

**CENTERS FOR DISEASE CONTROL AND PREVENTION,**

**FOOD AND DRUG ADMINISTRATION,**

**and**

**HEALTH RESOURCES AND SERVICES  
ADMINISTRATION,**

**DEPARTMENT OF HEALTH AND HUMAN SERVICES**

**convene the**

**WORKSHOP ON PREVENTING ORGAN AND TISSUE  
ALLOGRAFT-TRANSMITTED INFECTION:  
PRIORITIES FOR PUBLIC HEALTH INTERVENTION**

*June 2-3, 2005  
Atlanta, Georgia*

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**RECORD OF THE PROCEEDINGS**

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**ALLOGRAFT-TRANSMITTED INFECTION:  
PRIORITIES FOR PUBLIC HEALTH INTERVENTION  
*June 2-3, 2005, Atlanta, Georgia***

Executive Summary

The Centers for Disease Control and Prevention (CDC), Food and Drug Administration (FDA), and Health Resources and Services Administration (HRSA) convened a workshop entitled "Preventing Organ and Tissue Allograft-Transmitted Infection: Priorities for Public Health Intervention." The workshop was initiated by CDC's Blood, Organ and Other Tissue (BOOT) Safety Working Group, and was co-sponsored by FDA and HRSA. The proceedings, held on June 2-3, 2005 at the Sheraton Buckhead Hotel in Atlanta, were attended by about 75 participants representing over 30 external partners.

Front-line clinicians and persons representing tissue and organ procurement organizations (OPOs), tissue banks and processors, and regulatory and public health agencies were invited to attend the workshop. Critical points for intervention in preventing transplant-transmitted infection were outlined. The workshop was framed around four priority focus areas for intervention: (1) communication among OPOs, tissue banks, clinicians and public health agencies related to donors, samples and test results; (2) tissue bank systems approaches for tracking and notification of solid organs and tissues; (3) hospital systems for tracking organs and tissues; and (4) recipient adverse event recognition.

Background was presented on the following topics: an introduction to the workshop, by Matt Kuehnert and Tom Chapel, CDC; an overview on BOOT safety and availability by Jerry Holmberg, Office of the Secretary, HHS; the Futures Initiative and patient safety, by Dixie Snider, CDC; epidemiology of organ and tissue-transmitted infections by Arjun Srinivasan, CDC; current criteria for donor screening and disease reporting, by Laura St. Martin, HRSA; tissue donor requirements, by Ruth Solomon, FDA; testing requirements for human cell and tissue donors, by Melissa Greenwald, FDA; tissue standards in the healthcare setting, by Klaus Nether, JCAHO and Mike Strong, AABB; and tissue bank system approaches, by Scott Brubaker, AATB.

Breakout groups were formed around the four priority focus areas. Workshop participants discussed challenges and potential interventions. Recent transmission case studies (e.g., rabies, lymphocytic choriomeningitis virus) also were presented for illustration. It was agreed that there were readily identifiable gaps in organ and tissue safety, and recommendations on interventions were made with an emphasis on short-term solutions. The participants agreed on five most important interventions. First, communication networks should be improved. Second, a unique donor identifier bridging organs and tissues should be created. Third, education and dissemination of information to clinicians and transplant patients should be strengthened. Fourth, a framework for clinicians to report adverse events should be clearly delineated. Fifth, a notification algorithm for tracking organs and tissues should be designed.

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**WORKSHOP ON PREVENTING ORGAN AND TISSUE  
ALLOGRAFT-TRANSMITTED INFECTION:  
PRIORITIES FOR PUBLIC HEALTH INTERVENTION  
*June 2-3, 2005  
Atlanta, Georgia***

**Meeting Report**

The Centers for Disease Control and Prevention (CDC), Food and Drug Administration (FDA), and Health Resources and Services Administration (HRSA), Department of Health and Human Services (HHS), convened a workshop on "Preventing Organ and Tissue Allograft-Transmitted Infection: Priorities for Public Health Intervention." The proceedings were held on June 2-3, 2005 at the Sheraton Buckhead Hotel in Atlanta, Georgia.

**Opening Session**

Dr. Matthew Kuehnert of CDC opened the workshop by welcoming the participants to the proceedings, thanking FDA and HRSA for serving as co-sponsors, acknowledging the diligent efforts of the planning committee and administrative staff, and reviewing the agenda. The list of participants is attached to the report as [Attachment 1](#).

**Overview and Process of the Workshop**

Drs. Kuehnert and Thomas Chapel of CDC described the objectives and structure of the workshop. The CDC's National Center for Infectious Diseases formed a Blood, Organ and Other Tissues (BOOT) Workgroup in May 2004 to respond to the recent Institute of Medicine (IOM) report. The workgroup also coordinates CDC activities by providing updates on investigations of several different pathogens; overseeing current and planned projects of relevance to the field; identifying gaps and priorities for intervention; harmonizing efforts with other federal agencies; and collaborating with external partners to develop a BOOT safety agenda.

The workgroup's initial assessment showed that relevant expertise, partnerships and priorities would be needed to develop a BOOT safety agenda. Based on this finding, CDC, FDA and HRSA agreed to co-sponsor a workshop to improve organ and tissue safety. A planning committee was formed with federal agency representatives and external partners to identify appropriate experts to attend the workshop, specify priority focus areas for intervention, and determine gaps in data collection, detection and communication. The planning committee reached the following conclusions regarding the participants and structure of the workshop.

Front-line clinicians and persons representing tissue and organ procurement organizations (OPOs), tissue banks and processors, and regulatory and public health agencies will be invited to attend the workshop. The workshop will have a narrow focus limited to interventions for solid organs and selected tissues. Critical points for intervention in preventing transplant-transmitted infection will be outlined, such as donor evaluation and recovery; tissue processing, distribution and use; and the individual infection. The workshop will be framed around four priority focus areas for intervention: (1) communication among OPOs, tissue banks, clinicians and public health agencies related to donors, samples and test results; (2) tissue bank systems approaches for tracking and notification of tissues and solid organs; (3) hospital systems for tracking organs and tissues; and (4) recipient adverse event recognition.

Background presentations will be made on current partners, ongoing activities, oversight issues, promising interventions, and challenges, barriers and concerns. Updates will be provided on recent organ and tissue safety activities and progress. Breakout groups will be formed for the participants to engage in detailed discussions about the four priority focus areas for intervention. Feasible solutions will be proposed and roles, responsibilities and initial priorities will be identified for promising interventions on both short- and long-term bases. The participants will not be asked to reach consensus during the breakout groups. Instead, clear recommendations should be made in the four priority focus areas with an emphasis on short-term solutions to implement in the next year with existing resources, long-term solutions to conduct over the next two to five years with additional resources, and other solutions or dissenting opinions.

## **BOOT Safety and Availability**

Dr. Jerry Holmberg described HHS's perspective on this issue. HHS extensively partners with its agencies that play a critical role in blood safety issues, including CDC, FDA, HRSA, the Agency for Healthcare Research and Quality, Agency for Toxic Substances and Disease Registry, Centers for Medicare and Medicaid Services (CMS), and National Institutes of Health (NIH). The HHS agencies make strong efforts to deliver unified messages for surveillance, reporting and responsibility.

The HHS Secretary established an Advisory Committee on Blood Safety and Availability (ACBSA) with the following roles and functions. Policy recommendations are made and advice is provided on research of diseases involving blood, blood products and other health fields. Regulations are issued and enforced on the collection, preparation and distribution of blood and blood products. Regulations are developed on the transmission of communicable diseases.

HHS has identified several national issues. Important areas in blood safety include the reduction of bacterial contamination in platelet products, transfusion-related acute lung injury, reduction in errors, and current and emerging diseases. Key factors that are critical to blood availability include CMS reimbursement, donor testing and eligibility, access to treatment and emergency preparedness. HHS agencies have unique roles in creating a unified approach to reach common objectives and preserving the safety and availability of blood, organs, tissues and progenitor cells.

The newly-appointed HHS Secretary identified six essential actions for a 500-Day Plan, such as transforming the healthcare system; modernizing Medicare and Medicaid, advancing medical research; securing the homeland; protecting life, family and human dignity; and improving human conditions around the world. The 500-Day Plan is guided by several principles, including care for the truly needy, mechanisms to foster self-reliance, national standards, neighborhood solutions, collaboration rather than polarization, solutions that transcend political boundaries, markets before mandates, privacy protection, science for facts, a process for priorities, rewards for results rather than programs, changes in the heart and nation, and value of life.

The IOM report contained several recommendations to address threats. Advances should be made in health care related to blood, organ and tissue product safety. Surveillance should be improved through better reporting and innovative surveillance systems should be explored. Diagnostics should be developed and used. A multi-disciplinary workforce should be educated and trained. A comprehensive infectious disease research agenda should be developed. ACBSA is continuing its discussions on

the IOM report and will make recommendations to the HHS Secretary in the future. CDC, FDA and HRSA also maintain advisory committees to assess gaps in interventions in blood safety, blood products, emerging infectious diseases (EIDs) and organ transplantation.

CDC's strategic approach to BOOT safety and availability includes coordinating various programs, successfully responding to emerging threats, focusing on risk assessment and communication, incorporating a comprehensive strategy, and conducting interventions to improve "bio-vigilance." An integrated thought process, community collaboration, and clearly defined transfusion and transplant recipient health goals and outcomes will be needed to advance the "hemo-vigilance" strategy of blood and blood products to a bio-vigilance approach of blood, organs, tissues and other products from human and animal sources.

HHS agencies can take several actions to advance BOOT safety and availability. The domestic public health infrastructure should be assessed and strengthened. Promising products should be developed and tested. Surveillance systems should be integrated. Appropriate research should be funded, conducted and prioritized. Sample repositories for EIDs should be searched and information should be shared globally. Policies and processes should be open and transparent to the public. Risk communication should be improved with the development and delivery of effective messages based on lessons learned. Relationships with local and state governmental agencies should be built prior to the occurrence of an event. Public health at the grassroots level should be improved by ensuring clinicians have accurate information to make proper diagnoses.

### **CDC's Futures Initiative and Patient Safety**

Dr. Dixie Snider of CDC described the role of CDC's new organizational structure in patient safety. CDC previously operated with no overall measure of success, minimal customer segmentation and partnerships that were limited to state and local health departments. The Futures Initiative was designed to improve CDC's health impact on the population with clearly articulated goals and performance measurement, a segmented customer approach, and a strong partner network of revitalized state and local health department collaborations and new relationships with the media, businesses, healthcare organizations, communities and schools.

CDC's new architecture includes 26 goals with four overarching themes for persons, places, preparedness and global issues. The paradigm of the healthy places goals focus on communities, homes, hospitals and other healthcare settings, institutions,

schools, workplaces, and travel and recreational facilities. CDC acknowledges that advocates and other members of the public are increasingly interested in playing a larger role in efforts to improve policies and safety margins for all interventions. As a result, risk communication must be improved to ensure accurate information on interventions is delivered to the public.

CDC's road map to health is designed with goals, objectives, strategies and concrete actions. For example, a goal of a healthy hospital and healthcare initiative would be to increase the number of hospitals and other healthcare settings that provide safe, effective, patient-centered, timely, efficient and equitable care. An objective would be to increase the percentage of hospitals and other healthcare facilities with effective programs to protect patients and healthcare workers against adverse events. A strategy would be to reduce the number of adverse events related to the use of blood, organs, tissues or other biologic products. An action would be to eliminate major errors in infection transmission and compatibility between donors and recipients by improving biologic products with unique donor identifiers, bar coding, radio frequency or other technologies.

CDC will continue its strong focus on patient safety under the new organizational structure of coordinating centers and offices. Efforts are now being made to coordinate and replicate lessons learned from innovative and useful projects of various health issues throughout the agency. However, CDC recognizes that several challenges must be addressed. Outcome and performance measures must be established for all goals. Objectives and priorities must be identified to create a shared vision and the budget must be aligned with priorities. Collaborative efforts must be undertaken throughout CDC, HHS and other federal agencies to achieve goals.

### **Epidemiology of Organ- and Tissue-Transmitted Infections**

Dr. Arjun Srinivasan of CDC reported that "expected" infections in organ and allograft recipients occur in low numbers, but are not generally related to the actual allograft. Allograft- or organ-associated infections are aseptically processed and are not usually expected due to microbes on the graft. This definition can be applied to allograft tissues, but not organs. Organs cannot be reprocessed and will transmit microbes during transplants that result in disease to recipients. As a result, the workshop participants should focus on "unexpected" allograft- or organ-associated infections caused by an implanted allograft tissue or unanticipated transplanted organ.



Reports of unexpected pathogens have significantly increased since 2000. Florida and Louisiana reported cases in 2000 of septic arthritis following anterior cruciate ligament reconstruction using tendon allografts. Colorado reported a case in 2003 of Group A streptococcus (GAS) after allograft implantation. Germany, Massachusetts/Rhode Island and Wisconsin reported cases in 2003-2005 of transmission of rabies, lymphocytic choriomeningitis (LCMV) and West Nile viruses (WNV) from organ donors to transplant recipients. These problems will reoccur in the future unless the overall safety process is improved. CDC's investigations of organ and tissue-transmitted infections are summarized below.

An anterior cruciate ligament repair with a tendon allograft was performed on a healthy male 17 years of age in September 2003. The patient developed high fever and pain at the incision site and was readmitted to the hospital for removal of the allograft six days after surgery. GAS was detected in cultures of the patient's blood, wound aspirate and explanted allograft. The donor of the tissue presented to an emergency room three days prior to death with a diffuse rash believed to be a reaction to medication. The cause of death was attributed to an overdose of a muscle relaxant and analgesic medication. Several of the donor's tissues were cultured at the time of procurement and all were positive for GAS. However, the tissues were eventually distributed for transplant because post-processing cultures showed no evidence of infection.

CDC tested the samples and recovered GAS from the unprocessed tissues and donor serum sample, but did not find evidence of the infection in any of the recalled tissues. Pathologic examinations showed GAS in the skin, blood vessels and lung of the donor. Based on the test results and clinical history, CDC concluded that the donor's most likely cause of death was streptococcal toxic shock-like syndrome. Tissue and GAS isolates from the blood of the donor and recipient were all found to be genetically identical and confirmed a link to the allograft tissue. The American Association of Tissue Banks (AATB) now recommends that the totality of cultures be considered, the possibility of sepsis be addressed, and medical directors make an exclusion or deferral when multiple cultures are positive for a single organism.

A Texas pathologist reported cases to CDC in June 2004 of three patients who received one liver and two kidneys from a common donor and developed severe encephalitis. At the time of the report, two patients had died and one was critically ill. All three patients were readmitted to the hospital 20-25 days post-transplantation and eventually developed altered mental status and progressive neurologic deterioration. All standard tests for infectious agents performed by the hospital were negative, but mice developed neurologic dysfunction one week after CDC injected samples of the tissue. An analysis of nervous tissues in the mice showed particles resembling rabies virus. Viral testing

and inspection of brain tissue revealed that the virus was the same bat variant in all three cases.

The donor was admitted to a hospital with confusion, headache and a low-grade fever. A CT scan showed the presence of a cerebral hemorrhage that expanded after the donor was admitted and resulted in a coma and brain death. CDC found rabies antibodies in the blood and eventually learned a bat had bitten the donor. After the investigation, the Texas pathologist reported a fourth case to CDC. The deceased patient received a liver from the same donor one day after the initial three patients and showed clinical signs of rabies based on the autopsy report. CDC learned that during organ recovery, surgeons remove iliac arteries from donors to use in vascular reconstruction. Vessels that are not needed for the recipient may be stored in sterile conditions for later use. Vessels from the common donor were stored and used in the liver transplant of the fourth patient.

Several factors play a role in the frequency and number of organ- and tissue-transmitted infections that are now being detected. The severity of illness among all patients is increasing as healthcare advances. Immune suppressive medications with higher potency are used more often. Organ and tissue recipients may be sicker than in the past and more susceptible to infections. Heightened awareness of clinicians and improved diagnostic tests have enhanced the ability to detect unexpected tissue- and organ-associated infections. However, some cases are not detected and surveillance systems have not been designed to define the true incidence of these infections. Based on reports in the literature, the incidence of infections is estimated to be 0.02% from ~20,000 transplants per year and 0.0004% from ~900,000 allografts per year.

The estimates of incidence demonstrate that these infections are rare and uncommon, but the outcomes are severe. Most notably, 15 cases of organ-associated infections that occurred in 2002-2005 are equivalent to an attributed mortality rate of 67%. The 19 cases of tissue-associated infections that occurred in 1998-2003 resulted in one death, several hospitalizations, surgeries and prolonged courses of antimicrobial medications. Recent episodes of unexpected allograft- or organ-associated infections have improved awareness and understanding of the problem, but many aspects of the epidemiology of these infections are still unknown.

Comments by the workshop participants on the epidemiology of organ- and tissue-transmitted infections are outlined below.

- Use the definition of “allografts” for both tissues and organs, but distinguish between these two terms based on the recipient rather than

the donor. For example, the nature of immunosuppression primarily emphasizes viral pathogens in organ transplants and short-term bacterial fungal pathogens in tissue-based transplants.

- Develop a formal network for physicians to communicate and report adverse events because cases of organ- and tissue-transmitted infections are being missed with the current informal process.
- Improve reporting systems to include all settings where allograft transplants occur.
- Explore the technical feasibility of and costs associated with adding rabies antibodies screening to all collected tissues prior to distribution.
- Place more emphasis on preventing secondary infections from infected recipients because deaths will always occur from diseases transmitted by donors.
- Apply lessons learned and successes from CDC's investigations to enhance the overall organ and tissue safety process.

### **Current Criteria for Donor Screening and Disease Reporting**

Dr. Laura Saint Martin of HRSA explained that HRSA is an HHS agency with responsibility for regulating the national Organ Procurement and Transplantation Network (OPTN) and administering a contract with the United Network for Organ Sharing (UNOS) to conduct activities. Several OPTN forms were created to collect information on infectious diseases. The deceased donor registration form, living donor registration and follow-up forms, and donor histocompatibility form are used for donors. The transplant candidate registration form, transplant recipient registration and follow-up forms, post-transplant malignancy form and recipient histocompatibility form are used for recipients.

The deceased donor registration form asks whether the donor had HIV, human T-lymphotropic virus (HTLV), syphilis (as indicated by RPR/VDRL testing), cytomegalovirus (CMV), hepatitis B virus (HBV) or hepatitis C virus (HCV) infection; whether the donor had a clinical infection and its source; and whether the donor was in a "high-risk" category as defined by CDC. Information on HIV, CMV, HBV, HCV and the Epstein-Barr virus (EBV) is collected from the living donor registration form. Information on HIV, CMV, HBV, HCV and EBV is collected from both the transplant recipient registration and follow-up forms. Information on the BK virus is also gathered from the transplant recipient follow-up form.

UNet is a secure online database for the collection, storage, analysis and publication of all OPTN data regarding the patient waiting list, organ matching and transplants. All transplant programs, OPOs and histocompatibility laboratories use UNET. In addition to collecting data, UNet also serves as a secure mechanism for communication between OPTN members and dissemination of information to all transplant programs and OPOs. However, the OPTN database is limited in some areas. No data are collected on serious bacterial or fungal infections and consent for data collection does not extend to research.

The OPTN Board of Directors approved policy changes in November 2004 that established a formal system for OPOs and transplant centers to promptly report cases of transmissible diseases or medical conditions. Reporting of HIV, pituitary-driven growth hormones and HTLV was expanded to include infectious diseases and other communicable diseases related to malignancies. The new system has not been fully implemented at this time due to the need for additional data programming and education to OPOs and transplant programs about reporting requirements. However, several aspects of the system have been specified at this point.

The following diseases and medical conditions are required to be reported: encephalitis, meningitis, other unknown infections of the central nervous system, suspected encephalitis, HCV, herpes simplex or other encephalitis, JC virus infection, WNV infection, cryptococcal infection, rabies, Creutzfeldt-Jakob disease (CJD), other fungal or viral encephalitis, bacterial meningitis, HIV infection, herpes, active EBV or other active viremia, serologic evidence of HTLV I and II, active hepatitis A or B, infection with T. Cruzi, leishmania, strongyloides or toxoplasmosis, active tuberculosis, pneumonia, severe acute respiratory syndrome (SARS), bacterial or fungal sepsis, syphilis, multi-system organ failure due to overwhelming sepsis, and any new conditions identified by CDC as potentially communicable. The OPO Committee recommended the reportable diseases and medical conditions and released the list for public comment.

The following actions must be taken. A transplant center may use any non-HIV-infected organ at its discretion with informed consent of the recipient. A transplant center must notify the procuring OPO within one working day after receiving notification that an organ recipient in the program was confirmed positive for or died from a transmissible disease potentially from the donor's organ.

An OPO must communicate test results and diagnoses to any transplant center or tissue bank that received organs or tissues from the donor. An OPO must manage the investigation to determine whether a donor was diagnosed with a potentially

transmissible disease. An OPO must notify and submit a final report to OPTN within 45 days. OPTN must assist the procuring OPO in identifying transplant programs and recipients who received organs from a donor. OPTN must monitor the notification process and forward a copy of the final report to HRSA and recipient transplant centers. Transplant centers and OPOs will be required to comply with the new system.

HRSA views the new system as a solid step in creating a more robust and formal infectious disease reporting system. However, the process to report the transmission of confirmed and known infections does not capture undiagnosed or uncertain cases. As a result, HRSA and CDC are discussing the possibility of creating an “early alert” mechanism for programs to report suspicious symptoms of recipients and save specimens in the absence of a definitive diagnosis.

The workshop participants urged HRSA to revise the new reporting requirements to be reasonable and feasible. For example, 50% of liver transplant patients have had HCV. The majority of transplant patients develop septicemia or pneumonia. Requirements to report these conditions will be extremely burdensome to tissue centers and OPOs and will not assist in improving OPTN or producing meaningful data.

## **Tissue Donor Requirements**

Dr. Ruth Solomon of FDA outlined regulations for human cells, tissues and cellular- and tissue-based products (HCTPs). FDA defines HCTPs as “articles containing or consisting of human cells or tissues that are intended for implantation, transplantation, infusion or transfer to a human recipient.” FDA took the following actions from 1993-2005. Human tissues intended for transplantation were regulated and an interim final rule on communicable disease transmission was issued. A risk-based approach for all HCTPs was proposed and announced. Three proposed rules were published, released for public comment, finalized, became effective on May 25, 2005, and are now codified in federal regulations.

The three rules serve as the minimum for regulation of all HCTPs, act as the sole regulatory requirement for certain HCTPs, and supplement other existing requirements for HCTPs regulated as drugs, devices or biological products. The regulatory framework of HCTPs focuses on the following areas. The introduction, transmission or spread of communicable diseases by HCTPs and the use of HCTPs from infected donors will be prevented. Improper handling or processing that may contaminate or damage tissues will be prevented. Clinical safety and effectiveness will be assured for HCTPs that do not meet regulatory criteria.

HCTPs include bone, ligaments, tendons, other musculoskeletal tissues, skin, corneas, sclera, other ocular tissues, human heart valves, human dura mater, semen, oocyte, embryos, other reproductive cells, hematopoietic stem cells from peripheral blood and cord blood, chondrocytes, islet cells, other cellular therapies, and tissue/device and other combination therapies. HCTPs do not include vascularized organs, minimally manipulated bone marrow, xenografts, blood products, human milk, collagen, cell factors, other secreted or extracted products, ancillary products used in manufacture, and *in vitro* diagnostic products.

The federal regulations for HCTPs are divided into six subparts. Subpart A outlines the purpose, scope, definitions and general provisions of the regulations; describes exceptions to the requirements; and contains criteria for regulating HCTPs that do not require pre-market approval. Subpart A states that HCTPs require minimal manipulation, are advertised or labeled for homologous use, are not combined with another article, and do not have a systemic effect other than autologous or family-related use.

Subpart B outlines registration and listing procedures. Each tissue establishment must register with FDA within five days of initiating operations and annually thereafter even if no changes are made. Updates on changes in the organization, principal staff or products must be submitted to FDA every six months. A tissue establishment must complete and submit FDA's one-page Form 3356 by mail, facsimile or e-mail with its name and address; list of all HCTPs manufactured; and name, address and signature of the reporting official. Establishments that complete the registration and listing procedures are subject to FDA inspection.

Subpart C defines donor eligibility requirements for current good tissue practices (GTPs). Donor eligibility determination is based on donor screening and testing and required for all HCTP donors with some exceptions. HCTPs cannot be administered until the donor has been determined to be eligible with some exceptions. FDA defines "donor screening" as a review of the donor's relevant medical records and current medical history; a current physical assessment or examination; and evaluation of other available data, such as laboratory results, medical records, coroner and autopsy reports and information from other sources.

Subpart D outlines current GTPs that are necessary to prevent communicable disease transmission through methods, facilities and manufacturing controls. The GTPs are broadly described and can be applied to a wide range of HCTPs. The language provides each tissue establishment with flexibility to develop individual standard

operating procedures to meet goals. One GTP requires tissue establishments to design a quality program with the following functions. Procedures should be created and maintained to receive, investigate, evaluate and document data and describe all actions taken during HCTP manufacturing. Information should be shared on potential contamination of HCTPs or possible transmission of communicable diseases by HCTPs.

Data should be exchanged with consignees and other establishments that are known to have recovered HCTPs from the same donor or taken manufacturing actions. Records should accompany the HCTP when distributed that contain distinct donor identification codes with no personal identifiers, but with some exceptions. A statement on whether the donor was determined to be eligible or ineligible based on screening and testing results should be included. Records used to make the donor eligibility determination should be summarized. Manufacturing records should be retained for at least ten years after administration of HCTPs.

All tissue establishments that handle the HCTP must create a tracking system with the distinct donor identification code. The system must be designed to track the HCTP from the donor to consignee and vice versa and provide labeling information to facilitate effective tracking of the HCTP from the donor to recipient and vice versa. Files of procedures to review, evaluate and document complaints should be established, maintained and made available to FDA inspectors.

Subpart E outlines additional requirements for tissue establishments, such as those for labeling and reporting adverse reactions and HCTP deviations. FDA defines a "deviation" as an unexpected event potentially related to a communicable disease transmission or an action that is inconsistent with established specifications, applicable regulations or standards. Tissue establishments must investigate all deviations related to distributed HCTPs and report the event to FDA within 45 days of discovery. A follow-up report of corrective or preventive actions that were taken must be submitted to FDA as well. HCTP labels must contain the distinct donor identification code and the description, expiration date and required warnings of the HCTP. Additional information can be included on either the label or package insert, such as the name and address of the establishment that made the HCTP available for distribution, storage temperature of the HCTP, warnings and instructions to prevent communicable disease transmission.

Subpart F outlines inspection and enforcement of tissue establishments. FDA can issue orders of retention, recall, destruction or cessation of manufacturing to non-compliant tissue establishments. FDA is permitted to inspect tissue establishments at any reasonable time and manner with or without prior notice. Inspections are typically

conducted every two to three years, but the frequency is at FDA's discretion. Inspections can include questioning personnel, taking samples, and reviewing and copying records.

### **Current Testing Requirements for Human Cell and Tissue Donors**

Dr. Melissa Greenwald of FDA explained that the donor eligibility rule defines relevant communicable disease agents or diseases (RCDADs) and requires tissue establishments to screen or test for RCDADs. Federal regulations define and list particular RCDADs and describe situations where communicable disease agents or diseases can be added to the existing list, such as EIDs. With the exception of a public health emergency, FDA's process to expand the RCDAD list includes obtaining guidance, drafting language, releasing the document for public comment and finalizing the regulation. The current RCDAD list includes HIV types 1 and 2, HBV, HCV, human transmissible spongiform encephalopathies, CJD and *Treponema pallidum* for all HCTPs; HTLV types I and II for viable and leukocyte-rich HCTPs; and chlamydia trachomatis and neisseria gonorrhoea for reproductive HCTPs.

FDA's donor eligibility draft guidelines were published in May 2004 and added WNV, sepsis, vaccinia and SARS to the RCDAD list. However, the document has not yet been finalized. General donor testing requirements are outlined as follows. Donor testing must be performed at a laboratory that is registered with FDA and certified under the Clinical Laboratory Improvement Amendments or CMS equivalent. Donor screening tests rather than diagnostic tests must be licensed, approved or cleared by FDA; used in accordance with the package insert; and labeled for use in cadaveric donors if such a test is available. These recommendations are subject to change based on time or new technologies.

Test results should be interpreted only according to the manufacturer's instructions in the package insert. Triplicate testing is not recommended in any manufacturer's test kit instructions. Specimens should be gathered at the same time or within seven days before or after the collection of cells or tissues with certain exceptions. Donors who received transfusions or infusions 48 hours prior to specimen collection should be evaluated for plasma dilution or excluded as a donor. Clinical trials to support and test donor screening test kits should be conducted in a "pre-screened" or low-prevalence population with an emphasis on sensitivity. Clinical trials to support and test diagnostic test kits should be conducted in a symptomatic population with suspicion of a particular disease before testing is performed with additional emphasis on specificity.



Performance of a test kit in a low-prevalence population of pre-screened donors has not been established for diagnostic test kits. FDA's position is that tests specifically labeled for use in donor screening are the best tests to use in any donor screening situation. Recommended screening tests include those that are licensed or have been cleared by FDA for anti-HIV-1 and -2 or a licensed combination test; hepatitis B surface antigen and anti-hepatitis B core; anti-HCV; and the *Treponema pallidum* serological test for syphilis. FDA's guidance document specifies that persons with a reactive non-Treponemal screening test and non-reactive specific Treponemal confirmatory test are permitted to donate.

Additional screening tests for viable and leukocyte-rich cells or tissues can be used for anti-HTLV I and II and CMV. Additional tests for genitourinary diseases of donors of reproductive cells and tissues can be used for *Chlamydia trachomatis* or *Neisseria gonorrhoeae*. However, donor screening tests that are licensed, approved or cleared by FDA do not currently exist for either of these diseases. FDA published the donor eligibility draft guidance document before any nucleic acid tests (NATs) were approved for use in cadaveric specimens. At that time, only HIV and HCV test kits were licensed for use in screening blood or other living donors. The draft guidance contains two explicit statements on NATs and donor testing.

First, FDA may recommend NATs for use in cadaveric tissue donors as more information becomes available. Second, FDA recommends that living donors of HCTPs, such as semen donors or hematopoietic stem and progenitor cell donors, be tested with FDA-licensed NAT blood donor screening tests for HIV and HCV. Gen-Probe/Chiron, the National Genetics Institute and Roche Molecular Systems manufacture NAT kits for donor screening that have been licensed by FDA and can be used for blood, plasma, living and organ donors or cadaveric specimens. Gen-Probe is also developing additional NAT kits for donor screening of WNV and HBV.

FDA considers cadaveric specimens to be different than living blood donor specimens and requires additional validation studies to be performed. Claims may be obtained as an addition or supplement to previously approved test kits for those with an indication for use in screening blood donors. FDA published recommendations in November 2004 on obtaining labeling claims for communicable disease donor screening tests using cadaveric blood specimens from HCTP donors. FDA partners with industry to encourage the development of test kits for use in cadaveric donors and has noted several issues with these specimens.

Testing has not been validated for long-term specimen storage, but would be extremely helpful to the HCTP industry. Claims for HCTP donors can only include individual donor

testing and should not be pooled unless separate validation studies are performed. Turnaround times are often an issue with cadaveric HCTPs, such as the release of corneas in less than seven days. Claims for both serum and plasma are helpful for cadaveric donors due to the limited specimen volume. The organ and other living donor claim does not require data to be submitted. Language included in new test kits explicitly states that the test is not intended for use on cadaveric specimens, cord blood samples or as an aid in diagnosis.

FDA does not regulate organ donors or make decisions on screening and testing that should be performed for organ donors. The risk/benefit ratio for HCTPs and organs as well as screening and testing requirements are different. Overall, FDA's new testing regulations for human cell and tissue donors require that tissue establishments with knowledge of another organization performing infectious disease testing on the same donor obtain and consider those test results to make a donor eligibility determination.

The workshop participants asked FDA to consider two issues related to the testing requirements for human cell and tissue donors. First, the "cadaveric indication" language should be clarified to specify specimens taken after death. The current language is confusing because organ and transplant establishments frequently have cadaveric donors with both beating and non-beating hearts. Second, explicit recommendations should be included in the donor eligibility guidance document on using pre-processing bacterial and fungal cultures on tissue donors and applying results of post-processing cultures in the decision-making process to accept or reject donors or tissues.

### **New FDA Reporting Regulations for HCTPs**

Dr. Greenwald reported that GTPs for tissues contain reporting requirements for manufacturers and certain adverse events involving communicable diseases. Standards developed by the Joint Commission on Accreditation of Healthcare Organizations (JCAHO) will become effective on July 1, 2005 and will encourage organizations that store or issue tissues to develop procedures for the investigation and prompt reporting of recipient adverse events and post-transplant infections to the source facility.

Under FDA's GTP reporting requirement, a manufacturer must investigate any adverse reaction involving a communicable disease related to an HCTP that was made available for distribution from its facility. Manufacturers must submit reports to FDA of an adverse reaction involving a communicable disease that is fatal or life threatening; results in

permanent impairment of function or permanent damage to body structure; or necessitates hospitalization or medical or surgical intervention. FDA defines an “adverse reaction” as a noxious and unintended response to any HCTP for which a reasonable possibility exists that the HCTP caused the response.

A “manufacturer” is broadly defined as the entity that receives the report. Manufacturers must report an adverse reaction by submitting two copies of MedWatch Form 3500A to FDA within 15 days of receipt of information. Manufacturers must retain complaint files and review and evaluate each incident to determine if an event is reportable. Non-manufacturers can use MedWatch Form 3500 to promptly report adverse reactions to FDA and HCTP establishments. The MedWatch forms are being revised to be clearer and more understandable, but versions of the current documents can still be obtained from the FDA web site.

FDA forwards completed MedWatch forms to a triage contractor for entry into appropriate adverse event databases, including those for drugs, biologics and HCTPs; food, cosmetics and dietary supplements; and medical devices. Standard operating procedures for adverse reaction reports that were established by FDA’s Tissue Safety Team are followed. FDA cannot require end-users to submit reports, but the important role of MedWatch in HCTP safety can be critical to clinicians. Most notably, MedWatch prevents additional adverse reactions by detecting trends across the country that may not be identified at individual sites. FDA’s overall mission in this effort is to collaborate with diverse partners to improve human organ and tissue safety.

Comments by the workshop participants on FDA’s new reporting regulations for HCTPs are outlined below.

- Clearly delineate a formal communication and coordination process and identify a responsible entity to submit reports to FDA. For example, FDA’s broad definition of a “tissue manufacturer” is non-specific and can include screening entities, recovery agencies, storage facilities and processing organizations.
- Bridge gaps with clinicians by offering incentives and providing explicit guidance on recognizing and reporting adverse reactions. For example, clinicians are often confused about whether CDC, FDA, state and local health departments or suppliers should be contacted about an adverse event because governmental agencies have no regulatory authority over private providers.
- Revise complaint files to collect more information than is currently required to be reported to FDA.

- Strengthen requirements to report communicable diseases from MedWatch to state health departments and from manufacturers to state health departments.

### **Tissue Standards in the Healthcare Setting**

Mr. Klaus Nether of JCAHO explained that JCAHO is an independent non-profit accreditation organization that evaluates more than 15,000 healthcare programs in the United States and develops and revises healthcare standards. JCAHO reviewed its tissue storage and issuance standards in 2003 due to several factors. The standards were only applicable to laboratory programs. Incorporation of tissue standards into hospitals, critical access hospitals, ambulatory care settings and office-based surgery programs would allow JCAHO to survey all organizations accredited under these programs for compliance with the tissue standards.

The number of tissue transplants has tripled since 1990 and emphasizes the need to ensure quality and safety, while minimizing the potential risk of infection. Incidents of tissue-borne infections and other adverse outcomes in recipients of donor tissues are well documented. Over a 14-month period, JCAHO searched the literature, formed internal advisory groups, conducted an external field review with ~400 respondents, and revised and incorporated the tissue standards into other programs. Responses from the field review were strongly in favor of JCAHO's tissue standards.

Effective July 1, 2005, JCAHO's tissue storage and issuance standards will be applicable to hospitals, critical access hospitals, ambulatory care settings and office-based surgery programs. Laboratories will continue to comply with the standards as well. The standards do not apply to solid organs at this time, but JCAHO is currently discussing the possibility of undertaking this effort. JCAHO's schedule to survey its accredited organizations for compliance with the tissue standards will be every two years for laboratories and every three years for all other programs.

The standards address three major performance elements. First, organizations must assign responsibility for oversight of the tissue program throughout the establishment. Procedures must be developed to standardize systems and processes for acquiring, receiving, storing and issuing tissues. Second, organizations must maintain records for traceability to ensure sufficient retrieval of information in the event of an adverse patient reaction or manufacturer recall. Organizations must retain records for ten years on bidirectional tracing, staff involvement with the tissue, materials used and preparation

instructions. Organizations must develop a system to fully comply with the completion of tissue usage information to the source facility when requested.

Third, organizations must create a clearly defined process to investigate adverse events. Investigation and communication will be critical to this standard because prompt detection of an event will provide rapid response and treatment to recipients who are adversely impacted by an infected tissue. Effective communication of an adverse effect directly related to tissue use will enhance patient safety and assist in preventing disease transmission from an infected donor. Each organization can use its discretion in identifying appropriate entities to submit adverse event reports. JCAHO recognizes that the standard will be problematic in terms of tissue use in healthcare facilities, but will continue to evaluate all of its standards to address concerns and improve tissue quality and safety.

Some workshop participants did not agree with JCAHO's decision to include live vascular allografts in the tissue standards. This change will be extremely burdensome, will severely limit vascular allografts and may result in immediate termination of pancreas transplants. Participants representing the American Society of Transplant Surgeons were not aware of transplant surgeons who served on JCAHO's internal advisory groups to provide expert advice on this decision. Participants representing FDA noted that lawyers for the agency consider live vascular allografts to be HCTPs. However, FDA and HRSA are currently holding discussions to clarify this issue.

### **Tissue Standards for Hospitals**

Dr. Michael Strong, of the American Association of Blood Banks (AABB), conveyed that AABB was established in 1947 as an international association of blood banks, hospital and community blood centers, transfusion and transplantation services, and parentage testing laboratories. AABB's mission is to advance the practice and standards of transfusion medicine and related biological therapies. AABB's strategic mission focuses on standards and accreditation, education, technical and regulatory assistance, and consulting services. AABB's membership includes 1,800 institutions and 8,000 individuals from 50 states and 80 countries. AABB has developed standards in a variety of areas from 1958-2005.

AABB operates with >550 members who serve on ~60 committees, subcommittees, program units, task forces and workgroups. Two of the committees focus on cellular therapies and blood banks and transfusion services. A tissue task force was established to oversee tissue-related activities, identify areas where guidance or

standards are needed in hospitals and make recommendations. AABB administered a hospital tissue survey in 2005 in response to several issues. Interest in tissue use in hospitals increased. CDC's investigations highlighted the need for better communication and coordination. JCAHO proposed new tissue standards. The level of involvement of hospital blood banks in the handling of tissues needs to be determined. The development of educational programs and standards should be guided.

AABB's web-based tissue questionnaire collected data on the involvement of hospitals by tissue type, responsibilities of hospital departments, and the extent of responsibilities, such as ordering, storing, transporting and other handling duties; tracking, logging and other documenting duties; and investigating adverse events and other reporting duties. The tissue survey showed that musculoskeletal allografts were handled most often based on 325 respondents and surgical departments have the largest responsibility for tissues based on 402 respondents.

AABB then compared its May 1, 2005 standards to JCAHO's tissue standards that will become effective on July 1, 2005. AABB standards recognize that hospital blood banks or transfusion services may be required in some cases to store tissue products. The requirements do not apply if tissue banking is beyond the scope of these programs. AABB accreditation states that the blood bank is the owner and has responsibility for tissues stored in its facility. AABB standards are targeted to blood banks and transfusion services and cover seven major categories.

For "organization," a structure must be developed that clearly defines and designates responsible parties for key quality functions and the provision of blood, components, tissue, derivatives and services. For "resources," policies, processes and procedures must be created that ensure the provision of adequate resources to perform, verify and manage all activities in the blood bank or transfusion service. For "equipment," alarm systems and other equipment must be identified that is critical to the provision of blood, components, tissue or services.

For "supplier and customer issues," policies, processes and procedures must be developed to evaluate the ability of suppliers of critical materials, equipment and services to consistently meet specified requirements. This standard covers the incoming receipt, inspection and testing of tissues. For "process control," policies, processes and procedures must be created and validated to ensure the quality of blood, components, tissue, derivatives and services. This standard covers tracing, handling, storing and transporting tissues.

For “records and documents,” record systems must be designed to trace any tissue from its source to final disposition; review records applied to the specific component; and investigate adverse events manifested by the recipient. This standard covers the retention of tissue records. For “deviations, non-conformance and adverse events,” a process must be developed to investigate disease transmission or other suspected adverse events related to the use of tissues and derivatives. This standard covers procedures to promptly report cases to the source facility.

The evaluation showed that AABB standards cover the majority of JCAHO’s new tissue standards. However, AABB will need to address two prescriptive JCAHO standards related to assigning responsibility for oversight of the tissue program and coordinating tissue activities throughout the organization. The AABB tissue task force will take several actions to address these gaps. Changes to the AABB standards will be recommended. A workshop on tissue storage and distribution will be held for blood banks during AABB’s annual meeting in October 2005. A handbook, technical manual, guidelines and a chapter in the second edition of *Blood Banking and Transfusion Medicine* will be prepared. The AABB consulting division is strengthening its knowledge on management of tissue practices to assist under-funded and understaffed hospitals.

Overall, AABB is in a solid position to address issues related to JCAHO’s new tissue standards and continue its focus on patient and donor care and safety. AABB will make efforts to strengthen, increase and extend its educational expertise in tissues by creating alliances and advocating for transfusion medicine issues.

The workshop participants urged AABB and JCAHO to include state and local health departments in the requirement for facilities to report adverse events because these agencies are in a solid position to coordinate events in the field. The participants also emphasized the critical need to identify practical solutions at the individual level because communication among governmental agencies is not sufficient. Most notably, transplant clinicians must make rapid decisions to benefit patients.

### **Tissue Bank System Approaches**

Mr. Scott Brubaker of AATB presented information to guide the discussion for Breakout Group 2. The group is charged with addressing two key questions. First, what are the challenges to creating an additional unique donor identifier that allows trace-back and trace-forward of organs and tissues and extends to recipient medical records in the event of a suspected infection in the donor or recipient? The additional unique donor identifier can be similar to a UNOS number, but would be created for tissues. Second,

what detection control points should be identified to allow efficient identification, trace-back and trace-forward of tissues linked to a common donor, such as nodes for notification that may be used in the event of a suspected infection in the donor or recipient?

AATB administered a survey prior to the workshop to obtain input on the two questions from the top tissue banks in the country. The respondents noted both advantages and disadvantages in creating an additional unique donor identifier. On the one hand, tracking to one donor would be facilitated; complying with federal regulations on sharing donor records and cultures would be easier; and communicating between tissue banks and recovery agencies regarding shared donors would be improved.

On the other hand, logistical problems could arise related to the original or first tissue bank that would be assigned the unique identifier. Multiple numbers could be given to one donor. Communications between recovery agencies could be inaccurate. More errors in documentation or identification errors could occur. The process of matching and referencing an additional number would be burdensome. Additional cross-reference of records or the placement of new numbers on labels would be required. Major revisions and changes in software, standard operating procedures and staff training would be needed.

The majority of respondents pointed out that the current system of tracing donors and tissues is sufficient and no responsible parties have been identified to manage and pay for the service. For example, previous activities can be reviewed to estimate that unique identifiers will need to be issued to >30,000 potential donors per year. UNOS assigned 10,500 organ donor identification numbers in 2004. AATB-accredited tissue banks reported the recovery of ~24,000 deceased tissue donors in 2003. The Eye Bank Association of America (EBAA) reported that U.S. tissue banks provided 46,841 corneas for transplants in 2004.

AATB collected other information from the tissue survey in addition to the breakout group questions. The respondents identified two probable or proven cases of infection related to allografts that resulted in a tissue recall of a distributed inventory. In both cases, tissue remained in the inventory and was quarantined. Eight tissue banks received reports of suspected infections and were able to recall tissues in each case. Of these respondents, three reported tissues remained in the inventory that could be quarantined. Ten respondents reported using bar coding for donors or grafts. At the time of the survey, five respondents were considering incorporating the International Society of Blood Transfusion (ISBT) 128 bar coding system into tissue banking.



The respondents also provided feedback on FDA's tracking regulations and AATB's tracking standards for donors and individual allografts. Based on survey responses, incidences of suspected and probable or proven allograft-related infections were found to be ~0.014% and 0.00015%, respectively, for all tissue types. Tissue types represented in the survey from highest to lowest prevalence were musculoskeletal, soft tissue, skin, vessels, cardiac, semen, osteochondral and amnion.

The survey showed that respondents were most often notified about suspected infections in donors or recipients by telephone calls from hospitals. Symptoms reported for suspected allograft-associated infections from the most to least common were positive culture of an organism, drainage, inflammation, fever, positive serology and pain. *Staphylococcus aureus* was the microorganism most frequently reported, but none of the positive serologies were proven to be related to an allograft.

AATB proposed definitions for "suspected," "probable" and "proven" allograft-associated infections and asked the respondents to provide feedback on these terms. The "suspected" definition received the most comments. The most common links to a suspected infection due to an allograft were identified as the tissue type reported, processing method used and clinical procedure. Another portion of the survey collected information on obstacles to investigations. AATB's guidance document and changes to standards were published and posted on its web site.

The workshop participants expressed concern that only five respondents were considering incorporation of the ISBT 128 system into tissue banking at the time the survey was distributed. The system is a set of standardized data elements that can be used in any other system and should not be inaccurately defined solely as a bar coding system. ISBT 128 can identify the tissue bank, assign the donor a unique identification number, track the location of the donor globally and trace tissue-related processes. The system can eliminate the need for multiple unique donor identifiers and standardize data elements throughout the world. The participants urged Breakout Group 2 to explore solutions to gather more information and educate tissue banks throughout the country on ISBT 128.

### **Communication Between OPOs and Other Partners**

Dr. Marlon Levy, of the Association of Organ Procurement Organizations (AOPO), presented information to guide the discussion for Breakout Group 1. The group is charged with addressing two key questions. First, what are the needs and challenges for a communication network of organ and tissue procurement organizations? Second,

does a need exist for appropriate diagnostic algorithms using existing samples, such as a virtual repository? The group discussed these issues prior to the workshop and reached the following preliminary conclusions.

Recovery and transplant teams, tissue banks and processors, clinicians who use tissue allografts, and public health and regulatory agencies need to communicate. Potential transplant-transmitted infectious diseases should be communicated on a limited basis to a few participants. These pathogens should include HCV, HBV, WNV, rabies, LCMV and GAS. Notification of emerging issues affecting organ and tissue communities should be communicated and broadcast to many participants. These issues should include new policies, recall notices and new EIDs. Reportable events or notifiable infections should be targeted and communicated to fulfill reporting and regulatory requirements. These situations should include adverse events and tissue-associated infections.

The group noted several examples of communication networks for infectious diseases. The Emerging Infectious Network is represented by >800 infectious disease physicians who communicate opinions and anecdotal data through a moderated listserv. The network is used to periodically administer questionnaires to rapidly gather and distribute data on EID cases. The Epidemic Information Exchange (i.e., *Epi-X*) is CDC's secure and web-based communication network with strictly controlled access. The network distributes information to participants, allows persons to report events, maintains online surveillance and other tools, and provides automatic notification to beepers, cellular telephones and other personal communication devices.

UNet is a secure Internet-based transplant information database that is fully staffed and operated each day of the year. UNOS created the network for OPOs and organ transplant centers to register patients for transplants, match donated organs to transplant candidates on the waiting list, and manage critical data of all patients. The database has the potential for rapid communication and assessment of disease transmission. During the review of potential disease transmission, OPTN is notified, obtains initial information, reviews UNet, and collaborates with the donor OPO to contact all transplant centers associated with organ recipients. UNet then monitors progress, contacts HRSA and CDC, and communicates findings of the investigation.

The group identified several challenges to establishing a communication network. Organ and tissue communities have not traditionally communicated. Systems for tracking infections in organ recipients may not be suitable for tissue recipients. Linkages in terms of time and numbers between organ donors and recipients are more controlled than those between tissue donors and recipients.

For the second question, the group agreed that a repository is necessary and should be viewed as a priority. A repository can assess the prevalence of EIDs among organ and tissue donors, serve as a pool of available specimens for trace-back during investigations, and act as an accessible data set of pre- and post-mortem specimens to validate diagnostic tests developed for transplant evaluation.

The group listed factors to support the development of a virtual repository rather than an actual repository that is centrally located. Actual repositories are resource-intensive and expensive, but a virtual repository can maintain specimens that were previously collected and stored by OPOs and tissue banks. The need to collect specimens for testing may be infrequent. However, challenges associated with developing a virtual repository include Institutional Review Board approval for linked specimens, maintenance of various types of specimens by different OPOs and tissue banks, and increased costs and resource requirements related to the storage of additional specimens.

The group noted that the Retrovirus Epidemiology Donor Study Allogeneic Donor and Recipient repository can serve as a model in developing an organ and tissue repository. The database was established to identify EIDs related to transfusions and has created testing algorithms to determine the potential of infection from transmission. Current capacity of the repository includes 15 participating blood centers and hospitals and data of >3,500 recipients from >13,000 donors.

The workshop participants encouraged Breakout Group 1 to explore solutions to obtain endorsement of a communication network of organ and tissue procurement organizations from hospitals and physicians. Effective tools to facilitate the involvement of these groups in this process should be considered as well.

### **Hospital Systems for Tracking Organs and Tissues**

Dr. Bradley Eisenbrey of AABB presented information to guide the discussion for Breakout Group 3. The group is charged with addressing the issue of assigning and coordinating responsibility for acquiring, storing, tracing and investigating tissue-related adverse events to consignees in healthcare settings. The rationale for the group to address this issue is based on documented transmission of infectious diseases and the need for mechanisms to track tissues from donors and trace tissues from the recipient to donor.

The group acknowledged that hospital blood banks are uniquely qualified in this area due to experience with and an environment of current good manufacturing practices; solid inventory control; strong tracking and recall systems; an existing regulated environment; maintenance of monitored refrigerators, freezers and room temperature shelf space to store equipment; a computerized data management system; and a 24-hour per day/7-day per week operation for receiving, storing, issuing, retrieving and accessing tissues.

The group noted that some hospital blood banks have other unique capabilities as well. Existing and freestanding blood bank computer systems have been designed with bar code reading ability and the flexibility to create new product codes. Surgical departments regularly use blood bank freezers. Transfusion committees, hospital administration, risk management and surgical departments have expressed support of hospital systems to track organs and tissues. Hospital staff are aware of good manufacturing practices.

The group examined one model in this area to review lessons learned. The William Beaumont Hospital (WBH) in Royal Oak, Michigan developed a system because a standardized method had not been created to track organs and tissues. Moreover, several events triggered the need for this effort. A cornea was transplanted from a hepatitis B core antibody-positive donor with no documentation by the surgeon. The cornea was tracked to the surgeon only, but could not be traced to the patient for multiple events. Frozen bone and vascular tissues in an operating room were mishandled and resulted in waste. Instructions for reserved or special-order tissues were confused. Awareness increased about disease transmission cases involving tissues.

WBH took several actions to respond to these events. All bone, tissue and kidneys are now required to be centralized and accessioned in the blood bank inventory. Unique identifiers are assigned to the specific patient, bar codes are issued, and the correct product, intact shipping container and proper temperature conditions must be confirmed. The blood bank is responsible for ordering all non-renal tissues. WBH will not pay for tissue orders that are placed by persons other than the hospital tissue coordinator. This staff member is responsible for sending transplant reports to vendors, collecting and completing report forms or cards, tracking missing cards, obtaining audit reports from vendors, submitting reports to FDA, and serving as the liaison between the hospital tissue bank and epidemiology department to ensure no adverse events were overlooked.

WBH requires all vendors to be registered with FDA, licensed if applicable, and have membership in and inspected by AATB or EBAA. Vendors are subject to site visits for WBH to review processes, training procedures and documentation of donor criteria, recall policies and tissue tracking. WBH has assigned unique product codes and identifiers; developed a catalogue for surgeons; established a single access point for purchasers, vendors, surgeons and sales representatives; and created a computerized system for accessioning, issuing and tracking tissues and organs.

The workshop participants urged Breakout Group 3 to explore solutions to license transplant sites. These organizations frequently do not maintain logs or other systems to track tissues and organs from donors to recipients in the event of a recall or other problem.

### **Recipient Adverse Event Recognition**

Dr. Kent Sepkowitz, of the Infectious Disease Society of America and the Society of Healthcare Epidemiology of America, presented information to guide the discussion for Breakout Group 4. The group is charged with addressing two key questions. First, what elements of a minimum data set are essential when investigations of suspected infections occur, including epidemiologic and laboratory data? Second, what methods can be used to encourage documentation of tissue type, anatomic location and other routine clinical data in the medical record that are necessary for investigation and outcome analysis?

The group identified several challenges related to these issues. Unexpected pathogens that are transmitted through organ transplantation should be identified. Signs, symptoms or specific pathogens that serve of indicators of problems should be defined. Syndromes or organisms that imitate a disease should be determined. A process should be developed to convey appropriate information about the patient.

A decision should be made on whether all post-operative surgical site infections should be reported to the tissue bank that prepared the tissue. Appropriate patient information to include in adverse event reports should be clearly delineated. Efforts should be made to minimize fears of reporting adverse events to public health and regulatory agencies. Documentation procedures should be improved and standardized without additional burden. Strategies should be devised to encourage surgeons to include additional information on surgical allografts in patient charts.

The group intends to focus on four specific issues to fulfill its charge. First, what signs, symptoms and diagnoses of organ recipients should always be reported to OPOs? Second, what information should be included in a report to an OPO or tissue bank to facilitate an investigation by CDC or another entity? Third, what system can be developed to encourage reporting without adding extraneous data? Fourth, what processes can be implemented to assure patient safety and reduce the burden of completing unnecessary forms?

The workshop participants asked Breakout Group 4 to also focus on guidance to provide to sports medicine physicians who culture soft tissue allografts. These physicians are uncertain about whether the patient should be treated or if positive cultures should be reported.

Dr. Chapel recessed the meeting for the participants to report to their respective breakout groups.

### **Germany Experience of Rabies Transmission Through Organs and Tissues**

Dr. Werner Lauchart, of Deutsche Stiftung Organtransplantation, described a case that occurred in Germany related to the transmission of rabies through organs and tissues. A female 26 years of age presented to a hospital in December 2004 with a severe headache. A CT scan, EEG, cerebrospinal fluid test and nuclear magnetic resonance test revealed no pathologic signs and all laboratory values were normal. The patient reported visiting India in October 2004 for several weeks, taking speed and LSD the night before presenting to the hospital, and not using intravenous drugs. The patient was given Diazepam and discharged, but was admitted to the psychiatric department of another hospital with anxiety and psychiatric disorders two days later. The drug screen was negative with the exception of Diazepam.

The patient developed fever and pneumonia, went into cardiac arrest and was resuscitated twice, was referred to the intensive care unit and eventually developed signs of brain death. A family member consented to organ donation and postmortem examination. The donor was evaluated in accordance with German guidelines that are similar to U.S. and European OPS criteria. The assessment included tests for HIV, hepatitis B antigen, CMV and other pathogens. The donor's lung, kidney, corneas and kidney/pancreas were allocated to six recipients, but the heart was not distributed due to the two events of cardiac arrest and resuscitation. Myocarditis was suspected as the cause of the cardiac arrest, but could not be confirmed by pathology or biopsy. Microscopy did not reveal pathological signs, but gross autopsy showed that the heart

was dilated with a septal defect. The histology of cerebral tissue showed necrotising encephalitis in the brain stem, possibly due to Coxsacki B virus infection.

Recipients of the donor's kidney, lung and kidney/pancreas developed fever and similar neurological symptoms. Rabies was suspected, but could not be confirmed by re-analysis of the donor's brain specimens. However, reexamination of the donor's brain tissue showed Negri-bodies in the brain stem that were compatible with rabies infection. After a press release was issued, an individual confirmed that the donor had been scratched by a dog in India, but was not immunized or vaccinated against rabies during the trip.

Based on the new information, cutaneous neck samples, probes and blood serum specimens from the organ and cornea recipients and brain tissue and serum specimens from the donor were sent to German laboratories. The laboratory results showed that the donor's first brain biopsy was positive for rabies and the serum, CSF, and second through fourth brain biopsies were negative. No positive results were seen in recipients of the kidney, liver or two corneas. The lung recipient showed positive results in the saliva, skin biopsy and brain tests. The kidney/pancreas recipient showed positive results in the brain and all three saliva tests.

### **Global Safety of Organs and Tissues for Transplantation**

Dr. Luc Noel, of the World Health Organization (WHO), reported that the World Health Assembly (WHA) adopted WHO's 1991 guiding principles to ensure global safety of organs and tissues for transplantation. First, deceased persons should be viewed as the preferred source of tissues and organs, but living adult donors may be used with consent. Second, living donors should be genetically related to living recipients in general. Third, payment should not be given or received for tissues and organs, but may be allocated for recovery, preservation and supply costs.

Several groups identified ethical issues with WHO's guiding principles, including leaders in the field who urge policy changes to allow incentives to increase the number of organs for transplantation; organ donation programs with involvement in commercialized tissue operations; and the organ trafficking and transplant tourism industry in countries in WHO regions. Concerns were also expressed about the safety, quality, efficacy and access of WHO's guiding principles, such as infectious risk; short- and long-term outcomes of recipients and living donors; and the lack of access in under-developed countries and other areas to meet the needs of patients for kidney, cornea, skin, bone and haematopoietic stem cell transplants.

The WHO 111<sup>th</sup> Executive Board met in 2003 to underscore the need for WHO to address ethical and technical issues related to tissue banking. The importance of a portion of the WHO budget being dedicated to improving the quality of blood, blood products and transplant materials was emphasized as well. A background paper on human organ and tissue transplantation was submitted to support these requests. WHO convened a meeting in October 2003 with 37 clinicians, ethicists, social scientists and government officials representing 23 countries, all WHO regions and all levels of economic development to analyze global issues and concerns regarding the ethics, access and safety of tissue and organ transplantation. The meeting served as a foundation for WHA taking action in May 2004 to a resolution that was adopted in January 2004.

WHA recognized several problems in tissue banking and transplantation. Tissue trafficking occurs worldwide. The level of education, training and research in tissue banking at the global level is poor. Capacity does not exist to provide “origin-to-destination” traceability of tissues. Evidence of the efficacy of transplantation of some tissues is limited or entirely absent. Concerns were raised about the balance between ensuring non-profit tissue banks have capacity to sustain operations and preventing excessive income of for-profit tissue banks that use donated human materials. Approaches to donor consent are inconsistent and commercialization is unregulated. Harmonization of regulatory standards that deliver high costs for tissue banks is minimal.

WHA’s resolution on human tissue and organ transplantation is highlighted as follows. Member states were urged to implement effective national oversight of procurement, processing and transplantation of human cells, tissues and organs, including accountability for transplantation and traceability of human materials. Member states were asked to cooperate in formulating recommendations and guidelines to harmonize global practices in the procurement, processing and transplantation of human cells, tissues and organs, including the development of minimum criteria for suitability of tissue and cell donors. Member states were encouraged to form ethics commissions on cell, tissue and organ transplantation; extend the use of living kidney donations when possible, including those from deceased donors; and take actions to protect poor and vulnerable groups from transplant tourism, tissue and organ sales, and international trafficking in human tissues and organs.

The resolution also contained requests to the WHO Director General. The examination and collection of global data on the practice, safety, quality, epidemiology, efficacy and ethical issues of allogeneic transplantation should continue to be used to update WHO’s



human organ transplantation guiding principles. International cooperation should be promoted to increase access by citizens to therapeutic procedures. WHO should provide technical support, facilitate international cooperation, and develop suitable guidelines for transplantation of cells, tissues or organs. Guidelines to protect poor and vulnerable groups from becoming victims should be developed to assist member states in preventing organ trafficking.

WHO will also take advantage of other opportunities in addition to the resolution to increase its involvement in transplantation. The 11<sup>th</sup> International Conference of Drug Regulatory Authorities held a meeting in February 2004 that focused on human tissue problems and challenges for regulators. The meeting resulted in recommendations for WHO to develop clear guidelines for the quality, safety and efficacy of human cell, tissue and organ transplantation and facilitate surveillance activities by developing appropriate written standards and reference materials.

Essential requirements and minimal specifications were identified during the first global consultation on regulatory requirements and oversight of cell and tissue transplantation services in November 2004. Cell and tissue transplants that should be included in donor protection, patient safety and clinical efficacy were described. Responsibilities by health authorities and a comprehensive regulatory framework were outlined. A quality management system was recommended. Vigilance and surveillance beyond adverse event reporting through risk assessment, post-marketing surveillance and international collaborations with clinicians, operators, regulators and policymakers were proposed.

Cell and tissue transplantations were recognized as a specific class of health products during the consultation, but several limitations were acknowledged, including limited data in most countries, absence of a regulatory framework and oversight, and poor access to essential cell and tissue transplants. The benefits of implementing a comprehensive regulatory framework were found to outweigh costs of the investment. Components of the framework should include legally mandated standards, cell and tissue transplantation specifications, input from professional societies and other stakeholders, assurance of compliance and enforcement, a strong surveillance system, accreditation, and a process to address both public and private needs. Experiences in cell and tissue transplantation by more advanced countries were also described during the consultation. Core global specifications were drafted, submitted to experts and are now being considered by a WHO expert committee.

WHO is currently organizing regional meetings with health authorities of member states in Africa, Asia, Europe and Latin America with responsibility for transplantation to gather information, address cultural issues, identify priorities and develop a global network.

WHO will use the global knowledge base on transplantation as an overriding tool for its programs. The system will be designed with four components of activities and practices, a legal framework and organizational structure, xenotransplantation, and threats and safety measures. The fourth component will target infectious risks; analyze demonstrated to theoretical transmissible infections; rely on the national network of regulatory authorities and public health agencies; and allow models and data on epidemiology, preventive measures, risk assessment, alerts and other areas to be accessed and shared.

WHO programs will rely on national health authorities, scientific and professional societies, and partnering institutions to provide resources, input through regional meetings and questionnaires, and feedback through the global network. Information provided by stakeholders will be publicly available on the WHO web site. WHO acknowledges that adverse event reporting and vigilance are needed at every stage in the development of transplantation services to formulate strategies and policies. This effort must be active and comprehensive to result in collaborations among clinicians, operators, regulators and health authorities. Effective surveillance will also require international partnerships.

## Breakout Group Reports

Breakout Group 1. Dr. Levy reported that the group made general observations regarding communications between OPOs and other partners. Two separate communication networks should be developed for organ and tissue communities due to practical issues and different needs of the groups. Overlap between organ and tissue communities in donors, regulatory concerns, and public health and recipient health issues requires some areas to be similar, such as network design, process flow and data fields. The tissue community is not fully organized and may serve as an impediment to developing a communication network. Key outcomes from the group's discussion are outlined below.

### Short-Term Solutions

- Formulate targeted guidance to educate stakeholders, including surgeons, tissue banks and OPOs.
- Develop clear information flow diagrams to delineate and simplify communications for affected participants.
- Define "reportable events" to assist clinicians.
- Consider making tissue- and organ-association infections nationally verifiable diseases.

- Focus on in-hospital deaths and use OPOs as the common node to verify that all affected parties are notified and follow-up occurs.
- Charge AATB and EBAA with identifying appropriate points of contact and communication nodes for outpatient deaths in situations when OPOs are not notified or involved.
- Compile a list of points of contact at OPOs, tissue banks and other affected parties to facilitate direct contact during investigations.
- Create an inventory of OPOs, tissue banks, transplant centers, tissue processors or other organizations that currently archive specimens. Develop a list of materials archived by these establishments.
- Identify current archiving regulations and requirements.
- Develop algorithms to determine the number of specimens needed to prove the absence of emerging pathogens or infections.

#### Long-Term Solutions

- Develop a web-based system similar to UNet to track tissue donors and communicate.
- Create an oversight process to assure that all affected parties appropriately notify other groups and verify the investigation is complete.
- Design and maintain a database that can be used in studies, serves as a trace-back tool during investigations and specifies the availability and location of tissues. Explore the possibility of developing the database as a subset of tissue and organ databases.

Comments by the workshop participants on the Breakout Group 1 report are outlined below.

- Identify governmental or non-governmental groups that will be responsible for funding and supporting the communication network.
- Use UNet rather than OPOs as the common node to verify that all affected parties are notified and follow-up occurs because reports can be overlooked at the individual OPO level.
- Acknowledge that a communication network will not be effective without a regulatory arm to encourage OPOs, tissue banks, eye banks and other groups to recognize adverse events and take appropriate actions.
- Incorporate a universal donor identifier to link the two separate organ and tissue communication networks.
- Design the communication network and repository as simple tools with minimum data elements to increase the likelihood of broad implementation.

- Use the “William Beaumont Hospital tissue model” as the basis to develop communication networks.
- Use AATB as a mechanism to overcome communication barriers and obtain cooperation from major tissue bank programs.
- Urge regulatory agencies to mandate immediate notification of sero-conversion among recipients.
- Develop a process to communicate when an individual is NAT-positive because NATs are now being performed on tissues.
- Document the various communication flows between the organ and tissue communities to improve communication between OPOs and other partners.

Breakout Group 2. Mr. Brubaker reported that the group made several observations regarding tissue bank systems approaches. Tissue banks are interested in investigating tissue-associated infections. A standard currently exists that states positive serology “shall” be reported to all entities involved in the recovery of the donor within 24 hours. However, federal regulations now require information to be shared with all establishments that manufactured a cell or tissue.

The UNOS identification number is documented during tissue recovery to ensure the tissue bank can cross-reference the organ donor with the identification system for the tissue donor. AATB standards and federal regulations recommend that unused blood samples be archived for ten years. Repositories currently exist in several tissue banks for serum, plasma and lymph nodes. FDA requires tissue establishments to designate a responsible individual to follow specific steps in reporting tissue-associated infections and adverse events. Key outcomes from the group’s discussion are outlined below.

#### Concerns, Barriers and Constraints

- Determine whether the tracking number should be used internationally or domestically only.
- Decide whether organ and tissue numbers should be identical.
- Fill gaps related to tracing, such as the difficulty in tracing tissues from the end-user to the recipient and the time involved with locating other recipients.
- Identify a central location to fund and manage tissue bank systems.
- Urge federal agencies to develop a consistent process for regulatory oversight of organs and tissues.

### Short-Term Solutions

- Increase communication among AATB, AOPO, EBAA, UNOS and other groups to facilitate the development of an identification system. Engage FDA in this effort to provide guidance on a potential common donor identification number.
- Educate professional associations about the need to use MedWatch as the point of contact for tissues. Urge physicians to designate and train a clinical nurse or other staff member to record entries into MedWatch.

### Long-Term Solutions

- Continue to address the issue of tissue bank system approaches during industry, national or association meetings and within committees of each organization.
- Determine whether ISTB 128 or bar coding is the better mechanism to incorporate into tissue bank systems.
- Acknowledge that organ recipients offer the first opportunity to detect transmission of some infections, but this percentage is small.
- Emphasize the need for OPOs to be notified when a referral resulted in tissue donation. Include a list of specific tissues that were recovered in the notification. Use this approach to assist OPOs in maintaining a follow-up system by recording entries of referrals.
- Clearly define the process of potential infection transmission from organ donations and the role of tissue banks in this effort.
- Develop standardized definitions for “possible,” “probable” and “proven” allograft-associated infections to serve as a guide for reports of suspected infections.

Comments by the workshop participants on the Breakout Group 2 report are outlined below.

- Take caution in recommending tissue bank systems approaches due to insurmountable obstacles. For example, tissue and organ banks are extremely different and have no overlap or linkages in terms of reporting. Rigorous tissue regulations cannot be incorporated into organ systems at this time.
- Encourage professional associations to inform physicians of the importance of notifying tissue and organ establishments or FDA about organ- and tissue-associated infections. Clarify that FDA cannot regulate clinicians because its authority is limited to establishments and products.

Point out that physicians voluntarily submit reports, but this action is not mandated.

- Fill gaps related to tracking tissues in tissue banks because no government regulations have been established for this effort. Acknowledge that this disconnect has weakened the ability to recall non-implanted tissues and locate recipients.
- Address communication issues related to HRSA's new criteria for donor screening and disease reporting. Recognize that the regulations will increase competition among OPOs and decrease communication.
- Clarify the FDA regulations to specify adverse event data elements that should be reported from tracking systems. Encourage AATB to use this information to compile best practices and develop a guidance document.
- Make adverse events nationally notifiable conditions to strengthen reporting when initially recognized. Identify public health agencies that should have oversight of ensuring information is properly shared with appropriate parties.

Breakout Group 3. Dr. Eisenbrey reported that the group primarily focused on the need to educate industry about hospital systems for tracking organs and tissues. Key outcomes from the group's discussion are outlined below.

#### Concerns, Barriers and Constraints

- Identify appropriate groups to educate and responsible parties to pay for compliance mechanisms.
- Include risk management, infectious disease and epidemiology departments within hospitals in the communication process when adverse events are identified.
- Develop strategies to engage establishments or organizations that are not accredited by AATB or JCAHO.
- Explore solutions to address conflicting standards and the fragmented environments of tissue systems and regulatory agencies.
- Resolve issues related to using UNet as a model to develop a tissue system. For example, UNet is a fee-based service. Security mechanisms and strong barriers to access must be designed and maintained to prevent tissue establishments from reviewing information about UNet recipients, while still sending data about adverse events.
- Improve communication between OPOs and tissue procurement and processing agencies.

### Short-Term Solutions

- Use existing models to disseminate information and increase education about hospital systems for tracking organs and tissues, such as the *Morbidity and Mortality Weekly Report*, JCAHO newsletter and professional societies.
- Notify each accrediting organization of its respective obligation to enforce standards and ensure the process is fully implemented. Inform these groups that FDA has established a framework for accrediting organizations to use in enforcing standards.
- Form tissue user groups at the hospital level and reestablish transfusion committees. Use these structures to oversee tracking of events, ensure appropriate use of tissues and foster communication among surgeons who are involved in the use of tissues.
- Develop minimal uniform standards of practice that can be applied to all end-users.
- Establish tissue registries in each hospital.
- Convene an interagency tissue conference and use the meeting to form an interagency task force that will develop and publish guidelines for hospital systems to track organs and tissues. Model the meeting after the conference that was previously held by CDC, FDA, NIH and the Public Health Service (PHS) to ensure regulatory, medical, tracking and epidemiological expertise and knowledge are represented.

### Long-Term Solutions

- Develop uniform reporting requirements because non-accredited hospitals are not obligated to report.
- Provide education on quality tissue systems using critical elements and responsibilities from the “blood bank” model.
- Establish a system for tissues that is similar to UNet and includes unique identifiers for donors, a standardized numbering system based on the UNOS model, reimbursement capabilities, and a computerized registry system at both national and transplant facility levels.
- Urge regulatory agencies to create mandates that would require tissue orders to be placed by physicians and tissues to be treated as blood and pharmaceuticals.

Comments by the workshop participants on the Breakout Group 3 report are outlined below.

- Provide education to clarify that recovering tissue from a cadaver is an inherently different process than extracting blood from a living individual. Create reasonable strategies and diverse approaches to address contamination and other issues that will be different.
- Take caution in recommending additional regulations because numerous mandates will result in no actions being taken. Make strong efforts to obtain wide endorsement from clinicians of hospital systems for tracking organs and tissues and include incentives for participation.

Breakout Group 4. Dr. Sepkowitz reported that the group discussed the following issues to enhance the process of clinicians recognizing and reporting adverse events in tissue and organ recipients.

- Assign a unique identification number to deceased persons whose organs and tissues are harvested.
- Inform clinicians that three sentinel events should serve as triggers to recognize and report adverse events of tissues: removal of tissues due to a potential infection, patients who are re-hospitalized within three months after transplant surgery for management of possible infection, and organism-specific conditions.
- Inform clinicians that four unusual syndromes should serve as triggers to recognize and report adverse events of organs: encephalitis, hepatitis, myocarditis and endocarditis/endovascular infection.
- Design adverse event report forms as a simple four-line document to collect the unique identifier, contact information of the reporting official, and data on the syndrome that generated the report and number of days after transplant or implant the reaction occurred. Use a simple form to increase compliance because busy clinicians will be less likely to complete and submit complex or lengthy documents. Inform clinicians to submit the completed adverse event form to the source of the tissue or organ.
- Emphasize the critical need for microbiology laboratories to label and take other specific actions when tissues are removed due to infection.
- Develop a web-based system to provide immediate feedback to clinicians who report tissue-associated adverse events about similar or no events in other recipients who received tissues from the same donor. Use the input to decide whether a formal investigation should be launched.
- Create tissue and organ systems with similar elements to ensure the donor is the common denominator.



- Report HBV, HCV, HIV or other viral infections as “sentinel events” when sero-conversion of a recipient occurs after an organ was determined to be negative of these diseases.
- Notify the appropriate parties about rabies and parasitic organisms that present “late” after the transplant.
- Define a concrete, realistic, useful and meaningful time-line for sufficient follow-up and surveillance of recipients after the transplant.
- Discourage clinicians from culturing tissues before implantation.
- Identify agencies or organizations with responsibility for monitoring, taking action and financially supporting a system of tissue- or organ-associated adverse events reported by clinicians. Establish a syndromic surveillance system for organ or tissue transplants.
- Convene a group of experts to review successes and lessons learned from previous adverse events. For example, the transmission of CJD from transplanted tissues resulted in the establishment of effective regulations. Canada has made much more progress than the United States in engaging clinicians to recognize and report adverse events related to tissue or organ transplants.
- Develop a unified database that will serve as a centralized system for clinicians to submit adverse event report forms, learn about other events and input information.

Comments by the workshop participants on the Breakout Group 4 report are outlined below.

- Minimize barriers related to clinicians reporting tissue- or organ-associated adverse events. For example, federal agencies or accrediting organizations often punish and issue citations to establishments during an investigation instead of offering assistance.
- Expand the narrow focus of educational efforts to transplant surgeons to include nephrologists, internists, family practitioners and other providers who may treat recipients in the future.
- Create clear definitions of “possible,” “probable” and “confirmed” allograft-associated infections to assist clinicians in recognizing and reporting adverse events.
- Provide clinicians with a list of recommended peri- and post-operative antibiotics that should be administered in conjunction with non-sterile allografts.
- Clearly define “tissue” because this term encompasses all, live and dead tissues.

- Take caution in developing new regulations and designating agencies with additional oversight or legislative authority that may adversely impact patients. Acknowledge that patients throughout the world greatly benefit from thousands of tissue transplants safely and successfully performed each year by surgeons.
- Minimize reporting of prophylactic antibiotics due to the lack of evidence that antibiotics administered post-surgery prevent wound infections.
- Include a caveat in guidance to clinicians to clarify that most infections from large constructs are due to soft tissue envelope problems.
- Provide guidance to JCAHO-accredited facilities by specifying and clearly distinguishing between HRSA's tracking regulations for organs and FDA's tracking requirements for tissues.
- Treat vessels that accompany organ transplants as organs because tracking systems, UNOS identification numbers and other processes currently exist to address these issues.
- Review experiences and lessons learned by California and New York to define the role of health departments in reporting systems. For example, require physicians and healthcare providers to report outbreaks and "unusual" events to health departments. Explore the possibility of issuing citations and fines to non-compliant physicians. Establish strong linkages with tissue banks, blood banks, pharmacies and other programs throughout the state to ensure the health department is informed of non-reportable events and conducts post-investigation activities that are appropriate and helpful rather than punitive. Use the health department to provide onsite expertise to smaller facilities with less experience.

### **Open Discussion and Priority Summary**

Dr. Chapel led the participants in a review of the most common recommendations from the breakout group reports on the four priority focus areas for intervention. Overarching themes identified by the participants are outlined below.

#### Contextual Factors, Barriers and Tradeoffs

- Clearly define and distinguish between "organs," "tissues" and "infections."
- Acknowledge that improvements need to be made, but many aspects of the current system are effective. Utilize existing structures when possible, such as UNet or CDC's National Healthcare Safety Network that is used for reporting and communicating.

- Recognize that additional mandates may decrease the supply of some organs, particularly those with strict time-lines for transplants.
- Be mindful of time and financial burdens of reporting that will be placed on clinicians.
- Design approaches that emphasize improved quality of care rather than punitive measures for deficiencies.
- Be sensitive to entities that will implement and pay for increased costs of improved systems. Specify appropriate roles for public health and regulatory agencies.
- Engage tissue processors, diagnostic test kit manufacturers and other components of industry with significant investments and interest in interventions of organ-and tissue-associated infections.
- Emphasize that the Freedom of Information Act (FOIA) requires data to become public and may serve as a disincentive for participation in federally regulated interventions.
- Recognize that the Health Insurance Portability and Accountability Act (HIPAA) will limit data sharing and exchange of interventions.
- Be mindful of the current environment of silos and competitiveness among both organ and tissue procurement organizations.
- Acknowledge that industry does not fully participate in activities conducted by voluntary associations and organizations.

#### Preliminary Solutions and Concepts

- Improve communication networks and determine whether these processes should be separate, equal or linked.
- Develop a decentralized repository, but recognize that this type of system will not be feasible for eye tissue.
- Create a unique donor identifier.
- Design a notification algorithm for tracking.
- Strengthen education and dissemination of information to clinicians and transplant patients. Undertake these efforts on an ongoing basis due to frequent staff turnover in physicians' offices. For example, AATB can develop and distribute a best practices guidance document that provides advice on reporting probable infections, clarifies HIPAA exceptions, promotes MedWatch use, defines "possible" allograft-associated infections and outlines other operational issues. AATB can form a transfusion/transmitted diseases committee that is represented by medical directors, physicians, CDC, FDA, EBAA and AOPO to discuss EIDs. Clinicians should inform transplant patients prior to surgery of the potential for health problems to develop in the future from the organ or tissue.

- Establish a task force to develop specific guidance on the utilization of tissues in healthcare entities.
- Clearly delineate the framework for clinicians to report adverse events, including data elements to report, appropriate entities to receive reports and the overall process.
- Review the Canada model in which tools for epidemiological studies and other incentives are offered to physicians and hospitals for reporting emerging and reemerging diseases, nosocomial infections and medical device-related infections.
- Create a national biovigilance strategy with existing structures.
- Model interventions after blood bank activities.
- Establish a standardized labeling requirement. Review AATB's standards that contain guidelines on labeling content.
- Provide a forum for voluntary associations to identify actions that can now be taken to improve processes.
- Strengthen collaboration at the federal level. For example, form an interagency transfusion/transplant-transmitted diseases committee with CDC, FDA and HRSA. Place a stronger focus on organ and tissue safety during the monthly blood safety conference calls with CDC, CMS, FDA, HRSA, NIH and PHS.
- Identify actions that can be taken immediately. For example, CDC or the HHS Office of the Assistant Secretary for Health can serve as the "neutral" federal agency to provide a forum in which voluntary organizations are convened and goals that can be achieved on a short-term basis with existing resources are identified.
- Identify incentives that will encourage diagnostic manufacturers to design test kits for cadaveric donors, but be mindful of the tissue bank inventory of archived serum and plasma in developing new tests.

Of the preliminary solutions and concepts suggested, the participants agreed the following issues are the five most important interventions that can yield benefits on a relatively short-term basis. First, communication networks should be improved. Second, a unique donor identifier for both organs and tissues should be created. Third, education and dissemination of information to clinicians and transplant patients should be strengthened. Fourth, a framework for clinicians to report transplant-associated adverse events should be clearly delineated. Fifth, a notification algorithm for tracking among and between organs and tissues should be designed.

Dr. Chapel pointed out that federal agencies represented at the workshop will be involved in all of interventions, but he asked the participants to identify roles and responsibilities for additional organizations. Comments by the participants are outlined below.

- Designate UNOS as the lead for the organ component and AATB, AOPO and EBAA as the leads for the tissue component of the communications network.
- Designate UNOS as the lead for developing unique donor identifiers for both organs and tissues.
- Designate the American Academy of Orthopaedic Surgeons, American Orthopaedic Society for Sports Medicine, Association of periOperative Registered Nurses, clinical societies, transplant associations and nursing organizations as the leads for educating and disseminating information to clinicians and patients.
- Designate the Council of State and Territorial Epidemiologists and federal agencies as the leads for clearly delineating a framework for clinicians to report adverse events.
- Designate industry associations and public health agencies as the leads for designing a notification algorithm for tracking.

The participants also noted that the OPTN Ad Hoc Operations Committee is charged with developing a rapid notification system. A suggestion was made for OPTN to establish a new committee to create a tracking system or take other actions.

### **LCMV Transmitted Through Solid Organ Transplantation**

Dr. Boris Pavlin of CDC described results of a recent LCMV investigation. Of four patients who underwent transplant surgery in April 2005 at three hospitals in Massachusetts and Rhode Island, three died within four weeks after surgery and one became gravely ill. Patient 1 was a male 54 years of age with polycystic kidney disease who received a cadaveric kidney. The patient presented to a clinic on two separate occasions within ten days after hospital discharge with nausea, abdominal pain, watery diarrhea, shortness of breath, chills and a 35-pound weight loss. The diagnosis at hospital readmission was “volume depletion with abdominal pain.” Marked erythema at the incision site, elevated liver function tests, hepatomegaly, change in mental status and signs of renal failure were detected. The patient died two days later.

Patient 2 was a male 48 years of age with rapidly progressive glomerulonephritis and anti-glomerular basement membrane syndrome who received a cadaveric kidney. The patient presented to an emergency room nine days after hospital discharge with nausea, vomiting, abdominal pain and cough. The diagnosis at hospital readmission was "hyperkalemia." A reddened incision site, persistent diarrhea, chills and serosanguinous drainage from the incision were detected. The transplant clinician of patients 1 and 2 contacted the procuring organ bank and learned that one donor was the source of both kidneys and other organs to two additional recipients.

Patient 3 was a male 54 years of age with HBV, HCV, cirrhosis and hepatocellular carcinoma who received a cadaveric liver. The patient complained of abdominal and right shoulder pain following surgery. An initial rise in liver function tests and coagulation, fevers, seizure and unstable blood pressure were detected. The patient developed renal failure, required dialysis and died 26 days after surgery with hyperkalemic-induced erythema.

Patient 4 was a male 41 years of age with cystic fibrosis who underwent a double lung transplant and developed thrombocytopenia, renal failure, intermittent delirium and bilateral infiltrates within three days following surgery. Severe fatigue, abdominal distention and pain, ascites and small bowel wall thickening were detected. The patient went into respiratory distress and developed unstable atrial fibrillation. The patient was pulsed with steroids after a bronchoscopy revealed white fibrinous material, but the cardiac, renal and liver functions failed. The patient was allowed to die through comfort care 23 days after surgery.

Autopsies of all three deceased patients showed hepatic necrosis, but laboratory tests were negative for a common infectious agent. CDC tested specimens that were submitted by the Massachusetts and Rhode Island state health departments and found LCMV in tissues of all four recipients. LCMV is a single-stranded RNA virus with a natural reservoir in the house mouse. The prevalence of LCMV is ~5% in mice and humans. Infection in humans has only been linked to exposure to excreta of infected mice and pet hamsters.

LCMV is a biphasic illness with fever, myalgia and other non-specific symptoms initially, but aseptic meningitis or other neurologic problems eventually develop. LCMV acquired during the first and second trimesters of pregnancy has been linked to birth defects. Ribavirin has been used on an investigational basis to treat severe cases of LCMV. The health of patient 2 is continuing to improve after the LCMV diagnosis was made, intravenous Ribavirin was administered and immunosuppression therapy was decreased.

The common organ donor of the four patients was a healthy female 45 years of age who presented to a hospital in April 2005 with a headache, slurred speech and right-sided hemiplegia and was diagnosed with a right middle cerebral artery embolic stroke. The patient was given a tissue plasminogen activator, subsequently developed a hemorrhagic stroke, progressive edema and brain stem herniation, and declared brain dead. The patient's family consented to organ donation of the liver, lungs, kidneys, skin and corneas. Laboratory results of the organs showed no suspicion of infectious disease.

CDC performed an onsite investigation to determine the epidemiology of the LCMV cluster. Records from the organ bank, hospital and operating room were reviewed and revealed no common solutions for contamination or breaches in standard precautions. CDC determined that infection during or after organ procurement was highly unlikely. Interviews with family members revealed that the donor had contact with a pet hamster two weeks prior to death. Tests showed that the hamster was positive for LCMV, but laboratory tests of the donor's tissues revealed no signs of LCMV and the two cornea recipients were found to be asymptomatic. CDC retrieved the donor's skin and blood vessels accompanying the liver to prevent transplantation. The store that sold the donor's pet hamster terminated purchases of other rodents. CDC is continuing its testing and trace-back efforts.

The benefits of organ donation outweigh risks, but the investigation resulted in several lessons learned. The public should be educated about hand-washing, proper cleanup and other safe pet handling procedures to prevent LCMV and other infections. Rapid communication with OPOs, clinicians and public health agencies is critical. Real-time syndromic surveillance of adverse events in transplant recipients is needed and plays an important role in identifying clusters of illness from a common donor.

The participants made two recommendations based on the LCMV investigation. First, UNet should be programmed to require immediate entry of deaths. This strategy will assist in more rapid detection of deaths of recipients who undergo organ transplants from a common donor in multiple hospitals throughout the country. Second, transplant centers should redefine guidelines for autopsies because many transplant-related infections are discovered by the autopsy. Most notably, clinicians should inform family members who consent to organ donation about the critical need and importance of an autopsy on the deceased patient.

## **Closing Remarks**

Dr. Kuehnert confirmed that the participants will most likely be involved in future discussions and activities to advance the overall organ and tissue safety process. He thanked the participants for their valuable input and helpful recommendations during the workshop. The participants applauded Dr. Kuehnert, the planning committee and CDC's administrative staff for convening an extremely informative meeting.



## ATTACHMENT 1

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## ATTACHMENT 2

### List of Acronyms

AABB	—	American Association of Blood Banks
AATB	—	American Association of Tissue Banks
ACBSA	—	Advisory Committee on Blood Safety and Availability
AOPO	—	Association of Organ Procurement Organizations
BOOT	—	Blood, Organ and Other Tissues
CDC	—	Centers for Disease Control and Prevention
CJD	—	Creutzfeldt-Jakob Disease
CMS	—	Centers for Medicare and Medicaid Services
CMV	—	Cytomegalovirus
CSF	—	Cerebrospinal Fluid
EBAA	—	Eye Bank Association of America
EBV	—	Epstein-Barr Virus
EIDs	—	Emerging Infectious Diseases
FDA	—	Food and Drug Administration
GAS	—	Group A Streptococcus
GTPs	—	Good Tissue Practices
HBV	—	Hepatitis B Virus
HCTPs	—	Human Cells, Tissues and Cellular- and Tissue-Based Products
HCV	—	Hepatitis C Virus
HHS	—	Department of Health and Human Services
HIPAA	—	Health Insurance Portability and Accountability Act
HRSA	—	Health Resources and Services Administration
HTLV	—	Human T-Lymphotropic Virus
IOM	—	Institute of Medicine
ISBT	—	International Society of Blood Transfusion
JCAHO	—	Joint Commission on Accreditation of Healthcare Organizations
LCMV	—	Lymphocytic Choriomeningitis
NATs	—	Nucleic Acid Tests
NIH	—	National Institutes of Health
OPOs	—	Organ Procurement Organizations
OPTN	—	Organ Procurement and Transplantation Network
PHS	—	Public Health Service
RPR	—	Rapid Plasma Reagin
RCDADs	—	Relevant Communicable Disease Agents or Diseases
SARS	—	Severe Acute Respiratory Syndrome
UNOS	—	United Network for Organ Sharing

VDRL — Venereal Disease Research Laboratory  
WBH — William Beaumont Hospital  
WHA — World Health Assembly  
WHO — World Health Organization  
WNV — West Nile Virus