



DEPARTMENT OF HEALTH & HUMAN SERVICES

Public Health Service

Central Region

m24131

Food and Drug Administration  
Waterview Corporate Center  
10 Waterview Blvd., 3rd Floor  
Parsippany, NJ 07054

Telephone (973)

526-6006

February 24, 1999

WARNING LETTER

**CERTIFIED MAIL-**  
**RETURN RECEIPT REQUESTED**

Mr. Jorge Engel  
President  
Berlex Laboratories Inc.  
300 Fairfield Road  
Wayne, NJ 07470-7358

FILE NO: 99-NWJ-18

Dear Mr. Engel:

During August and September, 1998, the U.S. Food and Drug Administration conducted inspections of Schering AG Berlin-Wedding, Germany, and its subsidiary Berlex Laboratories Inc., Wayne, New Jersey, to determine compliance with the Postmarketing Adverse Drug Experience (ADE) reporting requirements of Section 505(k) of the Federal Food, Drug, and Cosmetic Act (the Act), and Title 21 Code of Federal Regulations Part 314.80.

Based on our review of the inspection reports, we conclude that your firm failed to comply with Section 505(k)(1) of the Federal Food, Drug, and Cosmetic Act, and 21 CFR 314.80 which require the reporting of postmarketing adverse drug experience reports.

Deviations from the ADE regulations include the following:

1. Failure to conduct prompt and adequate follow-up investigations of ADE's.  
For example:

a) 97-00950 USA: This case involved Betapace in which the adverse event was coded as "deaf". The narrative stated that the "hearing symptoms" continued, yet additional information regarding the outcome of the hearing problems was not obtained. Furthermore, this report was classified as Periodic, and reported as an unresolved hearing loss. Although there is no outcome stated, this unlabeled event should have been evaluated as medically significant (disability) i.e., a serious event, and submitted as a 15-day report. Prompt follow-up of this case should have been conducted to further clarify the event.

b) 98-00332 USE: This case involved a patient who was treated with Ultravist and stopped breathing. New information on the diagnosis of this medical event was obtained by your firm but no follow-up report was submitted to include this new information.

c) 98-02071 USE: This case involved Magnevist in which death was reported as the final outcome. Phone call attempts were made to contact the reporter, and the Department of Epidemiology and Medical Affairs (DEMA) was notified that the reporter would be gone for three days. No further attempts by phone or certified letter were made by Berlex.

Please note that this deficiency was first brought to your firm's attention during a previous FDA inspection on January 17-28, 1997.

2. Your firm failed to accurately report dates of receipt of ADEs. The following are examples in which the date received on the Medwatch form (box G4) does not match the actual date received:

Product	MFR #	Actual Date Received	Date on Medwatch form
Ultravist	98-00024 CDS	3/18/98	4/22/98
Magnevist	98-00071 FRA (follow-up)	6/4/98	6/19/98
Ultravist	98-00313 (follow-up)	6/18/98	7/8/98
Ultravist	98-00225 CDS	4/14/98	7/29/98

We have reviewed Mr. Robert Chabora's letter dated October 5, 1998, responding to the FDA- 483, Lists of Inspectional Observations issued to Berlex Laboratories, Inc., at the conclusion of the inspection. We noted that new procedures regarding handling of adverse drug experience reports will be implemented along with other corrective actions. We request that you reply in writing to this Warning Letter within 15 working days of receipt of this letter. Please be specific as to what steps are being taken to assure that all required reports have now been submitted and that similar deviations will not recur. If corrective actions are in process, please provide a timetable for completion of all such actions, including the implementation of system changes.

The above list of deviations is not intended to be an all-inclusive list of problems related to Postmarketing Adverse Drug Experience Requirements. It is your responsibility to assure adherence with each requirement of the Act. FDA expects drug manufacturers to establish reasonable mechanisms to assure that their foreign affiliates and corporate units rapidly transmit information to expedite reporting of serious and unlabeled adverse drug experiences to the FDA.

Berlex Laboratories, Inc.  
Wayne, New Jersey 07470

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**Failure to promptly correct these deviations may result in regulatory action without further notice. These actions include but are not limited to seizure and/or injunction.. It is your responsibility to assure compliance with the U.S. Postmarketing Adverse Drug Experience Reporting Regulations.**

**Your reply should be sent to the Food and Drug Administration, New Jersey District Office, 10 Waterview Boulevard, 3<sup>rd</sup> Floor, Parsippany, New Jersey 07054, USA (Attn: Diane Boucher, Compliance Officer).**

**A copy of this letter has been forwarded to Dr. Gaith McBride, Head of Corporate Regulatory Affairs, Schering AG, Mullerstrasse 178, D-13353, Berlin-Wedding, Germany.**

Sincerely yours,



**Douglas Ellsworth  
District Director  
New Jersey District**

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REVIEWED BY EB 3/4/99 DATE  
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