



DEPARTMENT OF HEALTH AND HUMAN SERVICES
Public Health Service

11 3916n

Food and Drug Administration
19900 MacArthur Blvd., Suite 300
Irvine, CA 92612-2445
(949) 798-7600

WARNING LETTER

AUG 24 1999

CERTIFIED MAIL
RETURN RECEIPT REQUESTED

WL- 41-9

Eugene Kaufman, President and CEO
Culture Technology, Inc.
864 South Robertson Blvd., Suite 101
Los Angeles, CA 90035

Dear Mr. Kaufman:

We are writing to you because on April 19-28, 1999, our investigators from the Food and Drug Administration (FDA) collected information that revealed a serious regulatory problem involving your product known as "LikeSKIN" and "LifeSKIN" which is made and marketed by your firm.

Under a United States Federal law, the Federal Food, Drug, and Cosmetic Act (Act), these products are considered to be medical devices because they are used to diagnose or treat a medical condition or to affect the structure or function of the body. Your human skin products (both allographs and autographs) are medical devices as defined by Section 201(h) of the Act. The law requires that manufacturers of medical devices obtain marketing clearance for their products from FDA before they may offer them for sale. This helps protect the public health by ensuring that new medical devices are shown to be either safe and effective or substantially equivalent to other devices already legally marketed in this country. You are also reminded of FDA letters of designation from the Office of the Commissioner FDA dated September 20, 1996, to your Attorneys [REDACTED] and [REDACTED], stating that your products were medical devices and the Center of Devices and Radiological Health would be your primary contact.

Our records do not show that you obtained marketing clearance before you began offering your products for sale. The kind of information you need to submit in order to obtain this clearance is described in the enclosed materials. The FDA will evaluate this information and decide whether your product may be legally marketed.

Because you do not have marketing clearance from FDA, marketing your product is in violation of the law. In legal terms, the product is adulterated under section 501(f)(1)(B)

and misbranded under section 502(o) of the Act. Your product is adulterated under the Act because you did not obtain premarket approval based on information developed by you that shows your devices are safe and effective. Your product is misbranded under the Act because you did not submit information that shows your device is substantially equivalent to other devices that are legally marketed.

Also during the inspection of your firm in April 19-28, 1999, our investigators found that your devices are adulterated per Section 501 (h) of the Act in that the methods used in, or the facilities or controls used for manufacturing, packing and storage, or installation are not in conformance with the Good Manufacturing Practice (GMP) for Medical Device Regulation, as specified in Title 21, Code of Federal Regulations (CFR) Part 820 as follows:

1. Failure to review associated data and documentation before release for distribution of the finished device, as required by 21 CFR 820.80 (d)(2); failure to establish and maintain procedures for finished device acceptance to ensure that each production run, lot, or batch of finished devices meets acceptance criteria, as required by 21 CFR 820.80 (d); failure to establish acceptance procedures to ensure that specified requirements for in-process product are met as required by 21 CFR 820.80 (c); and failure to document acceptance activities, as required by 21 CFR 820.80(e). For example:
 - a. Grafts of LifeSKIN Cultured Composite Autografts, lot #260Y90222, were prepared, cultured for sterility testing, and sent for patient application on the same day the culture was taken. The culture test results were received after [REDACTED] and were found positive for +1 coagulase negative staphylococci species. The release specification is "no growth."
 - b. There is no documentation to demonstrate that the Pyrogen Test and Endotoxin Test are performed during in-process and finished product testing.
 - c. There is no documentation to justify the release of finished devices based on sterility test results obtained after documented [REDACTED] laboratory incubation periods instead of 7-17 day incubation periods, as recommended in the United States Pharmacopoeia (USP) 23.
 - d. The endotoxin level concentration has not been established for the [REDACTED] Serum used in the manufacturing process.
 - e. There is no established testing for mycoplasma during in-process or finished device testing.

- f. There are no in-process tests for sterility, endotoxin, and pyrogen performed on the LifeSKIN Cultured Composite Autografts and the LikeSKIN Cultured Composite Allografts during the manufacturing process.
2. Failure to establish and maintain procedures for receiving, reviewing, and evaluating complaints by a formally designed unit, as required by 212 CFR 820.198(a); failure to evaluate complaints to determine whether the complaints represent an event which is required to be reported to FDA under part 803, Medical Device Reporting, as required by 21 CFR 820.198 (a)(3); failure to review and evaluate all complaints to determine whether an investigation is necessary, and to maintain a record that includes the reason when no investigation is made and the individual responsible for the decision not to investigate, as required by 21 CFR 820.198 (b); and failure to review, evaluate, and investigate any complaint involving the possible failure of a device to meet any of its specifications, as required by and 21 CFR 820.198 (c). For example:
 - a. The Complaint/Medical Device Reporting (MDR) procedure does not include the MDR process.
 - b. Patient files, [REDACTED] and [REDACTED], were not reviewed, investigated, and evaluated to determine if the complaint should be filed as a Medical Device Report (MDR).
 - c. Patient files, [REDACTED], [REDACTED] and [REDACTED] were not reviewed or evaluated as possible complaints to determine if an investigation was necessary when patient grafts failed to perform according to specifications, and no reason was documented for not conducting an investigation. The patients lost from [REDACTED] to [REDACTED] of their grafts; however, the LifeSKIN literature claims an "average 80% take."
 3. Failure to validate with a high degree of assurance and approvals according to established procedures, a process where the results cannot be fully verified by subsequent inspection and test, as required by 21 CFR 820.75 (a). For example:
 - a. The manufacturing processes for LifeSKIN Cultured Composite Autografts and LikeSKIN Cultured Composite Allografts have not been validated.
 - b. Cell culture protocol for the manufacture of LifeSKIN Cultured Composite Autografts and LikeSKIN Composite Allografts for patients with known sensitivity has not been validated.

- c. The sterility test method conducted on finished devices has not been validated to demonstrate that [REDACTED] containing a graft is equivalent to testing the actual graft for sterility.
 - d. The autoclave sterilization process for sterilizing equipment (glassware, forceps, and scissors) that is used in the manufacturing process has not been validated.
 - e. The deionized water system used in the manufacturing process has not been validated.
 - f. Cell growth incubators, [REDACTED] gas model [REDACTED], serial #1710-23, and model [REDACTED], serial #1820-10 have not been qualified.
 - g. Cell temperature growth incubators, model [REDACTED], serial #877100904 and 8771009014 have not been qualified.
 - h. [REDACTED] cell storage tank, model [REDACTED], serial #213, and [REDACTED] storage tank, model [REDACTED], serial #LTB921401JM-A110 have not been qualified.
 - i. Drying oven model [REDACTED], serial #SF64, and Oven Vacuum, model [REDACTED], serial #0991-b 1336, have not been qualified.
 - j. Autoclave model [REDACTED], serial #A4-36438, used to sterilize manufacturing equipment, has not been qualified.
4. Failure to periodically inspect environmental control systems to verify that the system, including necessary equipment is adequate and functioning properly, as required by 21 CFR 820.70 (c); failure to conduct periodic inspections in accordance with established procedures to ensure adherence to applicable equipment maintenance schedules, as required by 21 CFR 820.70 (g) (2); and failure to establish and maintain procedures for the use and removal of manufacturing material to ensure that it is removed or limited to an amount that does not adversely affect the device's quality; and failure to document the removal of manufacturing materials, as required by 21 CFR 820.70 (h). For example:
- a. The maintenance Policy No. 1028.002, Environmental Control, Release Date 1/97, requires [REDACTED] certification of the Class 100 laminar flow hood, and the Class 100 horizontal flow hoods used in the manufacturing process. The following hoods were last certified on 11/13/97:

1. Class 100 Laminar Flow Hood
[REDACTED], Serial #16992
[REDACTED], Serial #6C115F7332
 2. Class 100 Horizontal Flow Hood
[REDACTED], Serial #12995
[REDACTED], Serial #11201
- b. There are no written procedures for the removal of manufacturing material to assure that manufacturing materials such as penicillins, cephalosporins, and amino glycosides used in the cell manufacturing process are removed or reduced to an acceptable level before release of the product.
 - c. The removal or reduction of manufacturing material has not been documented.
5. 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 base the sampling plan for finished device testing on a valid statistical rationale, as required by 21 CFR 820.250. For example, one (1) graft out of [REDACTED] grafts per lot is sampled for sterility/viability check during finished device testing.
 6. Failure to analyze processes and other sources of quality data to identify existing and potential causes of nonconforming product, as required by 21 CFR 820.100 (a)(1). For example:
 - a. Contamination Report Forms dated 5/11/98, 4/8/98, 11/17/97, 10/2/97, 7/15/97, 6/9/97, 4/3/97, and 3/3/97, documented product and laboratory equipment/apparatus contamination by Streptococcus veridans, gram negative Staphylococci, Aspergillus, Group D Enterococcus, Flavobacterium, Penicillium species; however, no other potential causes of contamination such as the deionized water system and the testing laboratory environmental controls were reviewed or considered.
 - b. Skin grafts failed to meet specifications for patients [REDACTED], [REDACTED], and [REDACTED], and no investigation was conducted into the failures.
 7. Failure to establish and maintain the requirements, including quality requirements, that must be met by suppliers, contractors, and consultants, as required by 820.50 (a); and failure to establish and maintain data that clearly describe or reference the specified requirements, including quality

requirement, for purchased or otherwise received products and services, as required by 21 CFR 820.50 (b). For example:

- a. A supplier letter of quality assurance is the method by which quality standards are established for purchased materials used in the manufacturing process.
 - b. There are no written specifications for incoming manufacturing materials used in the manufacturing process.
8. Failure to make records not stored at the inspected establishment readily available for review and copying by FDA employee(s), as required by 21 CFR 820.180. For example, donor screening records used to determine donor suitability were not made available during the inspection for donors [REDACTED], [REDACTED], and [REDACTED].
 9. Failure to establish and maintain procedures to ensure that device history records (DHR's) for each batch, lot, or unit are maintained to demonstrate that the device is manufactured in accordance with the device master record (DMR) and the requirements of this part, as required 21 CFR 820.184. For example, the donor screening records for donor [REDACTED] did not include a screening interview with questions regarding behavioral and high risk criteria for HIV and/or hepatitis.
 10. Failure of the manufacturer to establish and maintain MDAR (Medical Device Reporting) event files, as required by 21 CFR 820.18. For example, the MDR handling procedure does not include the Medical Device Report (MDR) process.

In addition, 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 in 21 CFR part 803. Specifically:

11. Failure of the manufacturer to conduct an investigation of each adverse event, and evaluate the cause of the event, as required by 21 CFR 803.50(b)(2). Specifically, no investigation or evaluation was made to determine the cause of problems related by patient files [REDACTED] and [REDACTED] when the patient skin grafts failed to meet specifications, and if these events should be reported to FDA under the MDR requirements.

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 underlying problems in your firm's manufacturing and quality assurance systems.

We have received your response to the FDA-483 dated May 6, 1999. Our review indicates that with the exception of number eight (failure to make records readily available) your responses are inadequate. Specifically, your responses fail to address the stated issues and also fail to include documentation. You are responsible for investigating and determining the causes of the violations found by the FDA. If the causes are determined to be systems problems you must promptly initiate permanent corrective actions.

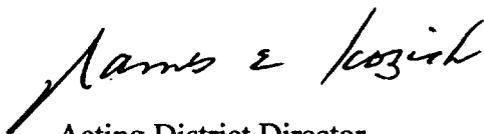
You should know that these serious violations may result in FDA taking regulatory action without further notice to you. These actions include, but are not limited to, seizing your product inventory, obtaining a court injunction against further marketing of your product, or assessing civil money penalties. Also, Federal Agencies are told about warning letters, such as this one, so that they may consider this information when awarding government contracts.

It is necessary for you to take prompt action on this matter. Please let this office know what steps you have taken to correct the problems within fifteen (15) working days from the date you receive this letter. We also ask that you explain how you plan to prevent this from happening again. If you need more time, let us know why and when you expect to complete your corrections. Please direct your response to:

Thomas L. Sawyer
Director Compliance Branch
Food and Drug Administration
19900 MacArthur Blvd., Suite 300
Irvine, CA 92612

Finally, you should understand that there are many FDA requirements pertaining to the manufacturing and marketing of medical devices. This letter pertains to specific issues of premarket clearance, Good Manufacturing Practices and Medical Device Reporting and does not necessarily address other obligations you have under the law. 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 1-(800) 638-2041 or through the Internet at <http://www.fda.gov>.

Sincerely,



Acting District Director

Enclosure