Quality activities associated with hospital tissue services

C.M. Hillberry and A.J. Schluetter

Quality assurance is a vital component of a tissue service that aims to meet regulatory requirements and provide safe and functional tissue for surgical procedures in the institution. Many hospital transfusion services have or are in the process of assuming tissue service functions for their institutions, and the concepts of tissue quality assurance requirements should be familiar to the transfusion service. This review discusses the key aspects of tissue service quality assurance, including requirements for FDA registration, selection and qualification of tissue suppliers, recordkeeping, management of occurrences and tissue recalls, adverse event reporting, audits, and quality control. Comparing the similarities and differences between tissue and blood component regulatory requirements suggests transfusion service processes can be readily adapted to incorporate quality assurance for tissue service activities.


Key Words: tissue service, quality assurance, records, recalls, adverse event reporting, supplier qualification

With the implementation of the US Food and Drug Administration (FDA) current Good Tissue Practices (cGTP) tissue regulations on May 25, 2005, and the introduction of the Joint Commission accrediting standards on July 1, 2005, many transfusion services are overseeing their hospital's tissue service functions. Additional accrediting agencies (e.g., AABB and College of American Pathologists) may also be inspecting tissue service activities as part of their overall laboratory inspection. Thus, quality assurance personnel in transfusion services, who are very experienced in activities related to qualifying suppliers, product tracking, recalls, and event reporting, are assuming similar tissue service responsibilities. Transfusion services can incorporate many of the tissue activities into their current procedures; however, some procedures may need to be created or modified. From registration to adverse event reporting, this review discusses aspects of quality assurance needed for a tissue service, with a focus on allograft tissue requirements, for comparison with similar functions required for a transfusion service.

FDA HCT/P Registration

Who must register?

Similar to the requirement for blood components, the FDA requires all manufacturers of products containing or consisting of human cells or tissues (HCT/Ps) intended for implantation, transplantation, infusion, or transfer into a human recipient to register. Manufacturing is defined as any step in the recovery, processing, storage, labeling, or distribution of any human cell or tissue, and the screening or testing of the cell or tissue donor. Hospital transfusion services that also provide tissue services commonly store purchased allograft bone, ligament, skin, heart valve, and cornea for use within their facilities.

Hospital tissue services are exempt from the FDA HCT/P (tissue) registration requirements if they only perform the following tissue activities:

- Autologous bone (or other autologous tissue) is removed during a surgical procedure and then stored until implantation into the patient at a future date within the same facility.
- Autologous tissue is removed and stored at another establishment until future implantation at the facility that harvested the tissue.
- Allograft tissue is received from a supplier and stored by the tissue service for use in surgical procedures only at that facility.

If the tissue service serves as a distributor to another facility or to another physical location under the same management, tissue registration is required. For example, if an autologous bone removed during a surgical procedure at one facility is transferred to another facility for implantation, or if purchased allograft tissue is shipped directly to another hospital, the shipping tissue service must register with the FDA.

What is the registration process?

If the tissue service performs a manufacturing step that is not one of the exempt activities, it must register with the FDA by using Form FDA 3356. The registration form can be obtained by writing to the Center for Biologics Evaluation and Research (CBER) or downloading the form at www.fda.gov/opacom/morechoices/fdaforms/cber.html. The tissue service, like the transfusion service, is required to provide facility contact information, types of tissues manufactured, manufacturing steps performed at the facility, and the contact information of the reporting official. Even though tissues may be handled or manufactured by various units within the hospital, one tissue registration may be submitted that includes all tissue activities performed at the facility. For example, allograft surgical tissue, hematopoietic stem cells, and reproductive tissue may be managed independently in the hospital, but all could be reported to the FDA in a single tissue registration. The tissue registration must be updated annually, in December, or within 5 days of initiating any new manufacturing function.
Qualification and Selection of Tissue Suppliers

Hospital transfusion services have policies and procedures for selecting and qualifying blood component and reagent suppliers that can be expanded to encompass tissue suppliers. A common difficulty encountered when qualifying tissue suppliers is that many of the companies selling tissue products are not the manufacturer but simply a distributor of the product. This makes it difficult to determine whom to qualify as the supplier, especially with the frequent buyouts and mergers that occur in the tissue industry. In some cases the distributor can be qualified independently, but in other instances the distributor will refer the tissue service to the parent manufacturing company for much of the information necessary to complete the qualification. When qualifying a supplier (either a distributor or manufacturer), predetermined selection criteria must be defined. Selection criteria are used to evaluate the quality of the products produced by the manufacturer by reviewing items described in Table 1. Additional secondary selection criteria may also be considered as described in Table 2. The secondary selection criteria assess factors that may facilitate administrative interactions with the supplier and can be useful in distinguishing among several companies that provide products of similar quality.

Many companies have information on their Web sites, including state licenses, product information, package inserts, and accreditation certificates. A public query function on the FDA Web sites (www.fda.gov/cber/tissue/tissreg-data.htm) allows anyone to search for a company’s tissue registration information. Product recalls can also be found on the FDA Web site at www.fda.gov/opacom/Enforce.html. It may be useful to contact the manufacturer’s quality assurance department through a phone call or by sending a supplier questionnaire to obtain any additional information needed to complete the qualification. In rare instances, the tissue service’s medical director may request an on-site audit of the manufacturer, after review of the Form FDA 483s received by the manufacturer or after a recall of any of its products. However, some tissue manufacturers may not allow customers to observe some of their practices, to protect proprietary processes.

Periodically after the initial selection and qualification, the tissue supplier’s performance should be reevaluated. Reevaluation may include items from the initial qualification as well as clinical feedback from the surgeons (e.g., ease of tissue use, clinical effectiveness of the tissue) and supplier performance issues (e.g., timely product delivery, product back orders).

Tissue Tracking Records

A key task in tissue management is accurate tracking of tissue movement in and out of the inventory. The tissue service must be able to track the tissue from the time of receipt into the facility until the final disposition (implantation, return to the supplier, or disposal), analogous to the requirement for blood component tracking for transfusion services. Tissue tracking should also include documentation of all instances in which the tissue was sent to patient care areas under established storage conditions and returned to inventory after meeting acceptance criteria. Tissue storage and transport conditions are based on the manufacturer’s storage and handling instructions and the storage time determined for the validated transport containers. This information must be communicated to the surgical areas and ideally incorporated into the nursing policies for tissue handling. The tissue service also establishes criteria for accepting returned unused tissues into inventory. The acceptance criteria may include the length of time in the validated transport container, inspection of package seals, tissue container integrity, and product temperature (e.g., product remains frozen).

The ability to track all tissue is essential in the event of a product recall that may require patient notification. Tissue tracking may use electronic or paper records, but any tracking method must contain several key pieces of information. These include the unique identifier (donor identification number, lot number), final disposition, tissue supplier, and the patient name and identifier if the tissue was implanted. The tissue service may receive several pieces of tissue with

Table 1. Qualification criteria

| Types of tissues manufactured |
| FDA Form 483 citations and corrective actions |
| Manufacturing processes (including current FDA registration for the manufacturing steps performed) |
| Qualifications of contract companies performing manufacturing steps (e.g., tissue recovery, laboratory testing) |
| Written quality program |
| Nature of product recalls |
| Clinical Laboratory Improvement Amendments (CLIA) certification |
| Licensed by the state if applicable (CA, FL, MD, NY) |

Table 2. Additional selection criteria for tissue suppliers

| Nature of tissue tracking system |
| Product cost and expiration dates |
| Customer service (product return policy, availability of product) |
| Method for monitoring contracted companies |
| Method of tissue recall notification |
| Accreditation by American Association of Tissue Banks (AATB) or Eye Bank Association of America (EBAA) |
| Method for adverse event reporting |
| Allowance for customer audits |
the same donor identifier and lot number from the same supplier. Each of these tissues must be tracked individually. If the tissue service decides to assign new identification numbers, the original identification number must remain part of the tracking record. Alternatively, a subunit number may be added to the original identification number so that the original number remains part of the final tissue identification.

Commercial tissue tracking software is available to assist the tissue service in tracking tissue inventory from tissue receipt to final disposition. Some programs have the capability of data entry through the use of bar code scanning. The data can be quickly retrieved from such programs in the event of product recall or adverse event.

For tracking, recall, and billing purposes, the definition of an implanted tissue and a wasted tissue must be clear for both the surgical team and the tissue service. A conservative approach is to track any tissue that has been exposed to the patient (e.g., package opened in the surgical suite, tissue placed on the patient and removed) similar to an implanted tissue because the patient may have been exposed to potential infectious agents from such tissue either by direct contact with the tissue or indirectly from surgical staff or instruments touching the tissue and then the patient during the surgical procedure. If this conservative approach is used for tracking purposes, the tissue service must still distinguish which tissues remained in the patient at the end of the case, as patients can only be billed for these tissues. Tissues to which the patient was simply exposed during the surgical procedure would be considered wasted for billing purposes. Thus, it is essential that the patient care staff communicate clearly to the tissue service whether the implanted tissue was left in the patient or the patient was only exposed to the tissue.

A key element in tracking tissues that is different from tracking blood component disposition is supplier notification of final tissue disposition. Many suppliers request that tissue services provide final tissue disposition information to them so that proper recall notification may occur if it becomes necessary. Some manufacturers use carbon copy notification forms, which facilitates retention of a copy of the completed form for tissue service records; however, currently there is no standard method or format for providing final tissue disposition information to the manufacturer. A variety of information may be requested such as patient demographics, surgeon name, date of final disposition, type of final disposition (e.g., implanted, wasted), facility contact information, and tissue identifier. Health Insurance Portability and Accountability Act (HIPAA) regulations allow the release of protected health information (PHI) to the tissue manufacturers without explicit patient consent for the purpose of routine product tracking and ultimately to enable product recalls, including locating and notifying individuals who have received recalled tissues. However, there is no requirement that the tissue service must release PHI when providing routine final tissue disposition information. If the tissue service chooses not to release PHI, in the event of a tissue recall it assumes responsibility for determining who received the recalled tissue, as the manufacturer would be unable to provide patient information with the recall notice.

The record retention time for tissue records is longer than the retention time for blood component records. The Joint Commission Accreditation Program standards require that several tissue records must be maintained for a minimum of 10 years or longer (if required by state or federal laws) beyond the date of distribution, transplantation, disposition, or expiration, whichever is latest. These tissue records include the tissue supplier, the original numeric or alphanumeric donor and lot identification, name(s) of the recipient(s) or the final disposition of each tissue, and the expiration dates of all tissues. Other records that are required to be retained for a minimum of 10 years are tissue storage temperatures, outdated procedures, manuals, and publications.

Management of Tissue Recalls

Tissue recalls are unlike blood recalls in that they often involve numerous tissues, and the tissues may have been handled by multiple companies at various steps between tissue procurement and distribution. Thus, for example, a tissue recalled by a parent company may have been distributed and labeled by a subsidiary, making the identity of the recalled item obscure. In the event of a tissue recall, the tissue manufacturer generally sends the recall notification to the entity that ordered the tissue (e.g., the hospital procurement service, the operating room, or the tissue service). The FDA also lists recalls at www.fda.gov/safety/recalls/default.htm and www.recalls.gov/. In addition, there are companies that compile recall notifications from multiple sources and distribute them to their subscribers. Subscribing to such a service may be useful to help ensure that the tissue service is aware of all pertinent recalls. The recall notification includes the reason for the recall, the description of the recalled tissue (catalog number, product name), and the tissue identification number and may also include how to handle any recalled tissue that may still be in inventory. Recalls are almost always voluntary on the part of the manufacturer, either because it discovered a problem or because the FDA raised concerns about the product. Only rarely does the FDA mandate a recall.

Regardless of whether the recall is voluntary or mandated, the same process should be followed by the tissue service. After receiving the recall notice, the tissue service should immediately check the current inventory for the recalled tissue and quarantine the tissue to prevent dispensing it for a patient. The quarantined tissue should then be discarded or returned to the manufacturer as instructed in the recall notification. After reviewing the available inventory, the tissue service should determine whether any of the recalled tissue was previously implanted.
The tissue service should have a recall policy that outlines how to handle the recall information and potential notification of the patients who have been affected. After reviewing the reason for the tissue recall, the tissue service medical director is responsible for determining when to notify the implanting surgeon. The medical director may determine that notification is not necessary in some circumstances, for example, if the patient is deceased or a minor error in labeling occurred that does not affect the tissue identity or integrity. Surgeon notification should include the reason for the recall, the patient information, recommendation regarding patient notification, and a request for information related to any medical complications from the implanted tissue. Patient notification may be deemed necessary by the tissue service medical director in the event that the patient’s health is at risk from the implanted tissue (e.g., positive microbial tested product, tissue donor tested positive for a communicable disease agent). If patient notification is deemed necessary and the surgeon does not want to notify the patient or no longer is on staff at the institution, the tissue service medical director should take the responsibility for notifying the patients. Notifications can occur through phone calls, hand-delivered letters to individuals at clinic appointments, or registered letters, depending on the specific situation. If the letters are sent to the patient through registered mail, the tissue service should be aware that a patient’s family member may sign for the letter and the patient may not be notified.7

Adverse Event Reporting

The FDA defines adverse reaction to tissue as a noxious and unintended response to any HCT/P for which there is a reasonable possibility that the HCT/P caused the response. Every hospital needs a process for identifying and reporting adverse events. Because adverse events may be acute or delayed in presentation the adverse event reporting process may involve several departments throughout the hospital.8 It is helpful to educate surgeons, the hospital epidemiology department, or even the patient’s primary care provider to encourage identification of potential tissue-related adverse events. Communication of the adverse event to the tissue service begins the investigation and reporting process.

One or more designated services within the hospital (e.g., hospital epidemiology, hospital quality assurance, tissue service) must be responsible for accumulating reports and investigating all tissue adverse events. In some hospitals, the tissue service is notified of any tissue-related adverse event and performs the investigation with consultation with other departments as needed. The tissue service medical director would then be responsible for review of the data related to the adverse event and determination of the likelihood that the tissue may be implicated. If tissue involvement cannot reasonably be excluded, the manufacturer should be notified.2 In turn, all manufacturers must report adverse events to the FDA if they are fatal, are life-threatening, result in permanent impairment of function or permanent damage to body structure, or necessitate medical or surgical intervention.4 Unlike tissue adverse event reporting, blood donor or recipient adverse event reporting only involves fatality reports. Adverse events may be related to either disease transmission or failure of intended tissue function. Examples of adverse reactions include bacterial or fungal surgical site infections, virus or cancer transmission, or increased intensity of medical care owing to the tissue implanted.

The manufacturer’s quality assurance department may request additional information from the tissue service including patient laboratory tests, patient medical history, and current patient status to assist them in their internal investigation. Again, all of this may be provided without violation of HIPAA regulations. It is ultimately the manufacturer’s responsibility to report the adverse event to the FDA; however, the FDA encourages health-care professionals to voluntarily report any adverse reactions related to a communicable disease through MedWatch using Form 3500 in addition to notification of the tissue manufacturer. If the tissue service is the tissue manufacturer (e.g., the harvesting facility for autologous tissue that has been shipped to another institution for implantation), the tissue service must submit a report within 15 days through MedWatch using FDA Form 3500A.9 The reporting process for adverse events related to blood components differs from the one for tissue in that the reports for transfusion-related fatalities are not submitted on a standardized form.

If the adverse event is related to the failure of a tissue to function as expected, the tissue service should begin its investigation by reviewing internal handling of the tissue. The investigation may include review of records related to the tissue integrity at set time points, including each time the product was issued and received into the inventory, as well as storage equipment temperature records. In addition to conducting an internal investigation, the tissue service should notify the manufacturer of the problem through the sales representative, a customer service line, or a manufacturer complaint form located on the manufacturer’s Web site.

It is essential that all adverse reactions be investigated and reported to the appropriate individuals. This information will allow the manufacturer to track recurring complaints about tissue problems and perform its own internal investigations. The FDA uses the information reported through MedWatch to determine whether a reaction is an isolated event or an emerging problem. Currently the United Network of Organ Sharing (UNOS) under a contract with the Centers for Disease Control and Prevention (CDC) is developing a system to allow easier reporting of adverse events and tracking of tissues between the tissue manufacturers and the hospitals. This system, called the Transplantation Transmission Sentinel Network (TTSN), will include five
key elements including registration of donors and recipients, reporting of adverse events, relay of information to regulatory and public health agencies, and community education. An electronic mechanism for tracking and sharing information between manufacturers and hospitals is being developed for TTSN. Pilot testing for this electronic reporting system occurred in the spring of 2008. A similar program, called the Hemovigilance Module, under the US Biovigilance Network, will track recipient adverse events associated with blood component transfusions.

Other Tissue QA Functions

The transfusion service can easily incorporate tissue into its current processes for auditing, occurrence management, and other quality control activities. Records can be audited for documentation of tissue receipt and acceptance into inventory, tissue implant information in the patient’s medical record, final disposition of the tissue (implanted, returned to the supplier, or wasted), and quality control of tissue storage devices. Observation audits can be performed for tasks such as preparing tissue transport containers, returning product into inventory, and notifying the tissue manufacturer of the tissue’s final disposition.

Occurrences involving tissues (e.g., equipment failures, deviations from standard operating procedures, supplier issues, documentation errors or omissions) can be tracked through the same occurrence management system currently used by the transfusion service for blood components. If the facility manufactures tissues, tracking may also include occurrences with product labeling, processing steps, and testing (microbial and infectious disease).

Quality control of equipment and testing is routine to the transfusion service, and similar functions are needed for the tissue service. In particular, monitoring of tissue storage conditions is essential as part of the verification that high tissue quality is maintained. The tissue service must store the tissues under the appropriate storage conditions as defined on the tissue package label. An accompanying review further discusses the intricacies of tissue storage. Some tissue suppliers require the tissue service to sign a statement that the tissues were maintained at the acceptable storage conditions. This acknowledgment may occur at the time tissues are returned to the tissue supplier or through a supplier consignment agreement.

Conclusions

Tissue service quality assurance functions are generally quite parallel to transfusion service quality assurance functions. They include tissue service registration with the FDA, qualification of suppliers, ensuring a robust tissue tracking process, management of recalls, and reporting of adverse events. With attention to minor differences between tissue and blood component requirements, tissue service quality assurance activities can readily be incorporated into the routine activities of a transfusion service quality assurance team.

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References


Christine M. Hillberry, BS, MT (ASCP), CQA (ASQ) Tissue Bank Coordinator, and Annette J. Schlueter, MD, PhD (corresponding author), Associate Professor, Department of Pathology, University of Iowa, 200 Hawkins Drive, Iowa City, IA 52242.