



DEPARTMENT OF HEALTH & HUMAN SERVICES
PUBLIC HEALTH SERVICE
FOOD AND DRUG ADMINISTRATION

PHILADELPHIA DISTRICT
Mossler

WARNING LETTER

900 U.S. Customhouse
2nd and Chestnut Streets
Philadelphia, PA 19106

Telephone: 215-597-4390

September 28, 1999

99-PHI-36

CERTIFIED MAIL
RETURN RECEIPT REQUESTED

Bernard J. Poussot, President
Wyeth-Ayerst Laboratories
Division of American Home Products Corporation
555 East Lancaster Avenue
St. Davids, PA 19087

Dear Mr. Poussot:

The agency has completed its review of the results of an inspection conducted at your West Chester, PA drug manufacturing facility from March 8 through May 5, 1999 by Philadelphia District Investigators Michael D. O'Meara and David J. Hafner and Northeast Regional Laboratory Pharmaceutical Microbiologist Dennis E. Guilfoyle, Ph.D. The inspection documented significant deviations from current Good Manufacturing Practice (cGMP), *Title 21 Code of Federal Regulations* (21 CFR) Parts 210 and 211, with respect to the manufacture of certain lots of epinephrine injection and meperidine HCl injection. At the conclusion of the inspection, the inspectional team issued form FDA 483, Inspectional Observations, to Robert R. Shemonsky, Managing Director. A copy of the FDA 483 is enclosed for your information.

These deviations cause certain lots of epinephrine injection and meperidine HCl injection, manufactured at this facility, to be adulterated within the meaning of Section 501(a)(2)(B) of the Federal Food, Drug, and Cosmetic Act (the Act) since the methods used in, or the facilities or controls used for, their manufacture were not operated or administered in conformity with cGMP, as follows:

1. Failure to assure that drug products meet all of their applicable quality standards throughout their labeled expiration date.

The inspection revealed that stability and retained samples of some lots of epinephrine injection, USP, contain individual Tubex syringe units that have become discolored over time such that they fail to meet your firm's stability specification for physical description which requires, in part, a "clear, colorless solution." Current good manufacturing practice requires that drug products meet all of their appropriate quality standards throughout their shelf life. Your firm has identified physical description as a quality standard, and your firm's data indicate that product older than 25 months does not consistently meet this quality standard. The caution against using discolored product that is contained in the product labeling does not provide an adequate remedy

since product older than 25 months may not meet its quality standard for physical description. Your firm's investigation into this matter found individual Tubex syringes of epinephrine, approximately 25 months of age or older, that failed to meet your firm's in-house [REDACTED] limit. In May 1998, Wyeth-Ayerst Laboratories (Wyeth) shortened the expiration date for epinephrine injection from 30 months to 24 months, and post-inspectional correspondence from Wyeth states that this action was taken to decrease the potential for discoloration in individual units. This decision did not, at that time, impact on commercially distributed product already labeled with the 30 month expiry date.

We acknowledge your firm's recent decision to voluntarily recall lots of epinephrine with the 30 month expiry date. However, your firm has not, to date, identified the chromophore causing the discoloration. We note that lots of epinephrine injection produced at West Chester appear to exhibit a more significant discoloration pattern than either the three lots manufactured to support the transfer of manufacturing operations for this drug from your Marietta, PA facility to the West Chester site, or the control lot produced at Marietta against which the three lots were compared.

The USP color and clarity test is included in your firm's stability testing specification for epinephrine injection; however, discolored units have not been subjected to this test. Rather, these units have been evaluated using your firm's in-house [REDACTED] test. This test has not been proven to be equivalent or superior to the USP test although we note your firm's opinion that the [REDACTED] test is superior to the USP color and clarity test.

2. Failure to assure that the system used to clean and disinfect processing areas in which sterile drug products, particularly epinephrine injection lot [REDACTED] and meperidine HCl injection lot [REDACTED] are filled consistently returns the rooms and equipment to aseptic conditions.

Your firm's investigations into failures of two media fill trials run on August 2, 1998 and September 28, 1998 identify inadequate disinfection and failure to remove a contaminated machine cover at the appropriate sequence in the disinfection process as the most likely causes of the failures.

Post-inspectional correspondence indicates that a sporicidal disinfectant was applied to and a routine disinfection performed in the applicable sterile areas prior to filling epinephrine lot [REDACTED] on September 21, 1998. During our inspection, review of the available cleaning and disinfection documentation for the filling equipment revealed that the "Hopper, Bowls, Rails" were disinfected [REDACTED] with [REDACTED] about [REDACTED] prior to the start of the fill. In contrast, available documentation for the filling equipment cleaning and disinfection done prior to the two failed media fills shows that the hopper, rails, and bowls were disinfected [REDACTED] with [REDACTED] prior to the start of the respective fills. Post-inspectional correspondence from your firm reports that the room equipment disinfection logbook documents that equipment disinfection was

performed in accordance with your written procedures. However, this logbook does not document that all of the machine parts and surfaces listed in the applicable procedures were disinfected or that the parts were disinfected in the required sequence. Your firm's correspondence also states that no action or alert levels for microbiological monitoring of air, surfaces, and personnel were exceeded during filling; our review of the applicable records found that no action levels for routine microbiological monitoring of air, surfaces, and personnel were exceeded during filling of the two failed media fills.

We have similar observations regarding filling of meperidine HCl lot [REDACTED]. In summary, your disinfection procedures and/or the manner in which you adhere to them were not sufficient to preclude the media fill failures that occurred and, by extension, call into question the assurance of sterility for epinephrine injection lot [REDACTED] and meperidine HCl injection lot [REDACTED].

You should be aware that this is not the first time we have raised concerns about recovery from non-sterile conditions to the attention of Wyeth management. An inspection conducted July 1 through August 9, 1996 documented the post-disinfection presence of microbial counts of greater than [REDACTED] CFU/plate on the floor of the aseptic corridor and on the floor inside the doorway to one of the sterile filling rooms.

3. Failure to thoroughly investigate exceeded environmental monitoring action levels in the sterile filling room in which meperidine HCl injection lot [REDACTED] was filled.

The inspection revealed that your firm's environmental monitoring found mold, [REDACTED] species, on the floor which exceeded your firm's action levels for that surface. Post-inspectional correspondence from your firm states that the exceeded action levels were associated with environmental sampling conducted prior to filling the meperidine HCl and that floor samples taken during filling were negative for growth. However, documentation for samples taken during filling shows that the areas where positive growth was found prior to filling (south, east, west, and center floors) were not sampled. There is no documentation that additional disinfection was done between samplings.

Although your firm believes that these floor counts did not impact the aseptic filling operations because of negative environmental monitoring results for critical surfaces, personnel, and air, such monitoring cannot provide a complete overview of the room conditions. Our review of the literature found that [REDACTED] spp. can contaminate water damaged, cellulose-containing building materials. The literature reports it can be an opportunistic pathogen in immunocompromised individuals and references a 1988 incident regarding [REDACTED] spp. contamination of the air system and the HEPA filters in a hospital's oncology-hematology

special care unit. Four bone marrow transplant recipients were subsequently infected.¹ We note that the West Chester facility has had water leaks above the ceilings in the sterile core, has had periodic breaks in sterile conditions (to change HEPA filters or otherwise access ceilings), and has identified the presence of [REDACTED] spp. as part of a trend in the sterile environment between [REDACTED] and [REDACTED]. Given that mold spores can become aerosolized, we have concerns regarding the source of the contamination. If it is above the sterile core ceilings, there is a potential for impact to the critical surfaces.

Your firm maintains that a ceiling or HEPA filter route of contamination is not likely because air and surface monitoring, with the exception of the floors, have been negative for [REDACTED] spp. contamination. We have not, to date, received any information from your firm regarding any investigation into possible contamination in the ceilings and/or HEPA filters or other potential source of this mold. We believe that cGMP requires additional vigilance in this area.

We have received and reviewed a letter dated May 25, 1999 from Mr. Shemonsky and Gerry Morris, Ph.D., Associate Director of West Chester Quality Assurance, which responds to the FDA 483 observations. We also met with Dr. Morris and other representatives from both Wyeth and American Home Products Corporation on June 9, 1999 regarding the inspectional findings. In addition, we had a second meeting with Mr. Shemonsky, Dr. Morris, and other Wyeth personnel on July 28, 1999 and are in receipt of a letter dated August 13, 1999 from Mr. Shemonsky regarding the status of your firm's corrective action commitments. As indicated above, these actions do not satisfactorily address all of the observations. We also have the following comments with respect to Mr. Shemonsky and Dr. Morris' responses to the following FDA 483 observations:

FDA 483 Observation 5.a.

The second paragraph of the response to this observation indicates that additional disinfection is performed prior to media fills that are conducted following a recovery from non-sterile conditions. As we pointed out during the June 9 meeting, it appears that this additional disinfection is not performed prior to filling the first lot of product following recovery from non-sterile conditions, which is a source of concern. The last sentence of that paragraph states that disinfection routines for media fills are designed to be equivalent to those for product; please clarify whether or not this will also pertain to disinfection routines employed following recovery from non-sterile conditions.

[REDACTED]

Page 5
September 28, 1999
Bernard J. Poussot

FDA 483 Observation 5.c.

On two occasions during the time period noted in the FDA 483 observation, the vacuum levels resulted in less than half the intended volume of air [redacted] cubic feet on March 6, 1998 and [redacted] cubic feet on March 9, 1998). Did these air volumes also result in a quantitative measure?

FDA 483 Observation 8

As mentioned previously, no environmental monitoring action levels were exceeded during filling of the two failed media fill trials. While environmental data are important, emphasis must also be placed on ensuring that your firm's procedures for recovering from non-sterile conditions consistently render the rooms and equipment suitable for aseptic processing regardless of the operations that require the break in sterility.

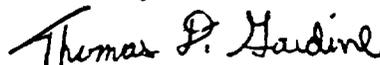
The above is not intended to be an all-inclusive list of deficiencies at your firm. As top management, it is your responsibility to assure that all of your company's operations are in compliance with the Act and its applicable regulations.

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. In addition, pending new drug applications (NDAs), abbreviated new drug applications (ANDAs), or export approval requests may not be approved until the aforementioned deviations are corrected.

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 and/or injunction.

Please advise this office in writing within fifteen (15) days of receipt of this letter as to the specific actions you have taken or intend to take to correct these violations, including an explanation of each step being taken to prevent recurrence of similar violations. Your response should specifically address any actions you intend to take with respect to epinephrine injection lot [redacted] and meperidine HCl injection lots [redacted] and [redacted]. If corrective action cannot be completed within 15 days, state the reason for the delay and the time within which corrections will be completed. Your reply should be addressed to Karyn M. Campbell, Compliance Officer, at the address noted on the letterhead.

Sincerely,



Thomas D. Gardine
District Director