



DEPARTMENT OF HEALTH & HUMAN SERVICES
Food and Drug Administration
New England District

purged
4/7/00
for
HFI-35 *M20321*

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April 6, 2000

WARNING LETTER

NWE-26-00W

Federal Express

David Miller, President
H.L. Bouton Co., Inc.
11 Kendrick Road
Wareham, Massachusetts 02571

Dear Mr. Miller:

During a recent inspection of your firm located at 320 Main Street, Buzzards Bay, Massachusetts, our Investigator determined that your firm manufactures sterile eye wash and sterile eye cups. The eyecup is a device as defined by Section 201(h) of the Federal Food, Drug, and Cosmetic Act (the Act). The eye wash is a drug as defined by Section 201(g) of the Act.

The above-stated inspection revealed that the device is adulterated within the meaning of Section 501(h) of the Act, in that the methods used in, or the facilities or controls used for, manufacturing, packing, storage, or installation are not in conformance with the Quality System/Good Manufacturing Practice (QS/GMP) for Medical Devices Regulation, as specified in Title 21, Code of Federal Regulations, Part 820 (21 CFR § 820).

Our Investigator also documented serious violations from the current Good Manufacturing Practices (cGMPs) Regulation (21 CFR § 210 & 211) for drugs. These deviations cause your sterile eyewash to be adulterated within the meaning of Section 501(a)(2)(B) of the Act as follows:

GMP Regulations for Drug Products

1. Failure to follow your written production and process control procedures for your sterile eye wash. Further you failed to document at the time of performance the execution of the various production and process control functions (21 CFR 211.100(b)). For example:

- a) The batch record for lot #1006 shows Hex (Chlorhexidine Gluconate) was added to the batch. This ingredient is not listed in the master batch record or product label. This batch was released and distributed.
 - b) The batch record for lot #1005B shows Hex was added to lot 1004. The records do not show how much Hex was added. The engineering manager stated the lot was discarded. There are no records to confirm the destruction of the lot.
 - c) Two (2) of [REDACTED] made since December 1999 have been reduced in size with no validations conducted. For example, batch #1006 was made to 1/3 the normal batch size; however the amount of each ingredient was not recorded. Batch #1005B was made to 1/2 the normal batch size, the amount of each ingredient was not recorded.
 - d) Various batches that you manufactured and recorded on the eye wash batch forms were actually concentrated eye wash, for example, batch #1011 indicates ten (10) times the amount of ingredients was added to [REDACTED] gallons of water. Further, the individual weights were not recorded.
 - e) Copies of labels are not maintained, and label reconciliations are not performed. Sterile Eye Wash, lot #1020 was being labeled on March 1, 2000. A portion of the lot was labeled with [REDACTED] labels; another portion of the same lot was labeled with [REDACTED] labels.
 - f) Batch record for lot #1000 could not be located for manufacture on December 8, 1999.
 - g) Batch #1002 was rejected due to an odor. There is no record of the disposition of the batch.
2. Failure to have adequate master production and control records (21 CFR 211.186).
For example:
- a) Neither the Batch Recipe nor the manufacturing procedure have been signed as approved or dated.
 - b) The first step of the Batch Record states to rinse the tanks. The Batch Record does not indicate how the tanks were rinsed.
 - c) The Batch Record includes an Optional step after filling, for flushing of the equipment with [REDACTED] and [REDACTED], if the system is going to be down for three (3) plus days. There is no way to indicate whether or not this step was performed after any given batch.
 - d) There is no explanation for determination of the expiration date. For example, the Engineering Manager said a two (2) year expiration date is applied, while the VP of Operations stated a three (3) year expiration dated is applied to the eyewash.

3. The master procedure has been changed at least two (2) times since December 1999 with no validations of the changes (21 CFR 211.100(b)). For example:
 - i. On January 27, 2000 additional equipment was added, e.g., two (2) charcoal filters and an additional UV sterilizer.
 - ii. On February 10, 2000 the re-circulation process was replaced with a mixer in one tank.
 - iii. On February 28, 2000 an optional equipment flush with [REDACTED] and [REDACTED] was removed from the system prior to manufacturing the next batch.
4. Failure to have strict labeling controls for use in drug product labeling operations. (21 CFR 211.125 & 211.130) For example:
 - a) There are no specifications for labeling.
 - b) There are no provisions for conducting labeling reconciliations.
 - c) Failure to constantly control packaging and labeling control operations, for example, three (3) of the five (5) bottles on the shelf from lot #1010 were missing both the lot number and expiration date.
5. Failure to control drug product containers and closures (21 CFR 211.80). For example:
 - a) There are no specifications for the bottles or caps. Some caps have been sterilized at the firm prior to use, others have not.
 - b) Bottle caps, eye wash ingredients, finished products, were all stored on shelves against the same wall with no clear delineations between in process and finished products.
6. Your procedure for Sterilization of Water Storage Tanks, Mixing Tanks, Transfer Lines and Filler fails to state when and how often the equipment must be cleaned. (21 CFR 211.67)
7. You failed to calibrate instrumentation at suitable intervals in accordance with a written program containing specific directions, schedules, and limits, (21 CFR 211.160(b)(4)). For example, the [REDACTED] scale used to weigh the ingredients for the eyewash has not been calibrated since purchased and moved from [REDACTED] to this location in July/August 1999.
8. Failure to follow your complaint procedures for your drug manufacturing processes. (21 CFR 211.198).

GMP Regulations for Medical Devices

9. Failure to conduct and have procedures for conducting audits of your device manufacturing processes (21 CFR 820.22)
10. Failure to follow your complaint handling procedures for your device manufacturing processes (21 CFR 820.198). Further your complaint handling procedure fails to address Medical Device Reporting (MDRs) (21 CFR 820.198(a)(c)).
11. Failure to have a device master record for the sterile eye cups. Further, you have no specifications for the eye cups, bags, or the labeling. (21 CFR 820.181)
12. Failure to maintain an adequate device history record for the eye cups (21 CFR 820.184). Your device history record for the eye cups consisted of only of a sterilizer printout.
13. Failure to adequately validate the sterilization of the eye cups (21 CFR 820.75), for example:
 - a) Validation of the [REDACTED] sterilization process has not been performed. There is no justification for the [REDACTED] hour exposure or aeration times. [REDACTED] lots of eye cups have been sterilized to date. Three (3) lots have been made with much shorter exposure times and two (2) lots have been made with shorter aeration times.
 - b) The aeration time for lot #23 was only one hour. The engineering manager said that aeration times have been shortened on Fridays when there are not [REDACTED] hours left on a shift, the product is left in the chamber with the door open over the weekend.
 - c) One sterilization lot had two (2) power interruptions, and resterilization was attempted twice (lots 37-39). Lot #42 had a power interruption but was not resterilized. There is no indication on the printouts of what phase the sterilization process was at during the power interruptions.
 - d) There are no specifications for allowable ranges for exposure temperatures or minutes. Generally, minimum exposure temperatures have ranged from [REDACTED].
 - e) The number of [REDACTED] integrators per load is not specified. Most of the [REDACTED] sterilization records include three (3) strips. Two (2) lots included only two (2) strips and one (1) lot included only one (1) strip and one (1) lot included four (4) strips.
 - f) There are no specifications for the large bag that two thousand (2000) bagged eye cups are placed into for sterilization.

14. Failure to adequately train personnel in the use of the sterilizer (21 CFR 820.25(a)). For example, there is no documentation showing anyone was trained in the use of the sterilizer. Further, all sterilization operations are either conducted by the supervisor of the Lens [REDACTED] Area or the engineering manager. The engineering manager could not explain how the exposure or aeration times were determined.
15. Failure to validate the heat sealer on the eye cup bagging machine. For example, there is no documentation of testing, no written procedure, or indication of which sterilization lots were tested or which of the two (2) type of bags were tested.
16. Failure to document which bag is used to package the sterile eye cups for any particular lot. For example, two different bags are used by your firm, one supplied by [REDACTED] and one supplied by [REDACTED]. There are no specifications for the bags other than size and labeling.
17. Failure to document corrective and preventative actions when the bags stuck to product during sterilization, or the investigation of the cause of the problem (21 CFR 820.100)
18. Failure to have design control procedures (21 CFR 820.30) for your sterile eye cups.
19. Failure to have procedures for conducting management reviews and no documentation of management review meetings (21 CFR 820.20(c)).

In addition, your sterile eye wash is misbranded under Section 502(o) of the Act, because your establishment is not registered according to Section 510 of the Act, and the drug product is not listed as required by 21 CFR Part 207.20(a).

Our inspection also determined that you have failed to update your device establishment registration. Federal regulations, 21 CFR 807.21, require that an establishment update its registration annually.

This letter is not intended to be an all-inclusive list of deficiencies at your facility. It is your responsibility to ensure adherence to each requirement of the Act and regulations. The specific violations noted in this letter and in the form FDA-483 issued at the conclusion of the inspection may be symptomatic of serious underlying problems in your firm's manufacturing and quality assurance systems.

H. L. Bouton Co., Inc.
320 Main Street
Buzzards Bay, Massachusetts
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We acknowledge receipt of your response to the FDA-483 dated March 17, 2000. Your response is currently being reviewed.

You are responsible for investigating and determining the causes of the violations identified by the FDA. If the causes are determined to be systems problems you must promptly initiate permanent corrective actions.

Federal agencies are advised of the issuance of all Warning Letters about devices so that they may take this information into account when considering the award of contracts. Additionally, no premarket for Class III devices to which the QS/GMP deficiencies are reasonably related will be cleared until the violations have been corrected. Also, no requests for Certificates to Foreign Governments will be approved until the violations related to the subject devices have been corrected.

You should take prompt action to correct these deviations. Failure to promptly correct these deviations may result in regulatory action being initiated by the Food and Drug Administration without further notice. These actions include, but are not limited to, seizure, injunction, and/or civil penalties.

Please notify this office in writing within fifteen (15) working days of receipt of this letter of the specific steps you have taken to correct the noted violations, including an explanation of each step being taken to identify and make corrections to any underlying systems problems necessary to ensure that similar violations will not recur. If corrective action cannot be completed within fifteen (15) working days, state the reason for delay and the time within which the correction will be completed.

Your reply should be directed to Compliance Officer Bruce R. Ota at the above address.

Sincerely,



David K. Elder
Acting District Director
New England District Office