DEPARTMENT OF HEALTH & HUMAN SERVICES

Public Health Service

93150

Food and Drug Administration
2098 Gaither Road
Rockville MD 20850

JAN 30 2003

WARNING LETTER
FEDERAL EXPRESS

Mr. Kirk Foley
Chairman & CEO
Activa Brand Products, Inc.
6845 Davand Drive
Mississauga, ON L5T 1L4 Canada

Dear Mr. Foley:

During an inspection of your firm located in Charlottetown, Canada, on July 29 -31 and August 1, 2002, an investigator from the Food and Drug Administration (FDA) collected information that revealed serious regulatory problems involving your manufacture of needleless insulin injectors. These products are devices as defined by the Federal, Food, Drug, and Cosmetic Act (the Act) (Section 201(h) of the Act, 21 U.S.C. § 321(h)). The above-stated inspection revealed that the methods used in, or the facilities or controls used for the manufacture, packing, storage, or installation of these devices are not in conformance with the Quality System Regulation (QSR), as specified in Title 21, Code of Federal Regulations (CFR), Part 820. These deviations from the QSR cause your products to be adulterated within the meaning of Section 501(h) of the Act (21 U.S.C § 351(h)). Significant deviations include, but are not limited to the following:

1. Failure to adequately establish and maintain a quality system that is appropriate for the specific medical device designed or manufactured and that meets the requirements in 21 CFR 820, as required by 21 CFR 820.5. For example, management has not ensured that quality system requirements have been effectively established and maintained.

   Your response to this observation is not adequate, and will not be until 21 CFR 820.5 has been fully met.

2. Failure to adequately establish and maintain an adequate organizational structure to ensure that devices are designed and produced in accordance with the requirements in 21 CFR 820, as required by 21 CFR 820.20(b). For example, the individual responsible for quality assurance and management representative duties is located off-site.

   Your response to this observation is not adequate. While an individual responsible for quality assurance is now located on-site, your response does not address whether this same individual will perform the duties of the management representative, and if not, whether the individual who will perform the duties of the management representative is now located on-site.

3. Failure for management with executive responsibility to review the suitability and effectiveness of the quality system at defined intervals and with sufficient frequency according to established procedures to ensure that the quality system satisfies the requirements in 21 CFR 820 and the manufacturer's established quality policy and objectives, as required by 21 CFR 820.20(c). For example:

   a. the president was not present at the annual management review conducted on January 22, 2002; and
   b. mandatory agenda items were not covered during the January 22, 2002 and April 28, 2001 management reviews.

   Your response to this observation overall, is not adequate. The observation pointed out that (1) the president was not present at an annual management review, and (2) mandatory agenda items, which included complaints, manual review, quality policy, supplier evaluation and corrective and preventive actions were not covered during certain management reviews. Your response does adequately address the absence of the president at an annual management review, and the lack of coverage of complaints at an annual review; however, it does not address the lack of coverage of manual review, quality policy, supplier evaluation and corrective and preventive action.

4. Failure to conduct quality audits to assure that the quality system is in compliance with the established quality system requirements and to determine the effectiveness of the quality system and failure to have such audits conducted by individuals who do not have direct responsibility for the matters being audited, as required by 21 CFR 820.22. For example:

   a. the Internal Audit Checklist utilized in conducting quality audits does not include all aspects of the quality system requirements, such as the complaint handling system; and
   b. the auditor conducting the March 14, 2002 audit audited areas for which he has direct responsibility.

   Your response to this observation appears adequate.

5. Failure to ensure that all personnel are trained to adequately perform their assigned responsibilities, as required by 21 CFR 820.25(b). For example:

   a. the manager of operations whose duties include implementing corrective and preventive actions (CAPA), nonconformance reporting and complaint handling has not been trained in the Quality System regulation; and
   b. the sales and marketing associate whose duties include complaint handling and implementing CAPA has not been trained in the Quality System regulations.

Your response to this observation appears adequate; however, it is recommended that you not only train your employees on an overview of the FDA requirements, as the response states, but also provide more in-depth training of the Quality System regulation (QS regulation), especially to those employees who have direct responsibility of ensuring that the requirements of the QS regulation are met.

6. 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). For example, there is a lack of procedures for design changes.

   Your response to this observation appears adequate.

7. Failure to adequately establish (define, document, and **implement**) and maintain procedures for receiving, reviewing, and evaluating complaints by a formally designated unit, as required by 21 CFR 820.198(a). For example:

   a. complaints were noted in the repair documents and telephone logs, but not incorporated into the complaint handling system; and
   b. customer complaint forms are incomplete in that serial numbers, identity of injector, and complainant's address is not recorded.

   Your response to observation "a" above is not adequate. Your response did not address the observation, which stated that the complaint handling system does not include complaints that come in through repair orders, telephone calls, etc.

   Your response to observation "b" above appears adequate.

8. Failure to process all complaints in a uniform and timely manner, as required by 21 CFR 820.198(a)(1). For example:

   a. complaint [redacted] was recorded on October 24, 2001 and still remains open;
   b. complaint [redacted] was opened on January 22, 2002 and still remains open;
   c. complaint [redacted] was opened on April 15, 2002 and still remains open; and
   d. complaint [redacted] was opened on March 27, 2002 and still remains open.

   Your response to this observation appears adequate.

9. Failure to adequately establish (define, document, and **implement**) and maintain procedures for receiving, reviewing, and evaluating complaints by a formally designated unit, which ensure that complaints are evaluated to determine whether the complaint represents an event which is required to be reported to FDA under part 803 or 804 of this chapter, Medical Device Reporting, as required by 21 CFR 820.198(a)(3). For example:

a. complaint [redacted] reports a complainant who went to the hospital because his "sugars were too high" and the complainant indicated that his injector never worked after repair, but there was no follow-up to ascertain whether this complaint was an MDR reportable event; and
b. 21 CFR 803, Medical Device Reporting, is referenced in procedure [redacted], Customer Service, for determining MDR reportability, but those regulations were not available at the firm.

Your response to this observation appears adequate.

10. Failure to review and evaluate all complaints to determine whether an investigation is necessary, as required by 21 CFR 820.198(b). For example, complaints are not evaluated to determine whether an investigation is necessary, nor is this required by procedure, [redacted], Customer Service.

Your response to this observation is not adequate. The complaint process does not state that when no investigation is made, a record shall be maintained that includes the reason no investigation was made and the name of the individual responsible for the decision not to investigate.

11. Failure to adequately establish (define, document and **implement**) 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 cause of nonconforming product or other quality problems, as required by 21 CFR 820.100(a)(1). For example:

a. Corrective Action Requests [redacted] were not closed out by the QC Supervisor, as required by [redacted] Corrective and Preventive Action, Rev. 1; and
b. [redacted] Corrective and Preventive Action, identifies repair reports as a source for identification of potential CAPA activities; however, repair reports are not being trended or reviewed for CAPA.

Your response to observation "a" above is not adequate. Your response states "all CARs are <u>not</u> subject to final review and closure by the Director of Quality Assurance or his delegate." The response also indicates that the Corrective and Preventive Action standard operating procedure has been rewritten and is included in the response; however, it was not included, and therefore, could not be reviewed to see if the word "not" in the quoted statement above was written in error.

Your response to observation "b" above is not adequate. Your response states that "effective immediately, all Repair Reports will be subject to review and evaluation by the resident Quality Assurance Representative for corrective and preventive action opportunities," but this requirement does not appear to be stated in any standard operation procedure that was provided with your response.

12. Failure to verify or validate a corrective and preventive action to ensure that such action is effective and does not adversely affect the finished device, as required by 21 CFR 820.100(a)(4). For example, three Corrective Action Requests [redacted] revealed that corrective actions are not verified.

    Your response to this observation is not adequate. Your response indicates that CARs are closed per [redacted] but does not state whether closing a CAR includes that the corrective action is verified or validated. [redacted] was not included as part of the response, and therefore, could not be reviewed.

13. Failure to adequately establish and maintain procedures for implementing corrective and preventive action that includes requirements for implementing and recording changes in methods and procedures needed to correct and prevent identified quality problems, as required by 21 CFR 820.100(a)(5). For example, [redacted], Packaging and Shipping, was not revised to indicate that the Tip Sheet, which was created as a corrective/preventive action for [redacted], is to be packaged with the new and repaired injectors.

    Your response to this observation is not adequate. Page 2 of [redacted], Packaging and Shipping, does not state that the Tip Sheet should be included with repaired injector kits.

14. Failure to review for adequacy and approve prior to issuance all documents established to meet the requirements of 21 CFR 820 and to promptly remove all obsolete documents from all points of use to avoid unintended use, as required by 21 CFR 820.40(a). For example:

    a. Corrective Action Request [redacted] resulted in the creation of a Tip Sheet with instructions on how to avoid dry firing and how to check for filling; however, this controlled document has not gone through the approval process; and
    b. [redacted] Rev. A, which was obsolete as of January 17, 2002 was utilized on February 25, 2002.

    Your response to this observation appears adequate.

15. Failure to review and approve document changes by an individual in the same function or organization that performed the original review and approval, unless specifically designated otherwise, as required by 21 CFR 820.40(b). For example:

    a. The [redacted] instruction manual has been revised to replace "sterilizing" terms with "disinfection" terms and the change did not go through the document control system; and
    b. [redacted] Document and Data Control, states that hand written changes to controlled documents are not permitted; however, [redacted], Calibration of Scales, has a hand written correction regarding the vendor utilized for calibration services.

Your response to this observation appears adequate.

16. Failure to adequately establish (define, document, and implement) and maintain procedures to control product that does not conform to specified requirements, as required by 21 CFR 820.90(a). For example:

    a. Instruction manuals are revised manually, and there is no system established to assure manuals are correctly revised;

    b. [redacted] Controlling of Nonconforming Product, does not address all disposition options identified on the nonconformance report form; and

    c. Nonconformance Reports are incomplete, in that, the QA review/comments section is not completed [redacted] and Nonconformance Repor[redacted] did not have inspection and closure section completed.

    Your response to this observation appears adequate.

17. Failure to adequately establish and maintain procedures to control labeling activities, as required by 21 CFR 820.120(b). For example, [redacted] Labeling of Injectors, does not require inspection of labels be documented, and there is no sampling plan for label inspection.

    Your response to this observation is not adequate. [redacted]states under procedure 1.1.1 that all labels will be inspected, but under 1.1.2 it states that only a sample of labels will be inspected.

18. Failure to adequately validate with a high degree of assurance and approve according to established procedures a process, where the results of the process cannot be fully verified by subsequent inspection and test, as required by 21 CFR 820.75(a). For example, [redacted] (sterility validation data) is incomplete in that the packaging integrity testing data has not been maintained.

    Your response to this observation is not adequate. A copy of the Packaging Integrity document was not included in the response.

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 form FDA 483 issued at the conclusion 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 FDA. If the causes are determined to be systems problems, you must promptly initiate permanent corrective actions.

Given the serious nature of these violations of the Act, all products manufactured at this facility may be detained without physical examination upon entry into the United States. In order to prevent your 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.

Federal agencies are advised of the issuance of all Warning Letters so that they may take this information into account when considering the award of contracts. Also, no requests for Certificates for Products for Export will be approved until the violations relating to the subject devices have been corrected.

We acknowledge your August 12, 2002, response to the FDA 483, and have addressed this response 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 15 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 correction 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. 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 II, 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,

George Koch for

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