

CENTER FOR DRUG EVALUATION AND RESEARCH

SPECIAL INTERST TOPICS

TITLE: Synthroid Meeting Minutes

DATE: 01/08/97



January 8, 1997

TRANSMITTED VIA FACSIMILE

Robert Ashwood, Ph.D.
Director, Regulatory Affairs
Knoll Pharmaceuticals
199 Cherry Hill Rd.
Parsippany, NJ 07054

Re: Synthroid
MACMIS ID#2380

Dear Dr. Ashwood:

This letter summarizes the December 12, 1996, meeting between Knoll Pharmaceuticals (Knoll) and the Division of Drug Marketing, Advertising and Communications (DDMAC).

Attendees:

Knoll

Robert Ashworth, Director of Regulatory Affairs
Robert Faulkner, Director of Pharmacology/Toxicology
Tim Seaton, Senior Director of Metabolic/Endocrine
Steven Goldberg, Senior Counsel, product and Trade Regulation
Jeffrey A. Staffa, Vice-President, Scientific and Technical Affairs
Gary D. Dolch, Vice-President, Quality Assurance
Nancy L. Buc, Esq., Buc and Beardsley, representing Knoll
Edward Parr, Buc and Beardsley, representing Knoll
Leonard Wartofsky, MD, Endocrinologist, Washington Hospital Center, representing Knoll

FDA

Patrick O'Brien, Regulatory Counsel, DDMAC
Norm Drezin, Deputy Division Director, DDMAC
Leah Palmer, Branch Chief, DDMAC
Kenneth R. Feather, Senior Advisor, DDMAC
Anne Reb, Regulatory Review Officer, DDMAC
Mark Askine, Regulatory Review Officer, DDMAC
Murray Lumpkin, Deputy Center Director for Review Management
Robert Temple, Associate Center Director for Medical Policy

Christine Rogers, Regulatory Policy Staff
James Bilstad, Office Director, Office of Drug Evaluation II (ODEII)
Solomon Sobel, Director, Division of Metabolic and Endocrine Drug Products (DMEDP)
Jean Temeck, Medical Officer, DMEDP
Stephen McCort, Project Manager, DMEDP
Mei-Ling Chen, Division Director, Division of Pharmaceutical Evaluation II (DPEII)
Hae-Young Ahn, Team Leader, DPEII
Mike Fossler, Pharmacologist Reviewer, DPEII
Yuan Yuan Chiu, Supervisory Chemist, Division of New Drug Chemistry II
Gurston Turner, Pharmacologist, Division of Scientific Investigations
Seth Ray, Attorney, Office of Chief Counsel

Points of Discussion:

1. Knoll presented its reasons for concluding that the Betty Dong study and the related manuscript are flawed. Knoll's conclusions are based on its own review of the facts, and on consultation with third-party reviews of the Betty Dong study:
 - A. Knoll has said that the pharmaceutical equivalence of the study medications was not established prior to patient administration. Knoll also stated that the assay used by the investigators to determine pharmaceutical equivalence was flawed, and that the investigators' reported values varied by 10-14%.
 - B. Knoll said that the patients enrolled in the Betty Dong study did not meet the disease-specific entry criteria, because the investigators did not have an adequate basis to determine subjects' thyroid status, and that 17 patients lacked evidence of two TSH levels prior to enrollment, as required by the protocol.
 - C. Knoll said that the Betty Dong study investigators failed to control for the effect of food consumption in relation to timing of drug doses and blood sampling.
 - D. Knoll said that tablet counts reveal that subjects in the Betty Dong study were noncompliant.
 - E. Knoll said that the Betty Dong study investigators failed to adequately evaluate study subjects' reports of thyroid-related symptoms.

2. FDA discussed its concerns relating to the circumstances surrounding the manuscript written by the Betty Dong study investigators and its relationship to the Berg/Mayor article. Specifically, FDA pointed out that it considers the findings of the Betty Dong manuscript to be material in light of representations made by Knoll with the Berg/Mayor article. To the extent that Knoll was disseminating reprints of the Berg/Mayor article after Knoll requested and received contradictory material information (the Dong study manuscript), FDA considers the Berg/Mayor article to be misleading labeling.

Knoll stated that it did not agree with FDA's analysis, but noted that the Betty Dong manuscript will be published pursuant to an agreement that Knoll recently reached with Betty Dong and her university. Knoll provided a copy of its recent press release announcing this agreement.

3. Knoll agreed to provide FDA with a written summary of the information it presented at this meeting. In addition, Knoll will consider providing FDA with copies of all raw data documents in Knoll's possession, and the report about the Betty Dong study that was conducted for Knoll by an outside auditor. Also, Knoll will consider waiving its right of confidentiality for the limited purpose of permitting clinical investigators involved in the Betty Dong study to speak with FDA about the study. FDA will review the information and arguments that Knoll has presented at this meeting, as well as any additional information that Knoll submits, and advise Knoll of its conclusions.
4. Knoll requested that FDA not release documents relating to this meeting to the public in response to requests under the Freedom of Information Act (FOIA). FDA will consider this request to be a designation of the information discussed in this meeting to be confidential and/or trade secret information, and FDA will notify Knoll a minimum of 5 business days prior to releasing copies of this letter.

Robert Ashwood, Ph.D.
Knoll Pharmaceuticals
Re: Synthroid

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Please review this summary carefully. If you believe this report is incomplete or otherwise inaccurate, contact me in writing at the Division of Drug Marketing, Advertising and Communications, Food and Drug Administration, 5600 Fishers Lane, HFD-40, Rockville MD 20857, or by telephone at (301)827-3901.

Sincerely,



Patrick C. O'Brien, PharmD, JD -
Regulatory Counsel
Division of Drug Marketing,
Advertising and Communications

cc: Nancy Buc, Esq.,

Robert Ashwood, Ph.D.
Knoll Pharmaceuticals
Re: Synthroid

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Draft: Reb Date: January 2, 1997
Revise: Obrien Date: January 2, 1997
Comments: Fossler, Temple, Palmer, Reb Date: January 6, 1997
Revise: Obrien Date: January 6, 1997
Comments: Ray, Drezin Date: January 8, 1997
Finalize: Obrien Date: January 8, 1997

CC:

HFD-40\Synthroid
HFD-40\Obrien\reb\palmer\drezin\baylorhenry
GCF-1\Kupchyk\Ray
HFD-02\Lumpkin
HFD-05\Axelrad
HFD-07\Rogers
HFD-101\Temple
HFD-102\Bilstad
HFD-344\Turner
HFD-510\McCort\Temeck\Orloff\Sobel
HFD-820\Chiu
HFD-879\Fossler\Ahn\Chen

MACMIS: 2380

MACMIS TYPE: Lett
MACMIS ACTION: NOAC

FOIA status: notify sponsor 5 business days prior to release