



Telephone (201) 331-2909

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

February 12, 1997

WARNING LETTER

Burton Greenblatt
President & CEO
G & W Laboratories, Inc.
111 Coolidge Street
South Plainfield, New Jersey 07080

File No. 97-NWJ-19

Dear Mr. Greenblatt:

During an inspection of your manufacturing facility located at 111 Coolidge Street, South Plainfield, New Jersey from December 2, 1996 through January 14, 1997, an Investigator from this office, documented deviations from Current Good Manufacturing Practice Regulations (cGMPs), Title 21, Code of Federal Regulations (CFR), Parts 210 & 211. These deviations, were noted on the Form FDA483, List of Inspectional Observations, issued to you at the close of the inspection.

The above stated inspection revealed that drug products manufactured at your facility are considered to be adulterated within the meaning of Section 501(a)(2)(B) of the Federal Food, Drug and Cosmetic Act (the ACT), in that the methods used in, or the facilities and/or controls used in manufacturing are not in conformance with cGMPS, as follows:

1) The Quality Unit is inadequate in the methods and procedures used to evaluate and investigate failures or discrepancies obtained during QC testing and manufacturing, for example:

o there was no investigation regarding stability test results for several lots of Indomethacin Suppositories 50 mg, in which repeated failing assays were obtained for room temperature and accelerated temperature studies.

o there are no impurity limits for Indomethacin Suppositories. During stability testing, impurity peaks were noted in several lots, ranging from 2 - 8% as compared to the active peak. There was no investigation into the source or identify of this impurity peak.

o there was no investigation regarding content uniformity failures for two of three process validation lots of Acetaminophen Suppositories 120 mg, Lots 6248-2 and 6248-3, conducted to qualify new fillers. Although the two lots in question were not released, there was no

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documentation to determine the cause of these failures.

1) Initial failing dissolution results for one lot of Prochlorperazine Suppositories 25 mg Lot 5173-1, at the 6 month stability station, was invalidated after retesting a QC retain sample stored below controlled room temperature, resulted in passing results. Additionally, there was no documentation to support that the dissolution method used for this product was validated.

2) there was no documentation to support invalidating initially failing results, based on suspected laboratory errors, for in-process testing of Morphine Sulfate Suppositories 5 mg, Lot 5078-9 and Flocinolone Acetonide Ointment 0.025%, Lot 6082-1.

3) there was no evaluation conducted regarding production deviations for several products that exceeded temperature specifications, nor were these lots placed on stability to monitor product changes throughout expiry.

4) there are no procedures in place to prevent contamination of bulk product from foreign particles. Specifically, there was no investigation conducted to determine the source of black spots noticed during the production of Greaseless Stainless Pain Relieving Rub, Lot 5027-2. The cause of black specks in Prochlorperazine Suppositories, lot 5231-8 was thought to be gasket material, however the source of this material was not determined.

2) Manufacturing process validation and re-work procedures for several product lines were found to be inadequate, for example:

there was no validation or extensive testing conducted to assure all product specifications were met concerning one lot each of Anusert HC-1 Ointment, Lot 5265-8 and Hydrocortisone 1% Cream, Lot 6078-7, which were reprocessed due to errors initially made in weighing the correct amount of raw materials.

the validation protocol for Prochlorperazine and Morphine Sulfate suppositories, written in 1993, uses a sample size to demonstrate content uniformity, that is not representative of the actual dosage form.

validation was conducted on only two lots of Morphine Sulfate 5 mg Suppositories.

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validation study of Triple Antibiotic Plus Ointment 1350kg batch size did not consider uniformity of the bulk solution with regard to levels of all three active ingredients. In addition, there was no validation data to support manufacturing of the 450kg batch size.

there was no investigation regarding the failure of an initial validation batch of Acetaminophen 120 mg Suppositories, Lot 4320-3, which was rejected for content uniformity.

3) Original batch records were not available for review during the inspection, for example:

validation batches for Promethazine Suppositories

batch records for Ergotamine Tartrate Lot 4104-2 (found to be on hold in the finished product warehouse, without explanation)

4) The stability testing program was not followed for some finished products, for example:

Triamcinolone Acetonide Ointment 0.025%, Lot 3092-1, was only tested initially and at 29 months

Trimethobenzamide Suppositories, Lot 4109-6, was tested initially, at 4 and 28 months

Aminophylline Suppositories 250 mg, Lot 2075-4, was tested initially, at 37 and 48 months. Lot 3049-4, was tested initially, at 26, 35 and 36 months

no lots of Indomethacin Suppository 50 mg made in 1994, were placed on a stability testing program

5) Analytic methods used to release finished products have not been adequately validated, for the following products: Trimethobenzamide Suppositories, Chloral Hydrate Suppositories, Morphine Sulfate Suppositories.

In addition, stability indicating methods have not been developed for the above products, as well as for Aminophylline Suppositories.

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6) There are no impurity profiles or established impurity limits for the drug substances used in the following finished products: Trimethobenzamide HCL, Aminophylline, Promethazine HCL, Fluocinolone Acetonide, Hydrocortisone Acetate, Chloral Hydrate and Morphine Sulfate.

7) The HPLC methods used for assay, release and/or stability testing are incomplete or inadequate, for example:

○ there is no data to support that the HPLC methods used for release and stability testing of Triamcinolone Acetonide and Indomethacin can detect all impurities identified by the drug substance manufacturer

○ there is no data to demonstrate that the in-house HPLC method used to release Miconazole Nitrate 2% Topical Cream and Miconazole Nitrate 2% Vaginal Cream is equivalent to compendial methods

○ there is no documentation regarding calibration and preventive maintenance for HPLC's used by the QC Chemistry Laboratory

8) Evaluation of microbiological activity is inadequate, for example:

○ there is no qualification program for media vendors
○ growth promotion is not performed on every media lot
○ positive controls are not routinely used

○ there is no microbiological evaluation of drug substances, containers, container closures and excipients used in product manufacturing

○ the contract microbiological laboratory used to conduct micro testing of ANDA and prescription cream and ointment products, has not been routinely audited

9) Cleaning validation regarding equipment used in manufacturing is inadequate, for example:

○ there is no data to demonstrate that drug substance and cleaning residues are effectively removed after cleaning

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there is no assurance that the sanitization procedures used once a week are effective to reduce product microbial levels

the written cleaning procedure is not consistent with the actual cleaning operation

10) Environmental assessments of the production areas for creams and ointments are incomplete, for example:

there is no surface monitoring of product contact surfaces

air samples are not representative of the entire production run

no evaluation was made of organisms isolated from air sample studies

there are no pre-established alert or action limits for microbial activity

The above list is not intended to be all-inclusive of deficiencies at your facility. It is your responsibility to ensure that the drug products you manufacture are in compliance with the Act and the regulations promulgated under it. Federal agencies are routinely advised of Warning Letters issued so that they may take this information into account when considering the award of contracts. You should take prompt action to correct these deficiencies. Failure to implement corrective measures may result in regulatory action, including seizure and/or injunction, without further notice.

We are in receipt of your written response, dated January 28, 1997, to the FDA483 List of Inspectional Observations. We are pleased that your firm has taken a proactive approach towards implementing corrections from a "Quality Systems" approach. You identified key positions within the QA Unit, Process Validation, Stability and Laboratory areas to be upgraded and/or expanded. You also reference the formation of a Validation Committee and a computerized stability management system, which will aid you in your efforts towards compliance. Your commitment to recall all Indomethacin Suppository lots in distribution is also acknowledged with this correspondence.

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Generally, your response to each FDA483 observation appears to be satisfactory in its concept. We recognize that efforts to revise procedures, upgrade process validation, conduct additional stability studies, and product specific cleaning validation will be implemented in the near future. A reinspection will be necessary to verify your planned corrective actions and evaluate your compliance with cGMPs.

We offer the following comments to specific responses as they relate to the FDA483 observations:

Item 4A) We disagree with your position that product uniformity is demonstrated by content uniformity in the finished product. Passing content uniformity result for a sampling of finished product is not an indication of blend uniformity. Samples taken from the mixing vessel are taken to demonstrate blend uniformity and they should approximate the size of the dosage unit. In-process blend sampling and testing is an important part of validation. Your response does not address our concern that blend samples taken during validation are not representative of the dosage unit.

Items 4C and 10) Your response does not address what QA procedures have been implemented to prevent misplacement of batch records in the future.

Item 9) When foreign particles are observed in a batch, it is important for the QA Unit to definitively determine the origin of the particles and implement steps to prevent recurrence. While the batch records documented that the affected lots were appropriately rejected, your response does not demonstrate what procedures are in place to protect products from potential contaminants in the future.

Item 21A) Your response does not indicate whether the QA procedures for sampling Purified Water will mimic actual use procedures or visa versa. Please provide additional information regarding procedures used to obtain QA samples and actual use.

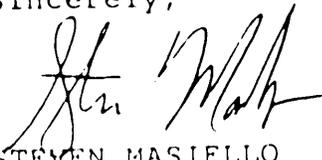
You should notify this office in writing, within 15 days working days of receipt of this letter, of the additional steps you have taken to correct the noted deficiencies, including an explanation of each step being taken to prevent the recurrence of similar conditions. If corrective action cannot be completed within 15 working days, state the reason for the delay and the timeframe

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within which corrections will be completed. Your reply should be sent to the New Jersey District Office, FDA, 10 Waterview Blvd., 3rd Floor, Parsippany, New Jersey 07054, Attention: Mercedes B. Mota, Compliance Officer.

Sincerely,



STEVEN MASIELLO
Acting District Director
New Jersey District

CERTIFIED MAIL -
RETURN RECEIPT REQUESTED

MBM:np