



DEPARTMENT OF HEALTH & HUMAN SERVICES

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Food and Drug Administration
Denver District Office
Building 20 - Denver Federal Center
P.O. Box 25087
Denver, Colorado 80225-0087
TELEPHONE: 303-236-3000

July 2, 2002

WARNING LETTER

CERTIFIED MAIL
RETURN RECEIPT REQUESTED

Mr. Thomas Cycyota
President and Chief Executive Officer
AlloSource, Inc.
6278 South Troy Circle
Centennial, Colorado 80111

Ref. # - DEN-02-13

Dear Mr. Cycyota:

An inspection of your firm located at 6278 South Troy Circle, Centennial, Colorado, was conducted between February 11 and April 3, 2002. This inspection determined that your firm processes human tissues intended for transplantation. Our investigators documented significant deviations of regulations for human tissue intended for transplantation set forth at Title 21, Code of Federal Regulations (21 CFR), Part 1270, promulgated under the authority of Section 361 of the Public Health Service Act. We found that your firm failed to prepare, validate, and follow written procedures for prevention of infectious disease contamination and cross-contamination during processing, as required by 21 CFR 1270.31(d). Our observations included:

1. Failure to follow written procedures based on a review of donor processing records, as follows:
 - a. There is no evidence that fascia lata tissue from donor ~~XX~~ was processed through the ~~XXX~~ procedure as required by your firm's SOP. This tissue was transplanted and subsequently the subject of a complaint involving a severe post-operative infection with *Enterococcus faecalis* and *Escherichia coli*;
 - b. Records indicate that the right tibia of donor ~~XX~~ was positive for *Clostridium perfringens*, a Category III microorganism, which is unacceptable for processing according to your procedures. Records indicate that this tissue was processed and released. AlloSource was unaware of this until our investigators discovered the

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discrepancy during our inspection. Tissue distributed from this donor was subsequently recalled.

- c. According to your procedures, tissues that are positive for Category II microorganisms are required to be irradiated and processed separately after processing the rest of the donor's tissues to prevent cross-contamination. Your records do not indicate that you always follow these procedures. For example, the ribs of Donor X X were positive for Group C *β-Streptococcus* and were processed through the X X X X before other tissues from the same donor.
- d. With respect to Donor X X your records indicate that on January 3, 2002, the Operations Processing Release Review form and a Notice to the file, required pre-debridement cultures to be taken on all tissues. These tissues were originally shipped to AlloSource on July 25, 2001, but were not received until July 27, 2001. Your firm returned the shipment on October 22, 2001, due to the delayed receipt and to the fact that the shipment was noted to have been received with "minimal or no dry ice." The tissues were returned to AlloSource on December 19, 2001 and were accepted, although there was no documentation of the rationale for acceptance. On January 3, 2002, the Medical Records Technician endorsed the records to indicate that the medical records and serology and microbiology review were found acceptable and did not require the Medical Director's evaluation, although the pre-debridement cultures were not performed until January 9, 2002. In addition, although procurement tissue cultures for the left and right ilia were positive for Category II microorganisms, pre-debridement cultures were not taken. Moreover, AlloSource processed the right anterior tibialis along with other tissues from this donor although there were no procurement culture results and the results of the pre-processing cultures were not yet known.
- e. Your firm continues to use the [REDACTED] system to process tissue although microbiological testing results indicate that, at times, the number of microorganisms exceed your specifications. Organisms including *Pseudomonas aeruginosa*, *Sphingomonas paucimoblis*, *Pseudomonas fluorescens*, and *Burkholderia cepacia* have been identified from point-of-use samples taken by your firm. These microorganisms are identified on your *Bacterial Reference List for Processing of Tissue* as bacteria that require secondary sterilization if recovered from tissue cultures. This water is used to process donor tissues including use as the final rinse in the purge and soak process. Your Document X X X X X X X X X X defines the acceptable limits for your high purity water system as X X X X. Review of your records indicated that your water system exceeded this limit on 29 out of 108 days monitored during the time period August 28, 2001 and February 13, 2002.

2. Failure to validate written procedures.

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There is no assurance that the ~~X X X~~ system used to conduct microbial testing will perform as you intend. The ~~X X X~~ system was developed originally for the analysis of clinical blood cultures, however, AlloSource is using it to conduct sterility testing of rinsates from aseptically processed tissues. There is no evidence that residue from solutions used during aseptic processing do not inhibit the growth of the sterility test media. Also, although you use up to ~~X~~ milliliters of sterile buffer solution to rinse tissue, only ~~X~~ milliliters of rinsate is used during testing. There is no rationale for this practice.

3. Failure to prepare written procedures.

There is no evidence that employees working in the cleanrooms follow appropriate practices. For example, our investigators observed that operators did not disinfect their hands after manipulating tissues for an extended period of time, and there was no disinfectant solution available in the cleanrooms for the operators to use. No procedures are in place to monitor the processing operators' hands after their shifts.

In addition, the following observations further showed that you either did not prepare or did not follow written procedures to prevent infectious disease contamination or cross-contamination:

- a. Several discrepancies were noted in the records for donor ~~X X~~. Procurement microbiological culture results were incorrectly recorded indicating that the right-side fascia lata was negative, when the tissue was actually positive for coagulase negative *Staphylococcus*; your records indicate that the left femur was positive for microbiological growth when the testing laboratory reported the tissue had "No Growth."
- b. All tissues from donor ~~X X~~ were to be irradiated per the Processing Plan as ~~X~~ of ~~X~~ tissues collected were positive for such organisms as *Enterococcus sp.*, *Aeromonas hydrophila*, and Group D *Streptococcus*. Final sterility results for tissues ~~X~~ and ~~X~~ were reported separately on the Aseptic Packaging Results record. The remainder of the tissues were reported on the Irradiated Packaging Results record. There is no evidence to demonstrate that tissues ~~X~~ and ~~X~~ were irradiated.
- c. Bulk demineralized bone matrix produced from Donor ~~X X~~ tested positive for *Propionibacterium sp.* Records indicate that this product was reworked and repackaged due to the presence of a "foreign body," however, there was no indication that the reprocessing included a ~~X X X X~~ to address this positive sterility test. The tissue was released for distribution after repackaging.

In addition to the deviations noted above, the inspection identified other issues of general concern which our investigators discussed with you at the conclusion of the inspection. In particular, during the inspection the investigators discovered that you had stopped the reprocessing of tissue that had been associated with a product withdrawal due to possible mold

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contamination based on your determination that the tissue was suitable for distribution without further action. Your decision appears to have been based on a scientifically unsubstantiated conclusion that the microbiological test media and not the tissue was contaminated with mold. Even after FDA informed you that your conclusions were not scientifically supportable, you took no action to either reprocess or destroy the recalled tissues.

As a result of the deviations identified during the FDA inspection in April and May 2001 and contained in FDA's letter to you dated October 9, 2001, AlloSource promised corrective actions, including the validation of various processes to prevent contamination or cross-contamination of tissue during processing. In letters dated April 5, 2002, and May 20, 2002, you notified FDA that some of the validations would not be completed by the times originally promised, including one critical validation concerning the ability of your tissue swabbing technique to properly recover microorganisms. As you know, the most recent inspection at AlloSource was initiated following a complaint that you had distributed tissue contaminated with bacteria. This inspection again identified significant deviations from the applicable regulations related to prevention of infectious disease contamination and cross-contamination of tissue during processing.

We acknowledge receipt of your written response dated April 24, 2002, which addresses the inspectional observations on the Form FDA 483 issued at the close of the most recent inspection. We have reviewed the contents of your response. Corrective actions addressed in your letter may be referenced in your response to this letter, as appropriate; however, your response was inadequate to address our concerns. Our comments regarding corrective action are detailed below. The items correspond to the observations listed on the Form FDA 483:

1.a. In your response, you state the tissue that was identified as not being subjected to your firm's ~~X X X~~ procedure had no associated safety issues. This tissue was later reported to you to be associated with a post-operative bacterial infection in the recipient and had to be explanted. Your February 13, 2002 memo to file submitted in response to this observation implies that as the ~~cultures~~ cultures taken had "No Growth," there does not appear to be a contamination issue by AlloSource or the procurement facility. However, as you stated in your April 5, 2002 letter to Mr. Steven Masiello, Director of the Office of Compliance, Center for Biologics Evaluation and Research, "...the swab method is known to have some limitations, especially in our application." Your conclusion that the tissue had no safety issues is inconsistent with the report from the consignee and the known limitations of the testing method employed by your firm.

1.b,

1.c &

1.d.1 Your response states that an additional review was effective April 9, 2002 and that Work Instructions being revised to address this additional review step will be revised to reflect this change no later than May 15, 2002. This Work Instruction should be written before the new procedure is implemented.

1.e.1 This observation involves the failure to follow written procedures. As stated in your

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response, the recovery agency's medical director classified this tissue as unacceptable due to the diagnosis of Alzheimer's Disease. Your Medical Director changed the diagnosis to "Senile Dementia" and the tissue was accepted. According to your procedures, Alzheimer's Disease was an exclusionary diagnosis and our investigators noted that hospital records for this patient listed this as an existing condition in 1993. We disagree with your statement that changing the diagnosis constitutes medical discretion. Your response states that the donor criteria that was in place at the time was directed towards donors that had an acute onset of dementia where there would be a concern of contracting a slow virus disease such as CJD. This is not evident in your written procedures. It is imperative that your staff, including your Medical Director, follows your firm's written procedures. Our observation concerns the lack of adherence to established criteria.

- 1.f Our review of the June 25, 2001, memorandum submitted with your response concerning the investigation of foreign particles in your product notes that your firm observed the lids and rims of carboys used to prepare buffer solutions were heavily soiled in what appeared to be mold. It appears from your response that you have made no attempts to analyze this "grime" and therefore you have no real knowledge as to whether this may be a source of potential microbial contamination.
- 1.g The rework documents submitted with your response for tissues X and X for donor X were not available or were not presented to our investigators at the time of the inspection. The purpose of our observation is to point out that it is essential that your firm perform an adequate review of your records immediately upon the conclusion of processing in order to detect discrepancies and/or errors to prevent the release of unacceptable product.
 - 1.i.1. This observation surrounded your acceptance of tissue in December 2001 that had been previously rejected in July 2001 due to the lack of dry ice in the shipping container. In your response, you state that the decision to accept the tissue was included in a deviation report and included the report in your response. We reviewed the deviation report and found nothing in it that provides a reasonable rationale for acceptance of the tissue.
 - 1.i.2. As a result of the issues surrounding the tissue accepted in the item above, your microbiology supervisor ordered additional microbiological tests, however, the tissue was deemed acceptable for processing before the tests were complete. In your response, you state that all required information was available for release of the tissue in accordance with your standard procedures. Based on the information you provided, your decision to consider the tissue suitable for processing prior to receipt of the additional tests is not compelling from a scientific standpoint.
- 1.i.5 In your response, you state that it was your decision to accept tissues with no procurement sample microbiological test results and process the tissues "at risk." Without the procurement sample results, you have no way of knowing whether the level and type of contamination present in the tissue is acceptable for introduction into the

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processing environment, and processing tissue "at risk" is inconsistent with manufacturing operations in a validated process.

- 1.j.2 The documentation attached to item 1.j.2 shows the results of your microbiology testing indicating no growth on tissue ~~X~~, however, there is no documentation attached demonstrating that this tissue was subjected to irradiation, as required by your processing plan. Our concerns involved the lack of evidence that this tissue was irradiated, not the fact that the cultures were incorrectly reported on the wrong form.
- 3.a The work instructions listed in your response, WI 321.01 and WI 1006.08 were not included. Therefore, we are unable to evaluate the adequacy of your proposed changes. WI 315.11, although attached to your reply, did not include the last page (page 3) and therefore, we are unable to comment on the adequacy of this procedure, as well. However, with regards to the suitability of a final ~~XXXXXX~~ after the ~~XX~~ ~~X~~ procedure, please be aware that all the steps preceding this final rinse would need to be fully validated to assure that all contamination, including all spore-forming organisms or endotoxins, is eliminated.
- 4.b In your response, you state that performance qualification studies were performed for the ~~XXX~~ microorganism test system, including seeded solution studies. However, the ~~XXX~~ system is intended to be used with blood and other normally sterile body fluids, and you are using the system to test rinse samples of tissue. You have not demonstrated that this application is an appropriate use of the ~~XXX~~ system. In addition, as you have not completed bacteriostasis/fungistasis testing on your sterility test process, it is impossible to conclude that the ~~XXX~~ system is appropriate for your use.
7. In your response, you state that AlloSource uses sterile technique practices as specified in the ~~XXXXXX~~ standards. As you are in the business of aseptic manufacturing of product intended for implantation into humans, we recommend that you also consult available resources concerning appropriate employee practices for aseptic processing of pharmaceutical and implantable device products.
10. Although you state that you have started to time the ~~XXXXXX~~ to ensure a minimum of ~~XX~~, your procedure does not indicate that there is any testing or monitoring of the potency of the ~~X~~ solutions used. Depending upon the bacterial/viral load of the tissues, the potency, and therefore the effectiveness of the solutions used, may be diminished. If the potency of the solution is not monitored, the ~~X~~ time must be validated to ensure that the worst-case (contamination) scenario will be addressed in the time allotted.

The above identification of deviations is 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, as well as other requirements of the Act, and Section 361 of the Public Health Service Act. The specific deviations noted in this letter and in the FDA-483, Inspectional

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Observations (copy enclosed) 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 causes of the deviations identified by the FDA.

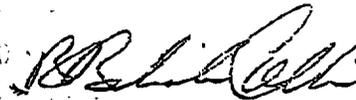
If the causes are determined to be systems problems, you should promptly initiate permanent corrective actions.

You should take prompt action to correct these deviations. FDA may take additional regulatory action without further informal notice. These actions include, but are not limited to an Order for Retention, Recall and/or Destruction, or such other measures reasonably necessary to prevent the spread of diseases as provided under 21 CFR §1240.30.

You should 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, including an explanation of each step being taken to prevent the recurrence of similar deviations. 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, Denver District Office, P. O. Box 25087, Denver, CO 80225-008, Attention: Regina A. Barrell, Compliance Officer. If you have any further questions, please feel free to contact Ms. Barrell at (303) 236-3043.

Sincerely,



B. Belinda Collins
District Director

Enclosure

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