

JUN -3 2004

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WARNING LETTER

VIA FEDERAL EXPRESS

Mr. K. Nakamae
President
Asahi Medical Company, Ltd.
MD Kanda Bldg., 9-1 Kanda Mitoshirocho
Chiyoda-Ku, Tokyo 101-8482
JAPAN

Dear Mr. Nakamae:

During an inspection of your facility located in Oita-Shin, Oita Japan, on [REDACTED], our investigator determined that your firm manufactures hollow fiber capillary dialyzers and plasma filters. These products are devices within the meaning of section 201(h) of the Federal Food, Drug, and Cosmetic Act (the Act)(21 U.S.C. § 321(h)).

This inspection revealed the following violations of the Act:

Quality System Regulation

These devices appear to be adulterated within the meaning of section 501(h) of the Act (21 U.S.C. § 351(h)), in that the methods used in, or the facilities or controls used for, their manufacture, packing, storage, or installation are not in conformity with Current Good Manufacturing Practice (CGMP) requirements, which are set forth in FDA's Quality System (QS) regulation, found at Title 21 Code of Federal Regulations (CFR), Part 820. Significant violations include, but are not limited to, the following:

1. Failure to validate with a high degree of assurance, and to approve according to established procedures, a process whose results cannot be fully verified by subsequent inspection and test, as required by 21 CFR 820.75(a).

Specifically, your validation documentation shows that your [REDACTED] sterilization validation was conducted according to the requirements of ISO [REDACTED] and the performance qualification was conducted using [REDACTED]. You failed to follow all of the validation requirements specified in the ISO standard and in your original 510(k). Review of validation data shows [REDACTED]. Data presented were for [REDACTED].

[REDACTED] It appears that you used [REDACTED] method, to develop the minimum six hour processing time to meet your [REDACTED] organisms. You performed the required [REDACTED]ns resulting in no [REDACTED] but failed to provide documentation that [REDACTED] duration from which [REDACTED] can be recovered to demonstrate the adequacy of the recovery technique. This is required by the ISO [REDACTED]

2. Failure to establish and maintain procedures for validating the device design, including risk analysis, where appropriate, as required by 21 CFR 820.30(g).

Specifically:

- a. Air leakage, abnormal pressure and function, leaching of plasticizer affecting the [REDACTED] and other possible hazards were not identified in your Failure Mode Effects Analysis (FMEA) table.
 - b. The FMEA [REDACTED] is not based on clinical effect such as death, serious injury, requirement for medical intervention, or temporary/permanent injury.
3. Failure to establish and maintain procedures for the identification, documentation, validation or where appropriate verification, review, and approval of design changes before their implementation, as required by 21 CFR 820.30(i).

Specifically, acceptance criteria were not established prior to the performance of validation activities conducted in [REDACTED] for a product design change. The change was intended to [REDACTED] from the [REDACTED] model dialyzer. You did not establish a formal design verification/validation protocol and acceptance criteria for the changes.

Trend analysis revealed that the [REDACTED] series dialyzers, intended for [REDACTED], identified an increase in frequency of [REDACTED]. You made changes to mitigate the problem. Specifically, there were three design changes made: modification of the [REDACTED] to minimize the [REDACTED] or [REDACTED] on the hollow fiber; modification of the shipping carton to [REDACTED] intended to lessen the [REDACTED] to the hollow fibers; and labeling modification intended to [REDACTED] of the dialyzer.

4. Failure to maintain a record of an investigation, including the dates and results of the investigation, and any corrective action taken, as required by 21 CFR 820.198(e)(6) & (7).

Specifically:

- a. Review of complaints [REDACTED] and [REDACTED] revealed that there was no failure investigation information other than written verification of the complaints. The complaints involved [REDACTED]. With further discussion about these complaints during the inspection, you located a similar complaint with more investigational information revealing a potential [REDACTED] problem that could result in [REDACTED] in dialysis tubing sets as the root cause of the [REDACTED] problem.
- b. Review of complaints [REDACTED] and [REDACTED] revealed reported [REDACTED] with limited investigation information. They are both for devices with the same product lot number. Complaint [REDACTED] notes that [REDACTED] was confirmed, whereas, [REDACTED] was not confirmed on complaint [REDACTED]. Testing was performed on the rest of the lot received from the complainant (120 units) and the lot passed. No [REDACTED] was performed, although you suspected the root cause of [REDACTED] was due to [REDACTED] the hollow fibers. The problem has been previously investigated, resulting in design changes to the [REDACTED] reduce potential hollow fiber [REDACTED] from [REDACTED].

Changes to Design and Instructions for Use

Additionally, we have reviewed information collected by our investigator about changes you made to the design of, and instructions for use for, the [REDACTED] hollow fiber dialyzers. Your written response to the FDA 483, dated [REDACTED], addressed these changes. You explained that you modified the design of the dialyzer by [REDACTED] the [REDACTED]. This design change was intended to [REDACTED] on the hollow fiber to help [REDACTED]. The instructions for use were also modified to provide specific guidance regarding the [REDACTED] to be used when [REDACTED] or [REDACTED] the device. A statement was also added [REDACTED] and [REDACTED] should be [REDACTED] to help prevent [REDACTED].

The Act requires that manufacturers of medical devices obtain marketing clearance from FDA for their products before they may offer them for sale. This helps protect the public by ensuring that new medical devices are shown to be both safe and effective or substantially equivalent to other devices already legally marketed in this country.

The [REDACTED] hollow fiber dialyzer that was cleared in the original premarket notification, [REDACTED], did not have the design features described above. These changes are significant modifications to your device and require a new 510(k) as described in 21 CFR 807.81 (a)(3)(i).

A review of our records has revealed that you did not obtain marketing clearance or approval for the [REDACTED] hollow fiber dialyzer with the design changes described above, which is a violation of the law. Specifically, this device is adulterated under section 501(f)(1)(B) of the Act because you do not have an approved application for premarket approval (PMA) in effect pursuant to section 515(a) of the Act, or an approved application for investigational device exemption (IDE) under section 520(g) of the Act. The device is also misbranded under section 502(o) of the Act because you did not notify the agency of your intent to introduce the device into commercial distribution, as required by section 510(k) of the Act. For a device requiring premarket approval, the notification required by section 510(k) of the Act is deemed satisfied when a PMA is pending before the agency. 21 CFR 807.81(b). The kind of information you need to submit in order to obtain this clearance is available through the Internet at <http://www.fda.gov/cdrh/devadvice/3122.html>.

For your information you may refer to FDA guidance documents "Deciding When to Submit a 510(k) for a Change to an Existing Device" (K97-1) and "510(k) Requirements During Firm-Initiated Recalls" (K95-1). We recommend that you submit a [REDACTED] [REDACTED] to the Agency to satisfy your premarket notification requirements. Please submit an actual sample of the modified device along with instructions for use to help expedite our review. The FDA will evaluate this information along with your new 510(k) and decide whether your product may be legally marketed.

Medical Device Reporting

The above-stated inspection also revealed that your devices are misbranded under section 502(t)(2) of the Act, in that your firm failed to furnish any material or information required by or under section 519 respecting the device. Specifically, you failed to submit a medical device report (MDR) to the FDA within 30 days of receiving information that reasonably suggested that one of your commercially distributed devices may have caused or contributed to a death or serious injury. [21 CFR Part 803.50(a)(1)]

Complaint record [REDACTED], dated [REDACTED], noted that one patient died after developing pulmonary edema while receiving [REDACTED] using your [REDACTED] Model [REDACTED] and that a second patient at the same hospital developed similar symptoms of pulmonary edema while receiving [REDACTED] with the same device of the same lot. You reported the patient death in MedWatch Manufacturer's report [REDACTED] [REDACTED] did not submit an MDR for the second patient. During the inspection you acknowledged that you failed to report the second event, and subsequently submitted MedWatch Manufacturer's report [REDACTED] [REDACTED] for this event.

The MDR report you submitted for the patient death, Medwatch Manufacturer's report [REDACTED] did not include all information that was reasonably known to you, as required by 21 CFR 803.50(b). Specifically, you failed to disclose that, in addition to the reported death, there was a second potential serious injury at the same hospital involving the same device of the same lot.

This letter is not intended to be an all-inclusive list of deficiencies at your facility. It is your responsibility to ensure compliance with applicable and regulations administered by FDA. The specific violations noted in this letter and in the Inspectional Observations, Form FDA 483 (FDA 483), issued at the closeout of the inspection may be symptomatic of serious underlying problems in your firm's manufacturing and quality assurance systems. You should investigate and determine the causes of the violations, and take prompt actions to correct the violations and to bring your products into compliance.

We received a response from [REDACTED] General Manager, QA & Product Safety, dated [REDACTED] concerning our investigator's observations noted on the FDA 483. It appears the response is adequate. However a follow-up inspection will be required to assure that corrections are adequate. We acknowledge receipt of your two-volume package, dated [REDACTED] submitted in response to the FDA-483. This information is currently under review. We will respond when our review is completed.

You should take prompt action to correct these deviations. Failure to promptly correct these deviations may result in regulatory action without further notice, which may include the refused entry of your affected products until the corrections are completed.

Please notify this office in writing within fifteen (15) working days from the date you receive this letter, of the specific steps you have taken to correct the noted violations, including an explanation of how you plan to prevent these violations, or similar violations, from occurring again. Include all documentation of the corrective action you have taken. If you plan to make any corrections in the future, include those plans with your response to this letter as well. If the documentation is not in English, please provide a translation to facilitate our review.

Your response should be should be sent to the Food and Drug Administration, Center for Devices and Radiological Health, Office of Compliance, Division of Enforcement A, OB/GYN, Gastroenterology, and Urology Devices Branch, 2098 Gaither Road, Rockville, Maryland 20850, USA, to the attention of Sharon Murrain-Ellerbe, Consumer Safety Officer.

Page 6 - Mr. Nakamae

If you need help in understanding the contents of this letter, please contact Sharon Murrain-
Ellerbe at the above address or at (301) 594-4616 or FAX (301) 594-4638.

Sincerely yours,



Timothy A. Ulatowski
Director
Office of Compliance
Center for Devices and
Radiological Health

Cc: Asahi Medical America (AMA)
3100 Dundee Road, Suite 201/202
Northbrook, Illinois 60062, USA

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OFFICE	SURNAME	DATE	OFFICE	SURNAME	DATE
HFZ-332	TIGROW	6-3-04			
HFZ-320	GKrehling				
HFZ-300	Reynold Fox	6-3-04			