



JUN 11 2003

Food and Drug Administration  
2098 Gaither Road  
Rockville MD 20850

WARNING LETTER  
VIA FEDERAL EXPRESS

Mr. Martin Madaus, Ph.D.  
President and CEO  
Roche Diagnostics Corporation  
9115 Hague Road  
Indianapolis, Indiana 46250

Dear Mr. Madaus:

During an inspection of Disetronic Medical Systems, AG located in Burgdorf, Switzerland, on January 27 - February 5, 2003, an investigator from the Food and Drug Administration (FDA) collected information that revealed serious problems involving the manufacture of external insulin infusion pumps. These products are devices as defined by the Federal, Food, Drug, and Cosmetic Act (the Act).

The above-stated inspection revealed that these devices 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 their manufacture, packing, storage, or installation are not in conformance with the Current Good Manufacturing Practice (CGMP) requirements of the Quality System regulation (QS regulation), as specified in Title 21, Code of Federal Regulation (CFR), Part 820. Significant deviations include, but are not limited to the following:

1. Failure to adequately establish and maintain procedures for implementing corrective and preventive action, which include requirements for analyzing processes, work operations, concessions, quality audit reports, quality records, service records, complaints, returned product, and other sources of quality data to identify existing and potential causes of nonconforming product or other quality problems, as required by 21 CFR § 820.100(a)(1). For example, review of the CAPA system document, RL 159, noted that all quality data sources have not been identified, such as the following:
  - a. production statistics do not identify all available in-process production test data sources and the routine analysis to be performed on these data sources;
  - b. various data sources for complaints, failure analysis, and repair data from in-house to distributors outside of Switzerland are not identified;

- c. the [REDACTED] Service system, which produces a custom generated report, lacked requirements and specifications for required data analysis and reporting for CAPA and management review; and,
- d. the [REDACTED] which produces a custom generated report, lacked requirements and specifications for required data analysis and reporting for CAPA and management review.

The responses submitted by Disetronic dated March 5, April 3, and May 6, 2003 are inadequate because Disetronic has not provided any revised CAPA procedures and has not submitted any data or documentation of implementing analysis for data sources that have been reviewed and analyzed under the CAPA system. Disetronic stated that CAPA procedures are under revision and that reviews will take place, but Disetronic did not provide any supporting documentation.

- 2. Failure to verify or validate corrective and preventive actions to ensure that such actions are effective and do not adversely affect the finished device, as required by 21 CFR § 820.100(a) (4). Your firm lacks documentation that verification or validation was performed of the corrective actions taken on the H-TRON products to ensure effectiveness of the changes. Further, review of the repair database identified H-TRONplus serial numbers [REDACTED] and [REDACTED] as having cracking at battery location C3; and, serial number [REDACTED] as having cracking at the H+M buttons following the corrective actions, which were implemented to alleviate these problems. Therefore, the effectiveness of the corrective action is uncertain. |

The responses submitted by Disetronic dated March 5, April 3, and May 6, 2003 are inadequate because Disetronic did not provide any validation procedures, plans, or data to ensure effectiveness of the changes to the H-TRON products. Disetronic stated that measures will be defined by March 15, 2003, but documentation has not been supplied, and the April response still has this action item marked as "Ongoing."

- 3. Failure to perform an adequate risk analysis, as required by 21 CFR § 820.30(g):
  - a. Risk Analysis procedure [REDACTED] has the probability of occurrence table with overlapping levels. There is not a scientific explanation or documented scientific rationale for how the level for frequency of occurrence was to be determined.

- b. The risk analysis for the Listron/D-TRON Version 1.5 and the risk analysis for the H-TRON plus 1100/1239 were not carried out to the anticipated lifetime for the devices as described in their respective design requirements. In both cases the previously established design life of the devices was [REDACTED] months, yet, the risk analysis was only performed for a product lifetime of [REDACTED] months.
- c. Review of the FMEA procedure [REDACTED] showed the severity and/or detection tables with more than one level selectable for a given severity and detection. For example, there are [REDACTED] selectable levels for Mittelschwerer Fehler per severity table and [REDACTED] selectable levels for Massig in the detection table. The selection of these levels will influence whether the RPZ (Risk index level) is below or above the predetermined FMEA acceptable value.
- d. Review of Listron/D-Tron/1252 for system analysis, hardware and Mechanik showed "Due to experience of DISETRONIC in creating FMEAs the acceptable value of RPZ was set to [REDACTED]." There was no documented rationale to support the use of [REDACTED] as an acceptable value or its relationship to the risk analysis of the device.

The responses submitted by Disetronic dated March 5, April 3, and May 6, 2003 are inadequate because Disetronic has not provided a copy of the revised Risk Analysis and FMEA procedures nor provided any evidence that a current risk analysis was performed according to the new procedures. Disetronic stated that procedures have been revised and current analysis is scheduled to be completed by April 15, 2003, but the firm did not provide any supporting documentation.

4. Failure to validate computer software for its intended use according to an established protocol, when computers or automated data processing systems are used as part of the quality system, as required by 21 CFR § 820.70(i):
  - a. Your firm lacks documentation of software requirements and specifications and documented evidence for software verification and validation activities for the complaint database, [REDACTED].

- b. Your firm lacks documentation of software requirements and specifications and documentation for software verification or validation activities for the program used to track failure investigations and repair data, [REDACTED]

The responses submitted by Disetronic dated March 5, April 3, and May 6, 2003 are inadequate because Disetronic has not provided any documentation addressing this observation or demonstrating the revision of procedures to ensure that software used throughout the quality system will be validated for its intended purpose. Disetronic promised some completion of software specifications by the end of April but stated that the software validation may not be implemented until the fourth quarter of 2003. Ten months to correct these deficiencies is unacceptable.

5. Failure to validate with a high degree of assurance, a process that cannot be fully verified by subsequent inspection and test, and failure to perform such validation according to approved established procedure, as required by 21 CFR § 820.75(a). For example, change number [REDACTED] to [REDACTED] and [REDACTED] and [REDACTED] and [REDACTED] and the D-TRONplus was implemented without process validation. Inspection found the automated adhesive dispensing process lacks a specification for the amount of adhesive to be dispensed. Without a volume or weight specification for the amount of adhesive to be dispensed, there is no adhesive specification and tolerance limits from which to validate the process.

The responses submitted by Disetronic dated March 5, April 3, and May 6, 2003 are inadequate because Disetronic has not provided any process validation procedures, plans, or data. Disetronic stated that validation is expected to be completed May 15, 2003, but evidence of initial qualification work or other specification data has not been supplied.

6. Failure to analyze service reports with appropriate statistical methodology in accordance with 21 CFR § 820.100, as required by 21 CFR § 820.200(b). For example, your firm lacks procedures for performing data analysis and how to report service and repair statistics.

The responses submitted by Disetronic dated March 5, April 3, and May 6, 2003 are inadequate because the firm has not provided any procedure(s) for the review and analysis of the

service and repair data. Disetronic stated that the revised procedures will be implemented by April 30, 2003, but evidence of procedure, training, or implementation was not provided.

7. 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 and failure to have written sampling plans, which are based on a valid statistical rationale, as required by 21 CFR § 820.250. For example:
  - a. There is no statistical rationale for the verification procedure used for the automated adhesive dispensing equipment to determine if the amount of adhesive dispensed using 50 samplings will comply with a [REDACTED] tolerance limit using only maximum and minimum data points.
  - b. Your firm lacks a statistical rationale for testing only 15 samples in a long term study, which is being done to determine the effect of using [REDACTED] for the H+M button assembly.

The responses submitted by Disetronic dated March 5, April 3, and May 6, 2003 are inadequate because Disetronic has not provided any procedure(s) for the use of appropriate statistics. Documentation of procedures, training, or implementation was not provided.

8. Failure to adequately establish and maintain procedures to control documents and document changes to include provisions for change records to record approval date, approval signature and when the change becomes effective, as required by 21 CFR §§ 820.40 and 820.40(b). For example:
  - a. Change control procedure [REDACTED] lacks a requirement for documentation of when a change is to become effective.
  - b. Change [REDACTED] lacked the date the change became effective. The change was implemented in Burgdorf in September 2001 and in Kiel in January 2002; however, signatures for document control and feedback to the person requesting the change were not signed and dated until January 28, 2003, during the FDA inspection.
  - c. Change [REDACTED] and [REDACTED] lacked a signature and date for approval of the manufacturing change and the document control file sign-off. The change documents also lacked the dates the changes became effective.

- d. Change [REDACTED] lacked the date for approval of the manufacturing change and lacked the date the change became effective.

The responses submitted by Disetronic dated March 5, April 3, and May 6, 2003 are inadequate because the firm has not provided a copy of the revised change control and/or process control procedure or any evidence of training or implementation.

- 9. Failure of the device master record (DMR) to include production process specifications, as required by 21 CFR § 820.181(b). For example, the DMR does not include or refer to the location of some production process specifications. Specifically, the procedure for the [REDACTED], lacks specifications for the amount of [REDACTED] to be dispensed and for the [REDACTED] for the dispensing equipment.

The responses submitted by Disetronic dated March 5, April 3, and May 6, 2003 are inadequate because Disetronic has not provided any process validation or software validation procedures, plans, or data. The firm stated that settings for automated equipment will be initiated by March 31, 2003, but documentation of any initial work or specifications has not been supplied. Further, Disetronic stated that it will review the Device Master Records by May 31, 2003, but further information or documentation was not provided.

- 10. Failure of management with executive responsibility to conduct an adequate review of the suitability and effectiveness of the quality system to ensure that the quality system satisfies requirements of part 820 and the manufacturer's established quality policy and objectives, as required by 21 CFR § 820.20(c). For example, Customer service data ending with December of 2001 was reviewed during the September 2002 management review. The data being reviewed by management in September was not current and up to date. In addition, other quality data only covered a time period from April 2001 to March 2002 and there was not any data present from March until August or September of 2002.

The responses submitted by Disetronic dated March 5, April 3, and May 6, 2003 are inadequate because Disetronic has not provided a translated copy of the revised Management review procedures nor provided any documentation that a comprehensive Management review has occurred to cover all necessary data to date. The firm stated that the procedure has been revised and that a meeting is scheduled for April 15, 2003, but documentation has yet to be submitted.

This letter is not intended to be an all-inclusive list of deficiencies at Disetronic. 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 form FDA 483 issued at the conclusion of the inspection may be symptomatic of serious underlying problems in the Disetronic 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 devices so that they may take this information into account when considering the award of contracts.

Given the serious nature of these violations of the Act, all products manufactured by Disetronic Medical Systems AG, Burgdorf, Switzerland may be detained without physical examination upon entry into the United States until these violations are corrected.

In order to prevent the devices from being detained without physical examination, your firm will need to respond to this Warning Letter (as set forth below) and to correct the violations noted in this letter. In addition, the agency usually needs to conduct a follow-up inspection to verify your firm's implementation of the appropriate corrections.

In order to remove the devices from this Detention Without Physical Examination, it will be necessary for you to provide a written response to the charges in this Warning Letter for our review. We acknowledge Disetronic's March 5, April 3, and May 6, 2003 responses to the FDA 483 and have addressed these responses above. After we notify you that you have submitted an adequate response, it will be your responsibility to schedule an inspection of your facility. As soon as the inspection has taken place, and the implementation of your corrections has been verified, your products may resume entry into this country.

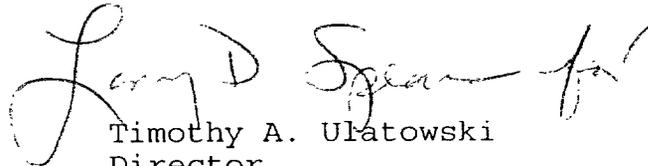
Please notify this office in writing within fifteen (15) working days of the specific steps you have taken to correct the noted violations, including an explanation of each step being taken to identify and make corrections to any underlying

Page 8 - Mr. Madaus

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. If documentation is not in English, please provide an English translation to facilitate our review. Please address your response and any questions to the Food and Drug Administration, Center for Devices and Radiological Health, Office of Compliance, Division of Enforcement A, General Hospital Devices Branch, HFZ-333, 2098 Gaither Road, Rockville, Maryland 20850, to the attention of Ms. Carolyn Niebauer.

Should you require any assistance in understanding the contents of this letter, do not hesitate to contact Ms. Leslie E. Caster at the letterhead address or at 301.594.4618 or FAX 301.594.4638.

Sincerely yours,

A handwritten signature in cursive script, appearing to read "Timothy A. Ulatowski".

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