



June 4, 1999

Chicago District  
300 S. Riverside Plaza, Suite 550 South  
Chicago, Illinois 60606  
Telephone: 312-353-5863

WARNING LETTER  
CHI-24-99

**CERTIFIED MAIL**  
**RETURN RECEIPT REQUESTED**

Daniel L. Peters, President  
Nycomed Amersham Imaging Americas  
101 Carnegie Center  
Princeton, NJ 08540-6231

Dear Mr. Peters:

During an inspection of your establishment, Medi-Physics, Inc., located at 3350 N. Ridge Avenue, Arlington Heights, IL, from March 1 - 9, 1999, our investigators, Tamara Alicea and Lisa A. Hornback, determined that your establishment manufactures implantable iodine seeds and radiopharmaceutical products. Implantable [REDACTED], manufactured at this facility, are devices as defined by Section 201(h) of the Federal Food, Drug, and Cosmetic Act (the Act). Radiopharmaceutical products manufactured at this facility are drugs as defined by Section 201(g) of the Act. The drug products covered in this inspection included Neoscan, Gallium Citrate Ga 67 Injection; Indium DTPA, In 111 Injection; Thallous Chloride Tl 201 Injection; Sodium Iodine I-123 Capsules; and Technetium Tc 99m Generator.

The inspection revealed that the devices manufactured at this facility are 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 Regulation for medical devices, as specified in Title 21, Code of Federal Regulations (21 CFR), Part 820, as follows:

1. Failure to adequately validate the ethylene-oxide (EtO) sterilization process used to process I-125 RAPID Strand™ no. 700, in EtO Sterilizer #1. This validation lacked a completed installation qualification and operation qualification. Performance qualification, performed in 1997, was found to be deficient by FDA in an April 24, 1998 inspection. No performance qualification was completed since the April 24, 1998 inspection.

The inspection covering production of drug products revealed significant deviations from current Good Manufacturing Practice regulations (cGMPs), 21 CFR Part 211. These cGMP deviations cause these drug products to be adulterated within the meaning of Section 501(a)(2)(B) 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 cGMPs. These deviations include the following:

1. Failure to establish adequate written procedures designed to prevent microbiological contamination of sterile products. For example, operators, who perform manual aseptic connections, were not routinely monitored for microbial load.
2. Standard Operating Procedure (SOP) #07-00-00, entitled, "Repeat/Retest", dated August 2, 1993, fails to assure that drug products conform to appropriate standards of identity, strength, quality, and purity because the procedure requires that, if an investigation is not able to assign the cause of a test deviation, the testing should be repeated in duplicate, on new, freshly drawn samples. This procedure fails to require the firm, before repeating the test on new, freshly drawn samples, to establish evidence that a laboratory or sample preparation error occurred and caused the initial test result to deviate from specifications.
3. Failure to establish an adequate training program for operators, conducting visual examination of finished injectable drug products, that includes testing the operator's ability to detect visual defects in vials that have a product label affixed.

The following represent significant deviations from both the Quality System Regulation for medical devices, as specified in 21 CFR Part 820 and the current Good Manufacturing Practice regulations for drugs, as specified in 21 CFR Part 211:

1. Failure to have sufficient number of personnel to conduct quality system functions. For example:
  - The firm failed to close the majority of complaints, reviewed during the inspection, within the 45-day limit required by the firm's complaint handling procedures for both medical devices and drug products.
  - The firm failed to close [REDACTED] of [REDACTED] discrepancy reports, reviewed during the inspection, within the 20-day limit required by the firm's failure/discrepancy investigation procedures.
2. Failure to adequately evaluate and investigate complaints. For example:

- Review of Complaint PCR #9809007 revealed that the firm failed to investigate returned [REDACTED] seeds to determine why the customer found [REDACTED] of [REDACTED] with radioactivity above specifications.
  - Review of Complaint PCR #9800012 revealed the firm failed to perform an investigation of the second lot of iodine capsules involved in the complaint.
3. Failure to complete investigations of discrepancies and failures within the specified 20 workday time frame.

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 Form 483 issued at the conclusion of the inspection to Christopher Manuele, Vice President of Nuclear Operations, may be symptomatic of serious underlying problems in your establishment'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.

In order to facilitate FDA in making the determination that corrections to the deviations from the Quality System Regulation have been made, thereby enabling FDA to withdraw its advisory to other federal agencies concerning the award of government contracts for medical devices, and to resume marketing clearance for Class III devices for which a 510(k) has been submitted, and Certificates to Foreign Governments for medical devices manufactured at your facility located in Arlington Heights, IL, we are requesting that you submit to this office on the schedule below, certification by an outside expert consultant that he/she has conducted an audit of your establishment's manufacturing and quality assurance systems relative to the requirements of the device Quality System Regulation (21 CFR Part 820). You should also submit a copy of the consultant's report, and certification by your establishment's CEO (if other than yourself) that he or she has reviewed the consultant's report and that your establishment, located in Arlington Heights, IL, has initiated and completed all corrections called for in the report. The enclosed guidance may be helpful in selecting an appropriate consultant.

The initial certifications of audit and corrections and subsequent certifications of updated audits and corrections should be submitted to this office on the following dates:

- Initial certifications by consultant and establishment: December 10, 1999 (or sooner)
- Subsequent certifications:
  1. March 27, 2000
  2. March 27, 2001

Federal agencies are advised of the issuance of all Warning Letters about devices and drugs so that they may take this information into account when considering the award of contracts. No premarket submissions for devices, to which the Quality System Regulation deficiencies are reasonably related, will be cleared or approved until the violations have been corrected. No requests for Certificates to Foreign Governments will be approved until the violations related to the subject devices have been corrected and verified. Additionally, pending NDA, ANDA, or export approval requests may not be approved until the drug cGMP violations are corrected and verified.

You should take prompt action to prevent a repeat of these deviations. Failure to prevent 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.

You should notify this office in writing, within 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 system problems necessary to assure that similar violations will not recur. If corrective action cannot be completed within 15 working days, state the reason for the delay, and the time within which the corrections will be completed.

We acknowledge the receipt of Dr. James T. Molt's response, dated April 19, 1999, concerning the investigators' observations noted on the Form FDA 483. Dr. Molt indicated that Nycomed Amersham has initiated a number of corrective actions in response to the investigators' findings and he provided estimated completion dates for these changes. You may reference Dr. Molt's response in your response to this Warning Letter. Please discuss the status of the corrective actions Dr. Molt indicated Nycomed Amersham was taking in your response.

Please send your response to Michael Lang, Acting Compliance Officer.

Sincerely,

/s/  
Raymond V. Mlecko  
District Director

Enclosure