



**PURGED** *RAK*

June 11, 1998

WARNING LETTER

Food and Drug Administration  
Minneapolis District  
240 Hennepin Avenue  
Minneapolis MN 55401-1999  
Telephone: 612-334-4100

CERTIFIED MAIL  
RETURN RECEIPT REQUESTED

Refer to MIN 98 - 37

Michael G. Guy  
President  
Guy & O'Neill, Inc.  
617 Tower Drive, P.O. Box 310  
Fredonia, Wisconsin 53021

Dear Mr. Guy:

We are writing to you because on March 16-19, 1998, an investigator from the Food and Drug Administration (FDA) collected information that revealed a serious regulatory problem involving products intended to flush in-dwelling catheters which are made by your facility located at 11815 West Dearbourn Avenue, Wauwatosa, WI, and marketed by 

Under a United States Federal law (the Federal Food, Drug and Cosmetic Act [the Act]), these products are considered to be medical devices because they are used to diagnose or treat a medical condition or to affect the structure or function of the body. Products intended to flush in-dwelling catheters are medical devices as defined by Section 201(h) of the Act.

The law requires that manufacturers of medical devices adhere to Quality System Regulations for Medical Devices as specified in Title 21, Code of Federal Regulations, Part 820 (21 CFR 820) in the methods used in, facilities or controls used for manufacturing, packing, storage, or installation of medical devices.

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Our inspection found your products are in violation of the law because of:

1. Failure to establish and maintain procedures for identifying valid statistical techniques required for establishing, controlling and verifying the acceptability of process capability and product characteristics (21 CFR 820.250). For example:
  - A. The media fill validation protocol does not establish microbial limits or Confidence levels.
  - B. The method used in the validation of the manufacturing process using media fills does not demonstrate adequate safety assurance levels because the statistical significance of the sample size has not been established.

We are concerned that your firm is releasing and shipping finished product prior to the completion of the sterility testing, especially in light of the inadequacy of your process validation.

2. Failure to establish and maintain procedures to prevent contamination of product by substances that could reasonably be expected to have an adverse effect on product quality [21 CFR 820.70(e)] in that no pyrogen testing has been performed and the device is designed to deliver saline solutions directly into the patient.
3. Failure to establish and maintain procedures for the control of storage areas and stock rooms for products to prevent deterioration or other adverse effects pending use or distribution and to ensure that no obsolete, rejected or deteriorated product is used or distributed (21 CFR 820.150) in that your firm has not established a written testing program designed to assess the stability characteristics of their products to be used in determining appropriate storage conditions and expiration dates. And
4. Failure to establish procedures for quality audits and conduct such audits to assure that the quality system is in compliance with the established quality

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system requirements and to determine the effectiveness of the quality system (21 CFR 820.22).

In legal terms, the products are adulterated under Section 501(h) of the Act.

We have received your March 16, 1998, response to our form FDA-483 dated January 7, 1998. Your responses to the concerns referenced in the form FDA-483 are noted and are being made part of the official file. The corrective actions that you are taking are appropriate for addressing the concerns raised during the January 7, 1998 inspection.

We are aware that your firm was informed of the registration, listing, labeling and 510(k) requirements for your products via a May 22, 1998, letter from FDA's Office of Compliance in the Center for Devices and Radiological Health. Please send us a copy of any correspondence that you have with the Center regarding these issues.

We also received your March 30, 1998, letter responding to the form FDA-483 issued at the close of the March 16-19, 1998, inspection. The corrective actions that you are taking are appropriate for addressing some of the concerns referenced on the form FDA-483. However, your response does not include the protocol and documentation requirements for the process validation that you are performing, and written procedures and documents associated with the pyrogen testing, internal quality audits, and stability studies.

This letter is not intended to be an all-inclusive list of deficiencies at your facility. As president, the most responsible individual at Guy & O'Neill, Inc., it is ultimately your responsibility to ensure that devices manufactured in your facility in Wauwatosa, WI, are in compliance with each requirement of the Act and regulations.

The specific violations noted in this letter and in the form FDA-483 issued at the close-out 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.

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If the causes are determined to be systems problems you must promptly initiate permanent corrective actions.

You should know that this serious violation of the law may result in FDA taking regulatory action without further notice to you. These actions include, but are not limited to, seizing your product inventory, obtaining a court injunction against further marketing of the product, or assessing civil money penalties. Also, other Federal agencies are informed about the Warning Letters we issue such as this one so that they may consider this information when awarding government contracts. Additionally, no pending applications for pre-market approval (PMAs) or export approval requests will be approved, and no pre-market notifications [Section 510(k)'s] will be found to be substantially equivalent for products manufactured at your facility until the violations have been corrected.

It is necessary for you to take action on this matter now. Please let this office know in writing within 15 working days from the date you received this letter of the steps you are taking to correct the problem. We also ask that you explain how you plan to prevent this from happening again. If you need more time let us know why and when you expect to complete your correction. Please direct your response to Compliance Officer Howard E. Manresa at the address indicated on the letterhead.

Finally, you should understand that there are many FDA requirements pertaining to the manufacture and marketing of medical devices. This letter pertains only to the issue of current Good Manufacturing Practices for your devices and does not necessarily address other obligations you have under the law. You may obtain general information about all of FDA's requirements for manufacturers of medical devices by contacting our Division of Small Manufacturers Assistance at 1-800-638-2041 or through the Internet at <http://www.fda.gov>.

It should be noted that the following guidance refers to validation and stability testing for drug products. Although your products are considered to be medical devices, the guidance for the manner in which you handle the saline and heparin solutions are amenable to the requirements for drug products because the issues and concerns regarding injectable drug products parallel those posed by your product which infuses solutions directly into the body.

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Additional guidance can be found at <http://www.fda.gov/cder/guidance/index.htm>:

Under the "Chemistry" heading of this web page you can find guidance on the following topics to help you bring your sterilization and stability operations into compliance.

Submission Documentation for Sterilization Process Validation in Applications for Human and Veterinary Drug products.

Submitting Documentation for the Manufacturing of and Controls for Drug Products

Submitting Documentation for the Stability of Human Drugs and Biologics

Beneath the ICH (International Conference on Harmonization) heading on this same web page, under the subheading "Quality," you will find the following guidance which may be helpful in accomplishing the stability studies for your product.

- Q1A Stability Testing of New Drug Substances and Products
- Q1B Photostability Testing of New Drug Substances
- Q1C Stability Testing for New Dosage Forms

We enclose a copy of the Guideline on Sterile Drug Products Produced by Aseptic Processing for your use.

If you have more specific questions about how FDA marketing requirements affect your particular device or about the content of this letter, please feel free to contact Mr. Manresa at (612) 334-4100 ext. 156.

Sincerely,

  
James A. Rahto  
Director  
Minneapolis District