Knoll's use of starting in 1994 and as late as 1996, and although FDA surely knew that Knoll, like Jones, was a member of the public with an interest in the agency's views on how to assess the bioavailability of levothyroxine, FDA did not in August, 1997, or by January 1998, or at any time in 1998, send Knoll a copy of the earlier version.

In November 1998, FDA gave notice in the Federal Register of its intention to publish a bioavailability guidance on levothyroxine.[7] I called the contact person listed in the Federal Register notice in December, 1998, and was advised that FDA had decided not to publish such a document. It was not until April 21, 1999 that another staff person at FDA told me that the information I had been given in December was incorrect and that FDA did intend to publish such a guidance.

Nor did FDA respond promptly to two FOIA requests I filed on Knoll's behalf which, had it responded, might have alerted Knoll to the fact that FDA was not just drafting a bioavailability guidance for levothyroxine but was seriously considering use of the very methodology FDA had objected to Knoll's using. Specifically, in November 1998, I submitted two FOIA requests, one requesting documents pertaining to a meeting between Jones and FDA in February, 1998, the other requesting a variety of documents, including guidances and drafts of guidances, pertaining to bioavailability.[8] (I was unaware of the existence of the earlier version of the draft guidance at the time I submitted these requests, much less that it had been provided to Jones a year or so earlier.) Because the Jones FOIA request was clearly relevant to a number of issues of concern to Knoll with respect to FDA's regulation of levothyroxine sodium tablets, I repeatedly pressed FDA for a response, both in writing and in telephone

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5. Solomon Sobel, M.D., was and is Director of FDA's Division of Metabolic and Endocrine Drug Products.

6. Ms. Cafmeyer's letter was produced to Knoll on April 20, 1999, under cover of a letter to me from Carolann W. Hooton in response to a FOIA request. A copy of Ms. Hooton's letter is attached.

7. Semiannual Guidance Agenda, 63 Fed. Reg. 59317 (Nov. 1998).

8. Letters from Nancy L. Buc to Freedom of Information Staff (HF1-35), Nov. 30, 1998 (copies attached).

discussions with FDA staff. But it was not until April 20, 1999 that FDA responded,[9] and it was only then that Knoll saw what FDA had provided to Jones sometime between August 1997 and January 1998.[10]

Argument

In light of the obligations imposed by the FDCA, FDA's regulations, and its GGP, FDA clearly had a responsibility to deal fairly and equally with Knoll and its competitors with respect to early versions of its draft guidance, notices of any draft guidance, and the draft guidance itself. It failed to do so. Instead, it gave one competitor a copy of the earlier version in the second half of 1997 or January 1998 and even met with that competitor in February 1998 to discuss bioavailability issues, all while failing to give Knoll any information as to the existence of such a document or FDA's position on bioavailability issues. The agency also affirmatively denied an intention to issue this bioavailability guidance; though that denial was apparently a mistake rather than intentional, it did happen.

Were these only problems of timing, they would be bad enough, but they are also problems of substance. The proposed guidance uses the Berg-Mayor model, including the same elements of Berg-Mayor to which FDA had taken vigorous exception in the form of an attack on Knoll's promotional use of Berg-Mayor.

Numerous FDA staff knew of the objections to Berg-Mayor and many of those same people must have been involved in preparation of the earlier version and the draft guidance. Many of those same people must have known that Jones got a copy of the earlier version sometime between August 1997 and January 1998, and many of them attended the February 1998 meeting with Jones at which bioavailability was discussed. All those people are bound by Section 701(h)(l) of the FDCA, 21 CFR § 10.80, and FDA's GGP. But FDA as an institution did not honor its obligations to the public, including Knoll, by making sure that Knoll knew what Jones knew, had the same documents as Jones, and had the same opportunity as Jones to participate in shaping FDA's policies on bioavailability.

The References

Page 7 of the draft guidance references the so-called Dong study and the editorial which accompanied its publication in JAMA, Thyroid Storm. Oddly, neither is referenced in the text of the draft guidance, and neither has any relevance to the issue of bioavailability of levothyroxine products in the context of preparation of an NDA or to the bioavailability model

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9. Letter from Carolann W. Hooton to Nancy L. Buc, supra note 6.

10. My November bioavailability FOIA request was not responded to until July 1999; curiously, the response does not contain a copy of either the earlier version or the draft guidance.

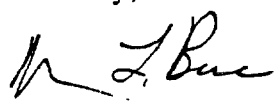
utilized in the draft guidance. It is especially puzzling why these two irrelevant references should have been included when FDA omitted to reference Berg-Mayor itself, the first publication of the model which the draft guidance utilizes. Knoll requests deletion of the references to Dong and Thyroid Storm.

Conclusion

In light of the 17-22 month gap between Jones' and Knoll's opportunity to consider adoption of Berg-Mayor despite FDA's prior rejection of it, Knoll should be entitled to at least a longer comment period than 60 days to level the playing field on this proposed guidance. It is not now making such a request, and in light of its familiarity with Berg-Mayor and other aspects of bioavailability for levothyroxine products, will endeavor to provide its comments by the original due date of August 9.

Knoll does ask that the agency commit more generally to even-handed treatment of marketers of levothyroxine sodium as work proceeds on the draft guidance, the August 14, 1997 Federal Register notice, and other aspects of its regulation of levothyroxine sodium products, so that what has happened here does not recur.

Sincerely,



Nancy L. Buc

& BEARDSLEY
919 EIGHTEENTH STREET, N.W.
SUITE 600
WASHINGTON, D.C. 20006-5503

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