

**Department of Health and Human Services**

**OFFICE OF  
INSPECTOR GENERAL**

**Oversight of Tissue Banking**



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# EXECUTIVE SUMMARY

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## PURPOSE

To provide a profile of the current external oversight system for tissue banking, and to identify limitations in that system.

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## BACKGROUND

Human tissue is an important resource for medical treatment. For example, it is used in burn treatment, reconstructive surgery, cancer care, and heart valve replacement.

Tissue from one donor can be processed into many forms and used to treat many people. The exact number of donors is not known, but it is growing. In 1999, more than 20,000 donors provided cadaveric tissue, up from perhaps 6,000 donors in 1994. It is estimated that tissue banks distributed more than 750,000 allografts for transplantation in 1999.

Human tissue can transmit disease. In the early 1990's two events raised major concerns. First, HIV was transmitted from one infected donor to several recipients of organs and unprocessed tissues. Second, investigators from the Food and Drug Administration (FDA) found instances of domestic suppliers accepting foreign tissue that had not been tested or screened; in one case the FDA found tissue that tested positive for Hepatitis B.

These concerns led FDA to issue an interim final rule in December 1993. FDA modified this regulation and reissued it as a new rule, effective in January 1998. It requires that tissue banks screen and test donors and that they maintain the appropriate records. The rule also provides for FDA inspections of tissue banks and retention, recall, and destruction of tissue that doesn't comply with these requirements.

This report responds to a request from the Secretary of Health and Human Services, asking the Office of Inspector General to examine the oversight system for tissue banking. We analyzed available data related to tissue banking, and we reviewed regulations, laws, and standards. We interviewed staff from FDA, from 30 tissue banks, and from associations representing various sectors of the tissue banking industry.

In this report, we use the term "tissue banks" to refer to entities involved in procuring, processing, storing, and distributing tissue. We use the term "tissue" to refer to skin, heart valves, and musculoskeletal tissue such as bone, cartilage, ligaments, and tendons. Our report does not address eyes and reproductive tissue.

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## PROFILE OF TISSUE BANKING OVERSIGHT

Oversight of tissue banking takes place at three levels:

- **The Food and Drug Administration** focuses on preventing transmission of

communicable disease by requiring donor screening and testing. FDA has conducted 188 inspections of 118 tissue banks since 1993. The agency has proposed two regulations and is developing a third that would expand its oversight of tissue banking. These regulations would require registration of all tissue banks, expanded screening and testing, and use of good tissue practices, akin to good manufacturing practices.

- **The American Association of Tissue Banks (AATB)** conducts a voluntary accreditation program. While AATB currently accredits 58 tissue banks, we identified another 90 that are not accredited. Accreditation addresses not only donor screening and testing practices, but operational and organizational aspects, such as qualifications of tissue bank personnel and banks' safety practices, equipment testing, facilities, labeling, and quality assurance programs.
- **New York and Florida** are the only two States to license and inspect tissue banks. In addition to screening and testing, these States require banks to report adverse incidents. They also address areas such as tissue procurement processes, tracking practices, emergency procedures, equipment standards, conflict of interest, community involvement, labeling standards, laboratory testing, and disposition of unused tissue. A few States, including California, Georgia, and Maryland, require tissue banks to be licensed by the State.

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## LIMITATIONS IN TISSUE BANKING OVERSIGHT

No new cases of disease transmission through human tissue have been identified since the FDA's 1993 regulation. This absence of new cases points to significant strengths and accomplishments in the current system which has focused on preventing the spread of communicable disease. Nevertheless, in the course of this limited inquiry, we identified situations that show the need for continued vigilance and monitoring. For example, FDA inspectors have found serious deficiencies in tissue banks' screening and testing practices. Banks have failed to meet basic standards of the AATB and been denied accreditation. States have received notification of adverse incidents involving tissue.

The rapid development of the tissue banking field means that traditional oversight methods may not keep pace with growth and changes in the industry. Consequently, thoughtful consideration needs to be given to the nature of any oversight approach.

Below, we outline limitations and vulnerabilities in current approaches, and we offer a combination of options that, taken singularly or in combination, could provide a way of enhancing oversight of the tissue banking field.

### FDA oversight

**Some tissue banks have never been inspected by FDA.** We found at least 36 tissue banks that have never been inspected, out of 154 tissue establishments that we were able to identify. FDA has indicated that regulation of tissue banks is an unfunded mandate, and that in order to carry out these inspections, the agency has had to borrow resources

from other programs, such as blood and plasma.

**FDA lacks a prescribed cycle for reinspection of tissue banks.** Of 118 tissue banks that FDA has inspected, 68 have been inspected only once. Due to limited resources, the agency has had to establish a priority list for followup inspections. The first priority is reinspection of firms whose previous inspection was classified as Official Action Indicated, the most serious level of deficiency.

**The number and location of tissue banks are unknown.** Information is lacking about the number of tissue banks in operation and the products they produce and distribute. FDA has proposed a regulation to require tissue banks to register and list their products. The regulation would address directly this limitation in knowledge about tissue banking.

**The scope of FDA's current regulation is limited.** Because the agency's current regulation focuses on donor screening and testing to prevent transmission of HIV-1 and -2 and Hepatitis B and C, other important aspects of tissue bank quality are not monitored. Until FDA's good tissue practices rule is finalized, tissue banks have no external requirements for quality and handling of tissue if they are not accredited by AATB or licensed by New York or Florida. Of the 154 tissue banks we identified, 67 are neither accredited by AATB nor inspected by Florida or New York.

### **Private accreditation**

**Many banks do not seek AATB accreditation.** AATB accredits 58 tissue banks. However, we identified 90 tissue banks that are not accredited. These banks are under no obligation to meet the standards or policies set by the association. For many tissue banks there is no real incentive to seek accreditation. There are a number of ways to encourage private accreditation of tissue banks. For example, FDA could provide technical advice and information that could be used in developing standards. FDA also could consider in what areas, if any, the agency could accept accreditation as showing compliance with FDA regulations. In such a case, legislation would be needed.

### **State oversight**

**Only two States inspect tissue banks.** In many ways, these inspections go beyond FDA requirements; yet the inspections are limited to banks that conduct business in Florida and New York. Other States could give consideration as to whether they wish to regulate tissue banking and, if so, how they would coordinate with other entities to limit redundancy and regulatory burden.

### **Information on supply and availability of tissue**

**Concerns about shortages.** There is no national system for tracking the availability of tissue. Two recent surveys by industry representatives raised concerns that skin may not be available when needed for treating burn victims. However, some shortcomings in these studies suggest that additional research is warranted to examine the extent and implications of shortages of tissues.

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## RECOMMENDATIONS

**The Food and Drug Administration should expedite the publication of its regulatory agenda that requires registration of tissue banks, enhanced donor suitability screening and testing, and the use of good tissue practices.**

At present, FDA is able to inspect only those banks that it knows about. Requiring registration of all tissue banks would ensure that the agency has a comprehensive list of tissue banks as a first step in assuring their compliance with standards.

In addition, many tissue banks are neither accredited by the AATB nor licensed and inspected by New York or Florida. Those banks that are not accredited or inspected do not have to meet any standards beyond the current FDA minimum requirements that they screen and test tissue donors for HIV and hepatitis.

**FDA should set a realistic, yet aggressive, date by which it would complete an initial inspection of all tissue banks.**

This could be accomplished under FDA's existing regulatory authority. Establishing a baseline of information will provide a minimum level of assurance that tissue banks are meeting basic public health and safety standards to prevent transmission of communicable diseases.

**FDA should determine an appropriate minimum cycle for tissue bank inspections.**

This, too, could be accomplished under FDA's existing regulatory authority. A minimum cycle for inspections would help ensure that tissue banks are meeting standards on an ongoing basis.

**FDA should work with States and with professional associations that have inspection and accreditation programs to determine in what areas, if any, oversight activities could be coordinated.**

FDA, the industry, and the States with regulatory programs could benefit from examining where standards are in agreement, as well as areas in which standards might conflict. Following such an examination, determination could be made of whether formal partnership or other arrangements would be appropriate to maximize the effectiveness of the oversight process. Such arrangements could require enactment of legislation.

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## COMMENTS ON THE REPORT

We received comments on a draft of this report from the Department of Health and Human Services. They are supportive of our findings and recommendations. The full text is included in Appendix B.

Our work in tissue banking continues. We will maintain an active watch on how the tissue banking community responds to the concerns that we have raised.

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# INTRODUCTION

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## PURPOSE

To provide a profile of the current external oversight system for tissue banking, and to identify limitations in that system.

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## BACKGROUND

### Transplantation of Human Tissue

Human tissue is an important resource for medical treatment. Physicians and dentists use cadaveric human tissue for a variety of medical purposes. Donated skin can meet critical needs in healing burn victims and in reconstructive surgery. Donated bone can be implanted to replace cancerous bone; it can be used in knee and hip replacements and for spinal surgery; and it can be processed into powder for use in dental surgery. Donated heart valves can replace defective valves in young children, saving their lives.

The exact number of tissue donors in this country is not known. It is clear, though, that the numbers are increasing. In 1999, more than 20,000 donors provided cadaveric tissue, up from perhaps 6,000 donors in 1994.

### Initial Concerns about Disease Transmission

Human tissue is capable of transmitting disease. Tissue from one donor can be implanted into many different people. Thus, if a donor has a communicable disease, using that tissue places multiple recipients at risk. It is estimated that tissue banks distributed more than 750,000 allografts for transplantation in 1999.

In the early 1990's two events occurred that raised concerns about disease transmission through tissue donation. First, HIV was transmitted to a number of recipients of organs and unprocessed tissues from an infected donor. Second, investigators from the Food and Drug Administration (FDA) found instances in which domestic suppliers were accepting foreign tissue that had not been adequately tested or screened; in one of these cases the FDA found tissue that tested positive for Hepatitis B.

Since these initial two cases, no other cases have been identified. However, without proper screening and testing, these problems could reemerge. As we discuss below, FDA continues to uncover deficiencies in the course of its inspections of tissue banks.

### Limited Federal Oversight of Tissue Banking

Tissue banks procure, process, store, and distribute human tissue. Federal regulation of tissue banking focuses on donor screening and testing to prevent the introduction, transmission, and spread of HIV-1 and -2, and Hepatitis B and C.<sup>1</sup> By way of contrast, organ procurement organizations (OPOs) must meet statutory requirements about their organization and operation; they are regulated and certified by the Health Care Financing



Administration. Furthermore, the procurement and allocation of human organs are governed by Federal statute and are administered through a contract with the Health Resources and Services Administration (HRSA). Likewise, legislation authorizes the operation of a national bone marrow donor registry, also administered under contract with HRSA.

## Recent Concerns about Tissue Banking

Several press reports in the Spring of 2000, appearing in the *Orange County Register* and the *Chicago Tribune*, raised concerns about tissue banking, including the extent to which the performance of the industry was monitored. Several members of Congress expressed their concerns to the Secretary of Health and Human Services. The Secretary asked the Office of Inspector General to examine two aspects of the tissue banking industry: consent for donation and the external oversight structure. This report responds to the second of those requests. Our companion report, *Informed Consent in Tissue Donation: Expectations and Reality* (OEI-01-00-00440), addresses consent for donation.

## This Inquiry

This report provides a profile of the oversight structure for tissue banks. We also identify limitations of current oversight efforts and steps that could be taken to address those limitations.

Throughout this report, we use the term “tissue banks” to refer to entities involved in procuring, processing, storing, and distributing tissue. We use the term “tissue” to refer to skin, heart valves, and musculoskeletal tissue such as bone, cartilage, ligaments, and tendons. Our report does not address eyes and reproductive tissue.

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## METHODOLOGY

Our inquiry is based on data analysis, document reviews, an observational visit, and interviews. We analyzed data from FDA’s Program Operations Data System which tracks information about FDA inspection activity across the nation. Our analysis examines this data from December 15, 1993 (following the issuance of the interim rule on tissue banking) through the end of Fiscal Year 2000.<sup>2</sup> Our analysis includes only tissue banks involved in procuring, processing, storing, and distributing tissues such as skin, heart valves, and musculoskeletal tissue. We do not include establishments that are involved in eye banking, or hospitals and laboratories inspected under the FDA tissue compliance program.<sup>3</sup>

We also reviewed pertinent FDA documents and inspection reports from the central office and from 3 of the 20 FDA district offices. We conducted interviews with FDA staff at both the central and district offices.

We reviewed AATB standards and accompanied an inspector on an accreditation visit to a tissue bank. We reviewed documents and data from the AATB and interviewed officials and staff from the association. We conducted interviews with senior staff from

30 organizations involved in obtaining, processing, and distributing human tissue.

We also interviewed officials and reviewed data, statutes, and regulations from New York, Florida, California, Georgia, and Maryland.

We conducted this study in accordance with the *Quality Standards for Inspections* issued by the President's Council on Integrity and Efficiency.

# PROFILE OF OVERSIGHT FOR TISSUE BANKING

Oversight of tissue banking occurs at three levels. At the Federal level, the Food and Drug Administration (FDA) has primary responsibility to set and enforce standards to ensure the safety of tissue. Within the industry, the American Association of Tissue Banks (AATB) operates a voluntary accreditation program. At the State level, two States — New York and Florida — license and inspect tissue banks. Below we provide a description of each of these activities.

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## Food and Drug Administration

FDA's regulation of tissue dates to December 1993. Operating under its public health authority, the agency issued an interim final regulation in response to evidence about transmission of HIV to recipients of organs and unprocessed tissues from an infected donor.<sup>4</sup> In a second case, FDA inspectors found imported foreign tissue that tested positive for Hepatitis B. In July 1997, the FDA reissued this rule with minor modifications, and the new rule became effective January 26, 1998.<sup>5</sup>

The FDA requires that tissue banks must ensure that donor screening and infectious disease testing are performed for HIV -1 and -2 and for Hepatitis B and C. Tissue banks must maintain and make available to FDA inspectors records that document screening and testing for each donor of human tissue. FDA has the authority to order the retention, recall, and destruction of tissue that doesn't comply with these requirements.

FDA has conducted 188 inspections of 118 tissue banks since 1993. In more than half of these inspections, FDA inspectors found deficiencies that needed correction. FDA issued 26 notices of official action — the most serious level of deficiency, in which the agency requires the bank to take corrective actions. In 72 other inspections, FDA issued a notice recommending that the bank take voluntary actions to meet the requirements.<sup>6</sup>

FDA is in the process of expanding its oversight of tissue banking. Regulations to expand that authority, however, have not yet been finalized. The components of expanded FDA oversight strategy comprise three regulations:

- **Registration of all tissue banks.** This proposed regulation would require tissue banks to register with FDA and list their products. The proposed regulation would apply to establishments engaged in “recovery, screening, testing, processing, storage, labeling, packaging, or distribution of human cellular or tissue-based products.”<sup>7</sup>
- **Expanded screening and testing for communicable diseases.** This proposed regulation would require donor screening and testing for diseases such as Human T-lymphotropic viruses (HTLV) and syphilis, and donor screening for Creutzfeld-Jakob Disease (CJD).<sup>8</sup>

- **Standards for “good tissue practices.”** These standards, akin to good manufacturing practices required of medical device pharmaceutical manufacturers, would cover areas such as proper handling, processing, and tracking of tissue.<sup>9</sup>

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## American Association of Tissue Banks

AATB currently accredits 58 cadaveric tissue banks.<sup>10</sup> Tissue banks perform a variety of functions. Of these 58 banks, 54 retrieve tissue, 34 process tissue, and 56 store and distribute tissue; 51 of these banks retrieve musculoskeletal tissues, 37 retrieve cardiovascular tissues, and 20 retrieve skin. Five banks are for-profit (three tissue processors, one tissue distributor, and one retrieval agency). The other 53 accredited banks are non-profit organizations. Eleven banks are OPOs. The number of donors recovered by accredited banks has grown substantially, from 6,132 donors in 1994 to 17,725 donors in 1999.

AATB’s standards are consistent with, but go beyond, FDA’s requirements. For example, in addition to screening and testing for HIV and hepatitis, AATB requires that tissue banks test for HTLV and screen for CJD. The standards also address operational and organizational issues. These areas include qualifications of tissue bank personnel and technical issues, such as safety practices, equipment testing, facilities, labeling, and quality assurance.

Accreditation involves a review of a bank’s written procedures and an on-site inspection. Since 1997, AATB has used contract inspectors to conduct accreditation visits.<sup>11</sup> Since 1997, an average of five new banks have sought accreditation each year.

A bank receives one of four recommendations. Banks that show no deficiencies receive immediate accreditation. A bank with minor deficiencies receives Level A accreditation, meaning that it must submit to AATB a written plan to correct the deficiencies found during the inspection. A bank with more serious deficiencies receives Level B accreditation, which means that it must take corrective action and be reviewed again through an on-site inspection. Finally, a bank could be denied accreditation outright. Accreditation is given for a three-year period, at the end of which the bank is subject to another review, including an on-site inspection. Since 1986, AATB has accredited a total of 98 tissue banks; 19 banks have been denied accreditation.<sup>12</sup>

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## State Regulation

New York and Florida are the only two States that operate oversight programs requiring that tissue banks be licensed and inspected. A few States, including California, Georgia, and Maryland, require that banks be licensed, either as tissue banks or as laboratories.

**New York’s** licensure law dates to 1990.<sup>13</sup> Currently, the State licenses 13 allogeneic tissue banks located in New York and 36 located out-of-State.<sup>14</sup> New York inspects both in-State and out-of-State banks prior to initial licensure and every two years thereafter.

Banks are licensed along two dimensions. One is a functional dimension: whether the bank procures or processes tissue. The second dimension relates to the type of tissue which the bank works with — cardiovascular, musculoskeletal, or skin. A bank may be licensed for any or all tissues and functions. At present, 29 banks are licensed to procure and 9 to process cardiovascular tissue; 39 to procure and 20 to process musculoskeletal tissue; and 33 to procure and 19 to process skin.

Licensure requires an initial application and on-site survey. Banks do not pay a fee for licensure. Tissue banks must disclose ownership and key staff. Banks must update this information annually and report statistics on procurement, processing, and distribution.

In addition to meeting FDA requirements to screen and test for HIV and hepatitis, New York requires banks to test for HTLV and syphilis. New York also requires tissue banks to meet specific standards for each type of tissue — musculoskeletal, cardiovascular, and skin — that the bank procures, processes, or stores. These standards relate to donor qualifications, tissue retrieval processes, laboratory testing, and disposal of unused tissue.

Banks must report any adverse incidents to the State. Since 1991, the State has received 8 reports from cardiovascular, 13 from musculoskeletal, and 6 from skin banks.

**Florida's** law was enacted in 1992<sup>15</sup> at the urging of the State's OPO, tissue banking, and eye banking community. Florida currently licenses 20 cadaveric tissue banks; 9 are located in Florida and 11 are based in other States. Another 2 banks have submitted applications that are now under review. The State inspects both in-State and out-of-State tissue banks prior to initial licensure and every two years thereafter.

Florida requires tissue banks to pay an initial application fee of \$1,000 and an annual fee of 0.25 percent of gross Florida revenues, with a minimum of \$1,000 and a maximum of \$35,000. The fees go to a State trust fund used for operating the licensure program, the State donation advisory committee, a donor registry, and donor education programs.

Applicants must disclose the bank's ownership, as well as information on equipment and donor selection and testing criteria. Florida requires tissue banks to comply with current FDA regulations. The surveying standards also address tissue tracking practices, emergency procedures, equipment standards, procurement processes, conflict of interest policies, community involvement, and labeling standards.

Florida requires tissue banks to report within 24 hours adverse events that could affect tissue recipients' medical conditions. Only three such incidents have been reported in the program's history.

# LIMITATIONS IN OVERSIGHT OF TISSUE BANKS

Today's tissue banking system is complex and rapidly changing. Tissue is processed into new forms and products that are put to a variety of important medical uses. New technologies using human tissue emerge constantly. No new cases of disease transmission through human tissue have been identified since 1993. This absence points to significant strengths and accomplishments in the current oversight system which has focused on preventing the spread of communicable disease.<sup>16</sup>

However, continued vigilance and monitoring are needed: FDA inspectors have found deficiencies in tissue banks' screening and testing practices. Banks have failed to meet basic standards of the AATB and been denied accreditation. States have received notification of adverse incidents involving tissue. Appendix A describes some safety problems that FDA inspectors have identified during inspection visits and adverse events that have been reported to the State agencies. These problems include distribution of tissue from donors who tested reactive for hepatitis, bacterial contamination of tissue, and repeat testing of donors as a way of qualifying their tissue as suitable for transplantation.

In the course of this limited inquiry, we identified some important vulnerabilities and limitations in the current tissue banking oversight structure. Rapid developments and innovation in the tissue banking field mean that traditional oversight methods have not kept pace with growth and changes in the industry. Under these circumstances, thoughtful consideration needs to be given to the nature of any oversight approach.

Below, we outline limitations and vulnerabilities in the current approaches, and we offer a combination of options that, taken singularly or in combination, could provide a way of enhancing oversight of the tissue banking field.

## FDA oversight

### **Some tissue banks have never been inspected by FDA.**

We developed a list of 154 tissue banks, based on data from three FDA district offices, AATB, Florida, and New York. We found that FDA had never inspected 36 (23 percent) of these banks. In addition to the 154 banks we identified, there are likely others that operate in States without licensing programs.<sup>17</sup>

FDA has indicated that regulation of tissue banks is an unfunded mandate. In order to carry out these inspections, the agency has had to borrow resources from other programs, such as blood and plasma.

### **FDA lacks a prescribed cycle for reinspection of tissue banks.**

FDA staff told us that their goal is to inspect tissue banks once every two years, but there is no required minimum cycle for these inspections.<sup>18</sup> Of 118 tissue banks that the agency

has inspected, 68 have been inspected only once since the FDA began its tissue program in late 1993.

FDA's compliance program acknowledges that there are insufficient resources to accomplish biennial inspections of all banks. As a consequence, the agency has established a priority list for followup inspections. The first priority for the program is reinspection of firms whose last inspection was classified as Official Action Indicated. This classification is the most serious level of deficiency, in which the agency requires the bank to take corrective actions.<sup>19</sup>

**The number and location of tissue banks are unknown.**

Information is lacking about the number of tissue banks in operation, and the types of tissue products that they produce. This lack of information limits the confidence with which assurances can be made that the supply of tissue is safe. These "unknown" tissue banks are likely to be new entities that may be in the early stages of operation. This situation does not inspire confidence that these banks are meeting basic standards of safety.

The FDA has issued a proposed regulation<sup>20</sup> calling for registration of tissue banks and listing of their products. Such a regulation would address directly this current limitation in knowledge about tissue banking.

**The current scope of FDA's regulations is limited.**

The agency's current regulations focus on preventing transmission of communicable disease. The regulations require tissue banks to conduct some donor screening and testing, to prepare and follow written procedures, and to maintain records. The regulations provide for FDA inspection of tissue banks, quarantine of imported tissue, and retention, recall, and destruction of tissue that doesn't comply with the regulations.

The current regulations, however, do not monitor other important aspects of tissue bank quality. FDA has proposed a regulation expanding donor suitability and testing requirements, and is developing a regulation on good tissue practices, akin to good manufacturing practices required of medical device pharmaceutical manufacturers. Until that regulation is finalized, tissue banks have limited requirements for quality and handling of tissue if they are not accredited by AATB or licensed by New York or Florida.

We were unable to document the extent to which banks that are neither AATB-accredited nor licensed in New York or Florida are involved in recovering tissue. The number, however, is likely to be substantial. For example, of the 154 tissue banks we identified, 67 are neither accredited by AATB nor licensed by New York or Florida.

## Private accreditation

### **Many banks do not seek AATB accreditation.**

At present, 58 tissue banks have AATB accreditation. Yet we identified another 90 banks that are not accredited. These banks are under no obligation to meet the standards or policies set by the AATB.<sup>21</sup>

Unaccredited banks include both large and small operations. For example, the country's largest processor of heart valves has never sought accreditation. Some OPOs that operate tissue banks are not accredited by AATB. Other unaccredited banks are small entities in the early stages of operations and do not yet feel that they can comply with the standards.

For many tissue banks there is no real incentive to seek accreditation. Hospitals and physicians regularly purchase tissue from unaccredited banks. The cost of accreditation may present a major barrier for smaller banks. For other banks, already subject to inspection by FDA and State authorities, a third inspection may seem burdensome.<sup>22</sup>

A number of steps could be taken to encourage a role for private accreditation of tissue banks. For example, FDA could provide technical advice and information that could be used in developing standards. FDA could also consider in what areas, if any, the agency could accept accreditation as showing compliance with FDA inspection regulations. To implement such a change, legislation would likely be needed.

## State oversight

### **Only two States inspect tissue banks.**

In many ways, these inspections go beyond FDA requirements. The State initiatives provide an important aspect of quality assurance. Yet the inspections are limited to banks that conduct business in Florida and New York. Those banks may be small, local entities that operate within each State, or they may be large national operations that are based elsewhere and that either process or distribute tissue in New York or Florida. For example, 15 of the 20 banks licensed in Florida also are licensed in New York, and 14 are accredited by the AATB; 29 of the banks licensed in New York have AATB accreditation. A few States, including California, Georgia, and Maryland, require tissue banks to be licensed by the State, either as tissue banks or as laboratories.

Other States could give consideration as to whether they wish to regulate tissue banking, and, if so, how they would coordinate with other entities to limit redundancy and regulatory burden.

## Information on supply and availability of tissue

There is no national system for tracking the availability of tissue and where there may be a shortage. Each bank maintains its own inventory and distribution records. Concerns have been raised that some tissues, such as skin, may be in short supply, and that donated



skin is processed into products that may be used for procedures that are not medically indicated. It is not clear how much tissue goes for such cosmetic uses; because physicians and patients determine how these products actually are used, tissue banks that manufacture them do not have that information.<sup>23</sup>

Recent concerns about shortages of skin have led to two surveys related to its availability. A survey of burn centers, conducted by the American Burn Association (ABA), found that 32 percent of respondents had delayed or altered treatment over the past year, and about half reported that they had difficulty obtaining allograft skin. The AATB survey found that banks recovered skin from over 6,000 donors in 1999. It also found that banks generally can meet the local need for skin, but when skin is requested by facilities outside their local area, meeting those requests is more problematic. Only 3 of 20 banks supplying cryo-preserved skin, and only 3 of 12 banks supplying fresh skin, can always meet requests from outside of their local area.

These initial surveys suggest that further research may be warranted to examine the extent and implications of a potential shortage of tissues. They provide the first systematic information about tissue supply and availability. The two associations deserve great credit for collecting and publicizing these data. However, there are limitations related to the source and specificity of information obtained. For example, the AATB respondents were accredited banks only; the ABA data do not allow one to determine if any patient actually was unable to obtain skin needed in a surgical procedure. These shortcomings and the limitations of an initial survey can easily be overcome in future refinements.

# RECOMMENDATIONS

**The Food and Drug Administration should expedite the publication of its regulatory agenda that requires registration of tissue banks, enhanced donor suitability screening and testing, and the use of good tissue practices.**

The FDA has been the lead agency within the Department of Health and Human Services for oversight of tissue banking. The FDA's current regulatory program focuses on preventing transmission of HIV and hepatitis by requiring that tissue banks test and screen donors to detect these conditions.

FDA has proposed and is refining three regulations that will enhance oversight of tissue banking. That regulatory agenda would require registration of all tissue banks, expanded screening and testing, and use of good tissue practices, akin to good manufacturing practices.

This proposed agenda is important for at least two reasons. First, at present FDA is able to inspect only those banks that it knows about. Requiring registration of all tissue banks would ensure that the agency has a comprehensive list of those banks that are in operation, as a first step in assuring their compliance with standards.

Second, many tissue banks are neither accredited by the American Association of Tissue Banks nor licensed and inspected by New York or Florida. Those banks that are not accredited or inspected do not have to meet any standards beyond the current FDA minimum requirements that they screen and test tissue donors for HIV and hepatitis.

**Within its existing regulatory authority, FDA should take two steps to enhance oversight of tissue banking:**

**FDA should set a realistic, yet aggressive, date by which it would complete an initial inspection of all tissue banks.**

As we show above, more than one of every five tissue banks has never been inspected. As we also note, the agency has indicated that regulation of tissue banks is an unfunded mandate, and that it has had to borrow resources from other programs to carry out current inspections. Nevertheless, we believe that it is important to establish a baseline of information. Such information would provide a minimum level of assurance that tissue banks are meeting basic public health and safety standards to prevent transmission of communicable disease.

**FDA should determine an appropriate minimum cycle for tissue bank inspections.**

A minimum cycle for inspections would help ensure that tissue banks are meeting standards on an ongoing basis. As we note above, FDA has established a priority list for

followup inspections to maximize available resources. We believe, however, that some minimum cycle, which the agency would determine, is important to ensure that tissue banks are subject to ongoing oversight.

**FDA should work with States and with professional associations that have inspection and accreditation programs to determine in what areas, if any, oversight activities could be coordinated.**

We recognize that resource constraints can put pressure on an agency's capacity to conduct inspections and reviews of tissue banks. In addition, we recognize that multiple inspection visits can place a strain on a tissue bank's operations. We believe that FDA, the industry, and the States with regulatory programs could benefit from examining where standards are in agreement, as well as places in which standards might conflict.

Following such an examination, determination could be made of whether formal partnership or other arrangements would be appropriate to maximize the effectiveness of the oversight process. Such arrangements could require that legislation be enacted.

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## **COMMENTS ON THE REPORT**

We received comments on a draft of this report from the Department of Health and Human Services. They are supportive of our findings and recommendations. The full text is included in Appendix B.

Our work in tissue banking continues. We will maintain an active watch on how the tissue banking community responds to the concerns that we have raised.

### Examples of Safety and Quality Problems Found in Tissue Banking

- Routine acceptance of tissue for further manufacturing without accompanying records from procurement agency documenting that donor's serum specimen had been tested and found negative.
- Confirmatory testing repeated until negative result was obtained for Hepatitis B surface antigen and Hepatitis C antibody, as a means of potentially qualifying donors as suitable for transplantation.
- Acceptance of foreign tissue with donor records not translated into English and without documented medical/ social histories.
- Lack of adequate controls to assure product sterility. Lack of standard operating procedures to prevent cross contamination of human tissue during manufacture.
- Failure to assure tissue was quarantined until all infectious disease testing and donor screening reviewed by a responsible official, and donor found to be free of risk factors for/ clinical evidence of Hepatitis B and C or HIV-1 and -2.
- Errors in calculating a donor's serodilution status. In retrospect, tissue bank determined that the tissue should not have been accepted because of indicators recorded on medical/ social history.
- Tissue bank notified that a donor had been incarcerated in the year prior to his death, nine months after tissue was tested, processed, and distributed.
- Distribution and implantation of soft tissue grafts from a single donor with possible bacterial contamination. The grafts came from a donor with no evidence of risk for HIV or hepatitis (confirmed through serological testing). Contamination appears to have occurred either at recovery or during processing.
- Positive test for the Hepatitis C antibody found by distributor, even though others who had handled the tissue had found negative test results.
- Tissue processing errors, such as use of expired processing reagents.
- Release and distribution of tissue from donors who tested repeatedly reactive for Hepatitis B surface antigen.
- Improper donor testing by the tissue bank's contract lab for HIV, Hepatitis C antibody, and Hepatitis B surface antigen.
- Culture-positive tissue or tissue lots distributed, then recalled.
- Adverse reaction in a heart valve recipient.

*From actual problems found by FDA inspectors and  
adverse event reports to States*

Comments from the  
Department of Health and Human Services

APPENDIX B



THE DEPUTY SECRETARY OF HEALTH AND HUMAN SERVICES  
WASHINGTON, D.C. 20201

DEC 26 2000

TO: Inspector General, HHS

SUBJECT: OIG Report on Oversight of Tissue Banking

I commend the Office of the Inspector General (OIG) for its prompt yet thorough response to my request to review the status of oversight of tissue banks. I recognize that the report does not address ocular and reproductive tissue.

The OIG report notes that "no new cases of disease transmission through human tissue have been identified since 1993", pointing to "significant strengths and accomplishments in the current oversight system." The Department agrees that the FDA should expedite its planned rule making activities related to tissues, specifically the final rule to require registration of tissue banks and listing of tissues and the proposed rule to require adherence to good tissue practice. Further, the Department finds considerable merit in the OIG's recommendations for an intensified inspection program directed toward entities that procure, process, and store tissues. As the OIG report recognizes, however, oversight of tissue banking is an unfunded mandate for FDA. Unless appropriations increase, FDA will have to make difficult choices in regard to its oversight in other areas of comparable or greater public health significance in order to increase its activity in the tissue banking area.

FDA has expedited development of the regulations needed to implement better oversight of tissue banks. A final regulation addressing registration of tissue banks and listing of tissues is nearing completion. FDA's proposed rule to require adherence to good tissue practice will be published in the near future.

A handwritten signature in black ink, appearing to read "Kevin Thurm".

Kevin Thurm

## Endnotes

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1. The FDA issued these regulations under the legal authority of section 361 of the Public Health Service Act. This section authorizes the Secretary to make and enforce regulations judged necessary to prevent the introduction, transmission, or spread of communicable diseases.
2. Since we obtained the FY 2000 data from FDA, seven additional inspections have been entered into the PODS data system. Because we cannot tell whether these are tissue banks as we define them here, or eye banks or some other type of establishment, we do not include these seven banks in our analysis.
3. When eye banks, hospitals, and other establishments falling under the FDA tissue establishment compliance program are included, the total number of inspections rises to 363 inspections of 251 establishments. These additional establishments include 79 eye banks, 29 hospitals, and 25 establishments, such as laboratories, that we classified as other entities.
4. 21 C.F.R., Parts 16 and 1270, added at 58 *Fed. Reg.* 65,514, December 14, 1993.
5. 21 C.F.R., Parts 16 and 1270, added at 62 *Fed. Reg.* 40,429, July 29, 1997.
6. Our analysis includes only those banks we identified as banks involved with procuring, processing, storing, and distributing skin, heart valves, and musculoskeletal tissue.
7. Proposed regulation at 63 *Fed. Reg.* 26,744, May 14, 1998.
8. Proposed regulation at 64 *Fed. Reg.* 52,696, September 30, 1999.
9. This proposed regulation has not yet been published.
10. The total number of AATB-accredited banks is actually 71; 11 of these are reproductive tissue banks, and 2 are based in Canada. In our analysis we use only cadaveric tissue banks located in the United States.
11. When AATB began inspecting banks in 1986, the association relied on volunteer staff from member banks to conduct inspections. The accreditation inspectors working with AATB since 1997 are former staff from FDA or the National Institutes of Health, who have experience in facility inspection. Using outside inspectors has helped to formalize the process and make it more professional. The contract inspectors are trained in audit and evaluation methodologies, and they have had years of experience in inspecting facilities. A second important difference is that the professional inspectors do not have any relationships with the banks they are inspecting; thus, they may be more objective in their evaluation.

12. Of the 19 banks, 8 were denied accreditation following Level B inspections. Five more failed to complete the process which requires a one-year waiting period after a bank receives a Level B accreditation. Inspections of four banks were aborted because of obvious non-compliance, and the inspections were not completed. Two banks would have been recommended for denial, but because current accreditation had expired, they withdrew from the process.

13. New York Public Health Law, Article 43-B, Sections 4364-4366; New York Code of Rules and Regulations, Title 10, Part 52. New York also licenses other types of tissue banks, such as hematopoietic progenitor cell banks, eye banks, semen banks, and tissue transplantation facilities.

14. New York actually licenses 60 tissue banks for procuring, processing, or storing skin, musculoskeletal, and cardiovascular tissue. Of these, 7 New York banks and 4 out-of-State banks procure or process autogeneic bone or infant foreskin, which are non-cadaveric tissues.

15. Florida Statutes, Title 29, Chapter 381.6021-381.6025; Florida Administrative Code, 59A (Health Facility and Agency Licensing), Chapter 59A-1 Certification of Organ Procurement Organizations, Tissue Banks, and Eye Banks.

16. It is important to recognize, however, that there are no requirements to track recipients of tissue. It is possible that cases of disease transmission could have occurred, but have never been reported to the tissue bank or to any government authorities.

17. The three FDA field offices are located in Dallas, Los Angeles, and Buffalo. We recognize that the number of banks we identify here (154) differs from the 148 banks we discuss below in the potential AATB universe. FDA can inspect any individual establishment involved in tissue banking; AATB accreditation applies to an entire organization. Thus, for example, a tissue bank that has a main office and two satellite offices would have one accreditation from AATB — but FDA inspections could be conducted at each of the three different offices.

18. In contrast, blood banks, mammography facilities, and medical device firms must be inspected every two years.

19. Food and Drug Administration, “Compliance Program Guidance Manual — Compliance Program 7341.002 - Inspection of Tissue Establishments,” November 3, 1999, part II, page 4. The priorities for inspection of tissue banks are:

1. Firms whose last inspection was classified OAI (official action indicated).
2. Firms about which FDA has received surveillance information indicating there is a potential violation of 21 CFR 1270.
3. Laboratories that perform required viral marker testing for tissue banks.
4. Firms which have never been inspected and which are known to lack accreditation by a standard setting organization such as the American Association of Tissue Banks.
5. Firms which have never been inspected.
6. Firms whose last inspection was classified as VAI (voluntary action indicated).

20. 63 *Fed. Reg.* 26,744, May 14, 1998.

21. We recognize that the number of banks we identify here (148) differs from the 154 banks we discuss above in the potential FDA universe. FDA can inspect any individual establishment involved in tissue banking; AATB accreditation applies to an entire organization. Thus, for example, a tissue bank that has a main office and two satellite offices would have one accreditation from AATB — but FDA inspections could be conducted at each of the three different offices.

22. AATB accreditation contrasts sharply with the situation for hospitals, where accreditation by the Joint Commission on Accreditation of Health Care Organizations (JCAHO) carries a definite benefit. Hospitals that receive accreditation are deemed to meet Federal requirements for certification as Medicare providers. Thus, hospitals have a very strong incentive to achieve that status.

23. The American Medical Association’s policy provides a useful framework for considering the differences between cosmetic and reconstructive surgery. That policy states that “*cosmetic* surgery is performed to reshape normal structures of the body in order to improve the patient's appearance and self-esteem. *Reconstructive* surgery is performed on abnormal structures of the body, caused by congenital defects, developmental abnormalities, trauma, infection, tumors or disease. It is generally performed to improve function, but may also be done to approximate a normal appearance.” (Policy H-475.992)