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DEPARTMENT OF HEALTH & HUMAN SERVICES

Public Health Service
Food and Drug Administration

Los Angeles District
19900 MacArthur Boulevard Suite 300
Irvine, California 92612-2445
Telephone (714) 798-7600

Certified Mail
Return Receipt Requested

WARNING LETTER

March 26, 1998

WL-21-8

Arthur J. Benvenuto
President/CEO
Advanced Tissue Sciences, Inc.
10933 North Torrey Pines Road
La Jolla, CA 92037

Dear Mr. Benvenuto:

During an inspection of your firm conducted between February 9 to March 13, 1998, our investigators determined that your firm manufactures human fibroblast-derived temporary skin substitute and bioengineered human replacement dermis. These products are devices as defined by Section 201(h) of the Federal Food, Drug, and Cosmetic Act (the Act).

Our inspection revealed that these devices are adulterated within the meaning of Section 501(h) of the Act, in that the methods used in, and the facilities and controls used for the design, manufacture, packaging, labeling, storage, installation, or servicing are not in conformance with the Good Manufacturing Practice (GMP) requirements set forth in the Quality System Regulation as prescribed by Title 21, Code of Federal Regulations, Part 820, as follows:

1. Failure to establish and maintain written procedures to adequately control environmental conditions that could reasonably be expected to have an adverse effect on product quality [21 CFR 820.70]. For example, our investigation disclosed numerous situations where your company discovered mold, yeast and bacteria contaminants during your routine environmental monitoring of your critical and controlled areas in your manufacturing facility but no thorough assessment was conducted to determine the potential impact that these contaminants may have had on your product or sufficient corrective actions to prevent their recurrence.
2. Failure to establish and maintain written procedures for implementing corrective and preventative action, especially identifying the actions needed to correct and prevent the recurrence of nonconforming product and other quality problems [21 CFR 820.100]. For example, our investigation disclosed numerous occasions in which your quality system failed to establish its authority and responsibility when investigation, corrective action, and follow-up were incomplete or inadequate to address the cause or resolution of the nonconformances.

3. Failure to establish and maintain written procedures for acceptance activities for in-coming, in-process and finished devices [21 CFR 820.80]. For example, our investigation disclosed numerous events where the initial test results exceeded your established specifications but in-coming, in-process, and finished devices were retested and released. Additionally, several lots of products were released without a measurement of cell viability.

4. Failure to maintain records of investigations of all complaints involving the possible failure of a device and/or records describing the reason no investigation was made. For example, our investigation disclosed that your firm had no written documentation describing the rationale for not performing investigations or documenting the results of investigations of several reported complaints, specifically complaints of infections of patients treated with your devices.

Additionally, our inspection revealed that your devices are misbranded within the meaning of Section 502(t)(2) of the Act, in that your firm failed to submit information to the Food and Drug Administration as required by the Medical Device Reporting (MDR) Regulation, as specified by 21 CFR Part 803. Specifically, you failed to submit an MDR after receiving information which reasonably suggested that one of your commercially distributed devices may have contributed to a death.

Your "Dermagraft-TC" is further misbranded within the meaning of Section 502(f)(1) in that it appears to lack adequate directions for use because the expiration date was extended beyond its original six month expiration period without the appropriate justification.

Although, your office met with representatives of our agency on March 17, 1998, we still have serious concerns about the significant deficiencies disclosed during our investigation. We have specific concerns about the number of occasions where your product failed to meet its pre-determined quality attributes but was released into commercial distribution without a thorough assessment to determine the reason for the nonconforming product. We also have serious concerns about your control of environmental conditions of manufacturing facility and the high endotoxin levels disclosed by your testing.

We acknowledge that you have submitted to this office two responses concerning our investigators observations noted on the form FDA 483. Copies of the responses have also been sent to the Center for Devices and Radiological Health (CDRH) for review. We will provide our comments to your responses, nevertheless, you should not delay in your response to this Warning Letter.

Additionally, please provide our office with a complete inventory of the product that has been commercially distributed to your domestic and international consignees and the amount of product that your firm has in your current inventory.

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 closeout 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 violation 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. Additionally, no premarket submissions for devices to which the GMP deficiencies are reasonably related will be cleared until the violations have been corrected. Also, no request for Certificates to Foreign Governments for Export will be approved until the violations related to the subject devices have been corrected.

You should take prompt action to correct these deviations. Failure to promptly correct these deviations may result in regulatory action being initiated by the Food and Drug Administration without further notice. These actions include, but are not limited to, seizure, injunctions, and/or civil penalties.

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, including 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 or any other items discussed at our meeting. If corrective action cannot be completed within 15 working days, state the reason for the delay and the time within which the corrections will be completed.

Your reply should be addressed to:

Dannie E. Rowland
Compliance Officer
U.S. Food and Drug Administration
19900 MacArthur Blvd., Suite 300
Irvine, CA 92612-2445

Sincerely,


Elaine C. Messa
District Director

cc: State Department of Public Health
Environmental Health Services
Attn: Chief, Food and Drug Administration
601 North 7th Street, MS-357
P.O. Box 942732
Sacramento, CA 94234-7320