DEPARTMENT OF HEALTH AND HUMAN SERVICES

Public Health Service

Food and Drug Administration
Atlanta District Office
60 Eighth Street N.E.
Atlanta, GA 30309

August 13, 2002

HAND DELIVERED

Steven G. Anderson
President and CEO
CryoLife, Inc.
1655 Roberts Blvd., NW
Kennesaw, GA 30144

ORDER FOR RETENTION, RECALL, AND/OR DESTRUCTION

Dear Mr. Anderson:

The Food and Drug Administration's (FDA) inspection of your facility on March 25 through April 12, 2002, covering human tissue intended for transplantation which is subject to the requirements of Title 21, Code of Federal Regulations, Part 1270 (21 CFR 1270), and our review of the information and records examined during the inspection revealed that certain human tissue received and distributed by your firm may be in violation of 21 CFR 1270, as indicated below:

- Your firm has not had validated procedures for the prevention of infectious disease contamination or cross-contamination by tissue during processing [21 CFR 1270.31 (d)] at least since October 3, 2001, as evidenced, in part, by tissues that were processed on and after October 3, 2001, and that tested positive for the same bacterial contaminant. One of these tissues has been associated with the death of a 23-year-old man.

Pursuant to 21 CFR 1270.43, the above referenced tissue must be:

- Recalled (if distributed), within five (5) working days of receipt of this order, under the supervision of an authorized official of the FDA, and/or
- Destroyed by an acceptable method of disposition, within five (5) working days of receipt of this order, under the supervision of an authorized official of the FDA, or
- Retained until it is recalled, destroyed, the safety of the tissue is confirmed, or an agreement is reached with the FDA for its proper disposition under the supervision of an authorized official of the FDA. Such agreement may include, but is not limited to, the reconditioning of the referenced tissue using validated procedures for processing of human tissues intended for transplantation. FDA has issued guidance for industry regarding validated procedures in a guidance document dated March 8, 2002, entitled

"Validation of Procedures for Processing of Human Tissues Intended for Transplantation".

CryoLife, Inc., its owners, employees, and agents shall not distribute or dispose of the tissue in any manner except to recall and destroy it consistent with the provisions of the Order. Any other arrangements for ensuring the proper disposition of the tissues must be agreed upon in writing by CryoLife and an authorized official of the FDA. Such arrangements may include assurance that the tissue has been recovered, processed, stored, and distributed in conformance with the attached regulations [21 CFR 1270]. In addition, FDA strongly recommends that CryoLife perform a retrospective review of all tissue in inventory that is not referenced in this Order to assure that it was recovered, processed, stored, and distributed in conformance with 21 CFR 1270.

All actions taken pursuant to this Order, or otherwise related to the tissue subject to this Order, shall be taken under the supervision of an authorized official of the FDA.

A joint inspection of your firm was conducted by FDA and the Centers for Disease Control and Prevention (CDC) from December 3-7, 2001. Subsequent to that inspection, your firm was notified on January 3, 2002, that additional tissue from the donor implicated in the death of a recipient had tested positive for the same bacterium, *Clostridium sordellii*. CDC also provided CryoLife with its recommendations to improve your tissue processing and testing procedures in this communication. Our inspection of March 25- April 12, 2002, revealed that your firm had not adequately investigated its validation of processing and testing methods nor implemented CDC's recommendations or any other procedures to ensure that tissue distributed by your firm was not contaminated. In addition, our investigators documented additional evidence of distribution of unsuitable tissue that resulted in infections in recipients. Your May 15, 2002, response to that inspection did not provide assurance that you would adequately correct these deficiencies in a timely manner, and address tissue in inventory or distribution. A warning letter was issued to your firm on June 17, 2002. Your latest response, dated June 25, 2002, did not provide assurance that you will adequately address these deficiencies in a timely manner, nor did it provide assurance that you would evaluate tissue in inventory or distribution. In addition, it has come to our attention that you were informed in March 2002, of a heart valve implicated in serious adverse reactions in a recipient, and finally acknowledged on July 6, 2002, that this heart valve, processed and tested using the same methods, is the likely source of this serious adverse event. Given these circumstances, it is our view that CryoLife has not promptly implemented appropriate corrective measures to address the serious deficiencies that have been brought to your attention.

Within five (5) working days from the receipt of this Order, the recipient of the written Order or prior possessor of such tissue may appeal the Order to the District Director, Atlanta District, Food and Drug Administration, 60 8th Street, N.E, Atlanta, GA 30309 and request a hearing on the matter in accordance with 21 CFR Part 16 (copy enclosed). Such manner of appeal is described in section 1270.43(e) of the attached regulations. Failure to request a hearing within the specified time period constitutes a waiver of the right to a hearing.

Please also be advised that the Center for Devices and Radiological Health is currently evaluating whether there are similar risks that may be posed by Cryolife's heart valves, and will take further regulatory action if appropriate.

Please contact Serene A. Kimel, Compliance Officer, at 404-253-1296, to arrange for supervision of the disposition of the tissues.

Sincerely,

Barbara A. Wood
Acting District Director

Enclosures:
A - 21 CFR Part 16 and Part 1270
B - Guidance for Industry: "Validation of Procedures for Processing of Human Tissues Intended for Transplantation" dated March 8, 2002