



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

d1209b

PHILADELPHIA DISTRICT

900 U.S. Customhouse
2nd and Chestnut Streets
Philadelphia, PA 19106
Telephone: 215-597-4390

WARNING LETTER

June 16, 1998

98-PHI-25

CERTIFIED MAIL
RETURN RECEIPT REQUESTED

Raymond Gilmartin, President
Merck & Company, Inc.
One Merck Drive (WS 3A-05)
Whitehouse Station, NJ 08889

GEN	SPEC.
RELEASE	
F# _____	DATE <u>6/18/98</u>
Reviewed by <u>Jay M. Campbell</u>	

Dear Mr. Gilmartin:

From April 6 through May 12, 1998, representatives from the Philadelphia District Office conducted a comprehensive inspection at your West Point, PA manufacturing facility. The inspectional team was led by Investigator Monica S. King and included Investigators Anthony A. Charity, Colleen A. Damon, Megan F. McLaughlin, Alicia M. Mozzachio, and Carol L. Rehkopf; Chemist Michael Gurbarg; Pre-Approval Inspection Program Manager Debra L. Pagano, and Compliance Officer Karyn M. Campbell. At the conclusion of the inspection, form FDA 483, Inspectional Observations, was issued to Ted B. Frank, Senior Director of Quality Operations, and those observations were discussed with Mr. Frank and other members of the West Point staff. A copy of the FDA 483 is enclosed for your information.

On May 28, 1998, we received a letter from Mr. Frank dated May 27, 1998 regarding Merck's response to the FDA 483 observations. We have carefully reviewed Mr. Frank's letter and find that, while it satisfactorily addresses some of the FDA 483 observations, it does not satisfactorily address others. As a result, these remaining observations represent serious deviations from current good manufacturing practices (CGMP's), codified at *Title 21 Code of Federal Regulations* (21 CFR) Parts 210 and 211, with respect to the drug products they affect. As a result, these drug products are adulterated within the meaning of Section 501(a)(2)(B) of the Federal Food, Drug, and Cosmetic (FD&C) Act.

1. Failure to adequately assess the stability characteristics of drug products in that samples representing all container/closure systems used in packaging in a given year are not included in the annual stability program (FDA 483 Observations Stability 1.A.-F. and 2.).

The inspection revealed that some solid oral dosage forms manufactured at West Point are packaged into high density polyethylene (HDPE) bottles of various sizes as well as blister packs.



Page 2
June 16, 1998
Raymond Gilmartin

However, West Point's standard operating procedure (SOP) for its concurrent stability program provides for product package configurations to be altered from year to year, so there is no assurance that the different packaging configurations are monitored annually. For example, our investigators observed that [redacted] lots of Pepcid® (famotidine) 40 mg tablets were packaged in blister packs in 1996 and 1997, yet no samples of the blister pack configuration were placed on stability in those years. Additionally, [redacted] lots of Noroxin® (norfloxacin) 400 mg tablets were packaged in blister packs in 1996, but no blister pack samples were included in the stability program for 1996. It also appears that this failure to include the blister packs in the stability program represents a deviation from the West Point SOP in that alternating product packages from year to year failed to include either of the aforementioned Pepcid® and Noroxin® blisters (for Noroxin®, our investigators observed that only bottles were included in the program for 1995). Further, the West Point SOP was not followed in that none of the [redacted] lots of Timoptic® (timolol maleate) 0.25% ophthalmic solution packaged in 1995 were included in the concurrent stability program for that year.

Mr. Frank's response to these two FDA 483 observations indicates that West Point's current stability program will be expanded to include "a minimum of one lot in each package type using different packaging material ... manufactured during a calendar year." This is acceptable; however, we are concerned about the timeframe within which this expansion will take place. Mr. Frank's letter states that the target completion date for the activities associated with this program enhancement is January 1, 1999 for domestic sites and March 31, 1999 for foreign sites. The Pepcid®, Noroxin®, and Timoptic® products listed above, as well as the other products included in the FDA 483 observation, lack stability information relevant to each packaging year. We are requesting, at a minimum, that all packaging configurations from the 1998 packaging year are included in the 1998 stability program.

We acknowledge that the CGMP regulations are not explicit about annual stability testing; however, it should be noted that the CGMP regulations are not all inclusive and that what determines a manufacturing practice to be "current" and "good" is if it can be considered feasible and valuable. In the case of annual stability testing, the agency has determined that such a practice is feasible and valuable and, thus, enforceable under Section 501(a)(2)(B) of the FD&C Act.

2. Failure to assure that incoming drug product closures, specifically, rubber stoppers, consistently conform with all applicable written procedures in that your firm has been unable to consistently meet the validation parameters identified for the [redacted] Stopper depyrogenation process (FDA 483 Observation Equipment 1.A.).

The inspection revealed that the West Point facility's most recent validation efforts for [redacted] in 1997 failed to achieve the specified greater than three log reduction in endotoxin. These failures were attributed to an accumulation of silicone on a screen that reportedly reduced the

Page 3

June 16, 1998

Raymond Gilmartin

effectiveness of the washing cycle; however, these failures were not investigated as per SOP, and it should also be noted that the screen had been cleaned at the specified frequency. Nevertheless, West Point continued to use [REDACTED] to process incoming stoppers.

Mr. Frank's letter indicates that [REDACTED] validation trials of this type have been performed since 1993 and that [REDACTED] of these trials met the specification for endotoxin reduction. However, our concern lies with West Point's inability to consistently meet its quality specification in this regard. While we acknowledge that the high temperatures involved in the stopper manufacturing process are not conducive to endotoxin growth, has Merck assured itself that the environment in which the stoppers are exposed after manufacturing does not add to any endotoxin load that may already be present?

Additionally, has West Point looked internally at a potential cause for the variance in results seen with the most recent validation effort? The 1997 validation trials exhibited a [REDACTED] log reduction and [REDACTED] log reduction; has West Point found a reason for the [REDACTED] difference between these results? We acknowledge West Point's interim plan to monitor pyroburden on incoming lots of stoppers until it can consistently achieve its specified greater than three log endotoxin level reduction; however, West Point also needs to assure itself during this time period that the maximum level of endotoxin found on incoming stoppers does not exceed the minimum amount of endotoxin removed during the [REDACTED] washing process. Also, we suggest that West Point consider the following items, if it has not already done so, in its next planned validation run:

- the successful and consistent adherence of the endotoxin challenge to the "spiked" stoppers;
- the validation of the endotoxin recovery laboratory method;
- the consistency of the sources (i.e. vendor and microorganism number) of endotoxin challenge used;
- the consistency of the stopper vendor's manufacturing process as well as the controls the stopper vendor has in place to reduce the endotoxin load on the stoppers post-processing;
- the endotoxin load on the silicone;
- the appropriateness of the frequency of screen cleaning.

Please include a copy of the protocol for the current [REDACTED] depyrogenation validation with your response to this letter.

In a related matter, we are aware that the West Point facility has [REDACTED] pieces of equipment related to the manufacture of drug products - some of which are old and were not initially qualified in accordance with the CGMP standards of today. In the absence of problems, we would not expect Merck to retrospectively run comprehensive installation, operational, and performance qualification studies on those pieces of equipment whose initial qualification work may not reflect current GMP standards. However, we do expect that Merck will respond

Page 4
June 16, 1998
Raymond Gilmartin

appropriately when faced with information that equipment is not functioning in accordance with written procedures and specifications.

This inspection found several atypical process reports associated with the Building 38 [REDACTED] dryers and [REDACTED] dryers [REDACTED] (see FDA 483 Observations Equipment 3. and 4., respectively). Our review of these reports determined that these dryers were not functioning as intended; however, they were still being used to process drug products. In response to our investigator's comments about the Building 38 [REDACTED] dryers, West Point management removed the dryers from service effective April 23, 1998. Our concern here is that the quality assurance unit was not proactive in removing these dryers from service despite the existence of atypical reports; the units were removed after comment during an FDA inspection.

We expect that the quality assurance system be comprised of an empowered and effective quality assurance unit that can identify quality problems and institute corrections in a timely manner. With respect to older pieces of equipment where internal deviation reports indicate that the equipment is not properly qualified and therefore cannot be utilized with some degree of assurance that the equipment will perform consistently and reliably, we expect that the quality unit will proactively ensure that this equipment is qualified in a timely manner and will not be used until the qualification is completed. We request that you perform a comprehensive evaluation of other equipment in the West Point facility so that those pieces of equipment that are not performing as intended are attended to in a timely manner.

3. Failure to ensure that manufacturing facilities are maintained in a clean and sanitary condition in that, on April 29, 1998, two lots of granulating solution for Prilosec® (omeprazole) delayed-release capsules were exposed to potential debris from on-going construction activities (FDA 483 Observation Written Procedures 1.).

We acknowledge the fact that these two lots were discarded as well as Mr. Frank's response indicating that an SOP covering third party CGMP orientation has been approved and implemented to prevent this observation from recurring. However, we are concerned about the timeliness of the "concurrent correction activities" that were underway at the time our investigator observed this condition: the department operator had to notify his supervisor who, in turn, had to notify the engineer in charge who could then interact with the construction workers to halt the construction operations. In this instance, it appears that neither the operator nor his supervisor was empowered to prevent the objectionable condition from occurring on his own although it looks as though the operator recognized the situation as an objectionable condition since he initiated the reporting process. Furthering our concern is information given to our investigator that indicates that the manufacturing of these two granulating solution lots began after construction activities had already started. We recommend that you consider the methods you have in place to prevent manufacturing from commencing under circumstances such as these where the product may potentially be exposed to dirt and debris.

Page 5
June 16, 1998
Raymond Gilmartin

We also have the following comments and/or requests for additional information with respect to Mr. Frank's responses to the following FDA 483 observations:

FDA 483 Observation 1.

Mr. Frank's response indicates that the atypical report and associated investigation for this incident could have been improved for clarity. We would like to emphasize the importance of accurate and complete documentation of drug manufacturing operations so that atypical events, like the one referenced in this observation, can be thoroughly investigated and release decisions can be based on facts and not hypotheses. In this particular case, there is no documentation in the batch record that the filter cartridge was dropped; this conclusion was based on the gross damage observed to the cartridge. In an unrelated but similar incident, our investigator also observed during this inspection an atypical report regarding an elevated reject rate for a Pepcid® I.V. (famotidine) Ten Dose Vial lot that was attributed to problems with low fills during processing. Our investigator's review of the corresponding batch record revealed that all fill checks were within specifications during processing and that there was no documentation included with the batch record indicative of mechanical or other problems during filling. We request that you consider methods of improving the level of detail of documentation in batch records and associated production records so that they accurately reflect the history of the batch and provide a better means with which to investigate atypical occurrences.

FDA 483 Observation Stability 4.

We acknowledge your intent to report all stability lots in annual reports but request that you clarify why this commitment will not begin until after September 1, 1998. If Merck has annual reports due to the agency before the September 1st implementation date, then those reports should contain information about all stability lots.

FDA 483 Observation Stability 5.

We acknowledge that your release specification for phenylethanol content in Decadron® Phosphate (dexamethasone sodium phosphate) ophthalmic solution is [REDACTED] and that you have data that indicate that the phenylethanol content can drop as low as [REDACTED] provided that the benzalkonium chloride remains at a concentration within its filed range. However, we suggest that you consider adjusting the stability specifications for phenylethanol to reflect the actual acceptable values [REDACTED]

Page 6
June 16, 1998
Raymond Gilmartin

FDA 483 Observation Stability 6.

First, we would like to clarify that our investigator's use of the term "degrade" comes from Merck's own characterization of the sulfite adduct as one of [REDACTED] degradation products. Second, we note that the corrective action identified in Mr. Frank's response, which involves the cessation of monitoring this by-product on stability, differs from the one initially offered to our investigators during the inspection, which involved an Analytical Change Request to tentatively revise the specification to conform to current process capability data until [REDACTED] lots of material can be evaluated. Is the decision to delete the monitoring of this by-product feasible in the absence of [REDACTED] lots of data?

FDA 483 Observation Equipment 2.

We acknowledge Mr. Frank's commitment to reassess all of the [REDACTED] inspection machines. Please advise what is being done in the interim until these reassessments are completed; for example, are the standard control sets being run each production day?

FDA 483 Observation Validation 1.

We suggest that the second field study also evaluate any other disinfectant application procedures that production uses that were not already evaluated in the first field study. This is because the laboratory studies represented "best case" conditions in that the study organisms were immersed in disinfectant; however, these conditions do not simulate the manual spraying and wiping procedures used in production.

FDA 483 Observation Validation 3.

Given the potential detrimental effect the build-up of silicone on the [REDACTED] screen has on washing effectiveness, we suggest that the current cleaning method and frequency with which the screens are cleaned be included in any additional cleaning validation performed.

FDA 483 Observations Investigations 2. B.-C.

Mr. Frank's response indicates that SOP's regarding the preparation of validation final reports will be revised by June 30, 1998; however, we request that you clarify if the 30 day timeframe indicated in the response pertains to 30 days for circulation of the report or 30 days for approval. If the 30 days pertains to circulation, then please identify a timeframe within which the report must be approved.

Page 7
June 16, 1998
Raymond Gilmartin

FDA 483 Observations Investigations 3. and 4.

We request that this review be expanded to ensure that the master batch records for all products are accurate.

FDA 483 Observation Written Procedures 2.

Please include a copy of SOP 236-335, Processing of Quarantines/Rejections for Pharmaceutical Laboratory Testing Failures, with your response to this letter.

FDA 483 Observations Laboratory 4. and 6.

Please confirm whether or not laboratory personnel have been trained in the revised SOP's discussed in the response.

FDA 483 Observation Laboratory 5.

Mr. Frank's response notes that a laboratory atypical investigation should have been conducted and indicates that laboratory personnel will be retrained in the applicable SOP. This is satisfactory; however, has a retrospective review of this event been conducted to evaluate what impact, if any, this event has on the validity of the results obtained?

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 FD&C Act and its associated 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 (NDA's), abbreviated new drug applications (ANDA's), or export approval requests may not be approved until the aforementioned violations 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 the recurrence of similar violations. If corrective action cannot be completed within 15 days, state the reason for the delay and the time within

Page 8
June 16, 1998
Raymond Gilmartin

which corrections will be completed. Your reply should be addressed to Karyn M. Campbell, Compliance Officer, at the address noted on the letterhead.

Sincerely,


for John W. Thorsky
Acting District Director
Philadelphia District Office

Enclosure

cc: Robert E. Bastian, Director
Division of Primary Care and Home Health Services
PA Department of Health
132 Kline Plaza, Suite A
Harrisburg, PA 17104

Ted B. Frank, Senior Director of Quality Operations
Merck & Company, Inc.
P. O. Box 4, WP38-4
West Point, PA 19486-0004