

Best Practices for Repositories I: Collection, Storage, and Retrieval of Human Biological Materials for Research

INTERNATIONAL SOCIETY FOR BIOLOGICAL AND
ENVIRONMENTAL REPOSITORIES (ISBER)

INTRODUCTION

THE DESIRE TO PRESERVE biological and environmental specimens for research purposes and to ensure species biodiversity require the development of methods for long-term storage that will enable their effective future use. Sharing successful strategies for accomplishing this goal was one of the early driving forces for the International Society for Biological and Environmental Repositories (ISBER). In addition, ISBER fosters education and research and promotes quality and safety in all activities relating to specimen collection, storage and dissemination.

ISBER's Best Practices for Repositories (Best Practices) reflect the collective experience of its members to provide repository professionals with a comprehensive foundation for the guidance of repository activities. These Practices reflect input from individuals within and outside ad hoc committees. Best Practices will be reviewed periodically and will be revised to reflect advances in research and technology. All revisions are subject to approval by the ISBER Council. These Practices reflect the most effective approaches to the establishment and running of specimen collection facilities and are not intended as required practices.

The focus of this first version of the ISBER Best Practices is on the management of human specimen collections. It is ISBER's intention to broaden the focus to include Best Practices surrounding other specimen types in subsequent versions. Likewise, because most of the initial contributions to this edition were from individuals based in the United States, the Practices described here primarily reflect U.S. perspectives. ISBER plans to broaden the scope of the Practices in future editions to include those from other nations in order to make this document more representative of international perspectives and experience.

These Best Practices are reviewed periodically and revised to incorporate improved application and research findings that would affect repository work. The reader is advised to check the ISBER website (<http://www.isber.org>) to ensure that the most recent version is available for use.

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SECTION A: GENERAL INFORMATION

A1.000 Adherence to ISBER best practices

Adherence to ISBER Best Practices is strictly on a voluntary basis. These Practices do contain references to U.S. regulations that are mandatory. The reader should refer directly to those regulations for the specific requirements contained therein, as appropriate.

A2.000 References to Best Practices

Throughout this document effective practices are presented for the management of specimen collections and repositories. In cases wherein a level of operation is indicated that is above the basic recommended practice, a designation of “Best Practice” is indicated.

A3.000 Definition of terms

Unless otherwise defined in another context in these Practices, important terms are defined below:

ACCIDENT—Any occurrence that deviates from Standard Operating Procedures (SOPs) or applicable government laws and regulations during specimen retrieval, processing, labeling, storage, or distribution that may affect subsequent use of those specimens.

ADVERSE OUTCOME—An undesirable effect or untoward complication consequent to or reasonably related to specimen integrity.

ALIUQUOT—A process wherein a specimen is divided into separate parts which are typically stored in separate containers as individual samples. The term aliquot may also be used as a noun to denote a single sample.

ASEPTIC PROCESSING—Processing of specimens using methods to restrict or minimize the potential contamination with microorganisms from the environment, processing personnel, and equipment.

AUDIT—A documented review of procedures, records, personnel functions, equipment materials, facilities, and/or vendors to evaluate adherence to written SOPs or government laws and regulations.

BATCH—A specific quantity of specimen that is intended to have a uniform character and quality, within specific limits, and is produced or processed according to a single processing protocol during the same processing cycle. (see LOT below)

CLEAN ROOM—A room in which the concentration of airborne particles is monitored and controlled to defined specification limits.

CODE OF FEDERAL REGULATIONS—Published by the Office of the Federal Register, National Archives and Records Administration, Washington, DC.

COLLECTION—See *RETRIEVAL*.

CONSIGNEE—Any individual, agency, institution, or organization that receives specimens and assumes responsibility for storage, dispensing, and tracking the disposition of specimens.

CONTAINER—Enclosure for one unit or units of specimen(s).

CONTROLLED AREAS—Restricted work areas of low microbial and particulate content in which nonsterile materials are prepared.

CRITICAL AREAS—Restricted work areas where containers and closures are exposed to the environment.

- CROSS CONTAMINATION*—The transfer of any part of one specimen to another specimen (e.g., microorganisms, blood, DNA, RNA, protein).
- CRYOPROTECTANT*—An additive that serves to minimize osmotic imbalances that occur with the progression of freezing fronts through a substance and is intended to limit the amount of cell damage due to cell shrinkage and intracellular ice formation.
- DEHYDRATION*—Removal of water from a tissue.
- DEVIATION*—An intentional or unintentional event that is a departure from a procedure or a normal practice.
- DISINFECTANT*—An agent that reduces the number of viable microorganisms.
- DISINFECTION*—A process that reduces the number of viable cellular microorganisms, but does not necessarily destroy all microbial forms, such as spores and viruses.
- DISPOSITION*—Final destination of specimens.
- DISTRIBUTION*—A process that includes receipt of request for specimens, selection of appropriate specimens, and final inspection, in conjunction with subsequent shipment and delivery of specimens to another repository, specimen collection center, or laboratory.
- DONOR*—Living or deceased individual who is the source of the specimen in accordance with established medical criteria, procedures, and privacy regulations.
- DRY ICE*—Solid-phase carbon dioxide.
- END-USER*—A health-care practitioner, scientist, or laboratory person who performs an appropriate procedure, test, or archival function for the specimen.
- EQUIPMENT QUALIFICATION STUDIES*—Protocols designed to adequately evaluate, prior to use, whether equipment will perform to expectations and function normally within tolerance limits.
- ERGONOMICS*—The science that explores human abilities and limitations and applies that knowledge to improve a person's interactions with their environment, tools, products, and practice.
- ERROR*—A departure from SOPs or applicable government laws and regulations during specimen retrieval, processing, testing, quarantining, labeling, storage, or distribution that might adversely affect the specimen.
- FREEZE DRIED/LYOPHILIZED*—Dehydrated for storage by conversion of the water content of a frozen specimen to a gaseous state under vacuum.
- INFORMED CONSENT*—A process by which information concerning the donation process is presented to the donor or donor's next-of-kin with an opportunity for them to ask questions, after which specific approval is documented.
- IN-PROCESS CONTROLS*—Any tests, samples, evaluations, monitoring, or measurements performed during processing or preservation that are designed to evaluate the processing or preservation procedure or the specimens subjected to processing or preservation for conformance to specifications in SOPs.
- IN-PROCESS MATERIAL*—Any material that is used in the processing of specimens, including, but not limited to, incoming specimens, water, alcohol, acid, containers, and closures.
- LABEL*—Any written, printed, or graphic material on or affixed to a specimen container or package.
- LIQUID NITROGEN DRY SHIPPER*—A container used for sending samples in the vapor phase of liquid nitrogen.
- LOT*—Specimens produced from one donor at one time using one set of instruments and supplies. Also refers to a quantity of reagents, supplies, or containers that is processed or manufactured at one time and identified by a unique identification number (see *BATCH* above).
- NEXT-OF-KIN*—Person(s) most closely related to a deceased individual as designated by applicable law, such as under the Uniform Anatomical Gift Act.
- PACKAGE*—A labeled carton, receptacle, or wrapper containing one or more containers and accompanying labeling material.

- PACKAGE INSERT*—Written material accompanying a specimen bearing further information about the specimen, directions for use, and any applicable warnings.
- POLICIES AND PROCEDURES MANUAL*—See Standard Operating Procedures Manual.
- POOLING*—Intentional physical contact or mixing of specimens from two or more sources into a single receptacle.
- PRESERVATION*—Use of chemical agents, alterations in environmental conditions, or other means during processing to prevent or retard biological or physical deterioration of a specimen.
- PROCEDURE*—A series of steps designed to result in a specific outcome when followed in order.
- PROCESS CONTROLS*—A system of checks and balances incorporated into standard operating procedures involving critical operations to prevent errors.
- PROCESS VALIDATION STUDIES*—The process of demonstrating that a specific procedure will consistently produce expected results within predetermined specifications.
- PROCESSING*—Any procedure employed after specimen collection but prior to its distribution, including preparation, testing, and releasing the specimen to inventory and labeling.
- PROCUREMENT*—See *RETRIEVAL*
- QUALITY*—Conformance of a specimen or process with pre-established specifications or standards.
- QUALITY ASSURANCE (QA)*—An integrated system of management activities involving planning, implementation, documentation, assessment, and improvement to ensure that a process or item is of the type and quality needed for the project. Same as Quality Management System (QMS).
- QUALITY CONTROL (QC)*—Specific tests defined by the QA or QMS Program to be performed to monitor procurement, processing, preservation, and storage; specimen quality; and test accuracy. These may include, but are not limited to: performance evaluations, testing, and controls used to determine accuracy and reliability of the Repository's equipment and operational procedures as well as monitoring of the supplies, reagents, equipment, and facilities.
- QUALITY MANAGEMENT SYSTEM (QMS)*—Same as Quality Assurance (QA) above.
- REMOVAL*—See *RETRIEVAL*.
- RETRIEVAL*—The removal, acquisition, recovery, harvesting, or collection of specimens.
- SAFETY*—Processes, procedures, and technologies to ensure freedom from danger or harm.
- SAMPLE*—A single unit containing material derived from one specimen.
- SHIPPING MANIFEST*—A written description of the contents of the shipped package.
- SPECIMEN*—A specific tissue, blood sample, *etc.*, taken from a single donor at a specific time.
- STANDARD OPERATING PROCEDURES (SOP) MANUAL*—A group of standard operating procedures (SOPs) detailing specific policies of a repository and the procedures used by the staff/personnel.
- STERILITY*—Absence of detectable, viable, contaminating microorganisms, as defined in the USP.
- STERILIZATION*—A physical or chemical process validated to destroy, inactivate, or reduce microorganisms to a sterility assurance level of 10^{-6} .
- STORAGE*—Maintenance of specimens for future use.
- T_g*—The Glass Transition Temperature. For cellular material, it is the temperature at which a cell is dehydrated to the degree that the remaining liquid within it is so viscous that molecules have insufficient energy to order themselves into a crystalline structure. Below this temperature (generally regarded as -132°C), no diffusion can take place within the cell and its surroundings. Without this diffusion, the biological "clock" stops.
- TOLERANCE LIMITS*—Limits that define a range of acceptable values that are established for each testing procedure, which, when exceeded, require the implementation of corrective actions designed to produce results within the acceptable range in future tests.

TRACEABILITY—The ability to locate a specimen during any step of its donation, collection, processing, testing, storage, and disposition.

A4.000 Abbreviations

Below is a list of abbreviations that are throughout this document:

2D—Two dimensional
ART—Administrator Responsible for Training
CDC—Centers for Disease Control and Prevention
CFR—Code of Federal Regulations
cGMP—Current Good Manufacturing Practices
CO₂—Carbon dioxide
DNA—Deoxyribonucleic acid
DOT—Department of Transportation
EDTA—Ethylenediaminetetraacetic acid
FDA—The United States Food and Drug Administration
GCP—Good Clinical Practices
GLP—Good Laboratory Practices
H&E—Hematoxylin–eosin
HIPAA—Health Insurance Portability and Accountability Act of 1996
IATA—International Air Transport Association
ICAO—International Civil Aviation Organization
IRB—Institutional Review Board
ISO—International Organization for Standardization
LN₂—Liquid nitrogen
MSDS—Material Safety Data Sheet
NIST—National Institute of Standards and Technology
NRC—Nuclear Regulatory Commission
OSHA—Occupational Safety and Health Administration
PEL—Permissible exposure limit
PHI—Protected health information
QA—Quality assurance
QC—Quality control
QMS—Quality management system
RBC—Red blood cell
RNA—Ribonucleic acid
SCBA—Self-contained breathing apparatus
SOP—Standard operating procedures
T_g—Glass transition temperature
UPS—Uninterruptible power supply
USP—United States Pharmacopeia
USPHS—United States Public Health Service

SECTION B: GENERAL ORGANIZATIONAL REQUIREMENTS OF A REPOSITORY

B1.000 General institutional requirements

B1.100 Institutional identity and affiliations: The purpose of the Repository should be clearly formulated and documented. It should be defined as to whether it is a freestanding entity, virtual, or part of an institution. The Repository should have sufficient professional staff and a com-

mitment to maintain, operate effectively, and preserve records and operating procedures for future reference and historical continuity.

B1.200 Contracted laboratory services: Repositories that contract for laboratory services should retain in their records the name and address of the contracted facility and documentation of the inclusive dates of the contract period.

B2.000 Functional components of a repository

B2.100 Director

B2.110 Qualifications: The Director should be qualified by training and experience to fulfill the scope of activities conducted by the Repository.

B2.120 General Operations: The Director should implement policies of the organization and should be responsible for all operations, including compliance with current and applicable regulations. This individual should ensure that repository activities are in compliance with national, state, and local authorities. Depending upon the Repository, the Director may have other responsibilities including: (i) ensuring that the Repository operates within budget (at an academic institution this would entail securing funding for the Repository either by writing external grants or securing contracts with clients); (ii) ensuring that all patient consent forms are updated annually to be in compliance with IRB regulations and serving as a liaison for the IRB; (iii) serving as a liaison for researchers within an academic setting, this would include ensuring that tissue needs are met in a timely fashion; (iv) serving as a liaison for hospital staff (surgeons, nurses, operating room staff, pathologists, and residents), this would include ensuring that patient issues are addressed and that Repository staff are responding in an appropriate manner.

B2.130 Personnel: The Director should construct and maintain a current organizational chart that delineates the functional relationships within the Repository. Members of the supervisory and technical staff should be appointed and directed by the Director.

The Director should approve and maintain job descriptions and should document staff responsibilities. The Director should ensure that personnel responsible for performing repository activities are adequate in number, have adequate experience, and should be assigned responsibilities commensurate with their capabilities.

The Director should also be responsible for developing and reviewing employee training programs and should ensure that there is an appropriate and acceptable safety program.

B2.140 Quality Assurance Program/Quality Management System: The Director or other responsible party should ensure that a Quality Assurance Program (also termed a Quality Management System) is in place to make certain that the entire operation conforms to the Repository's SOPs, necessary audits, and government regulations. It is good practice for the QA/QMS Program staff to report independently of the Director. The Director should, however, require regular documented internal reviews or audits to ensure compliance with the SOPs and regulations.

B2.200 Technical staff

B2.210 Qualifications: Staff must possess sufficient educational background, experience, and training to assure that assigned tasks are performed in accordance with the Repository's established procedures.

B2.220 Responsibilities: Technical staff should be responsible for implementation of policies and procedures as established by the Director. Duties of each staff member should coincide with

written job descriptions. Staff must demonstrate competency in operations for which they have received training and to which they are assigned. Authority and reporting relationships for each member of the staff should be clearly described.

SECTION C: RECORDS MANAGEMENT

C1.000 General

Each Repository should develop a record management system that permits detailed records to be made concurrently with the performance of each step in the collection, processing, and distribution of specimens. This may include, but is not limited to: informed consent, procurement, processing, preservation, quarantining, testing, record review, releasing, labeling, storage, distribution, and quality control of specimens. Records should be created and maintained in a manner that allows steps to be traced clearly. Record security systems should be adequate to ensure confidentiality and safety. It is recommended that confidential patient documents be stored in locked filing cabinets in locked rooms with limited access.

C1.100 Availability for inspection: Records should be readily accessible for inspection by authorized personnel from regulatory agencies and Quality Assurance (QA) personnel. Access to donor identity and medical, social, and other personal histories should be restricted to Repository staff with a need for access and inspectors from regulatory agencies.

C1.200 Record retention: Collection, processing, storage, distribution, and QA records should be maintained for a minimum of 10 years after the last expiration of the specimens involved. When there is no expiration date, records should be maintained for 10 years after the date of distribution.

C1.300 Security: Electronic records should be backed up daily on a network or remote server and weekly on a CD, diskette, or other appropriate media. Consideration should be given to establishing an arrangement with an offsite data security company that retrieves and stores all critical data at a remote location.

C1.400 Archival system: A Repository may develop a system for archiving records that are older than one year and fewer than 10 years as defined in Section C1.300. This system should be accessible for audits and inspection as defined in Section C1.200.

C1.500 Corrections and/or changes: Corrections or changes in a record should be made with a single line drawn through the altered text. Corrections should be initialed and dated by the individual making the correction or change. Changes in electronic records should be noted and tracked.

SECTION D: FACILITIES

D1.000 General

An efficient Repository has many design elements to ensure the safe keeping of the material being stored, support the equipment employed, and provide a safe and efficient working environment for the repository operators. Knowledge of the types of material being stored, the required storage conditions, the projected retention periods, and the projected use of the materials is essential to good repository design. The Repository design should include sufficient space

to accommodate the material being preserved and provide for the safe movement of people, equipment and specimens as needed.

D2.000 Heating, ventilation, and air conditioning (HVAC)

D2.100 Temperature: In most repositories ambient temperature is a major consideration. In most cases sufficient heating capacity must be provided to prevent freezing of water and drain lines. More commonly, heat is the problem. Where mechanical freezers and refrigerators are employed, sufficient air conditioning must be provided to maintain the ambient temperature equal or less than 72°F (22°C) at the level of the freezers/refrigerators. This is necessary to prevent excess load on the compressor systems and associated excess wear and early failure.

D2.200 Air flow and circulation: Sufficient air circulation and control must be provided to prevent excess moisture and condensation. Left unchecked, excess humidity can lead to fungal growth, which can render a repository great harm. Sufficient space for air circulation is required, especially in areas where freezers and refrigerators are employed, to prevent excess heat accumulation that may negatively affect compressor function. Adequate ventilation is also critical in liquid nitrogen (LN₂) repositories and where dry ice is used to ensure that sufficient oxygen levels are maintained (see Section E5.270 on oxygen sensors, as well as Section E5.600 on dry ice).

D3.000 Lighting

D3.100 General lighting: Lighting in a repository must be sufficient to provide a safe working environment and to allow materials to be put away and retrieved accurately. Lighting levels required will depend on the type of storage conditions, the size and type of material being stored, and the labeling/identification system employed. Lighting may be both general and task, depending on the situation. General area lighting may be incandescent, fluorescent, metal halide, or other. Some repositories may contain materials that are sensitive to light levels or frequencies/color temperature. In these instances, adjustments to limit levels or frequency must be made.

D3.200 Task lighting: Task lighting may be necessary to get sufficient illumination for tightly stored materials, reading small labels, or where overhead lighting is impaired. Where task lighting is employed, care must be taken that the lighting method does not adversely affect the storage conditions. For example, the heat from incandescent task lighting placed too close to stored material can cause thawing in samples. Fluorescent lighting is generally recommended for task lighting of frozen materials.

D4.000 Security systems

D4.100 General: The purpose of any repository is the safekeeping of the materials. To that end every repository should employ basic security systems. The systems must be monitored and alarms responded to 24 h per day, 7 days per week. Response systems must be in place such that a responsible individual can take the necessary action to respond to an alarm in a time frame that prevents or minimizes loss or damage to the collection materials. Systems should allow for calls to other key staff from a list of staff phone numbers when the first individual fails to acknowledge the alarm. Emergency contact numbers should be posted in prominent locations in the repository.

D4.200 Fire

D4.210 Sprinkler Systems: A fire prevention system is required by building codes for new construction, and compliance with code is normally required if a facility is being converted or renovated. The most common type of fire suppression is the water sprinkler system. The standard

system has water in the pipes at all times. Excess heat causes the system to activate, spraying water into the area.

When computer equipment and electrical systems are in place, a pre-action sprinkler system can be employed. In a pre-action system, the sprinkler pipes are dry until a fire is detected. This type of system prevents water damage from accidental activation of the sprinkler system.

D4.220 Non-water-based fire retardants: Due to the nature of certain equipment and stored materials, water is an unsuitable fire-suppression mechanism. In these instances, other chemicals are employed. The fire-suppression mechanism generally smothers the fire by cutting off the supply of oxygen. These systems are very effective. However, they are costly and pose some safety hazards. Personnel must be trained to evacuate the area immediately to prevent asphyxiation. For high-value materials and those samples that would be adversely affected by exposure to water, these nonaqueous systems are necessary.

D4.300 Access: Repositories should be equipped with a system that adequately limits access to appropriate staff and protects against physical intrusion. Doors should be locked. Keys should be controlled, with a record maintained of each person having access to the Repository. Keys that cannot be readily duplicated are highly preferred. Only persons assigned to the repository operations should have access to the material stored within. Freezers or environmental storage equipment that store valuable or sensitive specimens should be individually locked.

Best practice: Magnetic locks should be placed at critical entry points that control and record entry by individuals.

D4.310 Intrusion detection systems: When the facility is not occupied by authorized personnel, it should have an alarm system to monitor unauthorized entry. Motion detectors and door entry sensors should be integral components of the system. The alarm system should be monitored 24 h per day 7 days per week.

The most desirable set up is a Building Automation System that integrates all security and monitoring in a single system. The system should accommodate changes to security codes and keys when individuals leave the organization.

Best practice: A hierarchal system of security that employs multiple levels of physical, electronic, and procedural controls. For example, the repository material may be in a restricted area that employs electronic sensors when the area is unoccupied, where the freezers are locked, and the keys maintained in a cabinet which is locked.

D5.000 Back-up power

D5.100 Uninterruptible power supplies: Repositories, with exception of those that house only non-temperature-sensitive materials, require a constant source of electrical power. Given that all commercial power will fail at some time, a back-up power system is required.

Best practice: Computer systems and electronic systems, such as freezer controllers, should also be protected by an uninterruptible power supply (UPS) system.

D5.200 Generators: The most common type of back-up power is the motor generator. These units, typically fueled by diesel, natural gas, or propane, have automatic controls that start them when commercial power is lost. A generator must have a fuel supply to run continuously for a minimum of 48 h and preferably a minimum of 72 h, with an ability to resupply fuel storage supplies. Natural gas supplied by a pipeline may serve as an unlimited source, provided supply lines are not interrupted.

D5.210 Generator tests: For a back-up power system to function reliably when needed, it must be tested routinely to insure that the system will start on demand, and carry the required load. The generator system must be tested for automatic starting and power generation monthly and load tested quarterly.

Best practice: The power generator system should be tested for automatic starting and power generation weekly and load tested monthly (unless sensitive laboratory equipment is also supported by this generator. In this case, monthly load testing may be too frequent.)

SECTION E: OPERATIONS

E1.000 Standard operating procedures manual

E1.100 Purpose and design: Each Repository should develop written policies and procedures in a standardized written format that should be incorporated into a Standard Operating Procedures (SOP) manual. The SOPs should state policies and define and describe in detail all procedures. These SOPs should be utilized to ensure that all samples are appropriately stored so that they may be effectively disseminated for subsequent research and other uses.

E1.200 Contents: The SOP manual should specifically include, but should not be limited to:

- Specimen handling policies and procedures including supplies, methods, and equipment.
- Laboratory procedures for tests performed in house and any specimen aliquoting or other specimen processing.
- Policies and procedures for shipping and receiving specimens.
- Records management policies. This should include policies regarding the shredding of confidential documentation at the appropriate time.
- Quality assurance and quality control policies and procedures for supplies, equipment, instruments, reagents, labels, and processes employed in sample retrieval and processing.
- Policies regarding safety programs. These would include pre- and post-employment medical evaluations and immunization records.
- Emergency and safety policies and procedures, including reporting of staff injuries and exposure to potential bloodborne pathogens.
- Policies and procedures for the investigation, documentation, and reporting of accidents, errors, complaints, and adverse outcomes.
- Policies, procedures, and schedules for equipment inspection, maintenance, repair, and calibration for the purpose of maintaining equipment.
- Procedures for disposal of medical waste and other hazardous waste.
- Policies and procedures describing requirements of training programs for technical and QA staff.

E1.300 Implementation: Either the Repository Director and/or the individual responsible for the Quality Assurance Program should review and approve all SOPs and associated process validation studies prior to implementation. Upon implementation, all SOPs must be followed as written.

E1.400 Modifications: Each repository should have document control policies in place that govern modifications or revisions to SOPs. Prior to implementation, each modification should be approved by the Director and other appropriate individuals. Implementation dates should be recorded for all procedures.

E1.500 SOP review: All SOPs should be reviewed every 2 years.

E1.600 Staff access and review: Current copies of the SOP manual should be stored in designated locations and available to the staff at all times. New and revised policies and procedures should be reviewed by the staff prior to implementation. Documentation of staff review and any associated training should be maintained in a Training Record.

E2.000 Freezer and refrigerator monitoring

The operation of all freezers and refrigerators must be monitored. The function and temperature of each storage unit should be checked and recorded each work day. All storage units must have a mechanism to generate an alarm in the event established temperature ranges are exceeded.

All storage units should have a temperature-monitoring device that can be read and recorded. Dual or multiple temperature-sensing devices are preferred.

Continuous monitoring systems should be in place for all low-temperature storage units. Alarm conditions should be responded to in a time frame to ensure that no damage to the stored material occurs. Personnel with adequate training who can take corrective action should be on call 24 h per day, 7 days per week.

Best practice: Employ an automatic system that continually monitors all temperatures and critical parameters, creates logs, and can generate alarms and notify personnel to take action. The alarm notification should be active not passive; that is, the system should call or page the individual on call (or activate the “on call” list) rather than providing passive notification such as a message on a computer screen, which must be sought after by the monitor. It is recommended that more than one individual carry a pager at all times, in case the first pager called is not functioning or that the individual is in a location where they cannot respond to the notification.

E3.000 Inventory verification

A random check of the specimen inventory system (database) should be conducted on a small percent of samples on an annual basis. This verification will confirm that the appropriate specimens are in the correct freezer locations, as indicated by the computerized inventory system.

E4.000 Emergency preparedness

The facility should have in place an emergency preparedness plan that addresses a wide variety of unlikely, but possible, emergencies. This would include such natural disasters as earthquakes, hurricanes, tornados, flood, fire, terrorist activities, or political demonstrations.

E5.000 Storage environments

E5.100 Back-up storage capacity: Adequate back-up capacity for low-temperature units must be maintained in anticipation of possible equipment failure. Extra capacity equal at a minimum to the capacity of the largest single storage unit must be maintained at operating temperature at all times. This applies to each temperature storage condition. The total amount of back-up storage required for large repositories must be determined empirically, but will typically be 1.5–3% of the total freezer capacity.

Personnel must be trained in processes and techniques for rapidly transferring material to back-up units when necessary.

Best practice: A process should be in place for updating records of the specimen transfer, documenting the event, and corrective action taken.

E5.200 Cryogenic freezers

E5.210 Liquid nitrogen supply: Where LN₂ refrigeration is employed, an adequate supply of refrigerant must be maintained. For freezers filled from Dewars or supply tanks, a minimum 3-day supply of LN₂ at normal usage and replenishment intervals should be maintained, with the assumption that a resupply is readily available. The supply maintained on hand should be at least 20% more than the normal refill usage to allow for emergency situations. Bulk supply systems should maintain a minimum supply of 20% of the bulk tank capacity, or greater than 3 days working capacity, assuming a ready resupply system.

When bulk storage and piping systems are used, another hazard is potentially present. These systems require relief valves to prevent rupturing of the pipe and bulk tanks in the event of over pressure. If relief valves trip unexpectedly, a person near a valve can be sprayed with either the cold gas or the liquid. More likely, in the event of a blockage or overpressure event, a number of relief valves will vent nearly simultaneously. This can cause a “white-out” condition in a matter of a few seconds. Visibility drops to near zero and the oxygen level in the area may become less than that necessary to sustain life. Personnel must evacuate immediately. This unlikely event, which is usually caused by an error during the filling of the bulk tank, can be mitigated by well-designed procedures and practices.

Best practice: Self contained breathing apparatus (SCBAs or “air packs”) should be available for use in the event of a “white out” condition in the repository. If a SCBA or other respiratory protection gear is used, compliance with OSHA’s Respiratory Protection Standard is mandatory (29 CFR 1910.134). Certification of SCBAs is required. Personnel should receive training on the effective use of these units. In the event of an emergency, staff should evacuate the facility immediately and not return until the environment is safe.

E5.220 Liquid nitrogen freezers: The use of LN₂ freezers for long-term specimen preservation is optimal only if the operating conditions within the freezer are less than the critical storage temperature. The critical temperature for storage of sensitive organisms and cells is generally considered to be -140°C or below. Care must be taken that the desired temperature is maintained in the vessel in which critical material is stored. Many LN₂ freezers, especially older models, cannot consistently maintain -140°C at the top of the tank. Staff should be aware that the temperature of the freezer increases slightly (some newer freezer models are more efficient with respect to temperature loss) each time the freezer is opened and specimens are either placed in storage or removed from storage. Care must be taken to minimize the number of times a freezer is opened within a given time frame.

Best practice: Some type of temperature map of the freezer should be conducted on a periodic basis to verify the temperature at various locations within the freezer.

E5.230 Vapor-versus liquid-phase storage: Vapor-phase storage is preferred over liquid-phase storage. Properly selected and operated freezers provide sufficiently low temperature to maintain a good safety margin below T_g, and have sufficient refrigerant storage capacity to avert any accidental warming. Use of vapor phase avoids the safety hazards inherent in liquid-phase storage. Also, there is documentation of disease transfer via the liquid phase where primary storage containers were not hermetically sealed and the LN₂ became contaminated. Note that storage in either vapor or liquid carry specific requirements for freezer design that must be considered when the decision for vapor versus liquid is made.

E5.240 Selection of appropriate storage containers: LN₂ expands to 700 times its original volume when brought to a gaseous phase at room temperature. This situation produces a form of ex-

plosion hazard. Plastic and glass containers can easily explode if LN₂ is trapped when the container is removed from the freezer. Good practice dictates that any container that has potentially been in the liquid phase be allowed to equilibrate in the gaseous phase of the freezer prior to removal.

E5.250 Alarm systems: Alarm systems should be set to monitor the LN₂ level and temperature. Alarm set points should be established that will permit sufficient time for corrective action before significant warming occurs.

E5.260 Protective wear: Use of LN₂ as a refrigerant poses special safety problems. With a liquid temperature of -196°C , flesh freezes almost instantly if it comes in direct contact with the liquid. Because it is a liquid, it can splash, and therefore requires the use of face and eye protection. Heavy gloves, a face shield, and a protective garment should always be used when handling LN₂.

E5.270 Oxygen sensors: Because nitrogen displaces oxygen, care must be taken when LN₂ freezers are employed. The risk is inversely correlated with the size of the room. Oxygen level sensors should always be employed when LN₂ freezers are used in a repository. Both installed and mobile/personal monitors may be appropriate, depending on the size of the facility. Even when installed units indicate an alarm condition, it may be useful to employ a personal monitor to enter the room carefully to validate the alarm condition if the area is not visible from the outside. Mobile oxygen monitors may be the best to use in a secure area where LN₂ freezers operate because the sensors in installed units will degrade over time and sound false alarms.

E5.300 Mechanical freezers: Mechanical freezers are employed in a variety of storage temperature ranges, including -20 , -40 , -70 to -80°C , and occasionally -140°C . Mechanical freezers come in a wide variety of sizes, configurations, and operating electric voltages.

Because mechanical freezers are devices attached to commercial power systems, a back-up power plan and an emergency response plan must be in place. The length of time that results in the significant warming of the stored material will vary by the properties of the stored material, the thermal loading of the freezer, the ambient conditions, and the design and maintenance of the unit. It is incumbent on the facility operator to establish the critical temperatures and response times to alarms.

Common practice is to set the alarm point at about 10°C warmer than the nominal operating temperature of the unit. This allows for normal operating variation and some leeway for warming when the material is accessed.

E5.400 Refrigerators: Refrigerators are commonly employed where the life of the material being stored is enhanced by storage below ambient temperature. This is the preferred storage medium when the material must be kept cool, but is damaged by freezing. In refrigerator operation, it is important to ensure that the temperature is maintained within the specified operating range, not just below a maximum temperature. Some high-value materials, vaccines for example, must be maintained precisely between 2°C and 8°C . The facility operator must insure that high and low set points are monitored and that alarm response time is adequate to prevent excessive temperature excursions.

Best practice: For high-value materials, the refrigerators should be equipped with dual compressors that operate under an electrical alternating control system.

E5.500 Safety features for walk-in freezers and refrigerators

E5.510 Door release: Walk-in freezers and refrigerators entail special hazards. All building codes require that these units have safety releases to prevent a person from being trapped in a unit by accidentally closing doors (*i.e.*, interior door release mechanism).

E5.520 Floor covering: Refrigerators can generate slipping and falling hazards if water condenses on the floor. Freezers can occasionally create ice on the floor. Both types of units should have some type of mat or grate to prevent slipping.

E5.530 Dry ice: Walk-in freezers should be kept free of dry ice (*i.e.*, the solid phase of CO₂). CO₂ can rapidly build up, displace the oxygen in the room, and cause personnel working in the units to lose consciousness.

E5.600 General use of dry ice: Dry ice is frequently used as a refrigerant for shipping and emergency back up for mechanical freezers. Handling precautions (*e.g.*, wearing insulated gloves) should be employed when handling this material, the temperature of which is approximately -79°C. As dry ice sublimates, the CO₂ level in the surroundings can increase. In confined areas the CO₂ can displace oxygen, presenting an asphyxiation hazard. Where dry ice is employed, engineering controls to insure sufficient air or oxygen level monitoring are required.

E6.000 Maintenance

E6.100 General: A system for maintenance and repair of storage equipment, supporting systems, and facilities should be in place. Preventative maintenance should be in place for all operations and facility systems. System maintenance should be performed at regular, established intervals per manufacturer's recommendation.

Best practice: Maintenance records should provide a description of work that was done, tests that were performed, and the results compared to the standards.

E6.200 Calibration: A system for the calibration of all instruments should be in place. Any device that provides a readout, data, or has a meter movement, is considered an instrument, and requires calibration. Calibration should be done annually or per manufacturer's recommendation. Calibration should be performed against standards, such as those published by the National Institute of Standards and Technology (NIST).

Best practice: Calibration records should include the appropriate standard readings taken both before and after calibration.

E6.300 Validation: All equipment should be validated prior to use or following repairs that affect the instrument's measuring capabilities.

Best practice: A validation procedure should be in place to verify the operation of all new or repaired equipment. Documentation of the testing should be maintained.

SECTION F: QUALITY ASSURANCE AND QUALITY CONTROL

F1.000 Definitions

F1.100 Quality assurance: Quality assurance (QA) is an integrated system of management activities involving planning, implementation, documentation, assessment, and improvement to

ensure that a process, or item, is of the type and quality needed for the project.

F1.200 Quality control: Quality control (QC) is the system of technical activities that measures the attributes and performance of a process, or item, against defined standards, to verify that the stated requirements are fully met.

F2.000 Quality assurance program

Each Repository should have a Quality Assurance Program/Quality Management System (QA/QMS) or adhere to a QA program of the organization with which the Repository is associated. The program should describe the Repository's commitment to its QA and QC programs and describe approaches for ensuring that the requirements of the QA and QC programs are met.

The QA/QMS should describe procedures for conducting audits of the following areas:

- Equipment maintenance and repair
- Training records and adherence of staff to required training schedules
- Data management
- Record keeping
- Safety plan
- Adherence to cGMP, GLP, GCP, or ISO9001, as needed.

F2.100 Staff responsibilities: QA personnel should have responsibility for assuring compliance with all SOPs and regulatory requirements. QA/QMS staff should have the responsibility and authority to inspect and approve specimen handling, processing, and storage practices, as well as discontinue processing and/or release of specimens when errors warrant. QA/QMS personnel should be responsible for managing audits.

F2.200 Quality standards

F2.210 Current good manufacturing practices: (cGMP) are regulatory guidelines that should be interpreted by the Repository to fit its particular circumstances. cGMP may be more relevant to larger, corporate repositories, but academic and other smaller repositories may wish to aim toward cGMP guidelines. Generally, these standards are interpreted as follows:

- The facility is in a secure, locked area with limited access.
- Personnel must be trained in all procedures and such training is documented.
- The facility is subject to internal QA audits by external clients and agencies such as the FDA as appropriate.
- Policies and procedures are documented in SOPs that are approved by appropriate personnel and changed or updated only under strict document control rules.
- An extensive paper trail for all materials and equipment is maintained.
- Equipment maintenance procedures are performed as required and documented.
- Deviation reports are produced for all events that fall outside SOPs.

F2.220 ISO9001: ISO9001 was created through the International Organization for Standardization (ISO). ISO is a worldwide federation of national standards bodies with headquarters in Geneva, Switzerland. The organization was founded in 1946 to develop a common set of standards for manufacturing, trade and communications organizations.

ISO9001 is a system standard, not a product standard. Its primary purpose is to provide organizations with useful internationally recognized models for operating a quality management system. ISO9001 is a level of quality standardization that some Repositories are working to im-

plement. ISO is similar to cGMP, but is more recognizable in international settings. The international recognition of this system may make it attractive when an organization collaborates with international clients or colleagues.

F2.300 Audits: Repositories must be subjected to regular audits. The audit can involve a weekly check of freezer temperature logs for example, and a more complete review on a monthly or quarterly basis that includes random checks of SOPs for expiration and possibly pulling and checking random sets of specimens against the computer inventory listing. A designated individual familiar with the specific work being reviewed but not directly connected, should be responsible for each QA review. For this function the individual should report to the Director or another designated responsible party.

SECTION G: SAFETY

G1.000 General

Issues related to safe operation of an organization are complex and extensive and depend in most cases on the activities of the organization. For example, if the Repository stores and handles human material, then complex national regulations related to precautions necessary to protect employees from blood-borne pathogens and tuberculosis may need to be followed. In contrast, if no radioactive material is stored or handled in a repository, a safety plan dealing with radiological safety is unnecessary. Issues related to fire, electrical, and physical safety affect all organizations; however, there are no complex, extensive, or detailed regulations related to these areas of safety that are regulated primarily by state and local regulations. Thus, each organization must determine which areas of safety affect it and develop a safety program to protect its employees.

G2.000 Regulations: national, regional, and local

In developing Best Practices in safety, there are more aids than in other areas because of the extensive national, regional, and local regulations that must be met to protect the health and safety of employees. Along with these regulations, most national, regional, and local authorities provide guidance concerning how to meet these regulations. Some Web-based aids to understanding national regulations concerning safety are listed in Appendix A, whereas references are listed in Appendix B.

G3.000 Considerations

Safety plans are used to prevent or to minimize injuries to employees. To develop an effective safety plan, the likelihood and source of specific injuries for each employee must be identified. The sources and likelihood of specific injuries depends upon the procedures/activities that employees perform as well as the rooms in which the employee is likely to spend time. Each person and their supervisor should identify potential sources of injury and how the likelihood of injury can be minimized via changes in procedures or engineering changes, including the use of safety equipment or the improvement of ventilation within a specific area.

G4.000 Safety infrastructure

The Director or other designated individual (this may be the CEO in some private institutions) has total responsibility for the safe operation of all components of the institution. This individual may be subject to civil and criminal penalties depending on safety violations and the extent of any injuries resulting from safety violations/problems. Although the individual with this re-

sponsibility may be legally held responsible, the responsibility for safe operation lies with each and every employee.

The institution usually establishes a Safety Committee that is responsible for the overall safety plan of the institution and for periodic monitoring and updating of the plan. The Safety Committee usually appoints a Safety Officer to administer the program.

The Safety Officer establishes a safety training program and monitors and maintains compliance with the program, evaluates incidents and injuries, and recommends changes to the Safety Committee, as needed. The Safety Officer works closely with area supervisors to ensure local safety.

G5.000 Training

Training in safety reflects the same areas of focus as the general areas of concerns in safety. Of these areas, requirements for training in biohazards (*i.e.*, bloodborne pathogens), chemical hazards, and radiological hazards are the most demanding. Repository staff who come in contact with patients also need to be trained in Health Insurance Portability and Accountability Act of 1996 (HIPAA) regulations regarding the disclosure of confidential patient information to patients and others. Guidelines need to be established for interactions with patients when obtaining signed consent prior to procurement of tissues. Also, Repository staff needs to be made aware of risks associated with consenting patients such as infections and diseases that they could contract (*e.g.*, scabies, tuberculosis, *etc.*). As part of the bloodborne pathogen training, staff members are encouraged to get hepatitis vaccines.

General requirements of training programs include the following:

- Training in each area of safety should be given to employees before they begin their work.
- The training should be updated yearly for all employees.
- Training should be lead by knowledgeable trainers in a language that is appropriate for the employees being trained.
- The training should be at a level that is appropriate for the educational background of each employee and for the risks to which each employee may be exposed. Thus, there may be a need for different levels of training in safety based upon the needs and requirements of specific employees.
- Records of employee training should be maintained for at least 3 years, although this requirement may vary nationally, regionally or locally.

G6.000 Specific areas of concern

G6.100 Biological safety: All human specimens and to a lesser extent animal specimens, whether fixed, paraffin embedded, fresh frozen, or freeze-dried should be considered as biohazardous. As the extent of alteration of tissue increases (*e.g.*, fresh to frozen to fixed to paraffin embedded), the risk from various infective agents usually is reduced. However, certain agents such as prions (*e.g.*, the cause of Creutzfeldt-Jacob disease, scrapie, mad cow disease, deer/elk wasting disease) may still be infective even when tissues are fixed and processed to paraffin blocks. Thus, all human and animal specimen, independent of their state, should be treated with universal precautions, *i.e.*, should be handled as if infected with agents that may be pathogenic to humans (see Appendix B for references).

There will be two major U.S. regulations (29 CFR Part 1910.1030 "Occupational Exposure to Bloodborne Pathogens" and a second one in preparation), which address requirements for organizations to protect against bloodborne pathogens and tuberculosis, respectively. Any organization that deals with human specimens may need to meet the requirements of these regulations. The development of a biological safety program is outlined below in section G7.000.

G6.200 Chemical safety: There are several U.S. regulations related to chemical safety that may affect repositories. These include Occupational Exposure to Hazardous Chemicals in Laboratories (29CFR 1910.1450), The Hazard Communication Standard (29 CFR 1910.1200), and the Formaldehyde Standard (29 CFR 1910.1048). Most U.S. organizations that handle human specimens must follow the Occupational Exposure to Hazardous Chemicals in Laboratories law (29CFR 1910.1450). This law mandates that employers develop a written chemical hygiene plan; this is the core of the standard. The chemical hygiene plan must be capable of protecting employees from hazardous chemicals in the laboratory and capable of keeping chemical exposures below the action level or in its absence the Permissible Exposure Limit (PEL). Section G8.100 below lists the designated elements that a chemical hygiene plan must include. Organizations that fix tissues, for example, for quality control, must follow applicable areas of the Formaldehyde Standard.

G6.300 Electrical safety: Electrical injuries can be avoided by ensuring that all equipment is grounded; testing equipment when first purchased and then yearly will accomplish this. Similarly, all electrical base plugs must be in good condition and electrical work should be done with great care, ensuring that all areas are protected by removal of fuses and with written warnings at the fuse box. Surge protectors are recommended for stand-alone freezers if this is not part of the building electrical infrastructure. Frequently personal electrical appliances such as radios, hairdryers, *etc.*, may be ignored when testing for grounding and represent significant dangers. Also, great care should be taken with electrical appliances/equipment around water sources, especially sinks and bathrooms/showers. Again, applicable areas of national and regional laws will govern electrical safety for organizations outside the United States. These laws should be followed; however, explanations and guidelines for U.S. laws provide an excellent starting point. (See Web sites in Appendix A.)

G6.400 Fire safety: Fire safety can be evaluated by inviting an inspection by the local fire department. Prior to such inspections and at least yearly, fire drills should be practiced and emergency pathways should be posted at all room exits. Emergency exits should never be blocked, obstructed, or locked and hallways must not be obstructed or cluttered. Flammable agents should be stored appropriately, including storage of large amounts of flammable agents in fire cabinets if more than several quarts are stored in one area. Refrigerator/freezers can be purchased that are noncombustible, specifically for the research laboratory. Smoking should be regulated carefully; similarly, furniture, rugs, and equipment should be constructed of nonflammable material. Regulations for types of doors to serve as fire barriers should be followed as should fire requirements for construction of buildings that house specific activities (*e.g.*, laboratories). Much of what has to be done for fire safety will be governed by national, regional and local requirements. (see Web sites in Appendix A.)

G6.500 Physical safety: The physical safety of employees must be considered in all organizations and for all employees. Physical safety ranges from preventing falls to ensuring employees are not physically injured or intimidated by other individuals—either employees or nonemployees. Much of a plan for ensuring physical safety involves careful maintenance of the physical plant and facilities. Tears in rugs, broken steps, and water, soap, paraffin and other slippery substances on floors, and inappropriate use of ladders or chairs as ladders, all may lead to unnecessary falls. Similarly, unrestrained gas cylinders, unbalanced file cabinets, and inadequately secured shelves all can lead to injuries via falling or moving agents or structures.

Also included in causes of physical injuries are repetitive action injuries and back injuries resulting from inappropriate lifting and movement. For example, some LN₂ freezers are designed with metal racks that contain 10 storage boxes. Repository staff is required to stand on step stools and lift these huge heavy racks vertically out of the freezer to access specimens. In some repos-

itories, the task is compounded by the presence of LN₂ (instead of vapor phase) in each box. Back injuries can be avoided by installing an automatic pulley mechanism to aid in the removal of the racks from the freezers. By analyzing an employee's work environment and improving the proper placement of objects and/or provision of the proper tools, the potential for injury will be greatly reduced. When ergonomics is applied correctly in the work environment, visual and musculoskeletal discomfort and fatigue are reduced significantly.

Care should be taken with the overall security of the workplace; this includes limiting access to the workplace by unauthorized personnel. Keys should not be provided to delivery people (e.g., for the delivery of LN₂ or supplies). Instead, delivery people will be afforded entry into the locked area under constant supervision by repository personnel. Physical injuries that are difficult to avoid include minor cuts (e.g., paper) and bumps and strains due to inattentive actions. However, such minor injuries should not be compounded by exposure, for example of broken skin, to biohazards. The overall safety program should address other hazards that can be prevented or ameliorated. For instance, use of gloves to avoid thermal burns from both heat and cold (e.g., dry ice or LN₂). Check the occupational safety laws of your region. (See Web sites in Appendix A.)

G6.600 Radiological safety: Few Repositories will store or use radioactive material. For organizations needing a radiological safety plan, the personnel who utilize or come into contact with radioactive material require training, as well as specific monitoring equipment as do radiological safety personnel. Work with radioactive materials in the United States requires a license either from the Nuclear Regulatory Commission (NRC) or the individual state in which the facility is located. Refer to the NRC guidelines for your state, as appropriate.

G7.000 Key steps in developing a biosafety program

- Identify requirements related to biohazard safety promulgated by governmental and laboratory (repository) accrediting organizations and likely sources of up-to-date information as to biosafety. Use this information in developing an overall safety program and in training programs related to biohazards.
- Develop the organizational infrastructure necessary to develop and maintain a safety program.
- Identify risks and general issues of biosafety in the Repository; this includes identification of work activities and the safety issues of each activity as well as risks in various workspaces.
- Develop written guidelines to ensure biosafety based on published information, national, regional, and local regulations as well as local and consultant experience. These guidelines should be reviewed and updated periodically and modified as soon as possible to correct any identified problems. Maintain records of incidents involving safety of personnel as well as corrective actions.
- Develop and implement a training program of which a major focus is biosafety and maintain records of employee training.

The requirements of national regulations are listed in the Web sites and references provided in Appendices A and B. It is beyond the scope of this document to provide specific actions and details to improve safety in organizations handling human and/or animal specimens. Multiple books and articles are devoted to specific safety information, which is appropriate for safety training and for establishing or improving a safety program.

G8.000 Mandated elements of a chemical hygiene plan

G8.100 Safety and health SOPs

- A written emergency plan should be established to address chemical spills. The plan should include consideration of prevention, containment, clean-up, waste disposal, and disposal of chemically contaminated materials used during the clean up.
- Policies should be established concerning ventilation failure, evacuation, and medical care, reporting of chemical exposure incidents, and chemical safety drills.
- Policies regarding eating, drinking, smoking, gum chewing, and application of cosmetics in the laboratory should be developed.
- Policies should be developed to prohibit storing food and/or beverages in storage areas or laboratory refrigerators; eating and drinking should be limited to specified areas.
- Mouth pipetting and mouth suctioning for starting a siphon must be prohibited.
- Personal protection should be mandated; all persons, including visitors, must wear appropriate clothing (lab coats, long pants, and covered shoes; not shorts, skirts, or open-toed sandals) as well as eye protection. Long hair should be tied back and secured. Suitable gloves should be worn where there is a potential for contact with toxic chemicals. Inspect gloves before using and wash them before removing. Avoid the use of contact lens when possible in the laboratory.
- After handling hazardous materials, wash hands and other possible exposed areas of skin.

All chemicals used in repositories should have material safety data sheets (MSDS) available for reference for employees who potentially will come into contact with these chemicals. MSDS are available from manufacturers.

SECTION H: TRAINING

H1.000 General

Training of all personnel in the mission of the Repository and their functions in the Repository is very important. If training in some areas such as safety is not performed adequately, severe penalties may be imposed on the Repository and Repository personnel. Repository personnel must understand the goals of the function, how to accomplish the function, and how to evaluate the successful completion of the function. The training infrastructure needs to be defined at a high level of the organization. In some cases, support for training might include financial or time-off for general educational objectives (*e.g.*, university courses). The Director should appoint an Administrator Responsible for Training (ART) (see Section H2.200) who will be responsible for all aspects of training.

H2.000 Training infrastructure

H2.100 Training program: Each Repository should have a Training Program that is position, task, and location specific. For example, the training of cleaning personnel in janitorial training may be adequate for offices, but safety training also may be required if janitorial personnel clean laboratory areas containing toxic chemicals or biohazardous materials. Similarly, office personnel who enter hazardous areas may require some basic training in safety. Besides training in general occupational duties, personnel should be trained on any equipment that the personnel may use. This level of training should be appropriate with their contact with specific equipment.

The extent of training should be matched to operational needs of the position/tasks. In addition, for some types of training, the level must go beyond operational and functional requirements. For example, in some types of safety training, personnel must be trained in the history, symptoms and presentation, mechanisms, and outcomes of diseases to which someone might be exposed.

Training must be in a language with which the employee is conversant, and the level of train-

ing must not be above the educational level of the trainee; *i.e.*, it must be appropriate to the employee's level of comprehension.

Repository staff should be asked to review any written procedures for which they are responsible prior to the commencement of their "hands-on" training. A written record indicating that the employee has read the pertinent procedures should be kept in the employee's training file. This record should include the title of the procedure, the employee's initials, and the date upon which the procedure was read. It is preferable that a short test be administered to personnel concerning the material that is presented for the employee's review.

H2.200 Administrator responsible for training: Each Repository should have an ART who is responsible for all aspects of training. The ART will maintain the SOP Manual and will coordinate with the supervisor responsible for that particular procedure when any revisions are needed either due to the expiration of the SOP or because the SOP needed revision for technical reasons.

The ART will closely coordinate issues related to training in safety with the organization's Safety Officer and with other individuals responsible for specific areas of Repository procedures (*e.g.*, shipping and handling).

The ART is responsible for monitoring training and its appropriate documentation as well as the training of all supervisors and/or unsupervised employees. The ART will maintain records of employees who need to be trained in each required area and the time of their periodic updates of training. The ART will inform the employees of potential times of training and will monitor whether the training is completed according to the required timeframe.

The ART will closely coordinate documentation of training and extramural education with personnel who maintain employee records.

H2.300 Trainers: The trainer is one who regularly performs the procedures in question and has completed the training program previously. The trainer is responsible for assuring that the trainee understands each procedure and task fully. For special areas of training (*e.g.*, human subjects protection, privacy, safety), personnel with special expertise may provide the training. Experts via audio-visual methods, including Web-based technologies, may also provide training. This approach may permit employees to complete special areas of training at their own pace when time can be scheduled based on the employee's daily activities.

During the training period, the trainer will demonstrate, explain, and review the standards to be followed in conducting the procedure(s). The trainer should provide appropriate feedback, as necessary, on the trainee's performance of the procedure. The trainer should supervise the trainee in all tasks contained in the procedure(s) until the training phase has been completed. Upon successful completion of the training phase and after the appropriate documentation has been completed, the trainer should ask the trainee if they are comfortable conducting the procedure(s) without supervision, or if they feel that additional training is needed.

H2.400 Training documentation: Once the training is complete, a written record should be made of the trainee's signature as well as the trainer's signature indicating that the training is complete.

H2.500 Periodicity of training: Most U.S. regulations require training before the employee begins working and yearly thereafter. For example, training requirements in biohazards (blood-borne pathogens, tuberculosis) and chemical hazards (formaldehyde) are documented in Occupational Safety and Health Administration (OSHA) regulations in the Code of Federal Regulation (CFR). Because of U.S. requirements concerning yearly training, it frequently is convenient to refresh all training on a yearly basis. This approach is cost-effective when the same trainer can train large groups of employees concomitantly.

H2.600 Cross training: Repositories may find it advantageous to implement a system of cross training. Cross training is the practice in which staff is trained in a variety of procedures and no individual should perform only his/her designated tasks all of the time. Cross training alleviates staff burn out and reduces the staff turnover rate. Because some tasks require repetitive motion, cross training may minimize physical strain among those performing those particular responsibilities. Cross training also allows for critical procedures to be covered when regular staff is absent from the Repository.

H2.700 Training records: A Training File should be maintained for each Repository staff member and should include, but may not be limited to the following:

- Position description that includes the job title and responsibilities, as well as the educational experience required to perform the required task.
- Resume.
- Example of the employee's signature and initials.
- Copies of any certificates documenting that the employee has had specialized training. This should include training in shipping, safety, OSHA, and HIPAA. These records will permit an organized review to make certain that OSHA and other required training have been completed according to regulations.
- Documentation that an employee has read and understood all SOPs pertinent to the employee's responsibilities.

The Training File should be kept in the Repository and be available for QA or client review.

SECTION I: BIOLOGICAL MATERIAL TRACKING

11.000 General

To make certain that specimens can be tracked effectively from the site at which they are collected through their arrival and subsequent shipment from the Repository, certain systems must be in place. Such systems include the use of labels that identify the samples as they are transported and stored, shipping logs that document specimen arrival and departure from the Repository, and an inventory system that allows specimen location within the repository to be known to all appropriate staff.

Standardization of tracking methodologies for banked specimens will increase the efficiency of sample transport. It should facilitate interactions between organizations dedicated to sample procurement and institutions needing specimens for research purposes. Furthermore, the standardization of specimen tracking should expedite the exchange of scientific data among collaborating institutions.

Use of standardized labeling techniques such as the use of bar codes and sample identification information comprises the first step toward the standardization of sample identification and tracking across the industry.

12.000 Labels

Each specimen should receive a label that should adhere tightly under all projected storage conditions. Label printing should be resistant to all common laboratory solvents. Labels should include human-readable indications of contents. Flexibility should be allowed in the location of the label to allow for label legibility on a wide variety of containers.

Best practice: The adherence of labels to containers as well as the use of particular types of ink should be tested under the anticipated storage conditions before they are put into regular use.

I2.100 Bar coding: A base standard for labels is that they should be imprinted using a linear (one-dimensional) bar code that includes a human-readable indication of contents. It is not necessary that a standard system of symbols be implemented. Current bar code scanners are capable of reading a wide variety of symbols and the capacity of many scanners to read additional types of symbols can be expanded in many cases by the procurement of software upgrades. Under some circumstances two-dimensional (2D) bar codes may be desired. 2D bar codes have the added features that scanning error rates may be lower, more information can be contained on the label, they may be faster, and minimize physical stress for the technician from repetitive motion. Cost considerations will need to be made when procuring systems for reading and creating bar codes because scanners that read 2D bar codes are likely to cost more than those that read linear bar codes.

I2.200 Labels for human specimens: Recommendations for label and data transfer standardization of human biological specimens are in compliance with the HIPAA, Public Law 104-91 and with the Health Insurance Reform, 45 CFR, Parts 160 and 162. The Public Law 104-91 addresses the need for a standard identifier and other administrative requirements in HIPAA. The Health Insurance Reform, 45 CFR Parts 160 and 162, adopts standards for electronic transactions and requirements concerning the use of these standards by health plans and health care providers. Finally, the recommendations for standardization of bar code labels are in compliance with the U.S. Food and Drug Administration regulations for electronic records and signatures (21 CFR part 11). This regulation would amend the regulations governing format and content of professional labeling for human prescription drugs and biologic products.

The unique identifier for the specimen may reflect the date of collection/banking and/or sample type. (Under certain circumstances this information may need to be excluded to blind a laboratory that is performing tests on the sample.) This identifier should be a "license plate" number linked to a computerized inventory management system. If included, the date of collection/banking and sample type should be presented in human readable form on the label. (Including a date and sample type in a unique identifier that is bar coded requires the use of a very dense 2D bar code.) If space permits and appropriate circumstances exist, additional information such as the name or identifying number of the research/health-care institution from which the specimen was procured and the method of procurement may be included on the label. Whenever information is included on a label that may allow for re-tracement of a specimen to its donor, specific IRB issues must be considered by the repository.

I3.000 Inventory systems

An inventory system must be in place that tracks the location and status of every sample in the Repository. The inventory system should be capable of storing electronic signatures that meet 21 CFR Part 11 requirements, including a full audit trail of changes made to the database.

The computerized inventory system should ideally have the ability to generate configurable labels to provide the most complete information for the type of sample being stored, its originator, and its recipient. In addition, inventory system should have the linkage functionality with other established databases such as pathology, tumor registry databases, if additional data are needed.

Best practice: Access to the computerized inventory system should be tightly controlled. Defined levels of privileges should be afforded Repository staff and other users of the system. For example, some individuals may be able to determine specimen availability whereas others can enter specimen descriptions and record shipments to and from the Repository.

Best practice: Data should be convertible into formats that can easily be shared among collaborating institutions.

I3.100 Specimen location: Each freezer, refrigerator or room temperature storage cabinet should have a unique identifier. A convention should be established for numbering shelves, racks, boxes, as well as each location within the container.

I3.200 Other specimen descriptors: The inventory system should track sample identifiers such as sample ID, bar code ID (if different), date of collection, and sample type. Information should be included on the availability and volume of aliquots, the history of sample movement, sample thaws (as appropriate), and shipment to and from external sites.

I3.300 Additional information for human specimens: In addition to the information regarding specimen location, information relating to the following may be maintained (if relevant and/or available):

- Donor information: Age of donor at the time of donation; gender, occupation; race/ethnicity
- Diagnosis: Site, histology, stage at diagnosis, date of diagnosis
- Diagnostic procedures: Procedure, date of procedure
- Type of treatment (*e.g.*, chemotherapy, radiation, hormonal, immunotherapy) prior to specimen donation.
- Surgical procedure information: Surgery, primary site, metastatic site, stage of disease at time of surgery, diagnosis code (ICDO), diagnosis text.
- Medical history: Drug name, dose/frequency, date started.
- Family history: Relationship, diagnosis, age at diagnosis.
- Smoking history: Smoke type, smoke years, date quit.
- Vitals: Height (cm), weight (kg), alcohol history, recreational drug history, special diet, date of last menstrual period, date last follow-up, disease status at follow-up, cause of death.
- Clinical laboratory values (*e.g.*, calcium, hemoglobin, etc.).
- Availability of other biological specimens (*e.g.*, normal vs. diseased tissue, other tissues, blood, buffy coat, and plasma, paraffin-embedded tissue, H&E slide, formalin-fixed tissue, DNA, RNA, urine, feces, saliva, ascites fluid, and synovial fluid) from the same donor.

A repository may also incorporate digitally scanned documents into their database. For example, surgical pathology report, H&E slide of representative portion of the tissue, clinical lab reports, and the signed patient consent form.

I3.400 Validation: A system should be in place to maintain the accuracy of the inventory. The system can employ either periodic counts of inventory storage units or a cycle counting methodology. Formal validation of computer systems and software is required for some Repositories, including organizations subject to FDA regulations and by clients if it is a commercial operation. In addition, the inventory system should be subject to regular QA audits.

14.000 Shipping log

Each repository should maintain a Shipment Log to record the receipt and dissemination of shipments sent from the repository. The Log may be computerized or it may be kept in a log-book. If computerized, ideally it would be included in the functionality of the inventory management system described above. Each shipment entry should be given a unique shipment number. The Log should track the following elements:

- Shipment/invoice number
- Recipient/source

- Date received or shipped
- Courier name and ID# for tracking package
- Sample description
- Number of samples received or sent
- Study name if available
- Study number if available
- Key investigator name(s)
- Signature of individual receiving the specimen.

SECTION J: PACKAGING AND SHIPPING

J1.000 General

Packaging and shipping should conform to all regulations. Air shipments should conform to International Air Transport Association (IATA) standards. Ground shipments in the United States should conform to the Department of Transportation (DOT) standards. All personnel involved in the dangerous goods (including infectious materials) shipping process must be trained properly for both air and ground shipments.

Dry ice (solid carbon dioxide) and LN₂ employed for frozen shipments are hazardous materials, and appropriate labeling must be included. The rules for dry nitrogen shippers are less stringent.

Shipments of material that are subject to cold chain management should be shipped with sufficient refrigerant to maintain temperature throughout the shipping cycle.

J2.000 Transport specifications

The first step in the preparation of a shipment for transport is the determination of the specifications for the specimens that are traveling.

J2.100 Regulatory requirements: The shipper must first determine how to classify the specimens that are to be transported. Shipments of etiologic agents must be transported by the most expedient means possible per U.S. regulation. This is generally interpreted to mean overnight air shipments.

Specimens routinely shipped from repositories may be considered dangerous goods such as infectious substances, diagnostic specimens, biological products, genetically modified organisms and microorganisms, or toxic substances. The preservatives that have been applied to the specimens may be considered toxic, flammable liquids, nonflammable gases, or corrosives, all of which are dangerous goods. To properly classify the specimens to be included in a shipment, one should consult their U.S. Transport Regulations (49 CFR in the US) and the International Regulations (International Civil Aviation Organization [ICAO] and the IATA).

Training of personnel is required to transport dangerous goods.

J2.200 Temperature requirements: Specimens may be exposed to temperature fluctuations during transit. The following are typical temperature conditions required for transport of specimens and the insulation/refrigerant required to maintain that temperature:

- Ambient (20–30°C), insulated packaging to protect from extreme heat/cold ambient conditions.

- Refrigerated (2–8°C) gel packs designed for refrigerated temperatures, conditioned at –15°C or phase change material rated for refrigerated transport.
- Frozen (–20°C) gel packs designed for frozen temperatures, conditioned at or below –20°C.
- Frozen (–70°C) dry ice pellets or sheets.
- Frozen (at or below –150°C), LN₂ dry shipper.

J2.300 Humidity requirements: Specimens sensitive to humid conditions may need to be shipped in sealed bags with desiccant to prevent exposure to moisture during transit.

J2.400 Light sensitivity requirements: Light-sensitive material should be sent in packaging that does not allow penetration of light, such as amber vials or amber-coated bags.

J2.500 Arrival time requirements: Time-sensitive specimens such as fresh whole blood must be consigned to couriers with a proven reputation of successful on-time delivery. Time required for processing should be considered as well. For cold or frozen shipments, sufficient refrigerant should be included to allow for a 24-h delay in transport. For example, an overnight (24 h) shipment should have sufficient refrigerant for 48 h.

Temperature-sensitive material should be consigned with a courier capable of replenishing refrigerant in the event of a delay.

J2.600 Sample quantities: The quantity of specimens to be transported will affect the type of packaging and amount of refrigerant required to maintain appropriate temperatures for *all* specimens in the shipment.

J3.000 Validation of shipping conditions

J3.100 Review of packaging test report: The shipper is responsible for choosing appropriate packaging for the material being shipped. This includes a review of all test reports from the testing of the packaging to meet the regulation requirements.

Packaging that has undergone stringency testing must be used in the same configuration under which it was tested (*i.e.*, primary cryovials of equivalent rating, blood collection devices of equivalent rating).

J3.200 Validation of packaging: Packaging should be checked prior to use on specimens. These tests should include measuring all parameters that could influence specimen integrity (*i.e.*, temperature, humidity, light sensitivity, structural quality, and spill containment).

Shipments of specimens with high value or those with critical temperature requirements should include a temperature-recording device that can verify the temperature of the material being shipped throughout the transport cycle.

J3.300 Test shipments: In some situations, especially relating to extremely valuable samples, repositories may choose to send a test shipment that approximates the characteristics of the actual shipment. This may inform the shipper as to the adequacy of packing coolants and also to identify any potential obstacles for the successful shipment.

J3.400 International shipments: Special permits or other requirements may be unique to certain countries and regions.

Best practice: Identify all requirements for shipping to a designated country prior to the initiation of the shipment.

J4.000 Tracking shipments during transport

J4.100 General: The shipper and recipient should track all packages while in transit.

J4.200 Notification of shipment: The Recipient should be notified prior to the package being released by the Shipper to confirm that they are able to receive the package and have the proper facilities available for storage.

The Shipper should provide a 24-h emergency contact for all packages transporting Dangerous Goods.

J4.300 Shipping manifest: The Shipper should send a shipping manifest (preferably electronic) to the Recipient. A hard copy must also be included in this shipment itself to accommodate regulatory requirements.

J4.400 Confirmation of receipt: Confirmation of receipt and the condition upon arrival should be obtained for every shipment coming to or leaving a repository.

SECTION K: SPECIMEN COLLECTION, PROCESSING, AND RETRIEVAL

K1.000 General

Although specimen-processing practices vary according to the specific type of specimen being studied, collection and retrieval practices have many elements in common. Specimen type needs to be carefully considered prior to initiation of collection, based on availability and intended analytic objectives for the study. Many specimen collection protocols have special requirements for preservation of macromolecules (proteins, nucleic acids) and/or analytes of interest.

K1.100 Pilot studies and proof-of-performance studies: Whenever a new protocol, equipment, or laboratory is used for the collection and processing of specimens, repositories may wish to implement small-scale pilot studies for the validation of new methods or protocols. Pilot studies or feasibility studies can be helpful in the early identification of problems in the collection, handling, and processing of specimens before a larger study is undertaken.

Proof-of-performance studies are helpful for external or contract labs. They may include blinded samples for which levels of a target analyte are known from previous measurements, samples represented in duplicate (again blinded), and identical samples for which measurements are repeated on consecutive days. The results are evaluated to determine if a lab meets the organization's performance standards of reproducibility.

K2.000 Specimen types

A variety of specimen types may be collected for storage:

- Blood and blood fractions (plasma, serum, buffy coat, red blood cells)
- Urine
- Buccal cells/saliva
- Hair
- Nail clippings
- Breast milk
- Feces
- Exhaled air
- Tissues—surgical, autopsy, frozen, paraffin-embedded

- Cell lines
- Products of conception
- Cord blood
- Bone marrow
- Fluids from cytology (ascites, pleural fluid, synovial fluid, *etc.*)

K3.000 Collection procedures

K3.100 Special considerations for specimen collection protocols: Various protocols exist for the collection of different specimens. The protocol chosen should be suited to the particular needs of the study. Special considerations for specimen collection procedures are presented below. For reference see Holland *et al.* (2003) and Landi and Caproaso (1997).

K3.110 Timing of specimen collection: Biological marker levels may vary according to the time of day; however, a much greater effect may be the time and conditions associated with specimen processing.

K3.120 Specimen biological stability: The stability of specimens may be affected by any of the following:

- Anticoagulants used in blood collection (see Section K3.200).
- Stabilizing agents (*e.g.*, EDTA, ascorbate necessary to preserve folates and vitamins) should be included in the collection device or added as soon as possible after collection to assure stability of analytes.
- The time elapsed between specimen collection, or removal from a storage unit, and subsequent processing. Cell viability may be affected negatively as this period of time is extended.
- The temperatures at which specimens are collected and subsequently processed and stored are critical and must be carefully considered depending on the type of specimen and intended analyses. Warmer storage environment may be permissive for macromolecular degradation (RNA is particularly susceptible).
- The sterility of the instruments, surfaces, and equipment is an important consideration to prevent subsequent contamination. Sterility is particularly important if the intention is to collect RNA or to culture cells from the sample.
- Degradation—Enzymatic degradation affects many biochemical markers. RNA and proteins are particularly susceptible to enzymatic degradation and require special procedures to maintain their integrity during collection and processing.
- Containers/equipment—Collection containers and freezers or other equipment vary according to specimen types being collected.

K3.200 Blood: One of the primary decisions is whether to collect anticoagulated (plasma/buffy coat/RBC) or coagulated (serum/clot) blood. When multiple blood collection devices are involved there is a proscribed order of draw. (See Appendix A for internet resources.)

Depending on the amount of blood needed, collection of blood spots on treated or untreated cards is adequate or even preferable to collecting as above.

K3.300 Urine: Urine collections should be maintained on ice or refrigerated for the duration of the collection. Plastic or glass containers should be clean and dry, and have a 50- to 3000-ml capacity, a wide mouth and leak-proof cap. Depending on the analyte to be measured, a preservative may be needed. The type of preservative may differ according to test methodologies, time delay, and transport conditions. EDTA and sodium metabisulfite are examples of preservatives commonly used in urine collections.

K3.310 First morning: Subject voids before going to sleep and immediately upon rising collects a urine specimen. First-morning specimens are best for substances that require concentration; white and red blood cells and casts are more stable in concentrated urine.

K3.320 Random: Good for routine screening and cytology studies.

K3.330 Fractional: Fractional samples are used to compare concentration of an analyte in urine with its concentration in blood. First-morning urine (with solutes and metabolites from evening meal) is discarded and the second urine (fasting) is collected.

K3.340 Timed: Timed collections allow comparisons of excretion patterns. Typical collection times are 12 and 24 h. For the 24-h collection on day 1, the subject empties his/her bladder and for the next 24 h all subsequent urine is collected.

K3.400 Tissues: Specimen protocols for collecting human tissues vary greatly. Details and precise guidance are outside the scope of these Best Practices. Some guidance is available in the references listed in Appendix B (Grizzle *et al.*, 1999; Grizzle and Sexton, 1999; Jewell *et al.*, 2002).

K3.410 Essential considerations for collecting tissues: Tissues are typically collected prospectively to meet the needs of investigators, to populate a tissue bank, or as a combination of these. Regardless of the purpose of the collection, the following should be taken into consideration:

- Maintaining diagnostic integrity—The collection of samples for research must never compromise the diagnostic integrity of a specimen.
- Importance of a pathologist—The appropriate handling of tissues procured for research purposes is facilitated if a practicing pathologist supervises the actual procurement of the tissue; this is especially important to prevent the compromise of diagnostic specimens.
- Time constraints—The relative importance of the time lapse between receiving a specimen and processing it varies with the research application. Every molecule within a specific tissue degrades at a different rate. Thus, each class of molecule can be thought of as a biological clock that is started by a variety of signals or events. One clock may begin when the vascular supply to an organ is compromised during surgery, another when the tissue is removed and placed in a cold container. The speed at which the clock runs may depend upon the temperature at which the specimen is maintained. In determining the acceptability of time lapse, it is necessary to take into account the organ from which the specific tissue is obtained. Thus, the “best practice” is to collect and process specimens as rapidly as is possible (see Jewell *et al.*, 2002).

K3.420 Tissue sources: Depending on the needs of the investigator for whom the samples are collected, or the protocol of the repository, tissues can be collected from several sources.

K3.421 Surgery:

- Remnant samples may be collected from diagnostic procedures, or, with proper IRB approval, specimens may be resected specifically for research.
- Specimens should remain fresh, not fixed, and placed in a sterile container on wet ice for transport from surgery to pathology or to the repository.
- For the collection of remnant diagnostic samples, a pathologist should examine the specimen to identify tissue that can be made available for research without compromising diagnostic integrity.
- The optimal procedure would be to handle all specimens in a sterile manner; however, that is not always practical, as few surgical pathology gross rooms will have a sterile hood. In ad-

dition, many research protocols do not require that their tissue specimens be procured following sterile procedure. If a sterile hood is not available, the repository staff can set up a “clean” area on a sterile cloth towel. The prosector should be provided with sterile gloves and sterile instruments for resection of the tissue. Tissue provided to the repository should be placed directly in appropriately labeled sterile containers of saline or media (unless a researcher specifies otherwise) for transport to the repository for processing. If the tissue is to be frozen immediately, it is not necessary to place it in saline because this may cause ice crystals to form on the outside of the specimen when freezing.

- Specimens should NEVER be resected on a dry towel, or other absorbent material, as this rapidly desiccates the specimen and may compromise its usefulness.
- The prosector should be provided with fresh blades and instruments to use between different specimens and different areas of the same specimen (*i.e.*, the same blade that is used to dissect a tumor should NOT be used to dissect the associated uninvolved tissue).
- Specimens resected specifically for research may be either processed in the operating room, at the time of collection, or may be transported to the repository for processing, depending upon the requirements of the specific protocol.
- Specimens are useless if they are incorrectly identified. Thus, all samples should be labeled appropriately (Section I2, Labels) as to the identity of the patient, the location and perceived diagnosis (*i.e.*, primary breast tumor, metastatic breast tumor to a lymph node, uninvolved breast tissue), and the time of specimen resection and collection.
- Samples requiring snap freezing can be frozen in a Dewar of liquid nitrogen or on dry ice at the time of collection. Otherwise, it is recommended that samples be transported in saline, on wet ice, to the repository laboratory for additional processing.
- If a frozen section is cut for diagnostic reasons, then the Repository staff should make every effort to obtain an extra slide for QC. If sufficient amounts of tissue are available following a diagnosis, the Repository staff should save some of the tissue as snap frozen, and an adjacent section for making a paraffin block that will become the property of the Repository. An H&E slide can then be cut from each paraffin block that will serve as the QC for that specimen. If insufficient amounts of tissue are provided by the pathologist to allow for making a paraffin block, then the Repository staff should request an H&E slide to be made from the pathology department’s paraffin block (which will be used as the QC for the Repository).

K3.422 Autopsy:

- Remnant samples may be collected from autopsy procedures.
- Requests for tissue from autopsy procedures should specify a maximum time post mortem (interval between death and processing).
- Autopsy procedures may yield “normal” tissues (*i.e.*, normal lung), or large quantities of a specimen (*i.e.*, half a brain or a lobe of liver) that would not otherwise be available from surgical procedures.
- Specimens that are not removed as part of the routine autopsy procedure (*i.e.*, leg, arm, hand, foot, or face tissue) are not usually available as their procurement may result in disfigurement of the body.
- Tissue specimens collected at autopsy should be appropriately labeled as to the organ site, tissue type, and time of resection, and then placed immediately in a container of saline on wet ice for transport to the tissue repository for processing.

K3.423 Transplant: Occasionally, organs that are inappropriate for transplant may be offered or made available to a repository for research purposes.

- By the time transplant tissue is offered to a repository, it is not unusual for the organ to have been out of the body for many hours beyond the normal time frame identified for procure-

ment of samples. Because transplant tissue is, however, usually placed in a preservative to keep it viable for transplant, most researchers will still accept transplant tissue as it is likely to be of superior quality to either surgical or autopsy specimens.

- Information about the donor from whom the organ was procured should be obtained from the transplant center (*i.e.*, age, race, sex, time and date of death, cause of death, reason why organ could not be transplanted, results of any tests performed).

K3.500 Nail clippings: Nail clippings are used for trace metal analysis. These samples are simple to collect, store, and ship but present special washing, hydrolysis, and matrix problems for the analytic laboratory.

K3.600 Saliva: Collection devices include noncovered cotton roll, polypropylene-covered polyether roll, and paraffin wax chewing stimulation. Some researchers may request patients to provide saliva samples directly into a container; make sure that the opening is adequately large to facilitate this collection.

K3.700 Breast milk: Breast milk can be initiated when breast-feeding starts. It can be collected by manual expression or vacuum pump and should be collected in autoclaved bottles.

K3.800 Additional specimen types: Various protocols for collection and processing exist for rare or difficult to collect specimens such as bone marrow, cord blood, products of conception, and fluids from cytology (ascites, pleural fluid, synovial fluid, *etc.*).

Best practice: Collection of specimens for research must under no circumstances interfere with appropriate patient diagnosis.

Best practice: A pathologist must review all patient tissue specimens to determine what material can be made available for research. Blood and other body fluids not required for diagnosis can be collected in accordance with approved protocols and do not require pathologic review.

K4.000 Aliquoting frozen specimens

K4.100 Plasma, serum, and urine:

- All staff should wear protective equipment, as appropriate, such as lab coats, disposable gloves, freezer gloves, face shields, goggles (mandatory when working with LN₂).
- Assure that correct specimens are located; retrieve requisitioned specimens from the freezer using established QC procedures.
- Specimens in plastic cryovials should be thawed at room temperature.
- Specimens in glass vials should be thawed slowly overnight in a refrigerator to prevent cracking.
- Open all aliquot specimens in a biological safety hood. Sterile vials and pipettes are used to avoid contaminating samples.
- Determine the proper pipette and tip to use depending on required volumes.
- Use different pipette tip for each specimen and rinse pipette tip with 10% bleach solution before discarding.

K4.200 Freezing and thawing considerations: The rate and method of freezing and thawing specimens can have serious effects on the viability of cells. The following must be taken into consideration when freezing and thawing specimens for which cellular viability is important. Exact freezing and thawing protocols should be developed to ensure that the method used supports the known or anticipated use for the specimens.

- Rate of cooling—The rate of cooling controls the size of ice crystals and how fast they are formed, which may affect cell recovery. A uniform cooling rate of -1°C per minute from ambient temperature is effective for a wide variety of cells. The steady decline of temperature can be achieved by the use of commercially available freezing devices that control the rate of freezing.
- Storage—The temperature at which frozen preparations are stored affects the length of time after which cells can be recovered in the viable state. The lower the storage temperature the longer the viable storage period.
- Handling—In addition to temperature of storage, handling during removal from storage will affect the viability of cells and may result in degradation of cellular components. Every time an ampoule/vial is exposed to a warmer environment, even briefly, it experiences a change in temperature.
- Reconstitution (thawing)—Although slow cooling is generally best to insure cell viability, the opposite is required when thawing from the frozen state. Agitation of the vial/ampoule in a 37°C water bath is preferable, but may be detrimental to certain cell types if the process is too lengthy.
- Determination of recovered cells—There are several methods to accurately estimate the number of viable cells in a nonmotile population, usually by a dye exclusion method (*e.g.*, Trypan Blue).

K5.000 Specimen retrieval

The procedures recommended below assume retrieval of frozen specimens from freezers for distribution, but are applicable to other storage conditions and equipment.

Retrieval of specimens for shipment or analysis requires strict adherence to protocols for proper specimen inventory and tracking, as well as adherence to established safety standards in working with freezers and other storage equipment. Reference is made to other Best Practices as appropriate.

K5.100 Locating specimens in storage: Specimens to be retrieved must be located in the appropriate specimen inventory system (Section I3: Inventory Systems). A specimen requisition is generated according to procedures applicable to the institution's tracking and inventory system. The requisition is checked for accuracy before transmission to the repository, according to established SOPs (Section E1, Standard Operating Procedures Manual) and QC standards (Section F, Quality Assurance and Quality Control).

K5.200 Specimen retrieval:

- At the repository, locate and pull specimens as documented on specimen requisition.
- As required according to specimen type, maintain proper temperature of specimens during the retrieval process. For frozen specimens, keep vials on dry ice or in LN_2 during the process.
- Confirm that all requisitioned specimens are accounted for in the freezer or other storage container. If specimens are missing follow established protocols to locate the specimens; a deviation report should be produced to indicate that specimens listed in the inventory system could not be located.
- Place specimens in appropriate boxes or other containers and label according to standards established for the required shipping and storage conditions.
- All steps should be recorded in the record management system.

K5.300 Documentation of retrieval: Checklists and other forms are desirable to document the specimen retrieval process including steps taken above to confirm completeness of the process and steps occurring after retrieval to document shipment and quality checks.

- If specimens are to be shipped to an outside location, the recipient should be contacted at least 24 h prior to shipment.
- QC checks should be performed to confirm that all specimens listed on the requisition were retrieved. Confirmation at least a second time by a separate person is recommended.
- Records should be kept on any special considerations such as the number of times specimens have been thawed and refrozen if applicable.
- Records should be kept on problems noted with any individual containers, such as: no visible specimen, volume significantly less than documented in inventory system, container is cracked, label missing or unreadable.

SECTION L: HUMAN SUBJECTS

L1.000 General

Key discussions of ethics in human subjects' research are found in the Declaration of Helsinki adopted by the World Medical Association in 1964 and revised several times subsequently, most recently in 2000 and the Belmont Report published by the U.S. Department of Health and Human Services in April, 1979. There are several fundamental key concepts:

- Freely given informed patient consent is necessary before research on humans may be conducted.
- Research should be well designed, conducted by persons with appropriate expertise and lead to meaningful conclusions.
- Every measure should be taken to reduce the risk and ensure that the risk does not exceed the benefit of the expected finding.
- Studies in animals should provide reason to believe that the study of humans is needed and is the only way to get the necessary information.

L2.000 Applicable regulations

Repositories of human specimens for research must adhere to all applicable federal, state, and local regulations. In addition to the federal regulations, there are several recent state laws that extend the U.S. regulations to research in the state that is not funded by the U.S. government and state laws that impose additional consent requirements.

L2.100 Code of Federal Regulations: In the United States, most federally funded research on human subjects is regulated by the Code of Federal Regulations (CFR). The CFR is the codification of the general and permanent rules published in the Federal Register by the executive departments and agencies of the Federal Government. The U.S. human subjects' regulations do not specifically address use of specimens except by allowing exemption from the regulations for unidentified existing specimens and allowing expedited review of existing data, documents, records, pathological specimens, or diagnostic specimens. By practice, all other uses of specimens are subject to the regulations, though often considered minimal risk research that is eligible for waiver of the requirement for informed consent.

Title 45 (Public Welfare) Part 46 (Protection of Human Subjects) of the Code of Federal Regulations (45 CFR 46) or the 'common rule' applies to most federally funded research on human subjects and 17 U.S. agencies that support research. Research on human specimens is different from other types of human research in that there is generally no interaction with the patient and the risks are primarily from loss of privacy or confidentiality. Research that will lead to a filing with the U.S. Food and Drug Administration is subject to regulation by the FDA under 21 CFR 50 and 21 CFR 56.

The common rule and the FDA regulations state the requirement of institutions conducting federally funded research to utilize an Institutional Review Board (IRB) to review and approve any research involving the use of human subjects. In addition, the regulations state that no investigator may involve a human being as a subject in research unless the investigator has obtained the legally effective informed consent of the subject or the subject's legally authorized representative. Although there are substantial similarities between the common rule and the FDA regulations, the one essential difference is that the FDA does not allow waiver of consent.

L2.110 Institutional Review Board: An IRB is any board, committee, or other group formally designated by an institution to review biomedical research involving humans as subjects, to approve the initiation of and conduct periodic review of such research.

Best practice: A repository's processes and procedures for storage of human specimens for research should be available for review by an IRB to assure that they are appropriate to protect human subjects.

Best practice: Specimens should only be made available for studies that are expected to expand medical knowledge and contribute to the well being of the world's people. The rigor of the review should be related to the value of the specimens and data that are available. As a general rule, the greater the data annotating a specimen the more rigorous the review should be and the more important the expected result of the research should be.

L2.120 Informed consent: Informed consent should be obtained from each prospective subject or the subject's legally authorized representative. Consent should be sought only under circumstances that provide the prospective subject or the representative sufficient opportunity to consider whether or not to participate and that minimize the possibility of coercion or undue influence. The information that is given to the subject or the representative should be in language understandable to the subject or the representative.

Best practice: Subject consent should be obtained unless waived by an authorized IRB constituted in accordance with applicable law or regulation. Consent can be for a specific research use or for future unspecified uses. If the use is unspecified, an IRB review of the research must be conducted to assure that the use is consistent with the original consent.

Best practice: Subjects should always retain the right to withdraw consent and to have specimens and data removed from the repository once that consent is withdrawn. The logistics for such withdrawal of consent must be clearly defined and conveyed to all subjects at the time of consent. Even if an opt-out procedure is used, patient notification must include instructions for later withdrawal of consent.

L2.200 Health Insurance Portability and Accountability Act of 1996: In August of 2002 the Department of Health and Human Services published the HIPAA of 1996 with a compliance date of April 14, 2003. The HIPAA 'privacy rule' provides very specific requirements for the protection of patient data that apply to research uses as well as to a variety of other uses such as billing, insurance claim processing, etc. The Privacy Rule establishes a category of health information, referred to as protected health information (PHI), which may be used or disclosed to others only in certain circumstances or under certain conditions. PHI is a subset of what is termed individually identifiable health information.

Repositories may permit researchers to review PHI in medical records or elsewhere to prepare a research protocol, or for similar purposes preparatory to research. To permit the researcher

to conduct a review preparatory to research, the Repository must receive from the researcher representations that:

- The use or disclosure is sought solely to review PHI as necessary to prepare the research protocol or other similar preparatory purposes.
- No PHI will be removed from the covered entity during the review.
- The PHI that the researcher seeks to use or access is necessary for the research purposes.

L2.210 Release of de-identified data sets: The Privacy Rule permits the release of data that have been de-identified without authorization and without further restrictions because de-identified data is not PHI. PHI may be de-identified in one of two ways:

- The “safe-harbor” method is to remove all 18 identifiers enumerated at section 164.514(b)(2) of the regulations:
 - (1) Names of the individual or of relatives, employers, or household members of the individual
 - (2) All geographic subdivisions smaller than a state, except for the initial three digits of the ZIP code if the geographic unit formed by combining all ZIP codes with the same three initial digits contains more than 20,000 people
 - (3) All elements of dates except year, and all ages over 89 or elements indicative of such age
 - (4) Telephone numbers
 - (5) Fax numbers
 - (6) Email addresses
 - (7) Social security numbers
 - (8) Medical record numbers
 - (9) Health plan beneficiary numbers
 - (10) Account numbers
 - (11) Certificate or license numbers
 - (12) Vehicle identifiers and license plate numbers
 - (13) Device identifiers and serial numbers
 - (14) URLs
 - (15) IP addresses
 - (16) Biometric identifiers
 - (17) Full-face photographs and any comparable images
 - (18) Any other unique, identifying characteristic or code, except as permitted for re-identification in the Privacy Rule.
- The second way is to have a qualified statistician determine that the risk is very small that the information could be used, alone or in combination with other reasonably available information, by the anticipated recipient to identify the subject of the information. The qualified statistician must document the methods and results of the analysis that justify such a determination.

The Privacy Rule permits a Repository to assign to, and retain with, the de-identified health information, a code or other means of record re-identification if that code is not derived from or related to the information about the individual and is not otherwise capable of being translated to identify the individual.

L2.220 Release of limited data sets: Where only certain identifiers are needed, the Privacy Rule allows for a Repository to provide a researcher with a limited data set. Limited data sets may be used or disclosed only for public health, research, or health-care operations purposes. Before disclosing a limited data set to a researcher, the Repository must enter into a data use agreement with the researcher, identifying the researcher as the recipient of the limited data set, establishing how the data may be used and disclosed by the recipient, and providing assurances

that the data will be protected, among other requirements. The following 16 direct identifiers must be removed for PHI to qualify as a limited data set:

- (1) Names
- (2) Postal address information, other than town or city, state, and ZIP code
- (3) Telephone numbers
- (4) Fax numbers
- (5) Email addresses
- (6) Social security numbers
- (7) Medical record numbers
- (8) Health plan beneficiary numbers
- (9) Account numbers
- (10) Certificate or license numbers
- (11) Vehicle identifiers and license plate numbers
- (12) Device identifiers and serial numbers
- (13) URLs
- (14) IP addresses
- (15) Biometric identifiers
- (16) Full-face photographs and any comparable images.

Best practice: The collection, storage, and use of human specimens and associated data must be done in a way that respects the individual and maintains privacy and confidentiality.

Best practice: Users of the specimens and data must sign an agreement specifying how the specimens and data will be used and to whom they may be transferred. For unidentified specimens and data, users must sign an explicit agreement not to seek information about the subject's identity.

APPENDIX A: INTERNET RESOURCES

Subject	Web site	Organization	Topics
General safety	http://www.osha.gov	Occupational Safety and Health Administration, Department of Labor, USA	Current regulations and regulations under development; technical, prevention and training information; links
General safety	http://www.rmlibrary.com/db/lawosha.htm	Managerial Technologies Corporation	Occupational safety laws of all 50 states
General safety	http://www.med.virginia.edu	University of Virginia, International Health Care Worker Safety Center	Surveillance data
General safety	http://www.medicentrcenters/epinet	Exposure Prevention Information Network (EpiNet)	Surveillance information
General safety	http://www.cap.org	College of American Pathologists	General and technical information; lab management
General safety	http://www.lbl.gov/ehs/pub3000	Berkeley Lab Health and Safety	Health and safety manual
General safety	http://www.nccsls.org	National Committee for Clinical Laboratory Standards	General and technical information; forums; links
Biosafety	http://www.cdc.gov	Centers for Disease Control and Prevention, Atlanta, GA	Surveillance data; prevention and technical information; links. Proposed guidelines for working safely with <i>Mycobacterium tuberculosis</i>
Biosafety	http://www.cdc.gov/ncidod	National Center for Infectious Diseases	General and technical information; case information, teaching materials; research and resources
Biosafety	http://www.fda.gov/cber	Food and Drug Administration, Center for Biologics Evaluation and Research	Information on recalls, withdrawals, and safety issues concerning biologics
Biosafety	http://www.absa.org	American Biological Safety Association	Technical information
Biosafety	http://www.ace-osrt.edu	National Antimicrobial Information Network of Oregon State University and the EPA	Technical information on disinfectants; links
Biosafety	http://www.gjd.ed.ac.uk	UK Surveillance Unit for Creutzfeldt-Jacob Disease	Surveillance data on Creutzfeldt-Jacob disease; technical information; links
Chemical safety	http://www.cdc.gov/niosh/database.html	National Institute for Occupational Safety and Health (NIOSH)	Databases and information resource links and publications
Chemical safety	http://www.ilo.org/public/english/protection/safework/cis/products/icsc/dtasht/index.htm	International Occupational Safety and Health Information Center	Chemical database; International Chemical Safety Cards (ICSC)
Chemical safety	http://response.restoration.noaa.gov/chemaids/react.html	Chemical Reactivity Worksheet	Chemical database of reactivity of substances or mixtures of substances
Chemical safety	http://www.cdc.gov/niosh/chem-inx.html	Master Index of Occupational Health Guidelines for Chemical Hazards (NIOSH)	Guidelines for chemical hazards of specific chemicals
Electrical safety	http://ehssun.lb1.gov/ehsdiv/pub3000/CH08.html	Berkeley Lab Health and Safety	Electrical safety program
Electrical safety	http://www.princeton.edu/~ehs/labmanual/sec7-7.html	Princeton University	Laboratory electrical safety program

Electrical safety	http://www.ehs.uconn.edu/Word%20Docs/Electrical%20Safety%20in%20the%20Lab.pdf	University of Connecticut Environmental Health and Safety	Electrical safety in the laboratory
Fire safety	http://ehssun.lb1.gov/ehsdiv/pub3000/CH12.html	Berkeley Lab Health and Safety	Fire prevention and protection program
Fire safety	http://www.ehs.stonybrook.edu/policy/LabFireSafetyHazardAssessment.pdf	Stony Brook Environmental Health and Safety	Laboratory fire safety hazard assessment and work practices
Fire safety	http://ehssun.lb1.gov/ehsdiv/pub3000/CH12.html	Berkeley Lab Health and Safety	Fire prevention and protection program
Fire safety	http://www.ehs.stonybrook.edu/policy/LabFireSafetyHazardAssessment.pdf	Stony Brook Environmental Health and Safety	Laboratory fire safety hazard assessment and work practices
Human subjects	http://www.gpoaccess.gov/cfr/index.html	Office of the Federal Register, National Archives and Records Administration, Washington, D.C.	Code of Federal Regulations
Human subjects	http://www.hhs.gov/ocr/hipaa/	U.S. Department of Health and Human Services	Health Insurance Portability and Accountability Act of 1996 (HIPAA)
Human subjects	http://www.hhs.gov/news/press/2001pres/20010119a.html	U.S. Office of Human Research Protections	Stem cell guidelines
Packing and shipping	http://www.iata.org/index.htm	International Air Transport Association (IATA)	Standards for shipping human specimens by air
Packing and shipping	http://www.icao.int/	International Civil Aviation Organization (ICAO)	International Transport Regulations
Packing and shipping	http://www.myregs.com/dotrspa/	Office of Hazardous Materials Safety	U.S. Transport Regulations (49 CFR in the U.S.)
Packing and shipping	http://www.ehs.uci.edu/programs/dgoods/	Department of Transportation (DOT)	Standards for shipping human specimens by ground
Radiological safety	http://ehssun.lb1.gov/ehsdiv/pub3000/CH21.html	Berkeley Lab Health and Safety	Radiation safety program
Radiological safety	http://www.jmu.edu/safetyplan/radiology/advisorycommittee.shtml	James Madison University	Radiation protection program
Tissue procurement protocols	http://intranet.cc.nih.gov/dlm/specimensguidelines/orderdraws.html	NIH Clinical Center	Guidelines for the order of drawing blood specimens
Tissue procurement protocols	http://www.tubafrost.org	European Human Frozen Tumour Tissue Bank (TuBaFrost) project	Collection and storage of human tissues
Tissue procurement protocols	http://www.bd.com/vacutainer/	Becton-Dickenson	Newsletters and updates on blood collection tubes
Tissue procurement protocols	http://www.bd.com/vacutainer/products/venous/tubeguide.asp	Becton-Dickenson	Vacutainer tube application guide

(continued)

APPENDIX A: INTERNET RESOURCES (CONT.)

<i>Subject</i>	<i>Web site</i>	<i>Organization</i>	<i>Topics</i>
Tissue procurement protocols	http://www.bd.com/vacutainer/pdfs/plus_plastic_tubes_wallchart_orderofdraw_VS5729.pdf	Becton-Dickenson	Wall chart on blood tube order for blood collection
Tissue Procurement protocols	http://phlebotomypages.com/vac_blood_collect.htm	Phlebotomy Pages	Information on blood collection via vacutainers
Tissue procurement protocols	http://www.csmc.edu/5455.html	Cedar-Sinai Medical Center	Blood collection guidelines
Tissue procurement protocols	http://www.austin.cc.tx.us/kotrla/PHBLab2VenipunctureSum03.PDF	Austin Cancer Center, Austin, TX	Phlebotomy laboratory summary on venipuncture (see page 3 of Web site for table)
Tissue procurement protocols	http://medlib.med.utah.edu/WebPath/TUTORIAL/PHLEB/PHLEB.html	Internet Pathology Library for Medical Education	Phlebotomy procedures
Tissue procurement protocols	http://aacfg.s-3.com/virlab.htm	AIDS Clinical Trials Group	Protocols focused on specimen processing and handling
Tissue procurement protocols	http://www.who.int/emc-documents/surveillance/docs/whodscrdc2004.pdf	World Health Organization	Guidelines for collection of clinical specimens during field investigations of outbreaks.

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