



DEPARTMENT OF HEALTH & HUMAN SERVICES

Food and Drug Administration

July 19, 2002

Chicago District
300 S. Riverside Plaza, Suite 550 South
Chicago, Illinois 60606
Telephone: 312-353-5863

WARNING LETTER
CHI-21-02

CERTIFIED MAIL
RETURN RECEIPT REQUESTED

Mr. Miles C. White
Chief Executive Officer
Abbott Laboratories
100 Abbott Park Road
Abbott Park, IL 60064

Dear Mr. White:

From January 7 through January 28, 2002, and March 21 through April 3, 2002, investigators from the Food and Drug Administration's (FDA) Chicago District Office conducted inspections of your firm located at the above address. The purpose of these inspections was to determine your firm's compliance with the postmarketing adverse drug experience reporting requirements of Section 505(k) of the Federal Food, Drug, and Cosmetic Act ("the Act") and Title 21, Code of Federal Regulations (CFR), Part 314.80.

We note that several of the identified deficiencies arise from the product safety operations of Knoll Pharmaceuticals before Abbott Laboratories acquired the worldwide pharmaceutical business of BASF AG, which included the purchase of Knoll Pharmaceuticals, in March 2001. Knoll Pharmaceuticals is now a subsidiary of your firm, and you have completed integration of the Knoll product safety operations into Abbott's operations. As such, your firm has assumed the responsibility for reporting adverse drug experiences for that subsidiary.

Based on our review of the inspection reports and reports submitted by your firm to FDA, we conclude that your firm failed to comply with Section 505(k)(1) of the Act and 21 CFR 314.80. Section 505(k)(1) requires an applicant to establish and maintain records, and report data relating to clinical experience and other data or information for drugs for which an approval of an application filed under 505(b) or 505(j) is in effect. Deviations from the 21 CFR 314.80 include the following:

(1) In violation of 21 CFR 314.80(c)(1)(i), your firm did not submit serious and unexpected adverse drug experience reports in several cases to FDA within 15 calendar days of initial receipt of the information. For example, our investigator observed that for the period from January 1, 2000 to October 31, 2001, there were eighteen 15-day alert reports submitted late to FDA. These violative reports include, but are not limited to:

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<u>Product</u>	<u>Mfr. Control No.</u>	<u>Mfr. Receipt Date</u>	<u>Date sent to FDA</u>	<u>Days</u>
Norvir	[REDACTED]	2/27/01	8/7/01	161
Biaxin		3/2/01	10/16/01	228
ProSom		5/29/01	10/8/01	132
ProSom		4/26/01	10/5/01	162
ProSom		3/29/01	10/10/01	195
Norvir		2/16/00	4/19/00	63
Biaxin		7/10/00	7/23/01	377
Meridia			*	
Meridia			*	

*Your firm incorrectly categorized these reports as periodic adverse drug experience reports, which are required to be submitted to FDA at quarterly intervals for three years after the date of approval of an application. Because these adverse events were both serious and unexpected as defined in 21 CFR 314.80(a), you were required to submit these reports to FDA within 15 days, as required by 21 CFR 314.80(c)(1)(i).

(2) In violation of 21 CFR 314.80(c)(1)(ii), your firm in several instances did not submit followup reports for serious and unexpected adverse drug experiences to FDA within 15 calendar days of receipt of new information or as requested by FDA. The reports your firm failed to submit in violation of this regulation include, but are not limited to:

<u>Product</u>	<u>Mfr. Control No.</u>	<u>Mfr. Receipt Date (G4)</u>	<u>Date sent to FDA</u>	<u>No. of Days</u>
ProSom	[REDACTED]	F/U #2 4/3/01	10/3/01	183
Biaxin		F/U #1 8/10/01	9/20/01	41
Biaxin		F/U #2 10/31/00	10/18/01	352
Biaxin		F/U #1 5/15/01	10/15/01	153
Biaxin		F/U #2 4/26/01	10/29/01	186
Biaxin		F/U #1 8/31/01	10/29/01	59

The adverse drug experience information contained within the noted followup reports for Biaxin were originally received by your foreign affiliate in Japan, which forwarded the information to Abbott International. Abbott International subsequently forwarded this information to your Clinical Safety and Product Safety Division (D422), which submitted the reports to FDA. In many instances, there appears to have been a lapse in communications either before or after the transmission of information to D422, preventing timely submission of these reports to FDA by your firm. Under 21 CFR 314.80(c)(1)(ii), the applicant is required to promptly investigate all adverse drug experiences that are the subject of these postmarketing 15-day alert reports and

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shall submit follow-up reports to FDA within 15 days. We remind you that 21 CFR 314.80(c)(1)(i) require you to submit serious and unexpected adverse event reports, whether foreign or domestic, as soon as possible, but in no case later than 15 calendar days of receipt of the information by the applicant. Your foreign affiliate's failure to relay 15-day follow-up information to Abbott International in a timely manner appears to have been the cause of your late submission of expedited reports. This late submission is a violation of 21 CFR 314.80(c)(1)(iii).

(3) Again, in violation of 21 CFR 314.80(c)(1)(i), your firm failed to submit to FDA within 15 days of your firm's receipt of the information a serious and unexpected adverse drug experience report for a death associated with the drug product, Meridia. [REDACTED] was reported to you on November 20, 2000, but your firm did not report this serious and unexpected adverse event to FDA.

In your response letter to the Chicago District Acting Director, dated April 18, 2002, you indicated that your subsidiary, Knoll, reported all events that met the reporting criteria set forth in the CFR and FDA's Guidance for Industry, entitled: Postmarketing Adverse Experience Reporting for Human Drug and Licensed Biological Products: Clarification of What to Report. We do not agree with your response. According to 21 CFR 314.80(f), an applicant is required to submit FDA Form 3500A, otherwise known as the "MedWatch" form. Alternatively, another format for submission of adverse events is acceptable, as long as the content of the alternative format is equivalent in all elements of information to those specified in FDA Form 3500A, and the MedWatch program has agreed to the format in advance. The necessary data which comprise FDA Form 3500A are: (1) an identifiable patient; (2) an identifiable reporter; (3) a suspect drug; and (4) an adverse event or fatal outcome. These elements were present in the source documents for [REDACTED] but that event was not reported by your subsidiary, Knoll. Your explanation—that the caller mentioned this serious and unexpected adverse drug event was a "rumor"—does not affect the requirement to report this event. Since the necessary data elements were available, your firm was required to promptly report the serious, unexpected adverse event to FDA.

(4) In further violation of 21 CFR 314.80(c)(1)(i), you submitted adverse drug experience information in reports to FDA which was inaccurate in some cases, or did not completely reflect information available in the source documents, such as in three reports of death associated with the use of Meridia, as illustrated below.

Your response to this observation contained additional information that was not in the reports submitted to FDA, and presented explanations for your selection and presentation of data in these reports. These explanations do not adequately address either the omission of information or the inaccurate presentation of information in the reports submitted to FDA. These omissions and inaccuracies include those found in the following reports:

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Meridia		<p><u>Source Document</u> No mention of number of doses or length of therapy in source documents made available to investigator</p> <p><u>Submitted Form</u> Duration of therapy: one day/ a single dose</p>
Meridia		<p><u>Source Document</u> "autopsy did not reveal anything other than left ventricular hypertrophy"</p> <p><u>Submitted Form</u> No autopsy findings reported</p>
Meridia		<p><u>Source Document</u> Patient was in her early thirties and was not known to have any type of heart disease</p> <p><u>Submitted Form</u> Age unknown. No mention that patient was not known to have any type of heart disease</p>

(5) FDA compared the MedWatch forms in your computer to your paper files, and this comparison revealed inaccurate data in serious and unexpected adverse drug experience reports submitted to FDA. These inaccurate reports are a violation of 21 CFR 314.80(c)(1)(i). These violative reports include, but are not limited to:

<u>Product</u>	<u>Mfr. Control No.</u>	<u>Mfr. receipt date as reported to FDA</u>	<u>Mfr. receipt date in Mfr.'s source documents or database</u>
Norvir		10/26/00	7/17/00
Biaxin		9/10/01	8/10/01

(6) FDA's review of serious and unexpected adverse drug experience reports submitted to the agency revealed inconsistent reporting of the same dates in different fields of the same report. The submission of these inaccurate reports to FDA is another example of your firm's violation of 21 CFR 314.80(c)(1)(i). Your response did not address any actions your firm plans to take to correct this inaccurate reporting. These inconsistent reports include, but are not limited to:

<u>Product</u>	<u>Mfr. Control No.</u>	<u>Mfr. Receipt Date (as noted in Field G4)</u>	<u>Receipt Date (as noted in Field B5, 6 or 7)</u>
Biaxin		F/U #2 5/21/01	6/18/01
Biaxin		F/U #1 9/10/01	9/6/01
Biaxin		F/U #2 9/10/01	9/14/01
Biaxin		F/U #1 8/31/01	9/10/01

(7) Finally, in violation of 21 CFR 314.80(i), your firm did not always maintain records of raw data and correspondence related to adverse drug experiences. Raw data pertaining to followup investigations for seven deaths associated with Meridia [REDACTED] and [REDACTED] were not maintained and available for review. During the inspection, there was no case file for [REDACTED] and the case file for [REDACTED] did not contain any phone records or investigation records from the initial notification date of May 12, 1998 until March 22, 1999. Your response letter set April 30, 2002, as your target date for gaining access to the records. Please let us know if this has been completed.

Neither the above list of deviations, the Form FDA 483 "Inspectional Observations," which was presented to and discussed with Dr. Michael Beatrice, Vice President, Corporate Regulatory and Quality Science, nor the Form FDA 483 "Inspectional Observations," which was presented to and discussed with John Wolfinger, Deputy Vice President, Corporate Regulatory and Quality Science at the conclusion of the inspections, is intended to be an all-inclusive list of deficiencies at your facility. It is your responsibility to ensure adherence to each requirement of the Act and its regulations. FDA expects drug manufacturers to establish procedures to ensure that their foreign affiliates and corporate units rapidly transmit information to expedite reporting of serious and unexpected adverse drug experiences to FDA as required under 21 CFR 314.80.

You should take prompt action to correct these deviations. Failure to promptly correct these deviations may result in regulatory action without further notice. These actions include, but are not limited to, seizure or injunction. Federal agencies are advised of the issuance of all warning letters about drugs and devices so that they may take this information into account when considering the award of contracts.

We acknowledge receipt of the February 12, 2002 letter from Kay Peel and, as previously noted, the April 18, 2002 letter from Michael Beatrice to our Chicago District Office containing responses to the January 28, 2002 and April 3, 2002 Form FDA 483s issued to your firm. Although your firm has taken some corrective actions to address deficiencies found during the January and March-April 2002 inspections of your firm, you have not addressed many of our concerns. Of the deficiencies you address in your letter of April 18, 2002, we find many of your responses inadequate, as stated in this letter.

In addition to providing further response to the above noted items, we ask that you clarify your response to several of the items listed on the Form FDA 483, issued on April 3, 2002.

Observation 2

How has your firm modified its reporting procedures to determine that all adverse drug experience information has been reported to FDA consistent with criteria set forth in the Agency's regulations?

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Observation 3

What measures does Abbott have in place to ensure that the Standard Operating Procedures are fully implemented and reflect the actual practices used by the firm and its affiliates and contractors for adverse event reporting?

We request that you reply in writing within 15 working days of receipt of this letter. Your reply should be sent to the Food and Drug Administration, Chicago District Office, 300 S Riverside Plaza, Suite 550 S., Chicago, IL 60606, Attn: Richard Harrison, Director, Compliance Branch.

Sincerely,

**ls
Arlyn H. Baumgarten
District Director**