

DEPARTMENT OF HEALTH & HUMAN SERVICES

Public Health Service

Central Region

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Food and Drug Administration
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WARNING LETTER

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File # 00-NWJ-04

December 17, 1999

Patrick Zenner
 President and Chief Executive Officer
 Hoffmann-LaRoche, Inc.
 340 Kingsland Street
 Nutley, NJ 07110

Dear Mr. Zenner:

During inspections conducted at your firm located at the above address and at your 50 Madison Road, Totowa, NJ 07512 location from May 17 through August 26, 1999, our Investigators and a Microbiologist documented deviations from Current Good Manufacturing Practices for Finished Pharmaceuticals (Title 21, Code of Federal Regulations, Part 211). These deviations cause your drug products --

Xenical 120 mg Capsules,
 Xeloda 150 mg and 500 mg Film Coated Tablets,
 Versed 2 mg/ml Syrup,
 Rocephin for Injection 1g/18 ml,
 Accutane 40 mg Softgel Capsules,
 Mycelex-3 Cream,
 Naprosyn Suspension,
 Mestionon 60 mg and 180 mg TimeSpan Tablets,
 Bactrim Pediatric Suspension 16 oz.,
 Vesanoid 10 mg Capsules,
 Mestionon 60 mg Tablets,
 FUDR 0.5 g Lyophilized Vials,
 Roferon-A Injectable Solution
 HAS-Free Roferon-A 3 MIU / vial and 6 MIU / vial,
 Femstat 20 g DCA,
 Zenepax Concentration for Infusion Vials,
 Rocaltrol Solution 1 ug/ml, and
 Librium Sterile Powder 100 mg/5 ml

-- to be adulterated within the meaning of Section 501(a)(2)(B) of the Federal Food, Drug and Cosmetic Act (the Act) and/or misbranded within the meaning of Section 502 of the Act. An FDA-483 was issued to Mr. Edward Thiele, Vice President of Technical Operations on August 26, 1999 reporting those deviations.

The deviations disclosed during the inspection include:

1. Your firm released for distribution the packaged quantities of filling on days two and three (November 6 and 10, 1998) for lot 0128 of Mycelex-3 DCA Cream after day one filling (November 4, 1998) in-process testing showed out of specification results for the active Butoconazole Nitrate (actual results 93.5%; specification [REDACTED]), preservative methylparaben (actual results 87.2%; specification [REDACTED]) and preservative propylparaben (actual results 87.6%; specification [REDACTED]). The batch was manufactured as one homogenous unit; therefore any decision based on investigative results to accept or reject the batch should not lead to a partial release of the batch.
2. Your firm released for distribution the first 200 [REDACTED] cartons of lot 2 and the first 250 of [REDACTED] cartons of lot 9 of Naprosyn Suspension despite initial testing showing results outside release specifications. Repeat testing for those samples showed both lots exceeded USP specifications [REDACTED], and a third test on lot 2 again showed results exceeding USP specifications. This partial batch release was made without evidence to show the repeat OOS results were conclusively linked to only a portion of the batch.
3. Your firm rejected out-of-specification (OOS) results based solely on inconclusive laboratory investigations and retesting. Formal failure investigations should have been initiated and all results reported in making a decision whether a product conformed to relevant specifications. Specifically, the following OOS results were rejected based on inconclusive laboratory investigations:
 - a. Mestionon 60 mg Tablets at 36-month stability stations for lots 1354, 1355 and 1356
 - b. Bactrim Pediatric Suspension, lot 2143-2 (second half of testing in duplicate), for active and preservative assay at release
 - c. Tretinoin active pharmaceutical ingredient duplicate assay at 36-month stability station for lot 404015, used in the manufacture of Vesanoind Capsules lots 1 and 2
 - d. Pyridostigmine Bromide, active pharmaceutical ingredient duplicate initial assay for lot 980072, used in the manufacture of Mestionon 60 mg Tablets lots 1467 and 1468
4. Your firm failed to validate the manufacturing process for Mestionon Time Span 180 mg Tablets. Blend assay failures (results exceeding your upper specification of [REDACTED]) were noted for all three 1998 validation batches. Since 1990, 6 of [REDACTED] batches of this product have exhibited blend uniformity or blend assay failures. In addition, your firm has not determined the acceptability or unacceptability of the re-validation study conducted in 1998. These three validation batches with blend assay failures were conducted to support your commitment to our July 6, 1998 Warning Letter to successfully revalidate all existing products.

5. Atypical dissolution results encountered with Xenical Capsules were attributed to the active pharmaceutical ingredient, Orlistat. An unvalidated physical test (wetability) was used to predict batches of active ingredient that would result in finished product failures. However, Orlistat batches with physical test values that had previously resulted in a confirmed finished product dissolution failure, continued to be used in the manufacture of Xenical Capsules. Finally, the wetability method validation had not been performed at the conclusion of our inspection.
6. A reprocessed batch of Orlistat active pharmaceutical ingredient (lot BS9803U125) was used in the manufacture of Xenical Capsules, lots 413 through 417. This is contrary to verbal statements offered during the inspection. Firm officials stated that it was a Roche policy that reprocessed and/or reworked batches would not be shipped to Nutley for manufacture of Xenical batches destined for distribution within the United States. Upon receipt of the Orlistat batch at Nutley and again during your assignment of this batch to be used in Xenical 413-417, you failed to detect that the Orlistat lot had been reprocessed.
7. The Xenical "hybrid" manufacturing process, utilizing interchangeable portions from two different manufacturing trains, was not validated. Documentation of concurrence by senior management with the change in processing was provided, however you could not provide documented evidence that the decision not to validate was reviewed and approved by senior management or Regulatory Affairs. Internal commitments to conduct comparisons of lots resulting from single train versus dual train processing were not completed despite the current nearly exclusive use of the hybrid process. In addition, validation of this process was not proposed or implemented until our investigators apprised you of this deficiency.

NOTE: We acknowledge receipt of the hybrid process validation summary report at the exit meeting.

8. Your cleaning and maintenance for equipment used in the manufacture of Xenical Capsules are inadequate, given the production schedule and output for this product. Rust particles were detected in lot 355 on June 4, 1999. [REDACTED] additional lots of product were manufactured prior to the investigation being completed. A documented investigation into the rust particles did not commence until July 10, 1999, 36 production days after the particles were observed. Stainless steel residuals were identified in lot 299 on May 4, 1999. As of the close of the inspection on August 26, 1999, the investigation into the incident had produced only a draft report (including a reference to similar residuals noted in lot 288).
9. The protocol for the process validation of the Xenical MP4 manufacturing process train calls for three unique lots of Orlistat active pharmaceutical ingredient to be used. During validation of this train, only two lots of Orlistat were used without documented prior approval of the protocol change. The protocol deviation stated that the use of two lots was caused by the unavailability of a third lot of Orlistat.
10. In-process data for the manufacture of Xenical is not being generated and recorded for all manufacturing operations. Print-outs for extrusion, spheronization, fluid bed drying, and

end-of-production reports were not generated by operators for a total of 16 lots manufactured. In addition, your quality assurance unit reviewed and authorized the release of those lots despite the absent data and no ability to reproduce that data.

11. The report for the validation of the Xenical MP5 manufacturing train indicated no deviations to the protocol. Deviations did occur. In validation lots P001797 and P000048/commercial lots 131 and 133, significant manufacturing equipment deviations occurred, requiring rejection of a significant portion of P001797. Unit 2 of lot P000048 failed in-process moisture specifications. Unit 2 was blended with Unit 1 to obtain a passing in-process moisture result. Also, final blend sieve analysis for all three validation lots failed to meet historical/developmental ranges. The manufacturing deviations and in-process failure were not noted in the deviation portion of the validation report.
12. Multiple deviations to installation and operation qualifications for individual pieces of equipment in the Xenical MP5 manufacturing train were noted. In addition, no performance qualification was performed to address the impact of the deviations on future use of the equipment in the manufacturing process.
13. The manufacturing of Xenical capsules for "C" countries using reprocessed and reworked Orlistat was performed on equipment routinely used for production of Xenical Capsules and Xeloda Tablets destined for U.S. distribution. The material was processed despite the lack of change control documentation and with no prior evaluation of additional controls needed to prevent any possibility of cross-contamination.
14. The manufacturing process for Xeloda 150 and 500 mg tablets was not validated. Your first validation attempt encountered picking/sticking difficulties and the blend failed to compress. Those four batches (0001, 0002, 1001, and 1002) were converted to clinical trial batches. The second validation attempt (lots 003, 004, 1003, 1004) produced multiple predetermined criteria deviations (including loss on drying, moisture loss on drying for the final blend, sieve analysis, bulk and tap densities, final blend assay, final blend unit dose uniformity, kernel weight compression, hardness, thickness, friability, disintegration, and film coating for weight and thickness). The final page for the validation report of both product strengths contains the statement: *"All data is acceptable and meets predetermined criteria..."* along with the endorsement signatures of five responsible individuals with title designations relating to validation, production, and quality assurance. A third validation was attempted following a manufacturing change to the active pharmaceutical ingredient. Again, numerous predetermined criteria were not met. The two Xeloda 150 mg batches (006, 007), failed to meet approximately half of your acceptance criteria and multiple required samples were never collected for batch 007. The two Xeloda 500 mg batches (1045, 1046) failed approximately 80% of the predetermined criteria. The criteria included drying, final blend moisture loss on drying, tap density, sieve analysis, final blend assay, unit dose uniformity, kernel weight compression, thickness, friability, disintegration, compression assay, kernel dissolution, film coating, film coating assay, content uniformity after film coating, dissolution, and miscellaneous visual inspections. For one of the two 500 mg validation lots (1046), an over yield at the end of granulation was discovered. The overage was removed so as not to affect the lubricant; however, picking/sticking problems were noted with the

compression of the batch. The validation was deemed successful; however, the overage and its removal were not mentioned in the investigation of the picking/sticking difficulties. Finally, picking/sticking problems were also noted in one 150 mg validation batch (lot #006). The tooling punch tip was removed and treated to alleviate the problem, then compression resumed with the treated tool. The investigation into the picking/sticking problem did not mention the treatment of the tool, or that picking/sticking problems occurred with this lot. The yield overage and picking/sticking problems with Xeloda continue to occur in post-validation production lots and, at the conclusion of our inspection, still have not been corrected. In addition, low yields have also occurred. Also, equipment has been added to the Xeloda process which has not been qualified (specifically, [REDACTED])

NOTE: We recognize that you voluntarily ceased Xeloda production in July, 1999 until the re-validation could be completed.

15. Your firm's validation for Versed Syrup for Pediatric Use is inadequate. Your firm's quality unit endorsed the validation package on September 4, 1998, prior to the completion of the packaging and finished product testing on December 14, 1998. Meanwhile, the second and third validation lots failed the release specification for maximum levels of a known impurity on finished product assay. In addition, equipment (specifically, the [REDACTED]) was inadequately qualified, in that the testing did not duplicate actual filling times and no performance qualification was conducted on that device for the Versed Syrup's fill volume. Two post-validation complaints were reported for under fill volumes. Documentation was lacking to show that the push-in bottle adapters (PIBAs) were quantitatively tested for depth and diameter specifications. Complaints were received and a Field Alert generated as a result of the incorrect PIBAs being used in the first two validation batches.
16. Controls on your laboratory computer system software [REDACTED] allow saved chromatograms to be re-integrated without designation as a saved file. The saved chromatograms that are re-integrated then cannot be restored as original data.
17. Your firm's analysts performing sterility analysis on powdered products are inadequately trained. An analyst failed to fully dissolve the Rocephin lot 5387-07119 powder being analyzed for 12 of [REDACTED] vials, as witnessed on July 12, 1999, and as required by the method.
18. Media fills are not always being performed as required in your procedures either for regularly scheduled fills or fills required by a loss of sterility. All persons who enter the sterility core are required to participate in a yearly media fill. There were employees who did not meet this requirement. Your firm failed to execute a media fill following a sterility breach on April 2, 1999 during the manufacture of Rocephin 1 g/18 ml vials.
19. Your firm is not consistently performing stability testing at the frequency called for in your procedures or your New Drug Applications. In particular, stability stations for Versed Syrup, Xenical and Xeloda (all recently approved products) were performed late. Three, six, nine, and twelve months' stations for all three products were not executed on schedule, with the three-months' station for Versed Syrup not performed at all. All products have 24-month

expiration dates and there is limited accelerated stability data available for all three products, emphasizing the need to adhere to Agency-approved application testing stations.

20. Your Quality Management personnel authorized two investigation reports and the data contained therein as being acceptable, when those reports included erroneous information and the conclusions drawn from the investigation were unsupported by the actual information. The investigations concerned Rocaltrol Solution 1 ug/ml, lot 0001 and Accutane 40 mg Softgel Capsules, lot 478. The Rocaltrol investigation attributed data that was outside validation criteria to an improperly drawn baseline. The investigation report stated re-analysis was performed using a correct baseline and the results within acceptable criteria. However, review of the investigational data shows instead the standard response factor was recalculated and applied to the original chromatograms and no redrawing of the baseline occurred. The Accutane investigation found dark seams developing in the capsules. Your investigation states that no dark seams were encountered on visual examination, when the contract manufacturer's documentation on-site at your firm indicates the contrary, the presence of dark seams.
21. Microbiological issue investigations were not initiated or completed within a timely manner. A January 23, 1998 media fill for 10 ml/13 mm vials reported growth, yet the investigation took over two months and the media fill was not repeated as of the conclusion of our inspection. The total microbial count performed on Xeloda tablets, lot 1035, exceeded the action limit of [REDACTED]. The investigation into that deficiency was not initiated until 49 days later and not completed until the day our investigators requested the information pertaining to that investigation. As of August 16, 1998, the investigation failed to include any production scrutiny. HAS-Free Roferon -A 6 MIU/vial and 3 MIU/vial, lots 1007 and 0016 respectively, substantially exceeded the action limit of [REDACTED]. As of August 16, 1999, the investigation was incomplete and the report thereof in draft phase and unsigned, more than eight months after the investigation was commenced.
22. Production issue investigations were not initiated or completed within a timely manner. The production investigation into sticking problems with Xeloda Tablets 500 mg lot 1091 was not commenced until more than three months after the problem was discovered. The investigation into the discarding of two of the [REDACTED] granulation units for Xeloda Tablets 500 mg, lot 1090, did not commence for almost four months after the granulation units were discarded. The investigation into Bactrim tablets, lot 1604, for failing to meet hardness specifications took over one month to be approved by the Quality unit after the report was written. That same investigation called for corrective actions involving a batch record change and a dryer study to be completed by specified dates. On the dates our Investigators requested documentation of those corrective actions, memorandums were drafted and provided indicating the corrective actions were assigned new dates in the future with no reason or explanation for the additional time necessary to implement the corrections.

23. Inspection of the production facilities and laboratories as well as interviews of personnel revealed the following:
- a. Unlabeled laboratory sample bottles were noted in the chemistry laboratory. The Chemistry Laboratory Manager was unaware of the computer system for labeling and tracking laboratory samples, despite that system's operation since April 1999.
 - b. Stagnant water in a filling line prior to commencement of liquid-filling operations, with cleaning procedures silent on any time duration during which water may be allowed to remain in the filling line after cleaning.
 - c. Production personnel did not know which fluid bed dryer filter bags were dedicated for specific products.
 - d. A laboratory analyst failed to record/paste raw dissolution data into their notebook and that same analyst was seen recording data on scrap paper.
 - e. An employee working in the Class 100 Zenepax compounding area was observed to have her forehead exposed and to be wearing makeup.
 - f. A computer terminal used in the production area for Zenepax was observed to be operating constantly in alarm mode.
24. During the validation of Accutane 40 mg Softgel Capsules, 10.6% of lot SF096128 was rejected due to airfills and underfills. However, the Validation Task Report (the final validation report for that product and strength) states that there were no deviations for that validation lot.
25. There is no assurance that the required in-process testing was performed at the appropriate intervals for Femstat 20 mg DCA lot 0098. The in-process samples collected were not designated as beginning, middle or end of run. Documentation does not indicate that additional samples were collected and analyzed to correct the original sampling error.
26. Trending or systems prospective analysis of microbiological and analytical results for production water is not being performed.
27. There is no data to substantiate that your use of "double cleanings" following exceeded action levels, positive air pressure failures, maintenance, or construction assures that surfaces and systems cleaned in that fashion, are suitable for resumption of production. In addition, there are no procedures for performing "double cleanings".
28. During organism identification testing for Orlistat-Milled lot SI99050074, the microbiologist failed to update the computer database to include a new organism isolated from the sample analyzed. Due to that oversight, the presence of a different organism isolated from that sample was reported, an organism of the same genus already on file within the database.
29. Documentation of microbiological testing controls (e.g. media controls, lot numbers, product/strength, equipment) for your bacteriostatic and fungistatic tests were not consistently recorded during testing for Tensilon lots 0029, 0030, and 0031; Pegasys lot HC-30353-160; and Bactrim tablets [no lot number referenced].

30. The current Standard Operating Procedure for total plate aerobic count microbiological analysis for active pharmaceutical ingredients (API's), final dosage forms and raw materials calls for a minimum incubation period of three days' time, whereas the validation of this method was executed with a five day minimum incubation time.
31. The pH of the product-lysate mixture of the USP Bacterial Endotoxin test was either not performed or not recorded on validation product batches of Roferon-A (lot GN19578-180), HAS-Free Roferon A (lot 1007), and FUDR (lot 0282-09237) and active pharmaceutical ingredient Chlordiazepoxide HCl (lot 182097).
32. On four occasions, analysts failed to observe the [REDACTED] minimum pH of product in testing broth, as called for in your validation of the test method for API's, final dosage forms and raw materials, and failed to adjust to [REDACTED], also as called for in the procedure. The products involved were Cell Cycle Inhibitor (lot C193708), Vitamin B-12 (lot 079087), and Ticlid tablets (lot 0001 -- two analyses). Also, we observed one instance where, following incubation, the pH of the test mixture for Stearic Acid (lot 970021) was found to be less than [REDACTED] the minimum pH following incubation.

Similar observations relating to your investigations into out-of-specification findings and process validation have been reported to you in a previous Warning Letter, dated July 16, 1998 (98-NWJ-28), as well as in FDA-483's issued at the conclusion of recent inspections. Your response to that Warning Letter, and other subsequent submissions to the District, indicated that you had instituted comprehensive corrective actions to eliminate any future deviations in those two GMP areas. Clearly, that corrective action was insufficient, as process validation and out-of-specification deviations were documented for both older products and recently approved products during the current inspection.

The above discussion is not intended to be an all-inclusive list of violations. As a manufacturer of human pharmaceuticals, you are responsible for assuring that your overall operation and the products you produce are in compliance with the law.

You should take prompt action to correct the above violations and to establish procedures whereby such violations do not recur. Failure to do so may result in regulatory action without further notice such as seizure and /or injunction.

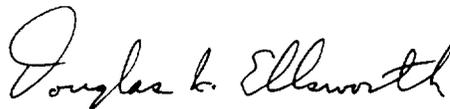
You should notify this office in writing within 15 working days of receipt of this letter of any additional steps you have taken to bring your firm into compliance with the law. Your response should include each step that has been or will be taken to correct the violations and prevent their recurrence.

The District acknowledges that your comments during the exit discussion, your September 2, 1999 response to the FDA 483, corrections verbally proposed at a meeting with District officials on September 8, 1999, your Corrective Action Plan submitted on October 15, 1999, and your most recent December 7, 1999 response, all indicate that you have taken corrective actions or are

in the process of correcting the above noted deficiencies. An inspection will be conducted in the future to verify your corrective actions and to evaluate your compliance status.

Your reply should be directed to the Food and Drug Administration, Attention: Kirk D. Sooter, Compliance Officer, at the address and telephone number above.

Sincerely yours,

A handwritten signature in cursive script that reads "Douglas I. Ellsworth". The signature is written in black ink and is positioned above the printed name and title.

Douglas I. Ellsworth
District Director