



DEPARTMENT OF HEALTH & HUMAN SERVICES

Food and Drug Administration  
Rockville MD 20857

FEB 25 1999

**WARNING LETTER**

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

Dr. Garth McBride  
Head of Corporate Regulatory Affairs  
Schering AG  
Mullerstrasse 178, D-13353  
Berlin-Wedding, Germany

Dear Dr. McBride:

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 (PADE) 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 Schering AG failed to comply with Section 505(k)(1) of the Federal Food, Drug, and Cosmetic Act, and 21 CFR 314.80 which requires the reporting of postmarketing adverse drug experience reports.

Deviations from the PADE regulations include the following:

Your firm delayed submission of report data to Berlex, which resulted in Berlex's failure to submit serious and unlabeled adverse drug experience reports within the 15-day timeframe.

- ◆ The following are recent examples of 15-day reports, which were submitted late to the FDA.

| Product   | MFR number                 | Date received by Manufacturer | Date sent to Berlex | Date sent to the FDA |
|-----------|----------------------------|-------------------------------|---------------------|----------------------|
| Magnevist | 96/00267 -JPN              | 8/15/96                       | 9/9/98              | 9/10/98              |
| Ultravist | 98/00520 -CDS              | 5/26/98                       | 9/9/98              | 9/10/98              |
| Ultravist | 98/00098- GBD follow-up #1 | 2/10/98                       | 5/12/98             | 5/14/98              |
| Fludara   | 98/00150- CDS              | 5/31/97                       | 3/5/98              | 3/6/98               |
| Magnevist | 98/00071-FRA               | 4/23/98                       | 5/18/98             | 5/20/98              |
| Fludara   | 98/00148-CDS               | 5/31/97                       | 3/5/98              | 3/6/98               |
| Ultravist | 97/00363-GBD               | 8/26/97                       | 1/7/98              | 1/7/98               |

- ◆ Several foreign, serious, and unlabeled ADE reports involving Magnevist and Ultravist, were submitted late due to incorrect classification as periodic reports. The reports were not submitted to the Agency until an FDA investigator brought it to the attention of the Berlex facility:
  - a) Magnevist (96/00267-JPN) was coded as "shock" as well as other events, and required initial/prolonged hospitalization.
  - b) Ultravist (98/00520-CDS) was also coded as "shock" and it was a life-threatening event.

The letter from you and Dr. \_\_\_\_\_ to FDA dated September 1, 1998 indicated that additional training would be provided to your staff and that other corrective actions would be taken. 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 to each requirement of the Act and its regulations. 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.

Failure to promptly correct these deviations may result in regulatory action without further notice. If you wish to continue to ship your products to the United States, it is Schering AG's responsibility to assure compliance with the U.S. Postmarketing Adverse Drug Experience Reporting Regulations.

Your reply should be sent to the U.S. Food and Drug Administration, 7520 Standish Place, Rockville, MD 20855-2737, Attn: Puri Subramaniam, CSO, Division of Prescription Drug Compliance and Surveillance (HFD-330).

A copy of this letter has been forwarded to Mr. \_\_\_\_\_ Laboratories, Inc. 300 Fairfield Road, Wayne, NJ.

of Berlex

Sincerely yours,



Lana Ogram  
Director  
Division of Prescription Drug Compliance  
And Surveillance, HFD-330

Enclosures

CC:

Berlex Laboratories, Inc.  
300 Fairfield Road  
Wayne, NJ 07470-7358