



DEPARTMENT OF HEALTH AND HUMAN SERVICES

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Food and Drug Administration  
Minneapolis District Office  
Central Region  
212 Third Avenue South  
Minneapolis, MN 55401  
Telephone: (612) 334-4100  
FAX: (612) 334-4142

June 14, 2004

**WARNING LETTER**

**CERTIFIED MAIL**  
**RETURN RECEIPT REQUESTED**

Refer to MIN 04 - 28

Bonita L. Baskin, Ph.D.  
Chief Executive Officer  
Apptec Laboratory Services, Inc.  
2540 Executive Drive  
St. Paul, Minnesota 55120

Dear Dr. Baskin:

The Food and Drug Administration (FDA) conducted an inspection of your firm, Apptec Laboratory Services (Apptec), located at 2540 Executive Drive, Saint Paul, Minnesota, between February 17 and March 4, 2004. This inspection determined that Apptec is a contract human tissue processor. During the inspection, the FDA investigators documented significant deviations from the regulations for human tissue intended for transplantation set forth in Title 21, Code of Federal Regulations (21 CFR), Part 1270, promulgated under the authority of Section 361 of the Public Health Service Act. The violations included the following:

1. Failure to prepare, validate, and follow written procedures for prevention of infectious disease contamination or cross-contamination by tissue during processing as required by 21 CFR 1270.31(d):
  - a. Your firm failed to validate written procedures. For example, there were no data to support the use of the processing parameters for the            soak step that was noted in standard operating procedure (SOP) TPR-0013A entitled "Decellularization and Freezing ." Additionally, there has been no evaluation of the effectiveness of the            soak.
  - b. Your firm failed to prepare written procedures or specifications describing the steps taken for prevention of infectious disease contamination or cross-contamination during tissue processing. For example:

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- i. There is no written procedure outlining the lyophilization process for human skin tissue.
    - ii. There is no written procedure for the re-lyophilization of human skin tissue. The FDA investigators documented ~~lots~~ lots of human skin tissues that have been re-lyophilized since you began processing human skin tissue.
    - iii. There is no written procedure for the storage of human skin tissue in a desiccator which is used to prevent moisture absorption prior to final cutting and packaging.
    - iv. There are no written procedures or specifications for the repackaging of human skin tissue that has undergone re-lyophilization.
  - c. SOP TPR-0013A entitled "Decellularization and Freezing ~~Form~~" was not followed, in that:
    - i. Your firm performed an additional processing step, which was not specified in the SOP. During the manufacturing of human skin tissue, Project 18776, the human skin tissue was ~~as an additional step~~ as an additional step in the procedure. There is no data supporting use of this additional step.
    - ii. Your firm failed to document the volume of wash solution utilized at various steps during processing, as required. Only the initial volume of wash solution is documented on Form TPR-0013-1A, Decellularization and Freezing Form.
2. Failure to prepare and follow written procedures for all significant steps for obtaining, reviewing, and assessing the relevant medical records of the donor as required by 21 CFR 1270.31(b), in that the SOP TPR-0014A entitled "Review of Donor Suitability" did not include specific provisions for the review of documentation or information, nor does the SOP establish acceptance criteria for use in determining the suitability of tissue donors. For example, the SOP does not include specific provisions for reviewing documentation including, but not limited to, the hemodilution formula and/or calculations to be used in determining blood loss and the transfusion/infusion of blood and blood products, colloids, and crystalloids; donor medical and social history criteria; and infectious disease testing criteria.

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3. Failure to prepare and follow written procedures for designating and identifying quarantined tissue as required by 21 CFR 1270.31(c), in that:
  - a. Your firm failed to prepare a written procedure for identifying in-process skin tissue not yet determined suitable for transplantation as being in quarantine status upon shipment to and from a contract manufacturer for lyophilization.
  - b. Your firm failed to prepare a written procedure for identifying in-process skin tissue not yet determined suitable for transplantation while stored in the  freezer. During the inspection, FDA investigators observed  packages of human tissue stored in the  freezer that bore no identification or designation such as donor, lot, or project identification, and quarantine status.

The above-identified violations are not intended to be an all inclusive list of deficiencies at your facility. It is your responsibility to ensure adherence with each requirement of the regulations and Section 361 of the Public Health Service Act. You are responsible for investigating and determining causes of the violations identified by FDA.

You should take prompt action to correct these deviations and to prevent their recurrence. Failure to do so may result in additional regulatory action without further notice. These actions may include, but are not limited to, an Order for Retention, Recall and/or Destruction.

We acknowledge receipt of your response letter to the inspectional observations received in our office on March 9, 2004, and the supplemental response received April 12, 2004. We have reviewed your response and we have the following comments.

- \* You identified that an audit of the lyophilization facility will be conducted to obtain procedures and to review validation data. However, you failed to indicate the corrective actions that you intend to take to address the issues related to the re-lyophilization of human skin tissue.
- \* Your revised SOP TPR-0016B entitled "Cutting And Packaging Of Lyophilized Dermal Tissue" does not specify the acceptance criteria for human skin tissue that is received from the lyophilization facility.
- \* Your revised SOP TPR-0016B entitled "Cutting And Packaging Of Lyophilized Dermal Tissue" does not provide specific steps for the storage of human skin tissue in the desiccator to prevent moisture absorption.
- \* The SOPs TPR-0040A entitled "Policy for Review of Donor Records" and TPR0014A entitled "Review of Donor Suitability" do not identify the

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algorithm or formula that your firm intends to use to calculate and determine hemodilution.

\* Your revised SOP TPR-0040A entitled "Policy for Review of Donor Records" is inadequate, in that:

- Section 3.1 entitled "Responsibility," provides, "[REDACTED]  
[REDACTED]  
[REDACTED]" While the procurement agency may perform the procurement and recovery functions of your operations under contract, it remains your responsibility under 21 CFR 1270.31(b) to prepare written procedures to be followed (by the procurement agency) for all significant steps for obtaining, reviewing, and assessing the relevant medical records of the donor.
- Section 5.5.3 entitled "Procedure," the SOP provides that "[REDACTED]  
[REDACTED]  
[REDACTED]" It is not appropriate to limit infectious disease testing of living donors to HIV. 21 CFR 1270.21(a) requires that all donor specimens must be tested for HIV, hepatitis B, and hepatitis C.
- Section 5.5.4 entitled "Procedure," the SOP provides that donors must meet age requirements. FDA regulations do not provide for any specific age requirements, however, your SOP fails to indicate any established age limits or specifications.

\* We acknowledge that process validation for human skin tissue currently being conducted by [REDACTED] is on-going. Please provide an update of the status of the validation study in your response to this letter.

We request that you notify this office in writing, within 15 working days of receipt of this letter of any additional steps you have taken to correct the noted deviations. This should include an explanation of the additional steps being taken to identify and make corrections to any underlying system problems necessary to assure that similar deviations will not occur. If corrective action cannot be completed within 15 working days, state the reason for the delay and the time frame within which the correction will be completed.

Your reply should be sent to the Food and Drug Administration, Minneapolis District Office, 212 Third Avenue South, Minneapolis, Minnesota 55401, Attention:

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Jane E. Nelson, Compliance Officer. If you have any further questions, please feel free to contact Ms. Nelson at (612) 758-7119.

Sincerely,

A handwritten signature in cursive script that reads "W. Charles Becoat".

W. Charles Becoat  
Director  
Minneapolis District

JEN/ccl

*JEN*