



**DEPARTMENT OF HEALTH AND HUMAN SERVICES**

Food and Drug Administration  
Atlanta District Office

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m3840n HPI-35

60 8th Street, N.E.  
Atlanta, Georgia 30309

June 9, 2000

**VIA FEDERAL EXPRESS**

Brian Haley, President & CEO  
Holox, Ltd.  
1500 Indian Trail Road  
Suite C  
Norcross, GA 30093

**Warning Letter**  
(00-ATL-44)

Dear Mr. Haley:

During an inspection of your firm located at 7390 Graham Road, Fairburn, Georgia, on April 11 - 21, 2000, our investigators determined that your firm still transfills compressed medical gases (drugs), and manufactures and distributes specialty gas mixtures (medical devices). The compressed medical gases (CMGs) filled at your facility include, but are not limited to: Oxygen, USP; Medical Air, USP; Nitrous Oxide, USP; Helium, USP; Carbon Dioxide, USP; and Nitrogen, NF. The specialty medical device gas mixtures manufactured at your facility include lung diffusion gas mixtures and calibration gases such as blood gas mixtures. During the inspection, our investigators documented serious deviations from the Current Good Manufacturing Practice (CGMP) regulations for drug products as set forth in Title 21 Code of Federal Regulations (21 CFR), Parts 210 and 211. In addition, our investigators documented deviations from the Quality System Regulation (QSR) for medical devices as set forth in 21 CFR Part 820. These deviations cause your CMGs (drugs) and medical device gas mixtures to be adulterated within the meaning of Section 501(a)(2)(B), and 501(h) of the Federal Food, Drug and Cosmetic Act (the Act), respectively. The deviations are as follows:

1. Your firm has failed to validate several of the analytical methods that are currently being used to test your drug and medical device products. For example:
  - a. Medical Air, USP - GC method for oil and hygrometer determination of water
  - b. Nitrogen, NF - Assay determination by fuel cell analyzer
  - c. Helium, USP - Assay determination by fuel cell analyzer
  - d. Carbon Dioxide, USP - Assay determination by gas chromatography
  - e. Blood Gas Mixtures - Assay determination by gas chromatography
  - f. Lung Diffusion Gas Mixtures - Assay determination by gas chromatography

2. Your firm has failed to maintain written procedures for the following analytical methods used for testing your drug and medical device products:
  - a. Medical Air, USP - GC method for oil and hygrometer determination of water
  - b. Nitrogen, NF - Assay determination by fuel cell analyzer
  - c. Helium, USP - Assay determination by fuel cell analyzer
  - d. Blood Gas Mixtures - Assay determination by gas chromatography
  - e. Lung Diffusion Gas Mixtures - Assay determination by gas chromatography
  
3. Your firm released several lots of medical devices, which upon initial testing had failed to meet acceptance criteria, without an adequate explanation of why the original results were voided, or why an investigation of the out-of-specification (OOS) results was not conducted.
  - a. Results obtained by your firm on 6/15/99 for two cylinders (X11425 & 734) from lot 0900J143 of a lung diffusion gas mixture failed to meet acceptance criteria for the carbon monoxide assay. Your firm voided the OOS results without an explanation, and released the cylinders upon retesting. No documentation was available to explain why an investigation of the original OOS results was not conducted.
  
  - b. Results obtained by your firm on 1/17/00 for three cylinders (190380, 542042, & D-12423) from lot 0900K014 of a blood gas mixture failed acceptance criteria for the carbon dioxide assay, and/or the oxygen assay. According to your firm, your customer was advised of the OOS results obtained and they agreed to accept the product "as is." However, there was no documentation to show why an investigation of the OOS results was not conducted. In addition, no record was kept that documents the customer's approval/acceptance of the OOS product. Please be advised that FDA considers the release of nonconforming product to customers who are willing to accept these products in spite of the OOS results, a violation of the Act.
  
4. Your firm failed to implement its own procedures in that it neglected to establish the suitability of the GC systems prior to their use in the testing of CMGs and medical device gas mixtures. Even though subsection 920.5.1.5(c) of the Medical Manual (MED-900) requires that your analysts perform a system suitability test of the gas chromatography system prior to each day of use, this was not always done. In the case of the analysis of lot 0900J143 (lung diffusion mixture), the analyst failed to calculate the percent relative standard deviation (%RSD<sup>1</sup>) for a series of standard injections. If he/she had done it, it would have been clear that the GC system did not meet the established limits of %RSD  $\leq$  ~~0.5~~. However, the analyst used this GC system to do the carbon monoxide assay determination for the referenced lot, which eventually led to the improper release of this lot for distribution.

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<sup>1</sup> Calculation of the %RSD for a series of five or six consecutive standard injections, and comparison to an established limit provides an indication of the precision (reproducibility) of the system and are part of the system suitability test.

Moreover, subsection 920.5.1.5(c) also requires that once system suitability is complete, the chromatogram must be reviewed and approved by a second qualified individual, who will sign and date the chromatogram. Again, in the case of lot 0900J143, this procedure was not followed.

Our review of the *Packaging Control Record* for lot 0900J143 revealed that the individual that signed it as the final record reviewer was also the analyst who performed the carbon monoxide assay testing for this lot. We believe that this type of review should be done by another qualified individual who is not directly involved with the analysis of the product under review.

The case of lot 0900J143 (lung diffusion mixture), where firm's procedures for testing and review were not followed, and no investigation into the causes of the OOS results was conducted, indicates to us that a breakdown has occurred in your firm's QA/QC system. In other words, the individual(s) in charge of reviewing production records and approving the release of finished products appears to have failed to perform those functions in accordance with the QSR.

5. Your firm released Lot 0900J248 (lung diffusion mixture) for distribution even though only one cylinder was tested for every minor component. According to subsection 7300.5 of your Medical Manual (MED-7000), every cylinder must be analyzed for every minor component. However, again your firm failed to follow its own procedure, and released the lot based on the test results of only one cylinder. In this case, the fact that this lot was transfilled from an "H" cylinder from lot 0900J143 raises additional concerns, since we consider the latter to have been inadequately tested and improperly released.
6. Your firm failed to establish adequate procedures for the evaluation and investigation (when necessary) of nonconforming product and out-of-specification test results.
7. Your firm has failed to establish a calibration and preventive maintenance program for the GC systems used to assay Carbon Dioxide, USP, blood gas mixtures, and lung diffusion gas mixtures.
8. Your firm failed to implement its own procedures with regard to the control of labels in the filling area. Subsection 400.5.2 of the Master Label and Tag Manual (LAB-001) requires that the working stock (labels) be transferred to a label control cabinet in the filling area and be kept under lock and key with access limited to authorized persons. This procedure has not been followed. In fact, the labels in the filling area were easily accessible by anyone in the area. Considering the large number of medical gas products that are filled in this area, this situation could lead to labeling mixups.
9. Your firm must establish and implement written procedures for the storage, maintenance, and use of filling adapters.

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 FDA 483 (copy enclosed) issued at the closeout of the inspection may be symptomatic of serious underlying problems in your firm's manufacturing and quality assurance systems. 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 drugs and/or devices so that they may take this information into account when considering the award of contracts. Additionally, no premarket submissions for devices to which the QSR deficiencies are reasonably related will be cleared until the violations have been corrected. Also, no requests for Certificates For Products For Export 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 FDA 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 assure that similar violations will not recur. If corrective action cannot be completed within fifteen working days, state the reason for the delay and the time within which the corrections will be completed. Your response should address any proposed actions regarding any finished drug and medical device products currently in distribution, which have not been properly tested.

We acknowledge receipt of a letter from Gregory P. Barnett, Director of Safety and Compliance, dated May 1, 2000, and addressed to FDA investigators, Penny McCarver, and Eric Weilage. That letter, which is currently under review, was in response to the Form FDA 483 issued to Allison Espy, Operations Manager, on April 21, 2000. You may refer to that letter in your response to this one.

Your response should be sent to Carlos A. Bonnin, Compliance Officer, Food and Drug Administration, 60 Eighth Street, N.E., Atlanta, Georgia 30309.

Sincerely,

  
Ballard H. Graham, Director  
Atlanta District

Enclosure

cc: Greg Barnett, Director of Safety and Compliance  
HoloX, Ltd.  
1500 Indian Trail Road  
Suite C  
Norcross, GA 30093