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Food and Drug Administration
2098 Gaither Road
Rockville MD 20850

VIA FEDERAL EXPRESS
WARNING LETTER

MAY 31 2000

Mr. Howard Bellm, Managing Director
Intersurgical Limited
Crane House, Molly Millars Lane
Wokingham, Berkshire, RG41 2RZ
UK

Dear Mr. Bellm:

We are writing to you because on February 14-17, 2000, an investigator from the Food and Drug Administration (FDA) collected information that revealed serious regulatory problems involving your class II breathing circuits, bacterial filters, and airway (extension) connectors. Under a United States Federal law, the Federal Food, Drug, and Cosmetic Act (the Act), these products are considered medical devices because they are used to diagnose or treat a medical condition or to affect the structure or function of the body (Section 201(h) of the Act).

The above stated inspection revealed that the methods used in, or the facilities or controls used for manufacturing, packing, storage, or installation of these devices are not in conformance with the Quality System Regulation, as specified in Title 21, Code of Federal Regulations (CFR), Part 820. In legal terms, the products are adulterated within the meaning of section 501(h) of the Act, as follows:

1. **Failure to implement corrective and preventive action where necessary by detecting recurring nonconforming product problems and utilizing appropriate statistical methodology, as required by 21 CFR 820.100(a).** For example, a) incomplete analysis and investigation into high scrap rates, concessions, complaints, etc.; b) complaints [REDACTED] referencing label issues do not show corrective and preventive action with regard to line clearance, label reconciliation, confirmation that training was satisfactory, or other label controls; c) appropriate statistical data has not been utilized to analyze complaints and other sources of information, such as production meetings, project lists and task lists, to identify emerging problems; and d) complaint [REDACTED] highlighted [REDACTED] units manufactured at Guernsey were defective (oversized taper) and returned to Guernsey.

In your written responses dated Feb. 25, April 3, and April 13, 2000, your firm stated that the staff involved would be retrained to follow procedures and that senior QA personnel would be involved. You did not provide documentation to substantiate that training had taken place to rectify the problem. This response is inadequate.

Also you stated that you are looking at revising your data collection and analysis system but no additional statistical techniques have been implemented. Furthermore, the CAPA procedure has not been updated. This is an ongoing corrective action. This response is inadequate.

2. Failure to identify the action needed to correct and prevent recurrence of nonconforming product and other quality problems, as required by 21 CFR 820.100(a)(3). For example:

- a) Complaint [REDACTED] – product [REDACTED] flutter housings, the design was changed due to a complaint, however, the disposition of stock was not reviewed.
- b) Complaints [REDACTED] and [REDACTED] – out of specification product resulting in leakage problem continued to be distributed without review for corrective and preventive actions.

In your written responses dated Feb. 25, April 3, and April 13, 2000, you reported having conducted follow-up on the complaints. However, to be considered adequate, the Corrective and Preventive Action Procedure should be changed to require review of potentially affected product in stock. This response is inadequate.

3. Failure to document corrective and preventive action activities, as required by 21 CFR 820.100(b). For example, there was no documentation for investigations of nonconformity, actions to correct or prevent recurrences of quality problems, verification and validation of corrective actions, or dissemination of information concerning quality problems to those directly responsible. The following serve as further examples:

- a) Complaint [REDACTED] – no documentation of equipment maintenance corrective action, review of devices in the field, or health hazard analyses for the cracked retaining rings due to [REDACTED] vending problems;
- b) Complaint [REDACTED] – no documentation for [REDACTED] design changes (reduce hole diameter) for leaking port caps resulting in increased complaints. There was no review of stock or health hazard analyses documented;
- c) Complaint [REDACTED] – no documentation for a review of stock or health hazard analyses for complaints of cracked swivel elbow bodies.

In your written responses dated Feb. 25 and April 13, 2000, you have committed to improve and expand the CAPA system. Follow-up on the complaints cited appears to have been completed. However, the corrective action is ongoing. This response is inadequate.

4. Failure to establish, maintain, investigate, and document procedures to control product that does not conform to specified requirements, as required by 21 CFR 820.90(a). For example, in process rejects of monitoring line tubing occlusion orders

relating to [REDACTED] and rectangular filter works orders [REDACTED] and [REDACTED] were rejected for leaks. The complainant reported nonconformance numerous times but no investigation or details of testing performed were documented. There were no records of scrapped tubes on the form [REDACTED] or the DHR for rejected components. The [REDACTED], however, revealed high scrap levels.

In your written responses dated Feb. 25, April 3, and April 13, 2000, you agreed to expand the CAPA system and to rectify the nonconforming product problem, however, the process has not been completed. This response is inadequate.

5. Failure to establish and maintain procedures for nonconformity review and disposition and to document the review and disposition of nonconforming product, as required by 21 CFR 820.90(b). For example, Complaint [REDACTED] – product [REDACTED] had deviation from the packing specifications with unauthorized concession by employee resulting in incorrect instructions for use (printed on the packaging).

In your written responses dated Feb. 25, April 3, and April 13, 2000, you stated that you conducted follow-up and took action to rectify the problem. This response appears adequate. The correction will be verified during the next inspection.

6. Failure to evaluate complaints to determine whether the event is required to be reported to FDA under part 803 or 804, as required by 21 CFR 820.198(a)(3). For example, complaints [REDACTED], product code numbers [REDACTED] (swivel elbow joints) involving breakage and fractures were not adequately investigated for the firm to know if a patient was involved in the event or the circumstances for the event. Complaint [REDACTED] discusses customer involvement, however, there is no evaluation to determine reportability on any of the events.

Your written responses dated Feb. 25, April 3, and April 13, 2000, Corrective and Preventive Action Procedure, [REDACTED], section 10, addresses more specifically what needs to be included in assessing whether a complaint is MDR reportable. This response appears to be adequate. The correction will be verified during the next inspection.

7. Failure to identify or to separate file complaints representing MDR reportable events, as required by 21 CFR 820.198(d). For example, complaint [REDACTED], involving a patient death, was listed on the product complaint form along with all other complaints and only identified with a “C” for “critical.” Complaint [REDACTED], subject of MedWatch [REDACTED] was not identified with a “C” as defined in procedure [REDACTED] issue 15, exhibit 4.1, clause 5. This procedure does not relate to the definition of a reportable event.

Your written responses dated Feb. 25, April 3, and April 13, 2000, the MDR procedure clarified that there will be a separate MDR file. This response appears to be adequate. The correction will be verified during the next inspection.

8. Failure to develop a standardized review process/procedure for determining when an event meets the criteria for reporting an MDR event, as required by 21 CFR 803.17(a)(2). For example, complaint procedure, [REDACTED] issue 15, does not specify MDR requirements such as responsibility for reporting or recording the reasons for the decision; Procedure [REDACTED] issue 13 gives details for European reporting, but not for FDA MDR requirements.

Your written responses dated Feb. 25, April 3, and April 13, 2000, demonstrate that you improved the MDR procedure. This response appears to be adequate. The correction will be verified during the next inspection.

9. Failure to maintain documents including deliberations and decision-making processes used to determine if a device-related death, serious injury, or malfunction was or was not reportable as an MDR event, as required by 21 CFR 803.18(b)(1)(i). For example, a) complaint [REDACTED] luer cap product [REDACTED] patient stopped breathing and an advisory notice was issued in UK and Europe and reported to the French Competent Authority; b) complaint [REDACTED] product [REDACTED], an occluded oxygen tube was returned to the Lithuanian manufacturer but there was no review of units distributed to customers, no health hazard analysis, and no product reconciliation documented; and c) complaint [REDACTED] product [REDACTED] (as well as 2 other similar complaints of the same nature), a death believed to be “patient misconnected [REDACTED] oxygen tube to IV line and died” resulted in a redesign of the product. There was no documentation to substantiate a review of documentation for MDR reportability for any of these events.

Your written responses dated Feb. 25, April 3, and April 13, 2000, discussed the 3 adverse events and made conclusions of MDR reportability on the follow-up. You included more specific information to conclude when an adverse event is reportable. This response appears to be adequate. The correction will be verified during the next inspection.

10. Failure to maintain procedures for approval of design changes and validation of a design change before implementation, as required by 21 CFR 820.30(i). For example, the Port Cap change requested in 1996 was signed as verified in 1998 without a review for potential problems. By the time the design was signed as successful in June 1999, the change had already resulted in several complaints. The design was changed to avoid further complaints. Also, the [REDACTED] filter material [REDACTED] relative to pad thickness and weight was changed, but never revalidated as the [REDACTED]

Your written responses dated Feb. 25, April 3, and April 13, 2000, stated that corrective action was ongoing but did not provide documentation to support re-validating the device after changes were made. Further, you stated that the verification and validated design changes would be improved, but did not supply the documentation to substantiate changes. This response is inadequate.

11. Failure to validate computer software for its intended use according to an established protocol, as required by 21 CFR 820.70(i). For example, the firm did not validate software for electronic records and electronic signatures.

Your written responses dated Feb. 25, April 3, and April 13, 2000, stated that you would formalize the policy regarding electronic data and signatures and notify the FDA. However, you did not provide documentation. This response is inadequate.

12. Failure to validate and approve a process, whose results cannot be fully verified by subsequent inspection and test according to established procedures, as required by 21 CFR 820.75(a). For example, the validation of the Nebulizer Humidifier was performed on the premises of the equipment supplier, however, the information on the “Weld Parameters and Validation Report for Nebulizer Humidifier Test Report” was not clear as to who did the validation and where, nor the lots product was taken from, whether they were production lots, the pass/fail criteria or the validation conclusion.

Your written responses dated Feb. 23, April 3, and April 13, 2000, stated that process validation would be expanded and that it was an ongoing effort. There was no documentation to substantiate a change. This response is inadequate.

13. Failure to document acceptance test results, as required by 21 CFR 820.80(e). For example, the frequency of in-process inspection for the tubing from Natvar is not documented. Although the tubing was stated to be 100% in-process inspected, occluded product was found but the findings were not documented.

Your written responses dated Feb. 25, April 3, and April 13, 2000, did not provide supporting documentation to substantiate appropriate changes to acceptance and in-processing of product. This response is inadequate.

14. Failure to fully implement procedures for control of all documents including electronic records and signatures, as required by 21 CFR 820.40. For example, the firm has not fully implemented procedures for control of all documents for their electronic record and electronic signatures.

Your written responses dated Feb. 25, April 3, and April 13, 2000, stated that you would formalize the policy regarding electronic data and signatures and notify the FDA. You have not provided this documentation. This response is inadequate.

15. Failure to review and approve documents by the designated individual, as required by 21 CFR 820.40(a). For example, the audit checklist (██████████) did not have an issue control or authorization.

Your written responses dated Feb. 25, April 3, and April 13, 2000, stated that the audit checklist sheet has an issue control number and is authorized. This response appears to be adequate. The correction will be verified during the next inspection.

16. Failure to conduct quality audits by an individual who is not directly responsible for the matter being audited, as required by 21 CFR 820.22. For example, since 1997, the QA Manager has conducted audits of areas for which she is responsible.

Your written responses dated Feb. 25, April 3, and April 13, 2000, indicated that internal audits will be conducted by trained auditors from the other European manufacturing sites so that the audit is conducted by someone other than an individual directly responsible. You also stated that three Guernsey site employees will be trained at the Internal Quality Systems Auditor course. This is an ongoing corrective action. You did not provide documentation such as in a policy change to substantiate the change. This response is inadequate.

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 issued at the closeout of the inspection may be symptomatic of serious 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.

We acknowledge that you submitted to this office February 25, April 3, and April 13, 2000, responses concerning our investigator's observations noted on the Form FDA 483. We have reviewed your responses and concluded that they are inadequate. An evaluation of specific responses is entered after each one of the deviations listed above.

Given the serious nature of these violations of the Act, the airway connectors and breathing circuits bacterial filters manufactured by Intersurgical Ltd. may be detained without physical examination upon entry into the United States (U.S.) until these violations are corrected.

In order to remove the devices from this detention, it will be necessary for you to provide a written response to the charges in this Warning Letter for our review. After we notify you that all responses appear to be adequate, we will request the establishment inspection at that time. As soon as the inspection has taken place, the implementation of your corrections have been verified, and you are notified that your corrections are adequate, your devices may resume entry into this country.

Please 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, include 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. Please include any and all documentation to show that adequate correction has been achieved. In the case of future corrections, an estimated date of completion, and documentation showing plans for correction, should be included with your response to this letter. Please address your response to:

Ed Santiago, Branch Chief
Food and Drug Administration
Center for Devices and Radiological Health
Office of Compliance
Division of Enforcement III (HFZ-343)
2098 Gaither Rd.
Rockville, MD 20850
USA

If you have any questions about the contents of this letter, please contact Brenda Hayden at the above address or at (301) 594-4659, or fax (301) 594-4672. 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 (301) 443-6597, or through the Internet at <http://www.fda.gov>.

Sincerely yours,



Lillian J. Gill
Director
Office of Compliance
Center for Devices and
Radiological Health

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