



Best Practices for Repositories:
*Collection, Storage, Retrieval and Distribution of
Biological Materials for Research*

**International Society for Biological and
Environmental Repositories**

Third Edition



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 web site (www.isber.org) to ensure that the most recent version is available for use.

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**INTERNATIONAL SOCIETY FOR BIOLOGICAL AND ENVIRONMENTAL
REPOSITORIES**

BEST PRACTICES FOR REPOSITORIES

Collection, Storage, Retrieval and Distribution of Biological Materials for Research

INTRODUCTION

The availability of high quality biological and environmental specimens for research purposes requires the development of standardized methods for collection, long-term storage, retrieval and distribution of specimens that will enable their future use. Sharing successful strategies for accomplishing this goal is one of the driving forces for the International Society for Biological and Environmental Repositories (ISBER). For more information about ISBER see www.isber.org.

ISBER's Best Practices for Repositories (Best Practices) reflect the collective experience of its members and has received broad input from other repository professionals. Throughout this document effective practices are presented for the management of specimen collections and repositories. **The term “Best Practice” is used in cases where a level of operation is indicated that is above the basic recommended practice or more specifically designates the most effective practice.** It is understood that repositories in certain locations or with particular financial constraints may not be able to adhere to each of the items designated as “Best Practices”. Repositories fitting into either of these categories will need to decide how they might best adhere to these recommendations within their particular circumstances. While adherence to ISBER Best Practices is strictly on a voluntary basis, it is important to note that some aspects of specimen management are governed by national/federal, regional and local regulations. The reader should refer directly to regulations for their national/federal, regional and local requirements, as appropriate.

ISBER has strived to include terminology appropriate to the various specimen types covered under these practices, but here too, the reader should take steps to ensure the appropriateness of the recommendations to their particular repository type prior to the implementation of any new approaches. Important terms within the document are italicized when first used in a section and defined in the glossary.

The ISBER Best Practices are periodically reviewed and revised to reflect advances in research and technology. The third edition of the Best Practices builds on the foundation established in the first and second editions which were published in 2005 and 2008, respectively.

SECTION A: REPOSITORY PLANNING CONSIDERATIONS

A1.000 GENERAL

A *repository* is defined as an actual or virtual entity that may receive, process, store or distribute *specimens* in support of a study or multiple studies and their associated data as appropriate. A specimen resource generally refers to the specimens collected for a particular study. Many issues touched upon in this section have been explored more fully in subsequent sections of these Best Practices. The reader should refer to the Table of Contents to identify sections appropriate to their particular interests.

A2.000 REPOSITORY DEVELOPMENT

A2.100 Models

The *collection* and *storage* of specimens may be performed in support of a variety of scientific endeavors. Specimens may be collected as a part of *prospective* or *retrospective* studies and the method of procuring these specimens will depend on the availability of resources and the particular scientific inquiry. There are several models for how specimens may be procured, stored and prepared for subsequent testing. A repository may take advantage of a single approach or multiple approaches to achieve its scientific mission. Once a repository is established in support of one model, it should be easier to expand the infrastructure to include other models as needed rather than to initiate a new repository from the beginning. This approach prevents duplication of efforts and allows more efficient utilization of resources. Regardless of the model employed, specimens should always be collected and processed according to the most current methods supported by scientific data and best practices, where possible.

A2.110 Procurement Service

A repository that provides procurement services, or request-based services, collects and processes tissue specimens for specific requests on an “as needed” basis. Investigators state what specimens they are seeking and frequently supply the protocol for collection, handling and storage. The repository attempts to collect specimens specifically for that request and process them according to the investigator’s specifications. A repository based on this model may not require long-term storage if the specimens will be transferred to the requestor within a short time after they are collected. Investigators initiating requests may not be able to follow *donors* over time and also must wait until the desired specimen has been obtained before testing can be initiated.

A2.120 Banking Service

Banking involves the storage of *samples* in anticipation of current and future needs. Investigators seeking a particular type of sample can approach a repository that has banked specimens to see if the desired samples are available among the existing collections. Banked specimens may be received into the repository through agreements with clinical sites, hospitals, or for non-human banks, through agreements with individuals who collect specimens routinely from field sites. Specimens are subjected to identical processing *procedures* using pre-defined

protocols to ensure standardized practices. Data associated with banked specimens may be limited to what is available at the time of collection.

One particular type of banking activity may be initiated by advocacy groups to advance research for a particular disease. Donors and families may direct hospitals and other clinical sites to send their specimens to these banks or specimens may be donated through specimen collection *containers* sent from the *donor's* residence (termed a donor's "self-collected" specimen). Advocacy-oriented banks often have associated registries containing detailed clinical and follow-up information. Samples and information from family members may also be associated with these banks.

A2.130 Population-Based Collections

Repositories that store specimen collections obtained for defined study purposes are typically collected and controlled by *custodians*. Decisions about which specimens and data are collected are typically made by an individual investigator or team of investigators as defined by the scientific goals of the study. Specimens are obtained and processed by trained field staff, clinical sites or hospitals according to best practices. Repositories of this type may be represented by a single laboratory or represent storage and processing capabilities for a large number of studies as a part of centralized repository services. These repositories may be operated by institutional staff or through contracted repository services.

A2.140 Virtual Repositories

Virtual repositories are ones that either store virtual depictions of specimens stored and analyzed elsewhere or that represent "clearinghouses" for specimens stored in repositories located elsewhere. Virtual depictions allow for new scientific questions to be addressed using specimens that have already been processed (*e.g.*, slides containing tissues prepared for immunohistochemical analysis). Publicly available data from Genome-Wide Association Studies (GWAS) would be included in this category.

Clearinghouses for physical biospecimens allow investigators to take advantage of specimens previously collected either through banking efforts or other collection activities. Information about available specimens is provided in the form of a searchable electronic inventory that can be used to identify the desired specimens. The repository provides contact information for an investigator to communicate directly with the study's custodian to learn of access policies required for the actual sharing of biospecimens. This type of repository allows investigators to be connected with resources that are currently available rather than having to initiate new collection efforts that can be time consuming and costly.

A2.200 Organizational Considerations

When planning a repository, it is important that the mission of the repository be clearly defined. The mission should address the purpose of the repository and the entities served by the collections obtained. The mission should be reviewed over time to ensure its appropriateness as conditions surrounding its implementation may change. It is important that the equipment, facilities, staffing and funding for a repository be established according to a structure that will support the mission and

activities during the anticipated lifecycle of the repository. Policies must be created, enforced and reviewed on a regular basis concerning specimen access, handling, *culling* and for the termination of the repository.

A2.210 Determination of Services to be Provided

Repositories will need to determine which services are to be provided and that the appropriate infrastructure is in place to provide them in such a way as to ensure that high *quality* specimens will be available for future research efforts. The infrastructure not only includes equipment and supplies but also the trained personnel to perform these services as needed. Services may include specimen collection, receipt into the repository, processing, storage and *distribution*. Particular *processing* may be required not only for each biospecimen type but also may depend upon the state of the specimen received (*e.g.*, fresh, frozen, fixed).

There are a number of additional services that a repository might provide in addition to the collection and storage of specimens. Examples of these include feasibility assessments to assist investigators with study planning and proposal submissions, the provision of letters of support or the establishment of collaborative relationships with investigators, *batching* of samples and inclusion of *quality control* specimens for specimens destined to be sent to a laboratory for testing, histology services, micro-dissection, nucleic acids extraction and analysis, *etc.* All services offered should be well-defined.

A2.220 Determination of Specimens to be Collected

The type of specimen that is best suited for a particular scientific investigation will depend on the goals of the particular research effort supported. Some material types are better suited for some types of analyses over others that may be less well-suited. Material type, specimen source and downstream testing plans will influence decisions surrounding how specimens are collected and processed. Repositories will also have to determine the most appropriate storage environment for the particular biospecimens it holds and ensure that the equipment and facilities are in place to support the storage of these biospecimens until they are needed.

Best Practice: Policies should be established for the acquisition of new specimens and for culling of collections (when specimens have fulfilled their original purpose or are no longer suitable for their intended purpose or if participants request the withdrawal of their specimens). See Section M3.000, Culling of Collections.

Best Practice: Effective planning efforts should consider the sources of specimen acquisition to be sure that the best specimens are obtained for the defined scientific purpose (*e.g.*, for human specimens examples could include surgical specimens or specimens obtained from autopsies). Decisions should be made early in the process to determine if any material types should be excluded from collection efforts.

A2.230 Determination of Customers Served

Repositories should develop a clear understanding as to the identity and needs of the investigators and scientific clients it desires to serve. Whenever possible, efforts should be made to understand the downstream testing planned to ensure that

the specimens being provided are collected and processed in a way to ensure the success of future research efforts.

Best Practice: Repositories should create a plan to receive feedback from users to make sure that customers' needs have been satisfied to the greatest extent possible.

A2.240 Communication

Policies governing repositories should be transparent and effective lines of communication established among stakeholders and research participants. Trust is an essential component among those donating, processing and storing the specimens, as well as among the investigators who use the specimens to pursue a scientific endeavor and efforts should be made to ensure that trust is developed and maintained.

Best Practice: Prior to the initiation of collection efforts, stakeholders should gather to talk about communication strategies to ensure that expectations are satisfied and transparency and trust can be firmly established.

Best Practice: Repositories should develop clear guidance as to what services are provided, the costs for the provision of those services, the hours services are available and contact information appropriate for each category of stakeholder for regular hours as well as for after-hour emergencies.

A3.000 FUNDING AND OTHER FINANCIAL CONSIDERATIONS

The cost for specimen collection, processing, storage and distribution can be considerable and it is important for repositories to develop a financial plan for the expected lifetime of the specimen storage and handling activities. Plans should be reviewed on a regular basis and adjusted as needed. See Section H, Cost Management for a full review of financial considerations when starting and implementing a repository.

A4.000 REPOSITORY PERSONNEL

A4.100 Director

The Director is the person with overall responsibility for management of the repository. The Director should be qualified by training and experience to direct and manage the scope of activities conducted by the repository.

A4.110 General Operations

The Director should implement policies of the organization and should be responsible for all operations, including compliance with current national, state and local regulations. Depending upon organizational structure of the repository, the Director may have other responsibilities including: (i) ensuring that the repository operates within budget, (ii) ensuring that the repository has adequate funding for operations which may require the development of cost-recovery strategies to ensure the repository's short and long-term financial stability, (iii) ensuring that an adequate policy is in place for access to the specimens stored in the repository and that requests for specimens are met in a timely fashion, (iv) serving as a liaison to key users (v) ensuring confidentiality of data and (vi) ensuring that SOPs and best practices are in place and in general use.

A4.120 Personnel Supervision

The Director should construct and maintain an organizational chart that delineates the functional relationships within the repository. Candidates for the supervisory and technical staff should be approved by the Director. The Director should also approve and maintain job descriptions and document staff responsibilities. The Director should ensure that personnel responsible for performing repository activities are adequate in number and experience, and are assigned responsibilities commensurate with their capabilities.

The Director should also be responsible for developing and reviewing employee training programs and should ensure that the repository is in alignment with all federal, state and local requirements.

A4.130 Quality Management System

The Director or other responsible party should ensure that a Quality Management System (QMS) is in place to ensure that operations follow the repository's manual of operations and standard operating procedures (SOPs) and comply with applicable requirements of governmental and regulatory organizations. The Director should require regular, documented, internal reviews or *audits* to ensure compliance with SOPs and regulations and satisfy end-user requirements (see Section D, Quality Management).

A4.140 Technical Staff

Staff should possess sufficient educational background, experience and training to assure that assigned tasks are performed in accordance with the repository's established SOPs. Technical staff should be responsible for adherence to policies and SOPs as established by the Director. Duties of each staff member should coincide with written job descriptions. Staff should 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.

A5.000 CONTRACTED LABORATORY SERVICES

Repositories that contract for laboratory services should retain records pertaining to the name and address of the contracted facility, the name and contact information for key personnel at the location where the services are being provided, documentation of the inclusive dates of the contract period and copies of the contract as well as any accompanying documentation. The scope of work for all contract services should be clearly articulated.

A5.100 Outsourcing Services

Careful planning during the development phase is critical to repository quality and cost-efficiency. Where internal resources are not sufficient to provide all necessary expertise, either during development or as a repository evolves, a repository may seek assistance from qualified external experts and consultants. Consultants should have documented successful experience (similar to that which would be sought for internal staff) in the area for which they are retained.

Repository consultants may provide expertise in areas such as strategic planning, equipment selection and decisions surrounding automation, SOP development, vendor selection, grants and cost recovery, contract management, *quality assurance* and regulatory affairs. Similarly, the repository may have contractual relationships with other institutions or service providers that provide access to facilities or services not available at the parent institution. In all of these situations, the Director should have clear documentation of the relationships, expectations, and responsibilities.

SECTION B: FACILITIES

B1.000 GENERAL

An efficient *repository* has many particular design elements to ensure the safe keeping of the material stored, support the equipment employed, and provide a safe and effective working environment for the repository staff. In planning the design of a repository it is necessary to know the types of material being stored, the required *storage* and handling conditions, the projected retention periods, projected growth of the *specimen* numbers, and the projected use of the materials. The design should include sufficient space to accommodate the material planned for initial, future and backup storage and also provide for the safe movement of people, equipment and specimens, as needed or as required by law and/or other regulatory agencies.

B2.000 HEATING, VENTILATION AND AIR CONDITIONING

B2.100 Temperature and Humidity

In most repositories it is critical to maintain ambient temperature within defined limits. Sufficient heating capacity should be provided to prevent the freezing of water in drain lines. Likewise, sufficient air conditioning should be provided to prevent excess load on the compressor systems of mechanical freezers and refrigerators that may result in excess wear and early failure. Humidity level restrictions may need to be considered when storing at ambient conditions.

Best Practice: For optimal life of the mechanical refrigeration equipment, repository ambient temperatures should be monitored and not allowed to exceed 22 °C (72 °F). This is particularly critical for rooms containing multiple mechanical units.

B2.200 Air Flow and Circulation

Sufficient air circulation should be provided to prevent excess moisture and condensation. Excess humidity can lead to fungal growth if left unchecked, which may affect specimen integrity and cause health problems for staff. Sufficient space for air circulation is required especially in areas where freezers and refrigerators are employed to prevent excess heat accumulation which may negatively affect compressor function (see Section C3.000, Mechanical Freezers). Adequate ventilation and monitoring are also critical in repositories where *liquid nitrogen* and *dry ice* are used to ensure that sufficient oxygen levels are maintained (see Section C2.400, Oxygen Sensors). Similarly, when services are performed in which potentially harmful vapors are generated (*e.g.*, formaldehyde) the ventilation system should ensure that personnel are protected and that regional and national standards for the removal of specific harmful vapors are met.

Best Practice: It is recommended that appropriate monitoring devices (*e.g.*, oxygen and CO₂ monitors) and exhaust systems are installed within areas where there is the potential for a low oxygen level to develop or harmful vapors to accumulate.

B3.000 LIGHTING

B3.100 General Lighting

Lighting in a repository should be sufficient to provide a safe working environment and to allow materials to be accurately put away and retrieved. The lighting levels required will depend on the particular spatial environment where the *samples* are stored, the type of activity that is being performed, the volume and specimen type, 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 appropriate source. Some repositories may contain materials or specimens which are sensitive to light levels or to particular frequencies of light.

Best Practice: Appropriate lighting should be planned for and used during the storage and handling of materials or specimens determined to have sensitivities to certain lighting conditions.

B3.200 Task Lighting

Task lighting may be necessary to have sufficient illumination for tightly packed materials, reading *labels*, or where overhead lighting is impaired. In situations where task lighting is employed, care should be taken that the lighting method does not adversely affect the sample integrity and the storage conditions. For example, the heat from incandescent lighting placed too close to stored material may cause a sample to thaw or partially thaw.

Best Practice: Fluorescent lighting or another type of lighting that does not create a source of heat is recommended for use in task lighting near frozen materials.

B3.300 Emergency Lighting

In case of power loss it is critical that emergency lighting be available to indicate exit routes from the repository and to provide an illuminated, safe environment to aid in monitoring equipment and responding to the needs of the emergency. Emergency lighting should have battery backup support and should be tied to backup generators. It may be beneficial to use small night lights that plug into outlets that have a battery component for low level illumination. Repositories should also have portable lighting (*e.g.*, flashlights) on hand to use as focused light sources, as needed. Focused light sources can be essential during an emergency for use in equipment diagnosis and repair. Emergency lighting should be tested on a regular basis and batteries checked on an annual basis and replaced as needed as a part of the overall *safety* and maintenance SOPs.

B4.000 FLOORING

Flooring surfaces used in repositories should be appropriate for the equipment and refrigerants used in daily repository activities. Flooring should be easy to clean and facilitate the movement of equipment when circumstances warrant. Special consideration should be given to the flooring in regions where liquid nitrogen is used, as vinyl tile will crack and cause a hazard if liquid nitrogen is spilled

directly onto it. Repositories should consider providing anti-fatigue mats for staff in areas where personnel stand for prolonged periods of time.

B5.000 BACKUP POWER

Repositories that store specimens in constant temperature environments require a constant source of electrical power. Given that all commercial power is likely to be interrupted at some time, a backup power system is required.

B5.100 Uninterruptible Power Supply

An uninterruptible power supply (UPS), uninterruptible power source or sometimes called a “battery backup” maintains a continuous supply of electric power to connected equipment when utility power is not available.

A UPS is inserted between the source of power (typically commercial utility power) and the load it is protecting. When a power failure or abnormality occurs, the UPS will effectively switch from utility power to its own power source almost instantaneously.

Best Practice: Computer systems and electronic systems, such as *environmental monitoring systems*, safety systems (e.g., oxygen sensors, ventilations systems) or controllers for liquid nitrogen freezers, should be protected by a UPS. UPSs used in repositories should be tested on an annual basis to ensure their proper backup capabilities.

B5.200 Generators

The most common type of backup power is a motor generator. Generators have automatic controls that cause them to produce electricity when commercial power is interrupted. Typically they are fueled by diesel, natural gas or propane. Where it is available and appropriate, natural gas supplied by a pipeline may serve as an optimal source, since it can serve as an unlimited source of fuel provided supply lines are not interrupted. The actual backup system employed should be determined based upon a risk management assessment of the facility, region and resources.

Dual fuel generators that can run on more than one type of fuel (e.g., natural gas and propane) provide a high level of flexibility for fuel supply sources. Manual transfer switches in addition to the automatic transfer switches can be installed which allow for set up of quick disconnects which enable portable generators to be brought in and connected in a matter of minutes. Each outage scenario and desired outcome needs to be evaluated up front to ensure expected infrastructure is in place. For large repositories, the decision to have one large generator or multiple smaller ones to support the facility will also come out of risk assessment exercises.

Based on risk tolerance assessments and financial stewardship, it may be determined that a backup generator support only designated pieces of equipment deemed critical.

Best Practice: A generator should have a fuel supply to run continuously for a minimum of 48 hours and preferably a minimum of 72 hours, with an ability to re-fill fuel storage supplies.

Best Practice: Repositories that utilize generators should have an established plan for sources to replenish fuel supplies in case of an emergency. This plan should include lists of suppliers and backup suppliers committed to provide the fuel as needed.

Best Practice: Repositories should contact suppliers to be placed on a list as an entity that receives a quick response should an emergency situation arise.

B5.210 Generator Tests

To ensure the likelihood that backup power systems will function reliably when needed, they should be routinely tested to ensure that the system will start on demand and carry the required load. Load tests should be performed to ensure that the generator can function within specifications under full load. Additionally, for facilities that have bulk diesel storage, annual testing and filtering of the fuel should be performed to ensure that excessive water or bacterial build-up which can affect performance of the generators has not occurred.

Best Practice: The power generator system should be included in a frequent preventative maintenance plan, which includes weekly testing for automatic starting and power generation and load tested monthly. If load testing places sensitive equipment at risk, the generator should be tested less frequently. Those systems that have an automatic transfer switch should also be tested on a periodic basis (e.g., every six months).

Best Practice: Repositories located in or associated with larger facilities (e.g., hospitals or universities) that automatically initiate backup power upon power interruption should link their freezers and other essential equipment into these emergency systems. The operational safety and testing should be performed by professional caretakers of the larger infrastructure.

Best Practice: Staging of the sequence of start-up of mechanical freezers and other systems should be considered to ensure sufficient downtime to allow the compressors to come to rest before restart.

B6.000 ACCESS

Repositories should be equipped with a system that adequately limits access to appropriate staff and protects against physical intrusion from unauthorized individuals. Doors should be locked. Keys should be controlled, with a record maintained of each person having access to the repository. Some repositories may employ magnetic locks which control and record entry. Only persons assigned to 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: Mechanical keys employed in a repository should be ones that cannot be readily duplicated.

B6.100 Visitor Access Policy

An access policy should be developed for individuals visiting the repository. Where feasible and appropriate, sign-in sheets or log books should be used to record the name, affiliation of the visitor, purpose of the visit, as well as track the time at which the visitor(s) enters and leaves the repository. Badges can be made available for the visitors that clearly indicate to staff that they have been formally received and their presence documented. Visitors should be accompanied by staff at all times during their visit.

Best Practice: When written or electronic records of repository visitors are maintained, the records should be maintained and archived according to the repository's established archive practices.

B7.000 SECURITY SYSTEMS

Every repository should employ basic security systems to ensure protection of the specimens stored therein. The systems should be monitored and alarms responded to twenty four hours per day, seven days per week. A responsible individual should be available at all times to take the necessary action(s) to respond to an alarm in a time frame that prevents or minimizes loss or damage to the stored materials. Systems should initiate calls to other staff trained in emergency response when the first individual fails to acknowledge the alarm.

B7.100 Intrusion Detection Systems

When either the repository or the building in which it resides is not occupied by authorized personnel, a system should be in place to detect unauthorized entry. Motion detectors, glass break and door entry sensors should be integral components of the system. As appropriate, the system should accommodate changes to security codes and keys when individuals leave the organization.

B8.000 FIRE PREVENTION

In many countries and municipalities a fire prevention system is required by building codes for newly constructed facilities and compliance with codes is usually required if a facility is being converted or renovated.

B8.100 Fire Prevention Plan

Repositories should have a written fire prevention plan. The plan should include a list of major fire hazards, potential ignition sources, proper handling and storage *procedures* for hazardous materials, and the type of equipment necessary to control each major hazard. The plan should address procedures for regular maintenance on equipment used to prevent or control sources of ignition or fires and name or job title of employees responsible for maintaining the equipment.

B8.200 Detection Systems

Automatic fire detection systems are used to quickly identify a developing fire and alert occupants and emergency response personnel before extensive damage occurs. Automatic fire detection systems do this by using electronic sensors to detect the smoke, heat, or flames from a fire and provide an early warning. Fire detection systems should be tested regularly to maintain proper reliability and

operating condition by a trained person knowledgeable in the operations and functions of the system. Fire detectors should be selected based on the burning characteristics of the materials present and the nature of location they will be used to protect.

B8.300 Fire Extinguishing/Suppression Systems

B8.310 Sprinkler Systems

The most common type of fire suppression is a sprinkler system that sprays water upon activation. 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 such a 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. Special consideration should be used if sprinkler systems are deployed in proximity to cold rooms where slip hazards could be an issue.

B8.320 Non-Water-Based Fire Retardants

Due to the nature of certain equipment and stored materials, water may be an unsuitable tool for fire suppression. In these instances, other chemicals may be employed. The chemicals used in these systems generally smother the fire by cutting off the supply of oxygen. While these systems can be very effective and may be critical for valuable *collections* adversely affected by exposure to water, they are costly and may present safety hazards. Although the majority of these suppressants do not represent a health risk to staff upon activation, personnel should receive appropriate safety training.

Most facilities provide dry chemical fire extinguishers. The suppressant is somewhat corrosive. If used in proximity of mechanical freezers the dry chemical released can be pulled into the compressor area and damage the unit. There is also risk of specimen contamination as it is difficult to fully remove and clean up the powder in these areas.

Best Practice: Use extinguishers that contain a non-corrosive gaseous suppressant in repository areas.

B9.000 EMERGENCY PREPAREDNESS

B9.100 Emergency Response Planning

Emergencies can cover a wide range of natural and man-made disasters, all of which may have varying effects on the facility and on the ability of the repository to carry out its essential functions. The type and duration of disasters may depend on the geographic location at which the repository is located. Depending on the “value” and the ability to replace certain samples, some repositories may decide to divide collections and store them in different environmental storage *containers* or even at different geographic locations so that a disaster affecting one component of the collection would not eliminate the entire collection.

Repositories should have a written disaster recovery/*incident* response and business continuity plan for responding to a wide variety of emergency situations. This plan should be tested periodically (*i.e.*, at least annually) to ensure that all personnel are trained and that the plan meets the anticipated needs. Copies of these plans should be distributed to all appropriate staff.

Key individuals should be identified who will serve as being “on call” or who will be able to respond to an emergency at the repository. Leave and vacation schedules should be monitored to ensure that coverage of essential responsibilities is in place should key individuals be unavailable. Emergency contact numbers should be posted in prominent locations in the repository and should be carried by staff members at all times who are “on call”. The contact information should be reviewed on a regular basis to ensure that the information contained therein is current.

Best Practice: The Director or appropriate staff member should communicate with local power providers before an emergency occurs to request that the repository be placed on a list of “high priority” users for power restoration following an emergency.

Best Practice: Repositories should have a check list of activities for “on call” staff to follow during an emergency. “On call” staff should be familiar with the location and operation of certain key equipment and controls (*i.e.*, circuit boards) that may need to be checked during an emergency. Telephone numbers for professional assistance should be clearly posted in the repository and accompanying administrative areas (*e.g.*, engineering or facilities personnel, power companies, fuel supply companies and transportation services).

Best Practice: Notification of security and environmental monitoring systems should be verified on a routine basis. Where possible, emergencies should be simulated to ensure proper follow-through for the established emergency plan.

Best Practice: If repository inventory systems are housed on a server located away from the repository, some consideration should be given to storing electronic inventory records on site. Otherwise, in an emergency, needed records may not be accessible.

Best Practice: In the event of an impending need for evacuation, repositories that utilize LN₂ bulk tank(s) should arrange to have them filled.

B10.000 RELOCATION OF A REPOSITORY

There are times that require repositories to be moved from one site to another. Such situations may be caused by the inability to renew a lease if repository space is leased or possibly because the special requirements have changed, either due to expansion or reduction of the collections housed within the repository. Since many considerations must be made to ensure an orderly transfer of equipment and supplies, planning should begin as early as possible to ensure the effective transfer.

The requirements for the new space should be well documented and complete and should meet the anticipated growth for the period of time for which it will be

occupied. Stakeholders and staff should be included in discussions to ensure that all details are attended to and that all training needs are met for handling the collections in the new location.

Move(s) should be planned over a period of time that will allow for effective responses to any challenge that may arise. Empty, cold, environmental equipment for all storage temperatures reflected in the collection to be transported should be operational and stabilized to receive specimens in the event of a failure of a particular unit during transit. Equipment maintenance professionals should be alerted to the date and time of the move to ensure the likelihood of their rapid response. To the greatest extent possible, repository staff should ensure that shippers, carriers and drivers follow all regulations for movement of hazardous and infectious materials.

Best Practice: A map should be created for the new site that will indicate the location of all equipment and materials that will be transferred prior to the initiation of the move.

Best Practice: Planning should include review of current processes to ensure that efficiencies can be incorporated into the new space.

Best Practice: The details of how the relocation is to be accomplished (*e.g.*, a description of the plan, timelines, roles of staff and contract support) should be documented to ensure that those involved are fully aware of schedules, costs and to ensure that the transition process is carried out effectively and appropriately.

SECTION C: STORAGE EQUIPMENT AND ENVIRONMENTS

C1.000 GENERAL

The variety of *storage* systems available for specimen *collections* continues to expand as technologies advance. Storage equipment selections should be based on the type of *specimens* to be stored, the anticipated length of time the specimens will be stored, the intended use for the specimens and the resources available for purchasing the equipment. Also important are the size and physical design of the *repository* and the number of specimens stored (as well as predictions for future growth in number of specimens stored). Some freezers and refrigerators now provide automated *sample* entry and *retrieval* components which may reduce long-term costs for the repository. Often these larger systems are accompanied by increased initial costs which may be more than smaller repositories are capable of supporting. Equipment selections should take into consideration staffing requirements, *quality* issues, available resources and equipment support and maintenance.

As costs for maintaining repositories have continued to rise, every effort should be made to keep the costs for operating equipment to a minimum. Recent developments in energy-efficient equipment can generate significant savings on facility costs. Several manufacturers are making use of compressor systems that are cooled either by water, where available, or by placing condensers on the exterior of the building so that the heat released from equipment does not have to be counter-balanced by heavy HVAC requirements. Other energy-saving storage solutions are being introduced to repositories that allow for ambient storage for some material types, eliminating the need for maintaining low-temperature storage environments to ensure specimen integrity (Section C6.000, Ambient Temperature Storage).

C2.000 LIQUID NITROGEN FREEZERS

The use of *liquid nitrogen* (LN₂) freezers for long-term specimen *preservation* is optimal for the storage of some types of biological material, provided that the critical temperature for storage of those materials is not exceeded. Cryogenic storage using LN₂ is an effective long-term storage platform because the extreme cold slows most chemical and physical reactions that cause specimens to deteriorate and because on-site LN₂ supplies reduce reliance on mechanical freezers that use electrical power.

While LN₂ storage has been traditionally reserved to *containers* that either hold LN₂ in the base of the freezer or which hold enough liquid for specimens that are submerged in LN₂, equipment is now available that allows for LN₂ to be used as a coolant to allow for storage temperatures in the -80 °C range. This type of cooling may have the advantage of being able to cool specimens in the event of a power failure. A comprehensive assessment of available choices in equipment design needs to be made prior to making any new purchases.

C2.100 Vapor or Liquid Storage

When considering storing in LN₂ vapor phase (≤ -150 °C) vs. submersion in liquid phase (-196 °C), vapor phase storage is preferred because it provides

sufficiently low temperatures to maintain samples below the T_g (*Glass Transition Temperature*; -132 °C) while avoiding the *safety* hazards inherent in liquid phase storage. Many commercially available vials are penetrable by liquid nitrogen so vials selected for storage should be tested before they are used. Certain containers, like cryogenic straws, are hermetically sealed and specifically designed for the safe storage of specimens in the liquid phase of nitrogen.

C2.200 Storage Containers

LN₂ expands 700 to 800 times its original volume when brought to a gaseous phase at room temperature. This situation may produce an explosion hazard. Glass, metal and some plastic containers can explode if LN₂ is trapped inside the container when it is removed from the freezer.

Best Practice: Any container used or stored at cryogenic temperatures should be rated for these temperatures.

C2.300 Liquid Nitrogen Supply

Where LN₂ refrigeration is employed, an adequate supply of LN₂ should be maintained. For freezers filled from *Dewars* or supply tanks, a minimum three-day supply of LN₂ at normal usage and replenishment intervals should be maintained, with the assumption that a re-supply is readily available. Bulk supply systems should maintain at least three days' working capacity. Bulk supplies should be checked for re-supply at least once a week. A *telemetry system* may be installed to allow suppliers to monitor liquid levels in real time to ensure stocks do not drop below agreed upon levels.

Bulk storage and piping 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 excessive pressure, a number of relief valves may vent nearly simultaneously. This can cause a "whiteout" condition in a matter of a few seconds. Visibility can drop to near zero and oxygen levels in the area may become less than that necessary to sustain life. Under these circumstances personnel should evacuate immediately. For this reason, O₂ monitoring should be installed in any areas of the facility where bulk LN₂ is utilized (See Section C2.400, Oxygen Sensors).

Best Practice: Daily LN₂ usage should be recorded either by monitoring the display levels or by manual means as excessive LN₂ usage can indicate problems with the vacuum component of the freezer.

C2.400 Oxygen Sensors

Because nitrogen displaces oxygen, care should 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. Normal levels of oxygen in ambient air should be ~21%. Most installed oxygen sensor units have batteries or sensor cells that should be replaced and re-calibrated every few years. Consult the manufacturer for recommended requirements.

Both fixed 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.

C2.500 Personal Protective Equipment

In addition to the oxygen deficit risks described under Section C2.400, use of LN₂ as a refrigerant poses special safety problems because of its low temperature and rate of expansion when placed at ambient conditions. Eye protection is mandatory every time LN₂ is handled to protect against splashes that inevitably occur. Face and eye protection is recommended when handling vials removed from a LN₂ freezer or when dispensing LN₂ from low pressure lines. Heavy gloves (appropriate for LN₂ use) should be worn to protect hands when handling samples stored within the liquid phase or when transferring LN₂ or other coolants to Dewar flasks. Normal laboratory personal protective equipment (*e.g.*, closed toed shoes, full cover of legs and feet and goggles) should be worn when handling coolants. The use of protective equipment, goggles and gloves, in particular, should be mandatory when handling cryogenics and the equipment should be placed in an easily accessible and visible location. Appropriate training in the safe handling of cryogenics should be provided and included in an SOP, describing the potential health hazards and required safety precautions.

C3.000 MECHANICAL FREEZERS

Mechanical freezers are employed in a variety of storage temperature ranges and come in a wide variety of sizes, configurations, and electric voltages. Because these are devices attached to commercial power systems, a backup power plan and emergency response plans should be in place (see Section B9.000, Emergency Preparedness). The length of time that results in the significant warming of the stored material will vary by the properties of the stored material, the temperature of the material stored in the freezer, the ambient conditions and the design and maintenance of the unit. It is the responsibility of the facility operator to establish and enforce the critical temperatures and response times to alarms.

Some mechanical freezers are equipped with emergency backup systems that automatically cool their contents with either LN₂ or liquid carbon dioxide (CO₂) in the event of an extended power loss. Any freezer implementing this type of emergency backup cooling system should be specifically designed to accommodate whatever coolants are utilized and adequate supplies of refrigerant gas should be kept on hand at all times to operate the system. Safety precautions with the backup system (O₂ or CO₂ monitoring systems) should be taken into consideration in the event of an emergency situation.

Independent of backup cooling solutions, efforts should be made to ensure that freezers (as well as refrigerators) are positioned in repositories to allow for

adequate air flow. Insufficient distance between units or between units and walls may lead to overheating of compressors that may shorten compressor life. In addition, inadequate air circulation may lead to the growth of mold and other harmful microbial contamination situations.

C4.000 REFRIGERATORS

Refrigerators are commonly employed where the longevity of the material being stored is enhanced by storage below ambient temperature. This is the preferred storage medium when the material should be kept cool, but does not require freezing. Refrigerators may also be used for storage of media and additives. 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 should be maintained precisely between 2 °C and 8 °C. The facility operator should ensure that temperatures are monitored.

C5.000 WALK-IN ENVIRONMENTAL STORAGE SYSTEMS

C5.100 Compressors

For the storage of valuable materials, walk-in refrigerators and freezers should be equipped with dual compressors that operate under an electrical alternating control system.

C5.200 Door Release

In most countries building codes require that walk-in units have internal safety releases to prevent a person from being trapped within a unit by the accidental closing of doors (*e.g.*, interior door release mechanism).

C5.300 Floor Covering

Refrigerators can generate slipping and falling hazards if water condenses on the floor. Freezers can occasionally create ice on the floor, or water if the unit is defrosting. Some type of mat or grate should be placed in front of these types of units to prevent slipping.

Best Practice: A warning sign should be posted at the entrance of walk-in cold storage areas advising that the area may be slippery.

C5.400 Dry Ice

Walk-in freezers should be kept free of *dry ice* (*i.e.*, the solid phase of CO₂). Carbon dioxide can rapidly build-up, displace the oxygen in the room, and cause personnel working in the units to lose consciousness. In confined areas the CO₂ can displace oxygen, presenting an asphyxiation hazard. Where dry ice is employed there should be adequate ventilation to ensure that sufficient air or oxygen levels exist. In these circumstances, it is recommended that walk-in freezers have both oxygen and CO₂ monitors.

C5.500 Motion Detection Devices

Because of the special hazards involved in personnel working in a -20 °C or colder walk-in environment, it is desirable that some form of monitoring system be employed. This is especially applicable if only one person is working in the

freezers. Systems which detect and alarm when motion does not occur are readily available (such systems are commonly employed by firefighters and other emergency personnel.)

Best Practice: For a -20 °C or colder walk-in environment engineering controls may be designed to support an audible alarm system coupled with a safety *procedure* to allow for the safest operating conditions.

C5.600 Contamination Issues

Contamination by fungus can frequently develop in cold rooms. This is facilitated by storage of non-specimen materials in containers such as cardboard boxes. It is, therefore, important to periodically survey the cold area to eliminate factors (*e.g.*, damp, unclean areas, cardboard boxes) that can facilitate fungal growth. Similarly it is not appropriate to use cold rooms to store hazardous or flammable material, or food. Periodic monitoring of cold rooms should be encouraged to visually monitor for fungal contamination and for items that may be inappropriately stored. Repositories should consider the use of built-in dehumidification systems.

C6.000 AMBIENT TEMPERATURE STORAGE

Recent developments have allowed for the identification of biological storage matrices that allow for long-term maintenance of certain biological components at room temperature. These matrices have been used for the storage of RNA and DNA and soon are expected to be available for other biological materials. They may be helpful when mechanical or cryogenic equipment is not available or may serve as an alternative method for back-up storage for some material types (Wan *et al.*, 2009). Prior to implementation, all matrices should be evaluated to be sure that they are appropriate for downstream applications. See also section D6.000, Validation of Sample Processing Methods.

C7.000 BACKUP STORAGE CAPACITY

Adequate backup capacity for low temperature units should be maintained in anticipation of possible equipment failure. If space and funds allow, backup storage should be available within the repository. Where this is not possible, repository staff should identify backup space in a nearby facility to allow for transfer of specimens in case of an emergency. Storage cabinets for ambient-temperature storage of biospecimens can be equipped with passive or active humidity controls to maintain biospecimens preserved at ambient temperature. These storage cabinets can be fully integrated with automation and robotic controls as well as tracking and sample management software.

Best Practice: Extra capacity equipment should be equal to the capacity of the largest single storage unit and should be maintained in reserve at operating temperature.

Best Practice: The total amount of backup storage required for large repositories should be determined empirically, but will typically be 1.5% to 3% of the total freezer capacity for liquid nitrogen storage and will be 10% for mechanical freezer storage. Backup space should be available in the repository, if possible.

Best Practice: Repositories should have a written procedure for transferring samples from a failed or malfunctioning unit (one that has exceeded or is on the verge of exceeding its acceptable operating temperature range or become over-filled) and for the return of the samples to their original location once it is considered safe to do so. The procedure should include the freezer or refrigerator name or number as well as the location within the freezer where the samples have been relocated.

C8.000 ENVIRONMENTAL MONITORING SYSTEMS

Acceptable temperature ranges should be determined for any specimen storage equipment that is designated for operation at a particular temperature before the equipment is put into service. Temperature ranges allow for normal operating variations and provide some variation for warming when the material is accessed. It is important to understand that temperature probes measure the temperature where the probes are located; therefore different locations in the equipment might exhibit different temperatures depending on the size and age of the unit as well as other factors. Also note that freezers and refrigerators that are full will likely display temperature readings that are different from readings taken when the equipment is empty.

Once placed in service, daily and continuous monitoring practices and systems should be used for evaluating the performance of all fixed temperature storage units. Storage units with defined environmental conditions should have temperature-monitoring devices that can be visually inspected on a regular basis (*e.g.*, a chart recorder or unit controller display).

In addition to regular temperature monitoring activities performed by repository staff, an automatic temperature monitoring system should be utilized that continually monitors temperatures of all critical equipment and other important parameters, creates logs, generates *audit* trails and generates alarms to notify personnel trained in emergency preparedness to respond. An option to have an audible alarm for those individuals physically present in the repository can be beneficial as well.

The alarm notification system should call or page the individual “on call” (or should activate the “on call” list) rather than simply providing passive notification (*e.g.*, provide computer generated notification which should be monitored by staff). This call should continue down the list of contacts until it is acknowledged.

Depending on the size of the repository and number of staff available, more than one individual should be available at all times, in case the first individual is in a location where they cannot receive or respond to the notification. Alarm conditions should be responded to in a time frame that minimizes the likelihood of damage to the stored material. Repository management should assure that personnel with adequate training who can take corrective action should be available or reachable 24 hours per day; seven days per week (see Section C9.000, Equipment Maintenance, Repair and Replacement).

One additional method for automated temperature monitoring involves the connection of thermocouple wires from the “dry” temperature contacts to the building security system. The wires may be run from one freezer to the next to minimize the number of wires and the length of wire needed. The alarm point for these probes should be set a few degrees higher than the alarm point of the automatic monitoring system. An alarm obtained through this type of backup system will not indicate which unit is in alarm, but will provide additional backup if a failure occurs in the monitoring system.

Visual inspection of equipment temperatures should be performed regularly (at least three times a week) and a record kept of the temperatures observed. Temperature records should be verified by supervisors on a monthly basis. In addition to monitoring the current equipment conditions, regular recording and review of temperatures provides a way to spot trends which may provide an indication of degraded performance or incipient failure.

Temperatures should be monitored during extended periods of freezer access to ensure that safe temperature ranges are not exceeded. Attention should be given to the fact that warming may not be immediately reversed by closing the freezer or refrigerator.

Best Practice: When possible, a temperature profile of the freezer or refrigerator should be performed prior to its initial use so that warm and cold spots that could be problematic for material storage can be identified (Section 9.200, Verification of Equipment Functionality).

Best Practice: In repositories where samples are stored in the vapor phase of liquid nitrogen, staff should regularly employ a technique whereby a physical measurement of the liquid nitrogen level is taken with a tool such as a dipstick to confirm the liquid nitrogen level. Alternatively, probes may be placed at various levels in the freezer to monitor liquid nitrogen levels (*e.g.*, temperatures below -196 °C indicate that the probe is submerged in liquid nitrogen and temperatures warmer than -196 °C indicate that the probes are in the vapor phase of the chamber.) If a tool is used to measure liquid levels it should be treated with ethanol, bleach or other *disinfectants* for the purpose of disinfecting the tool before and after it is used.

Best Practice: Alarms should be tested on a regular basis (*e.g.*, weekly or monthly) to ensure proper functioning and call-out to pagers and other notification devices used by staff that are “on call”.

Best Practice: In repositories that use an automated *environmental monitoring system*, periodic review of temperature profiles or trends should be employed to ensure consistency between the controller display values and the environmental monitoring system values. This practice will allow staff to proactively evaluate each unit’s performance and determine if any maintenance work is needed.

C9.000 EQUIPMENT MAINTENANCE, REPAIR AND REPLACEMENT

A system for preventative maintenance and repair of storage equipment, supporting systems and facilities should be in place. System maintenance should be performed at regular, established intervals per manufacturer’s

recommendation. Equipment exposed to infectious (or potentially infectious) materials should be properly disinfected. The choice of disinfectant to be used depends on the particular situation. Some disinfectants have a wide spectrum (kill many different types of microorganisms), while others kill a smaller range of disease-causing organisms but are preferred for other properties (they may be non-corrosive, non-toxic, or inexpensive). For example, bleach should not be used on stainless steel as it can result in pitting of the metal and damage to the equipment.

C9.100 Calibration

A system for the *calibration* of all instruments should be in place. Any device that provides analog or digital measurements is considered an instrument and requires calibration. Calibration should be done annually or per manufacturer's recommendation. Calibration should be performed against standards established for the country in which the repository resides.

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

Best Practice: A log of calibration records should be kept that includes the date of the calibration, the name of the individual performing the calibration, the name of the device used against which the instrument is calibrated, and a reference to the standard operating procedure used to perform the calibration.

C9.200 Verification of Equipment Functionality

The proper performance of all equipment should be verified or qualified prior to use or following repairs that affect the instrument's measuring capabilities. Documentation of the testing should be maintained and made available for audits. The repository Director should ensure that all required regulatory practices are implemented.

C9.300 Equipment Preventative Maintenance and Repair

Essentially all equipment comprised of multiple components wears out with time and exposure to various environmental conditions. The duration of the lifetime for equipment used in the repository may be significantly extended by performing routine assessments and modifications to the equipment according to the manufacturer's specifications. For mechanical freezers this may include a periodic changing out of fluids, cleaning of filters, calibration of probes, or manually removing ice from the tops and sides of the interior chamber of the freezer. Routine maintenance recommendations should be determined before a piece of equipment is put into service. Frost-free freezers should be avoided, since the daily heating cycle built into the doors of these models will gradually cause deterioration/*desiccation* of specimens stored near the doors and walls of the unit.

Maintenance records should provide a description of the cause of the equipment failure (where possible), the date on which the *incident* occurred and was observed (these dates may be different), the corrective action that was taken, tests

that were performed to verify proper functioning of the equipment, and the results compared to available standards and manufacturer recommendations.

Best Practice: Well-qualified personnel with expertise in monitoring and repairing repository equipment (especially freezers and refrigerators) should be used for regular and emergency repairs. These trained technicians may be on the repository staff, may be on staff within the larger organization within the institution in which the repository resides, may be available through a “fee for service” arrangement with a commercial entity with this expertise, or repair services may be obtained from a similar entity on a retainer basis.

Best Practice: Repositories should maintain spare parts for critical equipment, especially for aging equipment for which parts may not be readily available.

C9.400 Repair vs. Replacement

While most manufacturers of repository equipment offer projections for the expected lifetime of that equipment, actual lifetimes vary depending on a variety of factors including preventative maintenance, availability of replacement parts, environmental conditions in the area in which the equipment is located, etc. For example, manufacturers of mechanical freezers offer projections of lifetimes that range from 8-12 years, but actual lifetimes might run for a period of 5 to 15+ years. Liquid nitrogen freezers may have lifetimes extending through 10 to 35 years.

Long-range plans should be made to address the possible repair and replacement of equipment essential to the functioning of the repository. When multiple repairs are required, the additional cost of making those repairs may lead to a decision to have the unit replaced. Since replacement of freezers and refrigerators can be expensive, it is best to anticipate these costs and have some financial reserves available to address this when decisions to replace equipment are made.

Best Practice: Repositories should plan for the orderly replacement of equipment. If multiple pieces of the same equipment need replacement at one time, it might be best to use interim equipment or backup equipment while introducing the new equipment in over time. This allows for a gradual introduction of new equipment so that likely repair and replacement schedules are likely to be staggered.

Best Practice: Resources for equipment repair and replacement should be identified when the repository is being established before an emergency is experienced. These resources should be reviewed on an annual basis.

Best Practice: Before new equipment is purchased, an evaluation should be performed to identify the most energy-efficient equipment that effectively addresses the needs for that equipment. Attention should be given to the expected life of the equipment (*e.g.*, mean time between failures).

SECTION D: QUALITY MANAGEMENT

D1.000 GENERAL

The purpose of a *repository* is to supply biological materials and their associated data in a form that meets specific *quality* criteria and is provided in compliance with all necessary regulatory and statutory obligations. Therefore, a *Quality Management System* (QMS) that includes *Quality Assurance* (QA) and *Quality Control* (QC) programs should cover the full spectrum of a repository's operations. The implementation and maintenance of a Quality Management System contributes to the long term sustainability of repositories. These systems support the delivery of high quality services to end user communities and in doing so sustain the business, utility and research viability of *collections*.

Repositories must be able to carefully track each of the *specimens* that are received, processed and distributed from the facility. Accuracy and timeliness are critical to ensure their effective future use. Systems should be established to verify that all specimens are handled appropriately. Such systems involve standard operating procedures (SOPs) which are accurate descriptions of tasks performed and may involve the verification activities by more than one repository technician or by a supervisor. When manual processes are followed, double checking of records may be required to ensure that appropriate steps have been taken.

Quality Assurance is an integrated system of management activities involving planning, implementation, documentation, assessment, and improvement to ensure that a process, assay or product is of the type and quality needed for the project. Quality Control is the system of technical activities that measures the attributes and performance of a process, assay, item or product against defined standards to verify that the stated requirements are fully met. The QC process also confirms the authenticity of a collection's holdings (*e.g.*, reference strains and cell lines).

Each repository should have a Quality Management System (QMS) or adhere to the 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.

If it is not possible to have a formal Quality Management System with dedicated staff, then a policy should be in place to review *procedures* and records to assess the efficacy and quality of repository operations. This review should be conducted at least on an annual basis (Von Versen *et al.*, 2000; Betsou *et al.*, 2008).

D2.000 STAFF RESPONSIBILITIES

Responsibility for quality management should be assigned to a staff member whose responsibility is to ensure repository staff is trained to comply with quality standards and provide regular guidance and instruction to all personnel who should have a collective responsibility for assuring compliance with SOPs, policies and regulatory requirements. 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. A repository should have a clear policy and create a system for reporting, documentation and follow-up of any *deviation, incident* or failure and personnel should be trained and encouraged to report deviations. QMS personnel should be responsible for implementing both audits and accreditation processes.

D3.000 QUALITY MANUAL

A repository should create a manual which makes a clear quality statement and describes the roles and responsibilities of staff within and connected to the repository's operations and infrastructures in compliance with regulatory and health and safety obligations. Such a manual could be a separate Quality Manual, or could be incorporated into the repository's Procedures Manual or Manual of Operations. The manual may reference all the procedures which are required to ensure that QA/QC objectives are fulfilled.

Each repository should develop policies and procedures in a standardized written format (Standard Operating Procedures or SOPs) that are incorporated into a manual. These SOPs should be utilized to ensure that all *samples* are appropriately and consistently collected and stored so that they may be effectively disseminated for subsequent uses. Personnel should be trained in the use of the SOPs which should be reviewed on a regular and routine basis or in response to accidents, incidents and failure to conform to the QA/QC system.

Best Practice: Where possible, it is advantageous for a repository to share their quality practices to ensure commonalities for specimen integrity and associated data.

D3.100 Essential Components for Standard Operating Procedures

SOPs serve as the description of how tasks pertaining to repository operations should be handled by staff assigned to those specific responsibilities. SOPs allow for uniformity and reproducibility in specimen handling. SOPs should be written by an individual or group of individuals with experience in successfully performing the processes described and should be managed in a document management system (see Section G, Records Management). Draft SOPs should be reviewed before they are finalized.

Essential features of an SOP are included in the following list of components:

- Title – a unique name which captures the essence of the practice described.
- Number – a unique number that can be used for easy reference.
- Date – date the procedure was first introduced as well as the date of the most recent version.
- Version Reference – system for tracking version number and/or date to ensure the most recent version is used.
- Department/Division/Staff Covered – individuals to whom the SOP will apply.
- Purpose- brief description of the process(es) described in the SOP.

- Protective Wear – protective equipment that should be worn by staff when performing the procedure described.
- Equipment – list of the equipment needed to perform the procedure. Equipment description may include but is not limited to the name, model, date of purchase, serial number, inventory tracking number, and manufacturer.
- Supplies – all materials and supplies needed to perform the procedure should be recorded. The SOP may direct the user to maintain a record of the vendor, catalog number, lot number and expiration dates for the materials and supplies utilized.
- Step-by-Step Guidance – the procedure should be written in specific detail to ensure that it can be repeated in a reproducible fashion to include the order of steps that should be followed, the times allowed for each step (as needed) and the temperatures at which the steps are to be performed.
- Safety – describes any *safety* steps associated with the procedures and reference any relevant SOPs involving safety.
- References.

D3.200 Critical Topics for Manual of Operations

The manual should specifically include, but should not be limited to procedures regarding the following:

- Specimen handling.
- Laboratory procedures for tests performed in-house and any specimen *aliquoting* or other specimen processing.
- Where appropriate, human subjects protection documentation, including *informed consent*, privacy and confidentiality protections, and other legal, ethical and cultural issues.
- Where appropriate, access and sharing of specimens and associated data.
- Shipping and receiving of specimens.
- Relocation of specimens within a repository as equipment and environmental needs warrant.
- Records management practices. These should include policies regarding the shredding of confidential documentation at the appropriate time.
- Quality Assurance (QA) and Quality Control (QC) for instruments, reagents, *labels*, and processes employed in sample collection, processing, storage and *retrieval*.
- Equipment qualification, maintenance, repair, *calibration*, upgrading and replacement.
- Maintenance of essential support systems (*e.g.*, LN₂ supplies, electricity, extra power supply, temperature control system).

- Safety programs including documentation of staff *ergonomics*, safety-related incidents, injuries and exposure to potential human pathogens and notifiable animal/plant pathogens and agents under biological control.
- Investigation, documentation and reporting of incidents and near miss incidents, errors, complaints and *adverse outcomes*.
- Emergency response procedures.
- Disposal of medical and other hazardous waste.
- Training programs.
- Introduction of new personnel.
- Validation and documentation of the IT system including backup routines.
- Customer relations, forms and agreements.

D3.300 Implementation

Either the repository Director and/or the individual responsible for the QA Program should review and approve all SOPs and associated *process validation studies* prior to implementation. Upon implementation, all SOPs should be followed as written.

D3.400 Modifications

D3.410 Documents

Documents are materials that provide, publish and disseminate information. Each repository should have document control policies in place that govern retention and modifications or revisions to SOPs or other documents. Prior to implementation, each modification should be approved by the Director and other appropriate individuals. Implementation dates should be recorded for all procedures.

A system should be in place to ensure that only current versions of documents are available for use and that previous revisions are removed when new revisions are issued. Old versions of documents should be removed and archived when new revisions are issued.

D3.420 Records

Records ('historical footprints') comprise information compiled as registered and recorded evidence that is permanent and traceable. Records cannot be modified. Record keeping should be formalized and the person in charge of quality should ensure records are stored under secure/safe conditions and made accessible for inspection by authorized internal and external auditors (*e.g.*, regulatory, health and safety accreditation inspections).

D3.500 Review of Standard Operating Procedures

SOPs should be reviewed regularly (at least every two years or when policy or methods change) to ensure the current policy and/or method for performing the procedure is described. A system should be in place to document the revision number and date of release of the revised document.

D3.600 Staff Access and Review

Current copies of the SOPs should be stored in designated locations and available to the staff at all times. New and revised policies and procedures should be read by the staff prior to implementation.

Best Practice: A system should be in place to document staff review of the most recent versions of an SOP.

Best Practice: Training associated with SOPs should be maintained in a training record (see Section F2.700, Training Records).

D4.000 QUALITY STANDARDS

A variety of systems have been devised to allow for confidence and reproducibility in repository practices. Each system described in this section has been developed to ensure that good practices are in place, complete with careful documentation and traceability. While each of the standards described below are resources for repositories, there are costs involved in the attainment of each standard and all the standards may not be appropriate for every repository.

D4.100 Current Good Practices

Current Good Practices (cGP) are regulatory guidelines that should be interpreted by the repository to fit its particular circumstances. cGP may be preclinical (Good Laboratory Practice, or GLP), clinical (Good Clinical Practice or GCP) or manufacture (Good Manufacture Practice, or GMP). cGP may be more relevant to large corporate repositories, but academic and other small repositories may wish to aim toward cGP guidelines to instill confidence in the implementation of their SOPs. Generally, these standards are interpreted as follows:

- The facility is in a secure, locked area with limited access for unauthorized persons.
- Personnel should be trained in all procedures and successful completion of such training is documented with evidence of updates, if required, on a periodic basis.
- The facility is subject to internal QA audits and/or site visits by external clients and agencies as appropriate. The agencies that would audit vary by local, state, national or international regulations.
- Policies and procedures are documented in SOPs that are approved by appropriate personnel and are changed or updated only under strict document control rules.
- Records are maintained with respect to the purchase of new equipment, maintenance and repair activities, as well as equipment disposal. Examples of information tracked may include but are not limited to the name and model number for the equipment, name of manufacturer and contact information, serial number, date of acquisition, maintenance and repair, *etc.*

- Records should also be maintained for critical materials and reagents used by the repository. Examples of information tracked may include, but not be limited to; the item name, company from which the item was purchased, date of purchase, expiration date and all related Material Safety Data Sheets (MSDS).
- Deviation reports are produced for all events that fall outside SOPs.

D4.200 Best Practices

Best Practices reflect a consensus body of recommendations made by individuals working in and with repositories. These Practices are not binding but rather reflect the knowledge and experience of this community. Best Practices go above and beyond standard recommendations and may be cost-prohibitive in some cases. Repository management and other staff should decide which practices to adopt that best support their particular circumstances.

D4.300 International Organization for Standardization

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

- **ISO9001:2000 Requirements of Quality Management Systems** - 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. Specifies requirements for a quality management system where an organization needs to demonstrate its ability to consistently provide products that meet customers' and applicable regulatory requirements.
- **ISO/IEC 17025:2005 Quality Systems for Testing and Calibration Laboratories** - provides general requirements for producers of reference materials including tests and/or calibrations, and sampling. ISO/IEC 17025 covers the use of standard methods, non-standard methods, and laboratory-developed methods. This standard incorporates key requirements of ISO9001:2000.
- **ISO /IEC 15189:2007 Medical Laboratories**- includes particular requirements for quality and competence. Specifies requirements for quality and competence particular to medical laboratories.

- **ISO Guide 34:2000 General Requirements for the Competence of Reference Material Producers** - provides the general requirements that a reference material producer should demonstrate if they are to be recognized as competent to carry out the production of reference materials. References ISO/IEC 17025 as a normative document (Betsou *et al.*, 2008).

D4.400 Clinical and Laboratory Standards Institute (CLSI)

Different standards have been published by the CLSI which, although developed for clinical laboratories, may also be relevant to biorepositories. Relevant CLSI standards include the following:

- CLSI H3-A6 Procedures for the collection of diagnostic blood specimens by venipuncture; approved standard-sixth edition.
- CLSI H18-A4 Procedures for the handling and processing of blood specimens for common laboratory tests; approved guideline-fourth edition
- CLSI MM13A Collection, transport, preparation and storage of specimens for molecular methods; approved guideline.
- CLSI AUTO8-A Managing and validating laboratory information systems; approved guideline.

D5.000 AUDITS

Repositories should be subjected to regular audits. Audits cover the implementation of all SOPs that govern the repository. Audits may be done on a quarterly, semi-annual or annual basis, or in response to a non-compliant incident, accident or a change/deviation in procedure required in the light of new information or alterations to ethical, regulatory or health and safety issues. A designated individual familiar with the specific work being reviewed but not directly involved in that work should be responsible for each audit. For this function the individual should be someone who is not directly supervised by the Director (*e.g.*, they should report to a separate department or division responsible for quality assurance).

Regular audits for the inventory system should be performed and primarily directed at prevention of non-conformances as well as detection, corrective action and process improvement implementation (See Section I2.1000, Specimen Location).

D6.000 VALIDATION OF SAMPLE PROCESSING METHODS

Validation is the process by which a method or assay is ensured to be fit for purpose. This may be done by a single organization or by a number of partners cooperating on a systematic and formalized validation exercise (Dyer *et al.*, 2007; Reed *et al.*, 2007; Smith and Ryan, 2008).

Repositories should use validated processing methods for their biospecimens. Processing methods may be validated for the intended purpose either by the repository itself or by a third party. For the purpose of processing method

validation, the repository can use scientific literature, feedback from the end users, and/or laboratory quality control results. Technical training is also part of the validation of processing methods. The repository should list the circumstances requiring new validation measures to be taken (*e.g.*, new technicians, reagent *lot* changes, instrument changes, biospecimen type changes). Each processing method will be validated for a specific intended end use or for a group of intended end uses.

If no relevant scientific literature is available, the repository may have biospecimen research performed to assess the potential impact of the most important pre-analytical variables, following recommendations on biospecimen research. Implementation of a system to track pre-analytical variables such as Standard PREanalytical Coding (SPREC) will facilitate tracking and communication of the critical sample processing steps (Betsou *et al.*, 2010).

D6.100 Pre-analytical Variations

Features of biospecimen quality; including structure of proteins, function of enzymes, level of metabolites, gene expression levels, DNA methylation status, cell viability, microorganism viability can be affected by the specific procedures followed during sample collection, transport, processing and storage. *In vivo* pre-analytical variations include the patient's clinical condition, timing of collection (*e.g.*, pre-operative, post-operative), medication, diet, stress, circadian rhythms or the non-human specimen's environmental niche/ type of habitat, host, *axenic state*, season of *collection* and microbial phase variation which are difficult to control and standardize and should be considered as part of the inter-individual variation of the collection. These variations should be noted whenever possible and appropriate. *In vitro* pre-analytical variations include the type of collection tube, pre-centrifugation delay and temperature, centrifugation details for biological fluids, warm and cold ischemia times for solid tissues, type of sampling, type and time of fixation, time delay before placing into long-term storage, type of long-term storage and exact protocol of cryopreservation and of restoration for environmental specimens. These elements should be tracked in an appropriate manner (*e.g.*, SPREC, Betsou and the ISBER Working Group on Biospecimen Science, 2010).

D7.000 QUALITY CONTROL CONSIDERATIONS FOR SPECIFIC TYPES OF BIOSPECIMENS

Many of the QC processes are generic across all types of repositories and they concern the three “pillars” or responsibilities of all collections which are:

- **Authenticity:** correctly assigned identity
- **Purity:** freedom from contamination (when applicable)
- **Stability:** capability of a sample material to retain the initial value of a measured quantity for a defined period of time within specific limits when stored under defined conditions (Stacey and Day, 2007). For example, the stability of serum (“sample”) as pertaining to the Protein S activity (“measured quantity”) when stored at -80 °C (“under defined

conditions”) is the initial Protein S activity value (“the initial value”) plus or minus 20% (“within specific limits”) for 5 years (“for a defined period of time”).

Depending upon the molecular analyses that will be performed by the end-user, it may be advisable to extract and analyze matching molecular entities (*e.g.*, DNA, RNA or proteins) as a part of the biospecimen quality control testing (Day and Stacey, 2007; Stacey, 1999; Stacey, 2004).

QC measures for specific types of biospecimens can also be dictated by national/federal or international rules and regulations (*e.g.*, health and safety and bioethics) (Stacey and Doyle, 1998; Tomlinson, 2008; Fuller and Dijk, 2008; Budapest Treaty Regulations, 1977; FAO, 1996).

D7.100 Quality Control Consideration for Human and Animal Biospecimens

D7.110 Quality Control Considerations for Solid Tissue Biospecimens

QC examination of tissues designated for research should be appropriate for the research protocol. QC of tissue ranges from microscopic examination of an *aliquot* representative of a specific tissue by a pathologist or cell biologist, or an equivalently trained individual, to molecular quality control in which nucleic acids and proteins are characterized. The highest quality control measures (“platinum” level) involve enriching the diseased population of tissue through macro- or micro- dissection of frozen sections and potentially performing molecular analyses as well. Platinum-based approaches are, however, cost prohibitive and potentially exhaust specimen availability. A cost effective approach for tissue resources requires simple methods of QC that can be expanded per investigator request.

Best Practice: For pathology research, if tissue is prospectively removed from a patient with a particular diagnosis, verification of disease state criteria meeting the research request should be confirmed. The percent of specimen that is diseased should be documented along with the percent necrosis/fibrosis and percent of mucin formation present in the tissue. If tumor is present, tumor cellularity should be assessed.

Best Practice: For each tissue specimen collected, an aliquot, representative of that tissue specimen, should be microscopically examined by a trained pathologist or other trained professional experienced with the organism from which the tissue originated. This aliquot can be the diagnostic specimen from whence the research tissue was obtained, as long as the aliquot reviewed is as close as possible to the area where the tissue supplied for research was procured.

D7.120 Quality Control Considerations for Digital/Virtual Microscopy

D7.121 Virtual Microscopy

Virtual Microscopy (VM) is the method of producing a digital image of a tissue section or cytological preparation mounted on a glass microscope slide that is suitable for visual examination, *annotation* of regions of interest and interpretation. This method uses scanning equipment at a range of magnifications to produce digital images suitable for remote web-based

viewing and archiving. These digitized images can approximate the process of viewing slides microscopically, including the capacity to adjust viewing magnification and focus on specific regions of the image. When optimized, image quality may be sufficient for diagnosis or quality control to confirm the composition of banked research specimens. The use of this technology in certain situations may provide advantages compared with microscopic examination of slides, including: elimination of shipping glass slides, facilitating rapid review, reducing costs of tracking and replacing lost or broken glass slides, and allowing accessibility anytime via the Internet as well as allowing concurrent review of the same slide image by multiple viewers (Ramirez, 2007). Depending upon the availability and type of imaging systems, at some locations it may be more cost effective to provide a tissue section on a glass slide to investigators. Also, high quality images require optimal scanning and significant data storage capabilities; thus the storage capacity required for a large number of such images must be taken into consideration and only the most “diagnostically difficult” cases may necessitate digital storage.

D7.122 Digital Pathology

Digital pathology, built around the examination of digital virtual microscope images, is a workspace environment which integrates with other electronic applications such as laboratory information systems, electronic medical records, medical imaging, molecular testing systems and specimen tracking and receiving systems. Digital pathology also allows complex image analysis of both morphology and tissue based assays (*i.e.*, immunohistochemistry, immunofluorescence) and can allow simultaneous viewing of multiple different images concurrently. Image analysis of specimens could ultimately be used to automate quality control in tissue banks by augmenting or replacing the traditional morphologic review of actual tissue sections. It could aid in assessing tissue quality by detecting and measuring features such as % tumor, % stroma, % necrosis, % cellularity and other morphologic features.

D7.130 Quality Control Considerations for Fluid Specimens

The different collection, processing and storage procedures may adversely affect the structure and/or function of molecular components in fluid biospecimens. In some situations fluid biospecimens (*e.g.*, serum, plasma, urine, saliva, cerebrospinal fluid) may require assessment as to their integrity in view of the detection or measurement of specific *analytes*. Molecular markers to assess specific pre-analytical variables can be used, such as the hemoglobin content to assess hemolysis or the sCD40L content to assess exposure to room temperature (Betsou and ISBER Working Group on Biospecimen Science, 2009). In the absence of a sufficient number of such quality control tools, this is an ongoing field of biospecimen research. In many instances quality control can only be performed in reference samples and in a targeted manner once the end-use analysis is known. For example, if it is known that the specimens are going to be used for the measurement of a specific cytokine, the level of this cytokine in a

previously collected panel of control samples can be compared to the reference interval in a panel of freshly acquired specimens of the same type.

D7.140 Quality Control Considerations for Cell Specimens

Contamination control methods for eubacteria, fungi, mycoplasma and viruses can be applied to primary cell cultures or cell lines. Cell viability and/or purity of the cell suspensions can be assessed after thawing of a representative frozen aliquot (see Section K8.321, Assessment of Cell Viability). DNA fingerprinting methods can be applied for identification of established cell lines.

D7.200 Quality Control Considerations for Microorganisms

Phenotypic characterization includes both macroscopic and microscopic morphology assessment. Genotyping (*e.g.*, DNA sequencing, PCR-based profiling, microarrays), ribotyping, classical biochemical tests and/or serotyping methods can be applied for taxonomical identification purposes. Functional assays include viability assays, or assays for cytopathic effects.

Quality Control for purity can be performed; however, certain cultures need to be maintained in a non-axenic state (*e.g.*, obligate plant pathogens and assemblages of microorganisms, symbiotic and beneficial associates found in microalgae and cyanobacterial collections).

D7.300 Quality Control Considerations for Plant Specimens

The overarching QC process of plant biorepositories (*i.e.*, gene banks, culture collections, germplasm repositories, seed and field banks) ideally involves germplasm characterization before and after storage and at the point of dissemination as well as plant health (phytosanitary) checks, safety duplication and passport documentation with assignment of an accession number.

In the case of seed materials, the International Seed Testing Organization (ISTA) has the mission to develop and publish standard procedures in the field of seed testing and encourage and establish uniformity in seed testing world-wide.

For clonally propagated plants (and other non-seed genetic resources such as pollen and dormant buds) quality testing includes assessment of viability, phytosanitary status and disease management (*e.g.*, comprising quarantine, disease indexing and eradication).

Phenotype and genotype authentication can be a regulatory requirement for some crops and commercial forestry species and can include formal confirmation of certification status (trueness-to-type) by field-testing plants that are evaluated using specific phenotypic descriptors and as appropriate confirmation using molecular markers.

The detection, expression and stability of genetically modified materials may be necessary. The risk assessment and management of transgene contamination is a requirement for certain types of collections.

Post-storage QC measures include assessments of viability, *morphogenetic competence*, *totipotency*, regeneration, biochemical stability (*e.g.*, for secondary product producing cell lines) phenotypic and genotypic stability (*e.g.*,

characterization of somaclonal variation) and trueness-to-type assessment under field or glasshouse conditions using descriptors.

D7.400 Quality Control Considerations for Nucleic Acid Specimens

DNA and RNA can be assessed for integrity and fragmentation (*e.g.*, molecular weight; RNA Integrity Number), quantity/concentration and purity. DNA can be assessed for the absence of cross-linking, the absence of PCR inhibitors, the bisulfate conversion rate and the methylation status. RNA can be assessed for amenability to reverse transcription and the maximum length of the quantitative real time polymerase chain reaction (qRT-PCR) products.

D7.500 Validation of Quality Control Methods

Each QC method should be assessed by the repository or by the external laboratory performing the assays, for its accuracy and precision. Proficiency Testing programs using Reference Materials should be followed, when available, at least once a year (Schmehl, Bank and Cobb 1989; Day *et al.*, 2007).

SECTION E: SAFETY

E1.000 GENERAL

Issues related to safe operation of a *repository* are complex and depend on the particular activities of the repository. Regulations governing *safety* may be covered by national, regional or local statutes. Each repository should determine which areas of safety affect it and develop an appropriate safety plan to protect its employees (Grizzle and Polt, 1988; Grizzle and Fredenburgh, 2001; Grizzle, Bell and Fredenburgh, 2005; Grizzle, Bell and Fredenburgh, 2010).

Safety plans are used to prevent or to minimize injuries to employees. In order to develop an effective safety plan, the likelihood and source of specific injuries for each employee should be identified. These will depend upon the *procedures* and activities that employees perform as well as rooms in which the employees are likely to spend time (Grizzle, Bell and Fredenburgh, 2005; Grizzle, Bell and Fredenburgh, 2010). Each employee and their supervisor should work together to 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 (Grizzle and Polt, 1988; Grizzle and Fredenburgh, 2001; Grizzle, Bell and Fredenburgh, 2005; Grizzle, Bell and Fredenburgh, 2010).

E2.000 NATIONAL, REGIONAL AND LOCAL REGULATIONS

In developing an effective approach to ensuring safety in a repository there are many extensive national, regional and local regulations that should be met in order to protect the health and safety of employees. Along with these regulations, most regulatory authorities provide guidance concerning how to meet these regulations. Some web-based aids to understanding national regulations concerning safety are listed in Appendix A.

E3.000 SAFETY INFRASTRUCTURE

The Director or other individual with overall responsibility for the organization has primary legal responsibility for the safe operation of all components of the organization including a repository; frequently, the day-to-day responsibility for safety is designated to another individual and/or to a Safety Committee. While those with this responsibility may be primarily responsible, the responsibility for safe operation also lies with each employee.

The institution in which a repository resides 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 adherence to all safety regulations (Grizzle and Fredenburgh, 2001; Grizzle, Bell and Fredenburgh, 2005; Grizzle, Bell and Fredenburgh, 2010).

E4.000 TRAINING

Certain risks may be present when working with biospecimens. Employees should be advised of the potential hazards associated with all biospecimens and sign-off on their agreement to handle all *specimens* with the necessary safety methods. Individuals should be trained to follow universal precautions, i.e. to handle all biospecimens as though they are potentially hazardous, and should take appropriate precautionary measures. Additional risks may be present when field staff come in contact with patients during the consenting process (e.g., HIV or tuberculosis) or non-human species during the specimen *collection* process (e.g., zoonotic pathogens that are transmissible from animals to humans). See Section F, Training for a full discussion of training issues.

E5.000 PERSONAL PROTECTIVE WEAR

All persons, including visitors, should wear appropriate clothing (i.e., lab coats, long pants, and covered shoes; not shorts, skirts, or open-toed shoes) as well as eye protection. Appropriate gloves are recommended for handling any specimens, chemicals or hot or cold equipment and supplies. For example, chemically resistant gloves should be used when handling chemicals such as xylene. If exposure to hazardous materials occurs, hands and other exposed areas of skin should be washed. Laboratory coats may be laundered or disposed; this choice depends upon the type and extent of exposure.

Eyes and other mucous membranes must be protected from exposure to *biohazard* materials and chemicals. Depending on the likelihood of exposure, this protection may be accomplished via goggles, safety glasses, or face shields. These should be worn any time there is a likelihood of exposure of the face.

Respiratory protection is only necessary when the exposure to vapors to toxic chemicals exceeds the standard specified by regulatory agencies. If respirators are required, they must be individually fitted.

Appropriate safety equipment for specific tasks must be utilized by all staff as designated in the SOPs.

E6.000 SAFETY TOPICS

E6.100 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 potential biohazards. 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 (Grizzle, Bell and Fredenburgh, 2005; Grizzle, Bell and Fredenburgh, 2010). However, certain agents such as prions [e.g., the causative agent for Creutzfeldt-Jakob disease (“mad cow disease”), scrapie, deer/elk wasting disease, or other transmissible spongiform encephalopathies (TSEs)] may still be infective even when tissues are fixed and processed to paraffin blocks. Consequently, all human and animal specimens 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. Individuals should receive training so that they can

recognize symptoms that accompany the exposure to certain harmful compounds and diseases to which staff are exposed (Fleming and Hunt, 2006).

Facilities should develop a Bloodborne Pathogen Exposure Control Plan to eliminate or minimize occupational exposure to bloodborne pathogens. The plan should include a determination of employee exposure, methods to control exposure (*e.g.*, universal precautions, personal protective equipment, engineering controls), appropriate vaccinations, post-exposure evaluation and follow-up, communication of hazards and accurate recordkeeping. Applicable regulations covering occupational exposure to bloodborne pathogens should be determined.

Best Practice: Risk assessment should be carried out to assure that all regulations are followed.

E6.200 Chemical Safety

Many countries have developed regulations that govern activities relating to chemical safety that may affect repositories (see Appendix A). These laws may mandate that an organization develop a written chemical hygiene plan. The chemical hygiene plan should 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).

All chemicals used in repositories should have material safety data sheets (MSDS) available for easy reference for employees who potentially will come into contact with the chemicals and auditors who will look for these documents. MSDS are available from manufacturers and should be provided either in hard-copy or from a provided URL for downloading.

E6.210 Chemical Hygiene

Chemical hygiene plans should include the following (Grizzle and Fredenburgh, 2001; Grizzle, Bell and Fredenburgh, 2005; Grizzle, Bell and Fredenburgh, 2010):

- Approaches to prevent, contain, and clean up chemical spills. The plan should include a description of how waste and other chemically contaminated materials resulting from the clean-up are to be disposed.
- Approaches to the safe, lawful and appropriate disposal of all repository materials no longer deemed necessary.
- Approaches to ventilation failure, evacuation, medical care, reporting of chemical exposure incidents and chemical safety drills.
- A description of areas where eating, drinking, storing food and beverages, smoking, gum chewing and application of cosmetics are not permitted. This should include areas where specimens are processed, stored, handled, or where chemicals are used.
- Guidance on allowable pipeting methods (*e.g.*, mouth pipeting and mouth suctioning for starting a siphon should be prohibited).
- Guidance on the appropriate use of all chemicals used in fixation or *processing* of tissues.

- Requirements for the use of chemical fume hoods to minimize exposure to vapors from hazardous chemicals (*e.g.*, formaldehyde or xylene).

Best Practice: All regulations should be followed as to chemical safety.

E6.300 Electrical Safety

Electrical injuries can be avoided by ensuring that all equipment is properly grounded. Equipment should be tested for grounding when first purchased and yearly thereafter. Similarly, all electrical base plugs should be in good condition (grounding should be checked/verified) and electrical work should be done with great care ensuring that personnel in the affected work area are protected by removal of fuses and with written warnings at the fuse box. Also, care should be taken with electrical appliances/equipment around water sources in the repository/laboratory spaces, especially sinks. Electrical equipment should be unplugged prior to service, as appropriate, and staff should have visible control of the plug to avoid inadvertent energizing of the unit.

Mechanical storage units are rated to function at a specific voltage. Should the level drop below specified levels on board buck boosters will come on to stabilize the voltage. If conditions persist they can result in overheating of the wiring or components leading to failure or fire. Routine checks of facility voltages and/or noting of prolonged use of the buck boosters will alert staff to low voltage conditions.

Best Practice: Surge protectors or voltage regulators are recommended for stand-alone freezers if this is not part of the building electrical infrastructure.

Best Practice: All electrical equipment and base plugs should be tested for grounding.

E6.400 Fire Safety (See Section B8.000)

The local fire department or the organization's safety program can inspect a repository to evaluate fire safety prevention plans. Prior to such inspections and on a regular basis (*e.g.*, annually), fire drills should be conducted, fire suppression equipment and safety showers/eye wash units should be tested, and emergency pathways should be posted at all room exits. Emergency exits should never be blocked, obstructed or locked and hallways should 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 present in one area. Refrigerators/freezers that represent reduced dangers of causing combustion can be purchased for use in research laboratories. Smoking, if permitted at all, should be limited to designated external areas. Furniture, rugs, and equipment should be constructed of non-flammable 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). Fire safety will be governed by national/federal, regional and local requirements. (See Internet sites in Appendix A.)

Best Practice: Fire safety should be an important component of an organization's safety plan.

E6.500 Physical Safety

The physical safety of employees should be considered in all repositories. Physical safety ranges from preventing falls to ensuring employees are not physically injured by other means. Ensuring physical safety involves careful maintenance of the physical plant and facilities, such as handling and/or prevention of tears in rugs, broken steps and water, soap, paraffin and other slippery substances on floors. Power cords should be appropriately covered, and inappropriate use of ladders or chairs as ladders should be prohibited to prevent falls. Similarly, unsecured 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-motion injuries (*e.g.*, pipetting) and back injuries resulting from movement and inappropriate lifting. Repository staff members may be required to stand on step stools and lift heavy racks vertically out of the freezer in order to access specimens. 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 reduced greatly. When ergonomics is applied correctly in the work environment, visual and musculoskeletal discomfort and fatigue are reduced significantly. Where feasible, repositories may consider automated specimen input and *retrieval* systems to reduce physical strain on technical staff.

Physical injuries that are difficult to avoid include minor cuts (*e.g.*, paper), bumps and strains due to inattentive actions. However, such minor injuries should not be compounded by exposure to biohazards or chemical hazards. The overall safety program should address other hazards that can be prevented or ameliorated by wearing proper protective equipment and clothing such as the use of gloves to avoid thermal burns from both heat and cold (*e.g.*, dry ice or liquid nitrogen). Check the occupational safety laws of your region (see Appendix A.)

For equipment that may be located within a confined space (*e.g.*, large robotic stores for DNA samples), procedures should be developed to assure that the equipment is not moved or operated during routine cleaning, maintenance, or repair.

Best Practice: Physical safety should be considered in an organization's safety plan.

E6.600 Radiological Safety

Few repositories will store or use radioactive material. For those repositories that do use radioactive material, a radiological safety plan is needed. Specific training is required for personnel who use or come into contact with radioactive material as well as in the use of specific radiation monitoring equipment. Work with radioactive materials in many countries requires a license from a federal regulatory committee. Repository staff should refer to the appropriate guidelines for the country or region in which the repository is located.

E6.700 Dry Ice Safety

Prolonged exposure to *dry ice* can cause severe skin damage through frostbite. Those working with dry ice in the laboratory should use appropriate protective wear approved for low temperatures. Dry ice sublimates into large quantities of carbon dioxide gas which could displace oxygen and pose a danger of asphyxiation. For this reason, dry ice is assigned the S-phrase S9 in the context of laboratory safety and should only be exposed to open air in a well-ventilated environment (Annex IV of European Union Directive 67/548/EEC: Safety advice concerning dangerous substances and preparations).

Although dry ice is not classified as a dangerous substance by the European Union or as a hazardous material by the Department of Transportation (DOT) for ground transportation, when shipped by air or water, it is regulated as a dangerous good and IATA packing instruction 904 (IATA PI 904) requires that it be labeled specifically with a diamond-shaped black-and white label with the UN 1845 designation. Arrangements must be in place to ensure adequate ventilation so that pressure build-up does not rupture the packaging (See Appendix A for internet resources). The monitoring of carbon dioxide levels for areas in which dry ice is used is recommended to ensure that the areas are safe for employees.

E6.800 Liquid Nitrogen Safety

At atmospheric pressure, *liquid nitrogen* (LN₂) boils at -196 °C (77K; -321 °F) and is a cryogenic fluid which can cause rapid freezing leading to cryogenic burns or frostbite. Cryogenic burns can also be caused by the contact of skin with substances cooled with liquid nitrogen (*e.g.*, vials, hoses, storage racks.).

Since the liquid to gas expansion ratio of LN₂ is 1:694, a tremendous amount of force can be generated if LN₂ is rapidly vaporized. As LN₂ evaporates it will reduce the oxygen concentration in the air and cause a potential risk of asphyxiation, especially in confined spaces. Nitrogen is odorless, colorless and tasteless, and may produce asphyxia without any sensation or prior warning

Those working with or around LN₂ should use appropriate protective wear. A full face shield should be used to protect the eyes and face from splashes when working with large volumes of LN₂. Non-absorbent, insulated gloves (cryogenic gloves) should be worn when handling anything that is or has been in recent contact with LN₂. Cryogenic gloves are made to be used only in the vapor phase of LN₂ and should not be immersed in the liquid itself. A long-sleeved, buttoned lab coat should be worn at all times when working with LN₂ to protect the body. Non-absorbent cryogenic aprons can also be used and should be used when splashes may occur. Open pockets and turn-ups where liquid may collect should be avoided. Open-toed shoes should in no circumstances be worn when working with LN₂. Shoes should be sturdy and non-absorbent.

E6.900 Carbon Dioxide Safety

Carbon dioxide gas is a colorless, odorless non-flammable gas. In addition to presenting the risk of asphyxiation by displacing oxygen, carbon dioxide can present exposure risks such as changes in blood pressure, tinnitus, headache,

irregular heartbeat, difficulty breathing, etc. While eye protection is not required for working with CO₂ gas it is recommended; however employees should wear oxygen monitors while handling CO₂ cylinders or working with CO₂ gas. Cylinders should be stored in well-ventilated areas in compliance with appropriate regulations.

SECTION F: TRAINING

F1.000 GENERAL

All *repository* staff should be adequately trained to perform the tasks required by their particular position description. Proper training is important to ensure *quality* in *specimen* handling. In some areas of *safety*, adequate training may be mandated by federal/national law and severe penalties may be imposed on the repository and repository personnel if training is not provided as required.

Support for training is essential for adequate implementation of certain tasks and in some cases might require additional resources or time away from regular responsibilities to ensure that the training required is achieved in the most effective manner possible.

F2.000 TRAINING INFRASTRUCTURE

F2.100 Training Program

Every individual who enters the repository for the purpose of performing work should be trained in the particular functions or tasks which they are asked to complete. Training should be task and location specific and be designed for the particular position that is expected to carry out the work. Training should involve instruction in the use of any equipment used and involve appropriate *quality control* and *quality assurance* practices.

Training for some functions may be provided by departments outside of the repository (*e.g.*, maintenance staff, equipment vendors, infection control, professional air transport regulatory trainers) but repository staff should make sure that all individuals who enter the repository follow required safety and other policies in performing their particular tasks. Training must be in a language with which the employee is conversant and the level of training must be appropriate to the employee's level of comprehension.

Academic or other institutional training, in the form of courses, may be available by some institutions. The syllabus of such courses should be reviewed for correspondence with particular training needs and decisions made accordingly. Examples of areas covered by such courses may include legal aspects, management and financial aspects, cellular and molecular biology, statistical aspects, or quality assurance.

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 (see Section F2.700, Training Records). 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.

Best Practice: To ensure quality of repository activities, employee performance should be routinely monitored to identify needs for additional training between regular training intervals. Staff should be informed when first hired that routine

monitoring of employees' performance is a part of regular practices for ensuring quality and is applicable to all repository staff.

F2.200 Trainers

The trainer is an employee who regularly performs the procedures in question, has completed the training program previously and is skilled in explaining the elements of the task. The trainer is responsible for assuring that the trainee understands each procedure and task. 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 demonstrates, explains and reviews 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.

Best Practice: After the training has been completed, the trainer should be available to answer questions when the task is being performed by the trainee for the first few times.

F2.300 Training Coordinator

Each repository should have an individual responsible for training who is responsible for all aspects of training. The individual maintains the SOP Manual and coordinates with the supervisor responsible for that particular procedure when any revisions are needed either due to the expiration of the SOP or for technical reasons.

The training coordinator closely coordinates 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 training coordinator is responsible for monitoring, training and maintaining appropriate training documentation of all employees. The training coordinator maintains records of employees to be trained in each required area, tracks the time of their periodic updates of training, informs the employees of potential times of training and ensures the training is completed according to the required timeframe.

The training coordinator closely coordinates documentation of training and educational activities with personnel who maintain employee records, as needed.

F2.400 Frequency of Training

Training and repeat training should be conducted in accordance with applicable regulations and also in accordance with the needs of the particular tasks and positions held by repository staff. In many countries, regulations require training before the employee begins working and yearly thereafter (*e.g., biohazard and chemical hazard training*). Training for regular repository tasks should be implemented before staff is asked to perform those particular tasks and repeat training should be performed according to a defined schedule described by SOPs. Supplemental training (sometimes in conjunction with “corrective actions” or a protocol change) may be required following the evaluation of particular *incidents* in order to prevent their recurrence or to enhance staff performance.

F2.500 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 individuals are able to perform each of these at any time requested. Cross-training alleviates staff burn-out, reduces staff turnover, offers opportunities for advancement and allows for coverage of key activities if staffing levels change either on a temporary or a permanent basis. Also, since some tasks require repetitive motion, cross-training may minimize physical strain among those performing those particular responsibilities.

F2.600 Training Documentation

Once the training is complete, a written record of the completed training should be made that includes the trainee’s signature as well as the trainer’s signature. Electronic signatures should be used for documentation of any electronic training that is received.

F2.700 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 specified 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, and applicable regulations such as those required in the country in which the repository is located (see Appendix A).
- Documentation that an employee has read and understands all SOPs pertinent to the employee’s responsibilities.
- Documentation of analytical results obtained by a particular staff member to demonstrate proficiency in specified technical tasks. This should include results of reproducibility and/or quality control results.

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The training file should be kept in the repository and be available for Quality Assurance or client review. The training file should be archived according to the repository's SOPs after the employee is separated from the organization. If an employee moves from the repository to another department within the organization, the employee's training file should be transferred to the new department.

SECTION G: RECORDS MANAGEMENT

G1.000 GENERAL

Each *repository* should develop and maintain a records management system that permits detailed records to be made concurrently with the performance of each step in the *collection*, *processing* and *distribution* of *specimens*. Records maintained may include but are not limited to: training documents, protocols, standard operating procedures (SOPs), *informed consent* documentation, procurement documentation, processing records, testing, equipment maintenance, *audit*/review documents, specimen *storage* location information, *sample* distribution, and *quality control* activities. Records should be created and maintained in a manner that allows steps to be clearly traced and ensure sample chain of custody. Security systems should be adequate to ensure the confidentiality and security of all stored records. Access to records should also be on a “need to know” basis.

In some cases it may be necessary to either destroy or remove specimens at the request of study participants. Under these circumstances, records should be appropriately amended to indicate that the specimen is no longer part of the collection and the information management system should be adequately updated to reflect this event.

Best Practice: Paper files containing confidential donor or client information should be stored in locked, fire and water proof enclosures with controlled access.

G2.000 TEMPLATE FORMS AND SPREADSHEETS

A repository may develop a variety of forms to allow for effective record keeping. Uniform systems of documentation improve consistency in the tracking and monitoring of repository activities. Examples of effective forms include those to monitor equipment operations and repair, *incident* reports and activity check lists. Templates may also be developed to facilitate repetitive data entry into a specimen database; allowing for files to be translated into a compatible format for the repository’s database.

Best Practice: Forms or spreadsheets to record the most important pre-analytical variations that may affect the quality of the biospecimens are particularly important. For this, the Standard PREanalytical Coding (SPREC) can be used (Betsou *et al.*, 2010).

Best Practice: Forms should have a unique number and a distinct title and include the date that the version of the form was created (*i.e.*, version tracking).

G3.000 RECORD CORRECTIONS AND/OR CHANGES

Corrections or changes in a hard copy record should be made in ink 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. Changes tracked should include the name of the individual making the change, the time and date at which the change was made and the reason for the change.

Best Practice: Dates should implement a format that is unambiguous such as ddmmyyyy, where d stands for day, m stands for month and y stands for year.

G4.000 RECORD RETENTION

Unless otherwise specified by contract, corporate or government policy or other agreement, each repository should establish a period of time during which all records are retained. A policy should be in place for the destruction or return of records that no longer need to be retained. The length of time that records are maintained will depend on the nature of the record. For example, a repository may retire equipment maintenance and repair records following the retirement of the equipment. Records pertaining to a particular collection that is no longer active (*e.g.*, closed) or where the samples have been destroyed may also be retired, destroyed or returned to the sponsor.

G5.000 ARCHIVAL SYSTEM

A repository may develop a system for archiving records that are not needed as a part of daily activities that the repository requires to be maintained as defined in Section G4.000, Record Retention. This system should be accessible for audits and inspection as defined in Section D4.000, Audits. The system should meet all regulatory requirements for storage and access.

G6.000 SECURITY

Electronic records should be backed up daily on a network or remote secure server.

Best Practice: Arrangements should be established with an off-site data security company that retrieves and stores all critical data at a remote location.

Best Practice: Computers operated by repository staff should be password protected and should make use of automatic timeout mechanisms that lock the computer (*e.g.*, screensaver).

Best Practice: Permission levels should be created for staff at different operational levels as well as for users who are not repository staff, where this access is allowed.

G7.000 AVAILABILITY FOR INSPECTION

Records should be readily accessible for inspection by authorized personnel from regulatory agencies (these may vary for each state or country, depending on the regulatory agencies with jurisdiction over those activities) and *Quality Assurance* personnel. Access to privacy records or confidential client information should be restricted to specified repository staff members that are permitted to allow access for inspectors from regulatory agencies and other appropriate auditing groups.

SECTION H: COST MANAGEMENT

H1.000 GENERAL

In order for *repositories* to operate effectively for the fulfillment of their mission, it is critical that they have sufficient financial support to allow for proper functioning. The financial support available may vary depending on the type of institution with which the repository is affiliated, whether it receives public or private funding, and how much of the operational budget the repository itself will be asked to cover in order to remain operational. For example, some repositories may have part of their budgets covered by medical facilities or universities in which they are located.

Regardless of the funding source, repositories must be able to capture their costs in labor, materials and supplies, equipment, equipment support and facilities. It is only when these costs are known that accurate budgets can be prepared and sources for needed funding can be identified. Failure to accurately capture costs may lead to the early termination of programs.

Best Practice: Repositories should develop a business plan based on their objectives and strategy and based on known and estimated costs. Repositories should ensure that costs are captured effectively in order to support sustainability strategies. This plan should be reviewed regularly in order to account for changes in governance, organizational structure, labor, materials, supplies, etc.

Best Practice: In addition to annual budget plans, repositories need to have long term projections for sustainability. To ensure continued operations without compromising *quality*, specific plans for 5 years and beyond should be developed to anticipate long term costs and revenues.

H2.000 IDENTIFYING AND DEFINING COSTS

Developing an accurate assessment for the costs to support a repository can be complex and depend on possible overlapping functions undertaken in the repository setting. Cost assessments should be developed in cooperation with others involved with the financial management of the organization with which the repository is involved. Cost information for facilities, equipment and labor may be available from current and historical records. Where possible, information should be obtained from within the organization to determine current rates for overhead or indirect costs, facility costs (*e.g.*, costs for space, HVAC, utilities, labor) equipment depreciation and maintenance.

Critical costs for effectively initiating and developing a repository should be considered. For example, costs should be assessed for facilities, staffing (*e.g.*, payroll, benefits, training), administrative costs (*e.g.*, support, office equipment, supplies), monitoring equipment (*e.g.*, environmental monitoring systems, oxygen monitoring systems, pagers, cell phones), inventory management software and licenses, laboratory and specimen *processing* supplies (*e.g.*, barcode scanners, buffers, reagents, chemicals, disposables, *disinfectants*, laboratory *safety* supplies, personal protective wear) and *storage* supplies. The actual costs to be considered will depend on the function of the repository. For example, under some circumstances costs for collection should be included, whereas in others only the

costs for receiving and storing the *specimens* should be considered, since the repository may only serve as an intermediate storage facility. Likewise, costs for specimen testing may or may not need to be considered depending on the mission of the repository.

H3.000 COST ANALYSIS

Once all costs are accurately defined, it will be important to look at work processes and the ability to optimize work flow. Plans should be developed to share equipment with other, related activities, if possible. A variety of solutions may be possible to reduce labor costs while still performing the work of the repository with high precision and quality.

Best Practice: Routine repository activities should be examined to determine if automation may be incorporated to more rapidly process specimens with high accuracy. While automation typically requires an up-front expenditure of greater funds, reduction in labor and facility costs over time may result in lower overall costs. Automation strategies range from the simple to the complex, such as scanning bar-coded *labels* when *samples* are received or pulled from storage *containers*, versus automated entry and withdrawal of specimens from freezers. The former example is much less costly to implement than the latter, but both may be effective long-term cost reduction strategies.

Best Practice: Costs should be regularly reviewed to examine the actual costs (e.g., equipment purchase, repair and maintenance) versus the cost of acquiring new equipment that may be less expensive, more efficient, operate with fewer repairs, *etc.*

H4.000 COST RECOVERY

Repositories may require no additional funding, partial funding or complete recovery of costs from specimen *collection* through the entire life cycle of the specimen. External funding may be obtained through grants, contracts, other private funding mechanisms as well as user fees to cover the partial or full cost of collecting, maintaining and disseminating the specimen. Even repositories that have most of their costs covered may wish to consider a nominal service fee to promote good stewardship and judicious use of resources. Regardless of funding sources, it will be necessary for repository managers to prepare accurate, annual budgets to support orderly repository activities.

Best Practice: Policies on cost recovery should be determined in advance, as appropriate, with key stakeholders of the repository, potential recipients of the collected biospecimens, and with advocates for the study participants. Prices should be kept at a "market"-acceptable range in order to allow maximum use of the *biospecimen resource*.

Best Practice: Policies on cost recovery and actual expenses and revenue should be reviewed on a regular basis (e.g., yearly) to ensure the relevance of the projected prices, effectiveness of the costs recovered to accomplish the intention of the cost recovery plan, and to ensure that anticipated usage is being implemented as expected. Regular adjustments are likely to be required.

Best Practice: Services should be provided following business agreements based on quotations that include the length of time during which quotations for products or services will be honored.

Best Practice: Policies should be implemented to allow for the timely collection of fees and handling of non-payment.

SECTION I: BIOLOGICAL MATERIAL TRACKING

11.000 GENERAL

In order to make certain that *specimens* can be tracked accurately from the site at which they are collected through their arrival and subsequent *distribution* from a *repository*, effective tracking systems must be in place. Critical components of these systems include the use of unique specimen *identifiers*, appropriate specimen *labels*, electronic data inventory systems for specimen tracking and other features that are described in detail below.

12.000 INVENTORY SYSTEMS

A computer-based inventory system should be in place to track the location and pertinent *annotation* of every specimen in the repository. The system should also track significant events such as *sample* thaws, receipt and/or processing delays, destruction, *processing*, transfer of the sample within the repository, and specimen distribution and return (if applicable). Full query capability for all data stored should be provided.

The system should have the capacity to assign a unique ID to each specimen entered in the *database* and track its lineage (parent sample to child to grandchild, *etc.*). If an ID exists, but a new specimen ID reflective of the inventory system into which the specimen is being entered needs to be added, the inventory system should be able to track the original specimen ID as well as the newly assigned one.

Best Practice: Specimens received in the repository should be given a printed label with a barcode and specimen ID, if one is not already on the specimen *container*.

12.100 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 storage container. Each location combination (*e.g.*, freezer, rack, box, row, and column) should uniquely identify a location in the repository. The inventory system should support different storage environments for the same repository and also should record the container type (*e.g.*, vial, straw). The inventory system should be able to report on available storage space and able to assign and reserve space for incoming specimens.

To validate specimen location, a randomly generated specimen number/list or other appropriate randomized system should be checked on a subset of the samples on a regularly scheduled basis. This will ensure that the correct specimens are in the location specified by the inventory system (database). Certain storage systems (*e.g.*, straws) are stored in containers such as goblets and the database should be able to capture such containers that do not follow the normal box/row/column configuration.

I2.200 Additional Specimen Descriptors

The inventory system should track specimen type; vial or container type; volume or size; date and time of specimen removal from *donor*, *collection*, receipt and/or processing; processing method; storage temperature; preservatives and any other characteristics needed for the collection. Information should be included on the history of sample processing and movement, including the location of shipments to and from external sites. Finally, any information about the sample being compromised in any way should be recorded and available to the user.

I2.300 Additional Information for Human Repositories

In addition to the information regarding specimen location, information relating to the following data may be maintained for a repository depending upon the nature, purpose and type of the resource (if relevant, available or not stored in another interoperable information management system):

- Donor information: Age of donor at the time of collection, sex, race, ethnicity, occupation, etc.
- Diagnosis: Anatomic site (*e.g.*, breast), tissue type (*e.g.*, normal), diagnosis (*e.g.*, fibrocystic disease) and modifiers to provide additional detail regarding the diagnosis. It may be important to document the gross diagnosis (what the specimen was thought to be when collected, *e.g.*, breast-normal), the pathological diagnosis (diagnoses rendered by pathology for the actual resection, *e.g.*, breast-malignant-adenocarcinoma-ductal), *quality control* diagnosis of the specific sample obtained for research (*e.g.*, breast-normal-fibrocystic changes) and the pathologic stage at time of surgery. In some situations, it may also be appropriate to provide the diagnosis code (ICD10) and the text of clinical diagnosis.
- Diagnostic procedure: Type of procedure (*e.g.*, surgery), date of procedure, procedure details (*e.g.*, mastectomy), procedure identification number (*e.g.*, surgical pathology number).
- Type of treatment (*e.g.*, chemotherapy, radiation, hormonal, immunotherapy, anti-inflammatory) prior to specimen collection, amounts and dates (if known).
- Medication or drug 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, serum, plasma, paraffin embedded tissue,

H&E slide, formalin fixed tissue, DNA, RNA, urine, feces, saliva, ascites fluid and synovial fluid) from the same *donor*.

An inventory system may also be designed so that digitally scanned documents are included such as pathology reports, H&E slides of tissues collected, clinical lab reports, donor consent forms and *material transfer agreements* (MTAs, see Section M2.600, Material Transfer Agreements).

The information stored will vary according to the purpose, nature, and intended uses for the biospecimen collection. Since a repository may track samples of many different studies, consideration should be given to what the inventory database can contain and what should be stored in an external database and linked to the inventory.

I2.400 Additional Information for Non-Human Specimens

Many items listed in I2.300 can also be applied to the information tracked for non-human biological samples, specifically animal samples, as well as additional information not included above. The following information is important when collecting for animal/fungal/plant/microorganismal biobanks or environmental specimen banks (ESBs):

- Collection location: (latitude and longitude [and method of determination], altitude/depth, country/area/site/city, ocean/sea/bay, indoors/outdoors).
- Collection/gathering method, in whole specimens; also killing method.
- Collection conditions: weather, habitat/ecosystem characteristics, association with other species.
- Taxonomic and specimen information: life stage, sex of the specimen (where applicable), species/subspecies of specimen and/or higher taxonomic rank.
- Taxonomic detail focusing on wild organisms: taxonomic species authority, date the identification was made and name of identifier, previous identifications, (morphological) voucher ID and collection code of the specimen if sample is voucher-referenced in a natural history collection, type of association to this voucher (same specimen / same in-situ population / etc.), if specimen has been DNA barcoded, BOLD (Barcode of Life Database) IDs.
- Time tissue was removed from organism or site location, processed and frozen for storage.
- Processing location if divergent from collecting location, type of instrument used to collect and sub-sample, if necessary (*e.g.*, stainless steel blade, titanium knife, type of container used to store the sample (*e.g.*, Teflon®, polypropylene, glass, stainless steel)).

I2.500 Audit Trail

The inventory system should include a full *audit* trail of changes made to the database. This includes recording changes to both specimen data and system metadata. The audit trail should include but not be limited to: the original data; the changed data; who made the changes; how the change was made, date and

time of change, and if possible, why the changes were made. This audit trail should be automatically recorded and available for read-only access.

Record changes should not obscure previously recorded information in the Audit Trail. Such audit trail documentation should be retained for a period at least as long as that required for the electronic records and should be available for agency review and copying.

I2.600 Security

Access to the computerized inventory system should be tightly controlled. Passwords should conform to the minimum institutional standards regarding password length, strength, life cycle, recycling, etc.

Security roles with defined privilege levels should be assigned to individual users of the system. Some individuals may be able to view specimen availability whereas others can enter or modify specimen descriptions and make requests to have specimens shipped from the repository.

The system should provide a mechanism to log off users after a specified period of time during which the system is idle.

All database access attempts should be logged with the date and time of login and logout. Any failures to access the database should be logged with the date and time and reason for failure. The system should lock out a user after a specified number of failed attempts to access the system.

The inventory system should provide for single system sign-on utilizing the operating system's user name and password if possible.

User authentication information should always be encrypted.

All remote communication should be able to be conducted on an encrypted socket (*i.e.*, via a port that requires data encryption to prevent inappropriate access to secured data). For example, Web-based systems should be able to implement data encryption using a Secure Socket Layer (SSL) at the browser level.

All Protected Health Information (PHI) should be secured within the database through access controls and/or encryption.

I2.700 Interoperability

Within modern *biorepository* informatics systems, integration and interoperability are highly desirable. Systems should be able to integrate with other local applications such as electronic medical records, cancer registries, pathology systems and freezer temperature monitors. This allows other systems to be the single source of truth (SSoT) for appropriate data.

Integration and interoperability have many benefits which include, but are not limited to, the following:

- Reduced re-entry of data. Every time data is manually reentered from one system to another there is a risk of error. Re-entering of data can be costly.
- Data errors found and corrected in the SSoT system should be replicated to other systems.

Data should be electronically convertible into formats that can easily be shared among collaborating institutions, where possible and appropriate. The inventory management system should enforce all data integrity, security and audit trail requirements for external access. To achieve interoperability, inventory management systems should do the following:

- Have a public documented Application Programming Interface (API) to enable other systems to integrate with it.
- Use common public vocabularies for relevant data points (*e.g.*, Snomed, ICD9-CM, ICD10, ICDO).

I2.800 Reporting

The inventory system must have the ability to produce reports to support the repository workflow, document adherence to standards and practices and provide any business metrics required by the repository.

The system should provide the user with an interface for specifying display content and search criteria for the report. The exact nature of this interface can vary from full “what you see is what you get” (WYSIWYG) report designers to simple field selection for tabular reports. The query editor can also be presented utilizing several approaches, including simple data query forms, Query By Example (QBE) screens, customized query builders and text areas for native query specification.

The inventory system should have the ability to save reports for future execution. The inventory system should have the ability to generate report output and electronic data files (*e.g.*, in ASCII, XML, or Excel format). The system should provide full access to the database for reporting, provided that the system’s security rules are enforced. This access will allow users to generate reports on inventory status, freezer status, user access, audit trail entries, and other data tracked by the database to meet their needs.

If the database contains PHI records, the security model must restrict reporting on confidential data to only authorized users. Additionally, the repository should maintain SOPs about the generation, use, and destruction of reports that contain PHI to ensure that donor confidentiality is maintained.

I2.900 Validation

A closed system is defined as an environment in which system access is controlled by persons who are responsible for the content of electronic records that are in the system.

Persons who use closed systems to create, modify, maintain, or transmit electronic records should employ *procedures* and controls designed to ensure the authenticity, integrity, and, when appropriate, the confidentiality of electronic records, and to ensure that the signer cannot readily repudiate the signed record as not genuine. Such procedures and controls should include the following:

- Validation of systems to ensure accuracy, reliability, consistent intended performance, and the ability to discern invalid or altered records.

- Protection of records to enable their accurate and ready *retrieval* throughout the records retention period.
- Use of operational system checks to enforce permitted sequencing of steps and events, as appropriate.
- Use of authority checks to ensure that only authorized individuals can use the system, electronically sign a record, access the operation or computer system input or output device, alter a record, or perform the operation at hand.
- Use of device (*e.g.*, terminal) checks to determine, as appropriate, the validity of the source of data input or operational instruction.
- Determination that persons who develop, maintain or use electronic record/electronic signature systems have the education, training and experience to perform their assigned tasks.
- The establishment of, and adherence to, written policies that hold individuals accountable and responsible for actions initiated under their electronic signatures, in order to deter record and signature falsification.
- Use of appropriate controls over systems documentation including:
 - Adequate controls over the distribution of, access to, and use of documentation for system operation and maintenance.
 - Revision and change control procedures to maintain an audit trail that documents time-sequenced development and modification of systems documentation.

I2.1000 Quality Assurance

In order to provide high-quality information to serve the tracking system, standards, policies, and procedures should be used to ensure and maximize the quality, objectivity, utility and integrity of the data. Periodic reviews of data quality issues and adjustments to programs and processes will ensure continuous quality improvement. The electronic inventory system should comply with industry-applicable cGP guidelines (see Section D3.100, Current Good Practices). An established *Quality Assurance* program for the inventory system should be primarily directed at prevention of non-conformances as well as detection, corrective action and process improvement implementation.

Regular Quality Assurance audits and reviews should completely document:

- User requirements, as well as industry-specific certification requirements.
- Details of the review and approval process for software developed in-house, or obtained from a third party.
- Procedures followed to test the software functionality, compared with user requirements.
- Corrective actions or processes used to handle program errors and modifications.

- Training provided to personnel associated with the use (and development, if applicable) of the inventory system.

Best Practice: A periodic audit of the database should be performed to ensure accuracy of data.

I2.1100 Backup

Regularly scheduled backup procedures are an important security function that will enable the inventory system to be restored in the event original data is lost or corrupted, most typically due to drive or other hardware failures. The database should be backed up on a regular basis, depending on the institutional policies and frequency of data modification. The more frequent the data is changed, the more frequently the backups should be made.

The procedures to preserve the integrity of IT data should include (but are not limited to) steps to limit the extent of the destructive event, protocols for periodic backing up and storing of information, procedures for off-site storage of backup data, and protocols/procedures for restoring information from backed up media.

The procedures should specifically address the recoverability of information. Backups should be validated on a regular basis to ensure the data can be accurately recovered.

Changes to hardware and software commonly require review and reevaluation of these documented procedures. These procedures must specifically address the physical environment and equipment.

I3.000 LABELS

Each specimen should receive a label that tightly adheres under all projected storage conditions. Information printed on labels should be resistant to all common laboratory solvents. Labels should contain an ID linking to a database containing details about the specimen collection and processing information (see Section I2.000). Flexibility should be allowed in the location of the label to allow for label legibility on a wide variety of containers.

Material used in composition of containers for some specimens may pose special problems for label adherence and therefore in some cases, the label should be able to adhere to itself.

The adherence of labels to containers as well as the use of particular types of ink should be tested under conditions more extreme than the anticipated storage and processing conditions before they are put into regular use.

I3.100 Labels for Specimens

Human specimens should be labeled in such a way that protects privacy and confidentiality and is in compliance with applicable laws and institutional policies. Specimens should be labeled with a unique code or ID not derived from information about the donor. No other study or personal health information should be encoded in the specimen ID.

Best Practice: For all specimens, the repository's unique identifier for each specimen should be printed on the label in both barcode format and human

readable form. The ID should not be reflective of its storage location in the repository, as locations may change over time.

I3.200 Barcoding

Whenever possible, labels should be printed with a barcode that uniquely identifies the specimen. Linear (1D) barcodes are adequate for small values and/or larger labels. Under some circumstances, two-dimensional (2D) barcodes are necessary. 2D barcodes have the advantage that scanning error rates may be lower, more information can be included on the label and they may be optimal for use on smaller vials. Some containers can be ordered preprinted, such as straws and small vials that fit in 96-position racks. In certain situations, preprinted containers can have an ID structure that alleviates applying another label onto the container and save supplies and labor.

Best Practice: Each *aliquot* or container should be labeled with a unique barcode/number.

I4.000 SHIPPING LOG

Each repository should maintain a shipment log to record the receipt and dissemination of shipments sent from the repository. This log should be integrated into the functionality of the inventory management system described above. Each shipment entry should be given a unique shipment ID. The electronic log should be able to track the following elements:

- Shipment/Invoice ID.
- Source.
- Destination.
- Date shipped and date received.
- Courier name.
- Package Tracking ID, if applicable.
- Unique sample identifier.
- Sample type(s).
- Quantity sent and received.
- Study name and/or number if available.
- Shipping conditions (*e.g.*, dry ice, room temperature, etc.)
- Name/Signature of individual receiving the shipment.
- Any discrepancies between the *shipping manifest* and the actual shipment.
- Any indication that a specimen has been compromised (*e.g.*, record *deviations* in sample quality upon receipt).

SECTION J: PACKAGING AND SHIPPING

J1.000 GENERAL

Packaging and shipping should conform to all governing regulations. Air shipments should conform to International Air Transport Association (IATA) standards. Ground shipments should conform to applicable national/federal standards. All personnel involved in shipping biological materials should be trained properly for both air and ground shipments.

J2.000 TRANSPORT SPECIFICATIONS

The first step in the preparation of a shipment for transport is the determination of the specifications for the *specimens*. The shipper should determine what regulatory requirements are to be met as well as the physical requirements necessary to ensure proper shipping conditions.

J2.100 Regulatory Requirements

The shipper should first determine how to classify the specimens that are to be transported. Specimens routinely shipped from repositories such as infectious substances, diagnostic specimens, biological products, genetically modified organisms and microorganisms or toxic substances may be considered dangerous goods. Also, the preservatives that have been applied to the specimens may be considered toxic, flammable liquids, non-flammable gases, or corrosives, all of which are dangerous goods. In order to properly classify the specimens to be included in a shipment, one should consult their federal transport regulations as well as those from their International Civil Aviation Organization (ICAO) and IATA.

Many countries require that personnel involved in the transport of dangerous goods receive training in this area before they begin their shipping responsibilities. As regulations change, training may need to be updated.

J2.200 Temperature Requirements

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

- Ambient (20 to 30 °C) - insulated packaging to protect from extreme heat or cold ambient conditions.
- Refrigerated (2 to 8 °C) - wet ice or gel packs (conditioned at -15 °C designed for refrigerated temperatures 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, blocks or sheets. Note that dry ice (solid CO₂) employed for frozen shipments is considered a hazardous material and appropriate labeling should be included.
- Frozen (at or below -150 °C) - *liquid nitrogen dry shipper*. Dry nitrogen shippers are insulated *containers* that contain refrigerated *liquid nitrogen* that is fully absorbed in a porous material and is therefore considered a non-dangerous product and is not subject to IATA regulations as a dangerous good.

Best Practice: Shipments of cold or frozen material should be shipped with sufficient and appropriate refrigerant to maintain temperature throughout the shipping cycle with allowance for at least a 24-hour delay in arrival time.

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 Arrival Time Requirements

Time sensitive specimens such as fresh whole blood should be consigned to couriers with a proven reputation of successful on-time delivery. Time required for shipment *processing* should be considered as well. Shipments should be initiated when there are at least two working days left in the week, in case they do not arrive on the day scheduled for delivery. Shipments should also be scheduled so that they do not arrive at the recipient location on a holiday.

J2.500 Specimen 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. The container size should be appropriate for the amount of refrigerant needed and for the number of specimens that will be included in the container.

Best Practice: Shipments involving a large number of specimens should be divided into multiple, smaller shipments.

J2.600 Other Packaging Considerations

- Specimens should be positioned between the refrigerants used rather than being placed on top of or underneath the refrigerant.
- After the specimens and the refrigerant have been placed into the container empty space should be filled with Styrofoam or wadded paper to prevent movement of the specimens during shipment.
- Remove or mark through any *labels* remaining on the exterior of the shipping container from a previous shipment.
- Air-bills should not be reused.

J3.000 VERIFICATION OF SHIPPING CONDITIONS

J3.100 Review of Packaging Test Report

The shipper is responsible for choosing appropriate packaging for the shipped material. The shipper should review all test reports for the packaging to ensure that the packaging regulations are met.

Packaging that has undergone stringency testing should be used in the same configuration under which it was tested. Tests may include measuring all parameters that could influence specimen integrity (*i.e.*, temperature, humidity, light sensitivity, structural quality, and spill containment).

J3.200 Test Shipments

In some situations, especially relating to extremely valuable *samples*, repositories may choose to first 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 serve to identify any potential obstacles for the successful shipment.

Best Practice: When test shipments (as well as subsequent specimen shipments) are performed it may be helpful to use a temperature-recording device or an irreversible temperature indicator during the shipment to ensure that temperature requirements have not been exceeded.

J3.300 International Shipments

Special permits or other requirements may be unique to certain countries and regions. Some countries have regulations related to ethical issues which prohibit the import/export of certain types of human specimens or have specific requirements concerning the import/export of such specimens. If collecting non-human biological samples that are endangered or protected, special permits such as the Convention on International Trade in Endangered Species of Wild Fauna and Flora permit, as well as additional paperwork may be required.

Most international shipments also require a customs clearance note to be clearly displayed on the outside of the package. Check with the country of delivery for the customs information that needs to be displayed. Identify all requirements for shipping to a designated country prior to the initiation of the shipment. Use of a customs broker can be helpful or even critical. Certain couriers can provide this service which can be essential for transport to/from a foreign country.

Best Practice: Due to possible delays in completing customs requirements, temperature sensitive material should be consigned with a courier capable of replenishing refrigerant in the event of a delay. As a precaution, three additional days' worth of refrigerant is recommended for shipments in cases where customs clearance may be difficult.

Best Practice: International shipments should include a letter on institutional letterhead (as appropriate) documenting the contents and handling requirements. Copies of all import permits and sanitary certificates should be included, as needed.

J4.000 TRACKING SHIPMENTS DURING TRANSPORT

Both the shipper and recipient should track all packages while in transit.

J4.100 Notification of Shipment

The shipper should notify the recipient that a shipment is scheduled to arrive on a specific date. The recipient should confirm that they are able to receive the package and that they have the proper facilities for *storage* before the shipper releases the shipment. The shipper should provide a 24-hour emergency contact for all packages transporting dangerous goods.

J4.200 Shipping Manifest

The shipper should send a *shipping manifest* (preferably electronic) to the recipient prior to the release of the shipment. A paper copy should also be included with the shipment itself.

J4.300 Confirmation of Receipt

Confirmation of receipt and the condition upon arrival should be documented for every delivery or shipment of specimens. A form that records this information should be sent with the shipment/delivery. Information as to how the condition report should be returned to the shipper should be clearly indicated.

SECTION K: SPECIMEN COLLECTION, PROCESSING AND RETRIEVAL

K1.000 GENERAL

Specimen collecting and *retrieval* practices have many elements in common, although specimen *processing* varies according to the specific type of research activity, specimen *collection* and retrieval practices. Specimen availability and the intended analytical objectives for their utility should be considered prior to initiating a specimen collection. It is important to ascertain the sensitivities of different types of specimens to collection, processing, *storage* and retrieval *procedures*. These may vary, particularly between viable and non-viable *samples*; therefore, collection protocols should incorporate any special requirements necessary for the *preservation* of viability, functionality, structural integrity and stability of cells, tissues, organs, cell free fractions and macromolecules and/or *analytes*. In addition to specimen type, other factors include: status of the *donor* or population providing the specimen, collection method, sample vessel and security of containment.

Specific personnel responsibilities, training, risk management and skills may be required for specimen collection. Planning of collection logistics should take into account distance from the collection point to the processing lab, interim transport containment and security of the storage facility (if this is a different location). Protocols for stabilization and/or preservation of samples during transit may be necessary.

Due to the importance of pre-analytical processes (defined as those procedures undertaken between the time of specimen collection to the moment of their analysis) it will be important to apply strategies that maintain the stability and functionality of biospecimens and macromolecules of interest. Stringent procedures are similarly required for specimen labeling and tracking as initiated from the point of collection to receipt in the *biorepository*.

Based on the availability of specimens, a *repository* may collect and process many different specimens (*e.g.*, solid tissue, blood, saliva, urine) from the same case. Furthermore, a repository may process each specimen into a variety of formats (*e.g.*, formalin-fixed paraffin embedded, OCT blocks, snap frozen). Such redundancy of sample supply allows for optimized future usage; however, limitations of the repository's storage capacity must be considered when collecting multiple specimen types and processing them in a variety of formats.

K2.000 PILOT STUDIES AND PROOF OF PERFORMANCE STUDIES

Repositories should implement small-scale pilot studies to validate new protocols, equipment, laboratory tests or testing services when possible. Pilot or feasibility studies can identify problems or critical points and instigate preventative actions at an early stage of collection, handling and processing before a larger study is undertaken. Pilot studies can also help determine new processes and identify training required before implementing a new protocol. These studies are a requirement in some countries.

K3.000 TIMING OF SPECIMEN COLLECTION

The relative importance of the period of time between receipt and processing of a specimen varies with the research application. Cells, tissues and organs lose functionality and molecules degrade at different rates dependent upon type and status of donor and collection circumstances (Engel and Moore, 2011, Dey-Hazra *et al.*, 2010). It is important to identify critical factors which predispose different specimens to deterioration and contamination. For example, for specimens from vertebrate animals, cellular integrity and molecular degradation may begin when the vascular supply to an organ is interrupted during surgery or when tissue is removed and placed in a cold *container*. The speed at which the degradation occurs will depend upon many complex factors including: donor and/or organ health status, collection procedures and the temperature and hydration at which the specimen is maintained and the stability of molecules of interest (Jewell *et al.*, 2002). Every effort should be made to maintain tissue specimens at cold temperatures as soon as they become ischemic or are removed from the body. It is also important to prevent *dehydration* and *desiccation* of tissues during transportation by covering it with sterile gauze moistened in biopreservation media. In general, specimens should be processed as rapidly as possible.

Best Practice: The collection, processing, storage times, and procedures should be documented since pre-analytical variables may affect research and clinical outcomes.

Best Practice: End-users should be provided with the pre-analytical variables so that they can make informed, evidence-based assumptions and conclusions about their experimental data.

K4.000 TEMPERATURE

Because cold preservation is a critical stabilizing factor for many specimen types, the temperatures at which specimens are collected, processed and stored should be carefully considered (Benson, 2008). These range from chilling/hypothermic (2 - 8 °C) to low subzero (-4 °C to 0 °C), freezing (-20 °C to -150 °C) in mechanical/electrical freezers and storage at the ultra-low temperatures of liquid and vapor-phase *liquid nitrogen* (to a minimum -196 °C). Choice of collection and storage temperature depends upon specimen resilience to chilling, freezing and cold-induced dehydration, duration of exposure and tolerance to cryoprotective treatments, specimen type and use in intended analyses. The general rule is that a warm storage environment, even for a short period of time, can lead to physiological stress and macromolecular degradation. For this reason, it is necessary to maintain appropriate temperature(s) from the point of collection through processing and storage. Hypothermic temperatures (2 - 8 °C) should be considered as the default condition for specimen transport/storage when not frozen.

The type and duration of low temperature treatments are also dictated by specimen use. Blood samples collected to yield serum will need to be maintained at room temperature for a minimum of 30 minutes to allow clotting (Guder *et al.*, 2009). The collection and processing time should be documented and reported to

the end- user. This information is critical for *quality control* measures (*e.g.*, will help explain the presence of fibrin, a common occurrence when insufficient time is allowed for clotting to occur).

Biospecimens can also be collected, shipped and stored at ambient temperatures using new technologies that have been developed specifically for such purposes. Ambient preservation is available for purified analytes (RNA and DNA) as well as in complex systems (*e.g.*, saliva, blood, cells, tissue). Preservation can be for a few days and in some cases, for longer than 25 years (Doedt *et al.*, 2009). Technology for preserving dried blood spots on cellulose-based cards/filter papers at ambient temperature for longer than 15 years has been well described in literature (Belgrader *et al.*, 1995).

K4.100 Biopreservation/Cryopreservation

Biopreservation is a general term used to describe the preservation of all types (*e.g.*, viable and non-viable cells, blood, cell fractions, DNA) of biological materials using a range of low temperature and some ambient storage methods. Whereas, *cryopreservation* is a more specific form of preservation that involves the storage of cryoprotected living cells, tissues, organs and organisms at ultra-low temperatures, usually in LN₂ or its vapor to a minimum temperature of -196 °C. Cryopreservation involves the process of cooling cells or whole tissues to low sub-zero temperatures at which any biological activity, including the biochemical reactions that would lead to cell death, is effectively stopped. There are two distinct methods of cryopreservation: (1) preservation in the frozen state which can involve either ultra-rapid freezing (direct introduction into LN₂) or controlled-rate (slow programmable) cooling and (2) *vitrification*, which is preservation in the glassy, non-crystalline state. Both methods usually require the addition of *cryoprotectants* which have different protective properties (*e.g.*, colligative or osmotic) although generally they will lower the freezing temperature. Cryoprotectants are applied in different regimes, combinations and concentrations dependent upon the mode of cryopreservation (*e.g.*, frozen or vitrified).

Controlled-rate cooling minimizes the potential for lethal, intracellular ice forming during the freezing process; this is achieved by controlling extracellular *ice nucleation* (also termed ‘seeding’) and applying optimally slow cooling rates that allow sufficient water to leave the cell during the progressive freezing of the extracellular fluid. Controlled-rate cooling requires the careful control of cooling rate (*e.g.*, around 1 °C/minute is appropriate for many mammalian cells), ice nucleation temperature and terminal freezing temperature and hold time (*i.e.*, before specimens are transferred to LN₂); the optimization of which will vary between cells of differing size and water permeability. To circumvent cryoinjury caused by toxic cell volume changes and the excessive concentration of solutes the application of colligative cryoprotectants, such as DMSO, is required during controlled rate cooling.

In contrast, *vitrification* is a process that avoids the potential damage to cells caused by intracellular and extracellular ice formation. This is usually achieved by the addition of *cryoprotectants* at higher concentrations which increase the viscosity of the sample and prevent ice crystals from forming.

Common cryoprotectants, such as dimethyl sulfoxide (DMSO) are often toxic in high concentrations and care must be taken to limit the damage produced by the cryoprotectant itself. When possible, researchers should test available preservation solutions to determine what works best for their specific research activities and, as required, optimize the cryoprotectant strategy for their preserved samples. Using an appropriate cryopreservation media and cryoprotectant(s) will reduce the rate of degradation at hypothermic temperatures and offset the risks of inadvertent devitrification at ultra-low temperatures. When possible, researchers should test available preservation solutions to determine what works best for their specific research activities and, as required, optimize the cryoprotectant strategy of cryopreserved samples. Using an appropriate biopreservation media will reduce the rate of degradation at hypothermic temperatures and risks of inadvertent devitrification at ultra-low temperatures.

The temperature at which frozen and vitrified preparations are stored affects the length of time after which cells can be recovered in the viable state (generally, the lower the storage temperature, the longer the viable storage period). As temperature is reduced, metabolic and degradation processes in cells are slowed; however, they are not effectively slowed to allow for long-term storage (years to decades) until the temperature falls below the *glass transition* temperature of pure water (effectively $< -132^{\circ}\text{C}$ for most mixtures of cells and aqueous cryopreservation media). The T_g of some vitrification solutions can be higher and it may be prudent to determine the actual critical T_g using thermal analyses. In addition to storage temperature, handling during removal from storage will affect the viability of cells and may result in degradation of cellular components. Every time a sample is warmed above the glass transition temperature, it experiences a micro-thaw event. Repeated thermal cycling episodes lead to increased cell death via apoptosis and necrosis. The temporal nature of delayed onset cell death resulting from preservation stress may affect the quality of data obtained from these samples depending on the timing of experiments post-preservation and the ability of the cells to recover from cryoinjury in the long-term.

K4.200 Freeze/Thaw and Cooling/Re-warming Cycles

Freeze/thaw cycles for specimens cryopreserved in the frozen state and cooling/re-warming cycles for specimens in the vitrified state can be damaging to the macromolecules and cells intended for analysis. Damage can also occur via osmotic and dehydration injury during exposure and removal of cryoprotective additives and vitrification treatments. Therefore, it is important to select *aliquot* sizes that are appropriate for the intended uses for the specimens in order to minimize the number of times a sample is thawed and frozen or vitrified before it is used. Samples are often maintained at liquid/vapor nitrogen temperatures in order to achieve biopreservation of the sample below the glass transition temperature (below which the cell biochemical activity is virtually stopped). Thermal cycling intervals resulting in sample temperature increase above the glass transition temperature allows for repeated freeze/thaw cycles even within the sub-zero frozen state. For these reasons it is essential to limit the potential of

freeze/thaw and vitrification/devitrification cycles occurring when samples are introduced or removed from storage.

K5.000 SPECIMEN STABILITY

In addition to the issues of temperature discussed above, specimen stability may also be affected by other parameters such as the use of anticoagulants and stabilizing agents like EDTA and ascorbate (Wendland *et al.*, 2010, Isa *et al.*, 2010). It is important to know in advance, specimen collection requirements by manufacturers of customized assay kits. For some applications, rapid dehydration is an effective method to stabilize molecules. Dehydration methods may be more practical in field settings where access to refrigerants or chemical fixatives is dangerous or cumbersome. Where cold temperatures are applied it is essential to maintain the continuity of the *cold chain* from the point of collection to deposition in the repository.

Best Practice: Selected methods for collecting and preserving biospecimens should be followed when possible to ensure that any preservatives, dehydration or other protective treatments used do not have a deleterious effect on future analyses.

K6.000 COLLECTION AND STORAGE CONTAINERS

Collection and storage containers vary according to specimen types being collected and the analytical goals of the study. During selection of container type, consideration should be given to the long-term use, standardization and applicability to new platforms and automation. Also, the same containers used for specimen collection may not be suitable for specimen storage. In some cases contaminants associated with the container (*e.g.*, persistent organic pollutants or heavy and trace metals) may interfere with subsequent analysis. This issue is especially true for specimens stored for environmental analysis. Container *labels* should be permanent and able to endure excursions in and out of cold conditions and exposure to high humidity and ambient temperatures especially when samples are taken from extreme environments. Light sensitive material should be stored in containers that do not allow penetration of light such as amber vials or amber coated bags.

K6.100 Sterility

Risk assessments and mitigation exercises should be undertaken in the context of a specimen's requirements for asepsis. While complete sterile conditions may not be required for many specimen collections and processing, adequate consideration should be given to the cleanliness of instruments, surfaces and equipment used in specimen processing and handling. RNA is particularly sensitive to RNAses which may be present on tools and surfaces that have not been properly cleaned /sterilized. Where disposable instruments are used, every specimen should be handled with fresh new instruments and when non disposable instruments are used, they should be appropriately cleaned after each specimen processing. *Sterility* of preservatives, *cryoprotectants* and liquid nitrogen supplies should also be considered.

K7.000 COLLECTION PROCEDURES

A variety of protocols exist for the collection of different specimen types. The protocol chosen should be suited to the particular needs of the study. Special considerations for specimen collection procedures are presented below (Holland, *et al.*, 2003; Landi and Caporaso, 1997).

Staff should wear personal protective clothing/equipment, as appropriate, when working with specimens (see Section E5.000, Personal Protective Wear).

Depending on the needs of the investigator for whom the samples are collected or the protocol of the study for which the material is collected, tissues can be collected from several sources (*e.g.*, surgery or *autopsy*). Collection of specimens for research should under no circumstance interfere with appropriate patient diagnosis or care.

Best Practice: A pathologist should review all potentially diagnostic tissue specimens to determine what material can be made available for research. Blood, and other body fluids, as well as some other solid tissues not required for diagnosis or prognosis can be collected in accordance with approved protocols and may not require pathologic review.

K7.100 Solid Tissues

Tissues may be collected prospectively, as a part of a population-based study, or for general purposes for future research activities. The collection of samples for research should never compromise the diagnostic and prognostic integrity of a specimen. This is especially important when human solid tissue specimens are collected during surgery and where pathology is involved in the subsequent diagnostic process. This is because attributes of the sample (*e.g.*, the margin of the tumor or the number of tumor positive lymph nodes) may have a direct impact on the care that a patient subsequently receives (*e.g.*, chemotherapeutic treatment vs. radiation therapy vs. no treatment).

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. Information from the pathologist on the characteristics of the biopsy or surgical material (*e.g.*, % normal, % tumor, % necrosis and/or % fibrosis) should be recorded for future use so that the end user will be able to determine the usefulness of the tissue. Where possible, multiple sections or samples should be created to allow for greater use of the specimens.

K7.110 Surgical Samples

Remnant samples may be collected from diagnostic surgical procedures. With proper human subjects/ethics committee approval and appropriate *informed consent*, specimens may be resected specifically for research. When pathological diagnosis is required, a pathologist should first examine the specimen to identify tissue that can be made available for research without compromising diagnostic integrity.

Specimens should remain fresh, not fixed, and be placed in a clean or sterile container on wet ice (2 - 8 °C) for transport from surgery to pathology or to the repository. 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 have a sterile hood. Many research protocols do not require tissue specimens be procured or processed following sterile procedure. A “clean” area should be set up for specimen procurement/processing. During specimen procurement, contact between different specimens should be avoided (specimen contamination) and equipment used for procurement should be cleaned or disposable equipment replaced after each procurement. Fresh blades and instruments should be used with each new specimen as well as in different areas of the same specimen. The prosector should be provided with gloves and clean instruments for resection of the tissue. Specimens should not be resected on a dry towel, or other absorbent material, as this procedure rapidly desiccates the specimen and may compromise its usefulness.

Unless a researcher specifies otherwise, tissue provided to the repository may be placed directly in appropriately labeled clean containers of cold biopreservation media (2-8 °C) for transport to the repository for processing. If the tissue is to be frozen immediately, it is not necessary to place it in preservation media, which may cause ice crystals to form on the outside of the specimen when freezing. It is important to educate/train all personnel who will be handling the specimen on the specific handling requirements unique to each protocol.

Samples requiring snap-freezing or flash freezing (cooling at sufficiently high rates to limit damage to cell structure from intracellular ice formation or prevent compositional changes in labile molecules) can be frozen in a *Dewar* of liquid nitrogen or on *dry ice* at the time of collection. Where specimen morphology needs to be conserved, snap-freezing should be done in pre-cooled isopentane (at a maximum of -80 °C) or sub-cooled in liquid nitrogen. Data should be maintained and tracked on the time that elapses between relevant time points (*e.g.*, collection, processing, preservation, storage). A date and time stamp can be utilized for maintaining these records efficiently. This information can then be transferred into a *database*.

If a frozen section is cut for diagnostic reasons, then the repository staff should make every effort to obtain an extra slide for quality control (QC). If sufficient amounts of tissue are available following a diagnosis, the repository staff should save some of the tissue as snap-frozen and a representative section for making a paraffin block that will become the property of the repository. A hematoxylin and eosin (H & E) slide may then be cut from each paraffin block which 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 diagnostic paraffin block to serve as the QC material for the repository. All samples should be labeled appropriately (Section I.300, Labels) and all relevant accompanying data should be documented (Section I2.000, Inventory Systems).

Best Practice: Pre-label specimen collection containers with barcode/donor ID before surgery to ensure accurate labeling and specimen tracking.

Best Practice: All personnel who will be handling the specimen (*e.g.*, surgeons, nurses, pathologists and repository personnel) should be trained on the specific handling requirements of each protocol.

K7.120 Post Mortem Collection (Autopsy/Necropsy)

Remnant samples may be collected from *autopsy/necropsy* procedures consistent with relevant regulations, as appropriate. Requests should specify a maximum time interval post mortem prior to processing. Autopsy/necropsy procedures may yield “normal” tissues or large quantities of a specimen that would not otherwise be available from surgical procedures (*e.g.*, heart or brain). 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 into a container of cold biopreservation media (2 – 8 °C) on wet ice for transport to the tissue repository for processing. These organs could be dissected into smaller sections for processing and storage. Detailed information should be obtained about the decedent such as disease condition, age, sex, race, cause of death, time and date of death, and time of organ procurement. Information about the procured organ should include the condition (normal or diseased).

K7.130 Transplant

Occasionally, organs that are inappropriate for transplant may be offered or made available to a repository for research purposes. It is not unusual for the organ to have been out of the body for many hours beyond the normal time frame identified for procurement of samples. However, because transplant tissue is usually placed in a biopreservation media at 2 - 8 °C 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. Transplant organs may also be dissected into smaller sections for processing and storage. Information about the donor from whom the organ was procured should be obtained from the transplant center. All organs/tissues intended for research should be maintained in appropriate biopreservation media at 2 - 8 °C until processed. Isotonic saline or culture media may not be considered optimal for hypothermic biopreservation of viable cells/tissues/organs.

In general, it is important to remove as much blood and other native fluids from the resected tissue/organ as soon as possible prior to processing. The reason for doing this is because for larger or highly vascularized tissues in preservation solution, clot formation within the vasculature obstructs the penetration of the preservation solution into the tissue. This situation results in tissue specimens that are not homogeneously preserved and there could be localized tissue damage due

to ischemia. Also, tissue damage could occur because ischemia and the clotting cascade impact the molecular profile of the tissue. These activities produce changes in the molecular pathways and in the protein expression thus resulting in the tissue section being less representative of its original resected state.

K7.200 Blood Samples

One of the primary decisions in storing blood samples is whether to collect anticoagulated (plasma/buffy coat/RBC) whole blood or coagulated (serum/clot) blood. When serum is collected without anticoagulant, the blood clot obtained after processing can be used as a source of DNA for genotyping and other DNA related studies (Somari *et al.*, 2004). In similar fashion, blood collected with anticoagulant can yield a packed cell volume (containing both the buffy coat and RBC) to be used as a source of DNA.

When multiple blood collection devices/containers are involved there is a prescribed priority order of draw (see Appendix A for internet resources). The order of draw for clinical testing may be different from an investigator's requested order of draw. It is also important to determine which anticoagulants are acceptable for a particular downstream procedure. (See Section K5.000, SPECIMEN STABILITY).

Blood samples may be collected in different manners depending upon the amount of blood needed for a study and the distance between the sample source, processing location, and the repository. For example, blood samples may be collected at a location that is far away from the research site, in either small quantities as dried blood spots on treated or untreated matrices or collected in large quantities in tubes that provide stability at room temperature for several days.

Consideration should be given that cell viability and functionality from blood samples may be compromised during extended ambient storage/transport (Jansen *et al.*, 2009); however new technologies have been developed to significantly extend ambient storage/transport of blood samples for up to 1 year (Wilkinson, *et al.* 2011). Hypothermic temperatures (2 - 8 °C) may allow for extended stability of blood-derived cell products.

Best Practice: Blood samples should be processed and stored within four to twenty-four hours of draw, depending on the analytical endpoints (Tuck *et al.*, 2009.)

K7.300 Urine Samples

Urine samples should be maintained on ice or refrigerated after collection. Collection containers should be sterile and dry, and have a 50 mL to 3 L capacity, a wide mouth, and a leak-proof cap. Depending upon 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. Urine containers used for environmental toxicology assays should be high density polypropylene to minimize phthalate contamination. Because urine may contain cellular and other elements, a urine sample is typically centrifuged to remove cells

and debris. The acellular urine and separate cell pellet can then be analyzed and/or frozen as aliquots.

There are various methods of collection (*e.g.*, first morning urine, random, fractional, timed) depending on the type of analysis intended. The collection method should be documented in the sample record.

K7.310 First Morning Urine Samples

Before going to sleep, the donor voids a urine specimen. Immediately on rising, the donor collects the “first morning” urine specimen. First morning specimens are best for detecting substances in a more concentrated solution (*e.g.*, white and red blood cells or urinary hormones).

K7.320 Random Urine Samples

A random urine sample is good for routine screening and cytology studies.

K7.330 Fractional Urine Samples

Fractional urine samples are used to compare the concentration of an analyte in urine with its concentration in blood. First morning urine, which contains solutes and metabolites from the evening meal, is discarded and a second urine sample following a period of fasting is collected.

K7.340 Timed Urine Sample

Timed urine collections allow for comparisons of patterns of excretion of certain biomolecules. Typical collection times are 12 and 24-hour. For the 24-hour collection on day one, the donor empties his/her bladder and for the next 24 hours all subsequent urine is collected.

K7.400 Nail and Hair Clippings

Nail and hair clippings can be used for trace metal analysis to provide a longer-term measure of exposure. These samples are simple to collect, store and ship. They can also be used as a source of DNA.

K7.500 Saliva and Buccal Cell Samples

Saliva samples are used for drug testing, HIV detection or monitoring of hormone levels and as a source of DNA. Collection devices for these specimens include non-covered cotton roll, polypropylene-covered polyether roll and paraffin wax chewing stimulation. Some researchers may request donors to provide saliva samples directly into a container with an opening large enough to facilitate this collection. Saliva can be stored either as non-centrifuged aliquots or centrifuged, which results in supernatant and pellet aliquots which can then be analyzed and/or stored separately.

Buccal cell specimens may be useful as a source of DNA. A variety of collection techniques and containers have been developed specially for these collections. See references for several of these in Appendix A.

K7.600 Breast Milk Samples

Breast milk collection can be initiated when breast-feeding starts. Breast milk can be collected by manual expression or vacuum pump and should be collected in

autoclaved or specially cleaned bottles and are typically stored frozen. If certain analytes such as phthalates are of interest, the sample can be collected in a glass bottle with Teflon™ cap and stored in the participant's household freezer.

K7.700 Stool Samples

Samples are self-collected by participant into a container that can be lined with plastic wrap or placed inside another container to provide an impervious storage container. After collection the sample should be frozen. Some procedures will allow for lyophilizing the sample for long-term storage which provides a more inert (less odoriferous), smaller sample for analysis.

K7.800 Cervical Vaginal Lavage Samples

Cervical vaginal lavages (CVL) can be obtained and used for HPV studies.

K8.000 RETRIEVAL OF SPECIMENS FROM STORAGE

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.

K8.100 Locating Specimens in Storage

The location of specimens to be retrieved should first be verified in the appropriate specimen inventory system (Section I2.000, Inventory Systems). A specimen requisition is generated according to procedures applicable to the repository's specimen requesting, tracking and inventory protocols. The requisition is checked for accuracy before transmission to the repository, according to established SOPs (see Section D2.220, Critical Topics for Manuals Containing SOPs) and QC standards (see Section D3.000, Quality Standards).

K8.200 Specimen Retrieval

Specimens should be located and pulled from storage as documented on specimen requisition forms. If specimens are frozen or vitrified, speed is necessary during the retrieval process. Such speed may require that at least two individuals carry out the retrieval process. If possible, specimens being retrieved should be maintained at the storage temperature throughout the process (*e.g.*, specimens stored at -80 °C should be kept on dry ice during the retrieval process). Forceps may be used when withdrawing specimens stored at LN₂ temperatures to prevent warming of the specimens from contact with hands.

Once retrieved, staff should confirm that all requisitioned specimens have been accounted for. Quality control checks should be performed to confirm that all specimens listed on the requisition were retrieved.

If specimens appear to be missing, protocols should be followed in order to locate the missing specimens. Inventory systems should be updated to indicate that samples are in fact missing or that they were improperly located when placed in the inventory.

Best Practice: A second, independent quality control check should be performed to ensure that the correct specimens have been retrieved.

Best Practice: Mechanisms should be established to track before the last aliquot of a critical material is about to be used.

K8.300 Thawing, Re-warming and Aliquoting Specimens

K8.310 Liquid and Solid Tissue

Frozen tissue specimens should be thawed at room temperature for a brief period of time or at refrigerated temperature (4 - 8 °C) overnight. Specimens in resin straws can be thawed directly at room temperature or in a 37 °C water bath. Care should be taken that surface moisture from water baths does not enter the sample containers. In the case of vitrified samples, optimization of re-warming is critical and it may be necessary to apply a two-phase and/or rapid re-warming process to ensure that the samples do not form ice crystals as they pass through the *T_g*.

Large-volume liquid samples (*e.g.*, sera, plasma, urine) may need to be divided into smaller aliquots for *distribution* to multiple end-users. The proper pipette and tip to use is determined by the required volumes and eventual analysis. If analyzing for persistent organic pollutants, using a plastic pipette and tip may contaminate the sample further. A different pipette tip should be used for each specimen.

A new alternative to thawing a specimen for aliquoting is a drilling system that includes a motor that produces a sonic, linear oscillatory motion that removes a frozen biological sample from a stored frozen specimen without thawing the remainder of the specimen.

Best Practice: Specimen containers should be opened and the specimens aliquoted in a *biological safety hood*. Sterile vials and pipettes should be used to avoid contaminating samples.

K8.320 Viable Cells

The rate and method of freezing/thawing and cooling/rewarming specimens can have serious effects on the viability of cells. Exact freezing/thawing, vitrification and cooling/re-warming protocols should be developed, including the validation of appropriate biopreservation media (cryopreservation solution), devices and cooling rate to ensure that the method used supports the known or anticipated use for the specimens (see Section K4.100, Biopreservation/Cryopreservation).

Although slow cooling is generally best to ensure cell viability in frozen samples, the opposite process is required when thawing from the frozen state. Agitation of the vial/ampoule/straw in a 37 °C water bath for a brief period of time is preferable, but this process may be detrimental to certain cell types if the time required is too lengthy. Samples should be rapidly thawed just enough to thaw visible crystalline ice, and so that sample temperature is still hypothermic (2 – 8 °C). Cells should be further quickly diluted in appropriate media to minimize toxicity from the cryopreservation media; however, dilution protocols (which may include several washing steps in order to gradually dilute and wash out the cryoprotectant) should be optimized to circumvent damaging osmotic effects. In the case of vitrified specimens, optimizing cooling and re-warming regimes is critical for ensuring the formation and maintenance of a stable glassy state and

preventing de-vitrification and ice nucleation during re-warming. Therefore, in contrast to controlled rate freezing protocols, vitrification can involve rapid cooling and re-warming regimes.

K8.321 Assessment of Cell Viability

The number of recovered cells can be determined by several methods, including: dye exclusion (*i.e.*, Trypan Blue) or vital staining using tetrazolium salts, and fluorescent dyes such as fluorescein diacetate. Accurate measurement of the number of viable cells in a non-motile population can be difficult and it is essential to standardize viability assays and where possible back them up with unequivocal tests of functionality and clear evidence of cell division and growth. As indicated previously, the phenomena of delayed onset cell death results in a temporal disconnection between evaluations of viability immediately post-thaw and actual long term cell survival and functionality. As such, it would seem logical that post-thaw assessment of cell viability would need to be expanded beyond a singular assessment via Trypan Blue (or similar assays) immediately post-thaw or after re-warming in the case of vitrified samples. An outline for an expanded assessment of post-thaw recovery (this may be referred to as True Yield/Viability) would include multiple methods of assessment including Live/Dead assays, cell death mechanism assays such as Annexin/PI, metabolic assays such as alamarBlue or MTT, cell function assays (dependent on cell type), and assessment at multiple time points post-thaw/re-warming, especially within the timeline of delayed onset cell death.

K9.000 RECEIVING SPECIMENS

SOPs should be in place for receiving specimens into the repository. All specimens provided to the repository from outside sources should be confirmed and a record of the receipt should be maintained by the repository (see Section G4.000, Record Retention). Documentation should include the date and time the specimens were received, the tracking number assigned by the courier service, inspection of package and container for visible signs of damage, confirmation of the condition of the coolant used during specimen transport, confirmation that specimens received match those listed on the manifest, and documentation of all problems or discrepancies. If data loggers are enclosed in shippers, they should be checked to determine if adverse temperature spikes have occurred. Template forms documenting the above activities should be available and this can be modified as may be necessary. This form should identify the person making the entries (name/signature/date).

Best Practice: Any problems encountered with a shipment should be communicated to the sender to aid in the prevention of similar problems in the future. Particular note should be made of the stability of the cold chain for specimens shipped in the chilled, vitrified and frozen state.

SECTION L: LEGAL AND ETHICAL ISSUES FOR BIOSPECIMENS

L1.000 GENERAL

The *collection, storage, distribution* and use of biological materials in research raises many legal and ethical issues with repositories often serving as the intermediary between study participants and the scientific research community. On an international level, the collection and use of these materials is currently regulated by an amalgam of differing and occasionally conflicting laws and policies. Thus, repositories should proceed carefully, not only in their daily work, but also with respect to international exchange of *samples* and associated data. Regulations in some countries address the ethical issues related to collections and use of biospecimens and to import and/or export of *specimens* as well as shipping regulations (See Section J, Shipping and Packaging). References and links to applicable regulations and guidelines are included in Appendix A.

L2.000 COLLECTION OF HUMAN BIOSPECIMENS

Key discussions of ethics in human subjects research are found in a number of documents, including the Declaration of Helsinki adopted by the World Medical Association in 1964 and revised several times subsequently, most recently in 2008. These issues are also discussed in the Belmont Report published by the U.S. Department of Health and Human Services in April 1979 and include several fundamental key concepts:

- Freely-given informed 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 effort should be taken to reduce the risks to patients and ensure that the risks do not exceed the benefit of the expected findings.
- 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.

It is important to understand key terminology related to the legal and ethical issues for human specimens. Terms that describe whether and how specimens are linked to donor identity are often used in different ways and with different meanings in different contexts. Definitions of key terms have been included in the Glossary found in Appendix B.

The collection, storage, and use of human specimens and associated data should be conducted in a way that respects the individual and maintains privacy and confidentiality. In addition, repositories should adhere to and keep up-to-date on relevant national human subjects regulations, privacy regulations and other relevant national, state and local laws. For example, some regions prohibit the use of fetal tissues, embryos, or embryonic stem cells in biomedical research. Regulations that govern the collection and import and/or export of human specimens, including those mandated by the Convention on Biological Diversity should also be observed.

L2.100 Human Subjects Review Board/Ethics Review Committee

A human subjects review board (institutional review board or ethics review committee) is any board, committee, or other group formally designated by an institution to review biomedical research involving humans, to approve the initiation of the research and conduct periodic review of such research. As a component of a human subjects/ethics review, the processes and *procedures* for collection, storage, distribution, and use of human specimens for research should be evaluated to ensure that these procedures are appropriate to protect human subjects.

L2.200 Informed Consent

Informed consent for the collection, retention and use of specimens is a process that offers donors information sufficient to allow them to make an informed choice about whether to provide specimens and data to the *repository* and agree, where applicable, to future research use. Consent should only be obtained under circumstances that provide the prospective donor or the donor's representative sufficient opportunity to consider whether or not to participate and minimizes the possibility of coercion or undue influence. The information that is given to the donor or the representative should be understandable to the subject or their representative.

Consent may be obtained for a specific research project, such that the details of the project can be specifically outlined. Alternatively, consent may be obtained for unspecified future research, in which case general information about the possible future research uses are provided, in accordance with applicable national or local regulations and policies. Mechanisms should be in place to assure that future research uses of specimens are consistent with the original consent (*e.g.*, through review by a human subjects/ethics review committee or other mechanisms consistent with applicable regulations and guidelines).

Donors should have the right to withdraw consent and to have their unused specimens and data removed from the repository unless the specimens and associated phenotypic or demographic data are *anonymous* and cannot be linked by the repository to donor identities. The conditions under which a donor may make this request as well as the logistics for how a donor initiates this request should be specifically outlined in the informed consent document and process.

Best Practice: Donor consent should be obtained unless waived by an authorized human subjects/ethics committee constituted in accordance with applicable laws or regulations.

L2.300 Protection from Research Risks

Care should be taken to minimize the risks to subjects, and ensure that risks do not outweigh the benefits of the expected findings from studies using the specimens. This includes minimizing physical risks and psychosocial risks associated with the collection of specimens and/or data and ensuring that the collection of specimens and data does not affect patient care.

The repository should follow well-documented procedures to protect the privacy and confidentiality of the donors from whom the specimens and/or data are obtained. Such procedures may include: completely anonymizing specimens and data; assigning a unique code and/or removing all identifying information from the specimens and data; storing specimens and data securely; restricting access to specimens and/or data; and providing firewalls between the subject identity and the recipient investigator. Such firewalls prevent inappropriate data from passing in either direction through the firewall (*e.g.*, identifying information to the researcher or specific research results that have not been validated to the donor). In addition, identifying information should be removed before allowing the recipient investigator to have access to specimens and/or data, unless the investigator has human subjects/ethics committee approval to have access to this information.

Best Practice: The collection of specimens and/or data for research must never adversely affect patient care.

Best Practice: Every effort should be made to protect the privacy and confidentiality of data associated with the specimens.

L2.400 Specimens Obtained from Mentally Impaired Persons

Extra care and attention should be given to the consent process when donors are incapable of signing the consent form themselves. Patients in this group would include those under heavy sedation, patients with dementia, or patients with syndromes of impaired consciousness, such as coma, brain death, locked in syndrome, and persistent vegetative state. Ethical guidelines for the management of patients in these conditions have been published by the British Medical Association (1996) and the American Neurological Association Council on Ethical and Judicial Affairs (1999). In cases of demented or mentally incompetent donors, a relative or legally authorized person could sign the consent form on the donor's behalf. In some countries, the donor must be informed regardless of their age, medical, or mental condition.

L2.500 Specimens Obtained from Autopsies

Biospecimens may also be obtained during *autopsy* from pathologists at hospitals, institutions, or the coroner's office. Full consent or authorization should be obtained from the *donor* (*e.g.*, a signed agreement to donate their body for scientific research), the next of kin, or a legally authorized person. In the U.S., some states require consent from the next of kin even if the consent was obtained from the donor prior to death. It is important to rapidly harvest organs and tissues soon after the donor has deceased (*i.e.*, a "rapid autopsy"), since mRNA and many proteins are sensitive to enzymatic degradation.

European countries have adopted legal frameworks in order to improve the accrual of tissues for research from autopsies. An "opting in" system has been devised whereby potential donors must register in advance. Alternatively, an "opting out" system has been developed, in which it is presumed that people give their consent for donation unless they register their objection (Jacob, 2006).

L2.600 Specimens to be used for Genetic Analyses

Some repositories either use a “tiered consent” form (one that allows participants to consent to some aspects of the research but not others) or require a separate consent form to be signed by donors when their biospecimens may be used for genetic testing or for mutation analysis. When genetic information generated from biospecimens is stored in a *database*, it is important that confidentiality is maintained and that the database server is secure. In some cases, national standards have been set for such security. Complex ethical issues arise when genetic testing is performed on biospecimens, such as whether to inform donors of their research results, whether to inform donors’ families when heritable genetic factors are identified in tissues, especially post-mortem tissues, whether to inform families about possible disease risks, whether to ask relatives to collaborate on heritable genetic testing, and whether to advise relatives to seek genetic counseling. These ethical issues are currently unresolved and are especially difficult if there is no known treatment or cure for the disease at hand. Furthermore, in some jurisdictions there are laws that prohibit the return of results unless conducted in an approved laboratory. Even then, the results or their interpretation may be incorrect and their use in medical decisions might cause harm to patients. Thus, it is essential to discuss these issues with the human subjects/ethics review committee during the design of a repository protocol and informed consent and before returning any research results to subjects, their families, or physicians.

L2.700 Consideration of Perspectives of Communities, Populations, Ethnic and Social Groups

In some cases, there may be risks to ethnic and social groups or communities due to the release of aggregate research findings even when no individually identifiable information has been revealed. In addition, some populations or groups have specific beliefs about the *disposition* and use of their specimens, which should be respected.

Best Practice: When research focuses on a particular community it is best to seek input from representatives of the group on relevant aspects of the design of the study, the consent process, appropriate uses of specimens and dissemination of collective research findings.

L2.800 Special Considerations for Collection of Pediatric Human Biospecimens

L2.810 Enrollment of Pediatric Subjects

The collection, storage and distribution of specimens from pediatric subjects create additional ethical considerations, particularly in the areas associated with the gathering of informed consent from subjects (Kaufman *et al.*, 2008). All elements described above associated with the use of samples from adult subjects should also be adhered to when working with pediatric subjects, including securing human subjects/ethics review board approval for all processes and procedures, the minimization of risk associated with subject participation including the risks associated with the loss of privacy and confidentiality, and the

termination of specimen resources. The age of pediatric participants may be critical and require more detailed documentation (*e.g.*, days, months, years). Policies and legal requirements may differ by country and region.

L2.820 Parental Permission and Pediatric Assent

Subjects below a certain age (which may differ by region or country) are not able to provide informed consent. Instead, parental permission and pediatric subject *assent* (in cases where assent may be given), is obtained in lieu of informed consent. Assent should include helping the patient understand the nature of their condition, informing them of what they can expect with tests and treatment(s) and obtaining an expression of the patient's willingness to accept the proposed care (American Academy of Pediatrics Committee on Bioethics, 1995).

The documentation associated with obtaining parental permission is similar in nature and content to a document used to obtain informed consent from an adult with the exception that the documentation contains references to the minor child as the donor. The components of the parental permission documentation must include a complete and understandable description of the procedures associated with the collection, storage, and distribution of the specimens, risks and benefits (if any), options other than participating, and opportunities to withdraw permission. The process of securing parental permission should include the opportunity for the parent or guardian to discuss and question the pediatric donor's potential involvement in the research until a level of full understanding is reached.

Once parental permission is obtained, the process of securing pediatric assent may be undertaken if the donor in question is at an age and developmental level where assent may be given. The assent process should be conducted through the discussion of the research, procedures, and processes with the child in age appropriate language, including the opportunity for the child to ask questions. As with the securing of parental permission, key topics must be covered with the child, including the facts that they do not have to participate and that they may withdraw their assent to participate at any time in the future. For children who are either not yet old enough to read or not able to read, this assent process may be conducted orally, assuming that the appropriate human subjects/ethics committee has approved the enrollment of children of that age. For children of reading age and ability, a pediatric assent document should be utilized. Assent documentation should be drafted in language that is age appropriate, easily understood, and likely to encourage questions and discussion. As with the process to obtain informed consent and parental permission, the process associated with obtaining pediatric assent should be an interactive process where information is freely shared and decisions are made in an informed fashion.

L2.830 Age Considerations

Until the subject in question is of legal age, parental or guardian permission is required for the pediatric subject to participate in research. The question, however, of when to progress from using a pediatric assent document to using an informed consent document is less clear and tends to be institution and/or human

subjects/ethics committee dependent. The process and documentation must be designed with the emotional, developmental and cognitive abilities of the pediatric population in question. If the pediatric subjects are adolescents, it may be possible to use the same documentation as is used to secure informed consent from adult participants, with the caveat that parental permission is still required as a necessary first step. A new consent may be required from the participant once he/she reaches the age of majority.

Best Practice: Repositories should consult with human subjects/ethics committee for guidance on whether subjects that have reached the age of majority should be re-consented or whether a waiver of informed consent by the human subjects/ethics committee is appropriate.

L2.840 Withdrawal of Assent and/or Permission

Pediatric subjects and their parents or legal guardians must be informed that they are able to withdraw their assent or permission, respectively, at any point and decline to further participate in the process.

L3.000 ETHICAL COLLECTION OF ANIMAL BIOSPECIMENS FOR RESEARCH

Scientific researchers who work with animal models generally agree that experiments that follow the best animal welfare procedures result in the best science. Three Rs (reduction, refinement and replacement) in animal procedures should be an integral part of any research project, to help minimize animal use and suffering and to facilitate good scientific practice.

The refinement of scientific procedures carried out on animals to minimize adverse effects and to maximize the scientific benefit gained is a legal and ethical requirement under the Animals (Scientific Procedures) Act 1986, the Animal Welfare Act 2006, the Animal Health and Welfare Strategy for Great Britain and also in the wider European and worldwide context. Nevertheless, refinements are not always implemented for a variety of reasons (Hartley *et al.*, 2004; Karas, 2006).

The ‘five freedoms’ concept announced by the British Farm Animal Welfare Council in 1979 (FAWC, 1979) can be taken as general indicators of laboratory animal welfare. These five freedoms are: (1) freedom from injury and disease; (2) freedom from discomfort, hunger and thirst; (3) freedom from pain; (4) freedom to express normal behaviors; and (5) freedom from fear and distress. In any animal resources facility, researchers must implement actions to minimize the impact of the procedures they perform on these five freedoms.

Currently, animals are sacrificed in laboratories or breeding establishments for a variety of reasons including:

- When animals have passed the age of being suitable for breeding.
- To provide blood and other tissues samples for a scientific analysis.
- At the completion of an experiment or due to continuing adverse effects.

- To end an experiment because the levels of pain, distress and suffering are likely to exceed a certain level.
- In situations where the health or welfare of the animals are a matter of concern.
- To eliminate animals with improper characteristics such as type or sex.

In terms of animal welfare, the primary criteria for euthanasia should follow the rules: the method should be painless, achieve rapid unconsciousness and death, require minimum restraint, avoid excitement, should be suitable for the age, species, and health of the animal, must minimize fear and psychological stress in the animal, should be reliable, reproducible, irreversible, simple to administer (in small doses if possible) and safe for the operator. The use of carbon dioxide (CO₂) for the sacrifice of mice and rats is widely accepted because of its low cost and easiness. However, the use of CO₂ has been recently contested and additional measures, such as anesthetizing the animal to avoid panic or pain or performing cervical dislocation to ensure that gassed mice are dead, are being proposed.

The limitation of the number of animals for experimental procedures might be disadvantageous, since strategies that reduce the numbers might produce a disproportionate increase in the pain and distress caused to the animals that are included in the experiments. Therefore, researchers should think in terms of minimizing, rather than reducing, the numbers of animals used.

Through the harmonization of procedures among animal resource centers it is expected that minimization/elimination of pre-analytical confounding variables and the resulting comparability of studies will result in a reduced number of animals used for experimental research. Such harmonization will result in better animal welfare standards in a way that both animals and science benefit from harmonization.

L4.000 COLLECTING PERMITS FOR WILDLIFE SAMPLES

Collecting wild organisms is controlled by international directives and national laws. Failure to heed these laws can be damaging for biodiversity and can circumvent fair access and benefit sharing among countries. It should be checked before leaving on a field trip which permits are needed.

National and/or regional collecting permits, and potentially CITES permits (for species covered by the Convention on International Trade in Endangered Species of Wild Fauna and Flora) are usually necessary. Export and import permits should also be considered. Some of these permits can take many months to get. Permits are often highly specific and attention should be paid to include the target sample derivative(s) (whole specimen/viable cells/fixed tissue/DNA/etc.)

L5.000 SHARING AND DISTRIBUTION OF SPECIMENS AND DATA

Repositories should provide responsible custodianship of the specimens and data that they collect, maintain and share. Mechanisms should be in place to maintain the *quality* of specimens and data, protect donor privacy and confidentiality and to ensure that specimens are shared in a manner that is consistent with any consent obtained for the specimens (see Section M2.000, Access and Utilization).

The benefits derived from international transfer of biological material extend beyond the physical specimen to include benefits such as training and capacity building. In 2011, the Secretariat of the Convention on Biological Diversity recommended the resources on Access and Benefit Sharing (ABS) prepared by the Swiss National Academy of Sciences. These include a sample ABS agreement as well as case studies and a Step-by-Step guide to compliance.

Best Practice: Specimens and/or data should only be made available for ethical and scientifically appropriate research that is expected to contribute to scientific discovery.

L5.100 Termination of Repositories

Repositories should develop plans at the time of their establishment for the disposition of specimens and/or data should the repository be terminated for any reason. The disposition, including any transfer of specimens and/or data to third parties, should be consistent with the informed consent under which specimens and/or data were obtained.

L5.200 Ethical Disposal of Biospecimens

For some populations, disposal of biospecimens may have ethical considerations. Depending upon the nature of the study population and the repository, repositories and recipient researchers may be required to dispose of unused specimens according to local, legal, ethical and *safety* rules for the disposal of human remains. Alternatively, recipient researchers may be requested to return unused specimens to the repository.

SECTION M: SPECIMEN ACCESS, UTILIZATION AND DESTRUCTION

M1.000 GENERAL

Rights to a *specimen* may vary as it passes from patient/participant to clinical caregivers, to a *repository*, and finally to the researcher. Specimens that are required for clinical care should not be made available for researcher use.

Biospecimen repositories should ensure that mechanisms are in place to maintain specimen and data *quality*, protect *donor* privacy and confidentiality and to ensure that specimens are shared in a manner that is consistent with the consent and privacy standards under which such specimens and data were obtained (Ravid, 2007). They should provide access to these policies to sponsors, donors and if appropriate, to the general public.

Best Practice: Repositories should train staff on policies related to specimen access and utilization.

M2.000 ACCESS AND UTILIZATION

M2.100 Access and Use Policies

Repositories should have well-established written policies for sharing and distributing specimens as well as *procedures* for determining what constitutes appropriate research use of the specimens and data.

Access policies should be in compliance with existing rules, regulations, policies and applicable laws. When investigators are required to obtain human subjects or ethics committee review and approval for the research use of specimens and/or data, documentation of such approval should be obtained prior to specimen or data *distribution*.

Best Practice: Human specimens and associated data should be distributed without information that could identify the donor, unless identification is absolutely necessary and the human subjects or ethics committee review has granted permission for inclusion of identifying information.

M2.200 Review of Specimen Use Requests

Requests for specimen use should undergo some level of scientific and/or administrative review to ensure proper utilization. Considerations may include scientific merit and potential impact of the proposed research, whether the research use is appropriate to the nature and purpose of the repository, availability of specimens of a specific type, adequacy of the research design and funding, public health benefits and risks of the proposed research, legal and ethical considerations and qualifications of the research team and research environment. Review should also consider requests for studies requiring rare specimens, specimens annotated with large amounts of data and those that require additional *processing*, pre-analysis or special handling by the repository staff.

Best Practice: Use of specimens and associated data should be consistent with *informed consent* and authorization.

Best Practice: *Biospecimen resources* should have a well-documented and clearly defined process for sharing specimens and data, prioritizing requests for access to specimens and data with limited availability and a mechanism for evaluating competing requests for scarce resources. Requests should be reviewed in a timely manner by qualified individuals.

M2.300 Data Sharing

M2.310 Types of Data

Two kinds of data may be associated with specimens: specimen-specific data and *donor* or subject-specific data. Both types may include identifying and non-identifying information.

Specimen-specific data is uniquely associated with a particular specimen (*e.g.*, *aliquot* of tissue, vial of fluid). Examples of specimen-specific data include *sample* quantity (*e.g.*, volume, weight), quality indicators (*e.g.*, RIN numbers, ischemic times) and *storage* conditions (*e.g.*, stored in media, preservative, paraffin-embedded).

Donor-specific data includes clinical or biological data gleaned from existing records (*e.g.*, diagnoses, treatment history, family history, risk factors, lab results), *databases* such as patient registries, donor identifiers (*e.g.*, names, field identifications, health record numbers, species) and exposure data (*e.g.*, air pollution, geographic particularities, natural and man-made toxic substances, volcanoes and waste dumps).

M2.320 Transfer of Data

Samples are often more useful for scientific research when accompanied by subject specific data that characterizes the sample and its source. Therefore, repositories often provide a set of associated data with each sample to aid with the interpretation and analysis of the scientific user's experimental results. It is important to ensure that such data will be used in accordance with appropriate legal requirements including consent, protocol, and other documents governing the repository. In the case of human samples, it is important to protect subject/donor identity and privacy. Whenever possible, human subjects data should have all identifying information removed.

Best Practice: Repositories should develop policies consistent with applicable laws and regulations including those related to transfer of intellectual property, informed consent, ethical and privacy standards and formal agreements covering specific data sharing arrangements.

M2.330 Data Security

Repositories that send data to users should carefully consider available data distribution methods. Internet transmission for example, is convenient but requires special consideration of security technologies such as encryption. Security concerns also arise when transmitting data using physical formats (*e.g.*, disks, tapes).

Data distribution via courier for example, is preferable to standard postal service when use of a reliable tracking mechanism is confirmed. Encryption is recommended when using couriers since there is always the chance of delivery error or interference.

Best Practice: Repositories should ensure that the data is transmitted securely, minimizing the possibility of interception or unauthorized use, particularly if information is included that could potentially identify individual donors.

Best Practice: Repositories should instruct data recipients regarding data security measures including the use of password protection and encryption, where appropriate.

M2.400 Benefit Sharing

Benefit sharing is another important consideration, particularly when dealing with specimens or data from developing countries. Sharing the "benefits" from specimen research is important to ensure that providers of resources are treated in a fair and equitable way. The concept of benefit-sharing grew out of discussions about developing countries profiting from plant and animal materials collected in developing countries without benefit to those who provided the raw material. An international protocol, the Convention on Biodiversity was signed by 150 countries. How the concept applies to specimen research is not always clear, but certainly involves avoiding exploitation (*e.g.*, in developing countries). There are numerous ways that "benefits" can be shared. These include sharing of technology or sharing benefits of research with the study population or providing security backup of stored specimens in an established repository with quality practices in place. Some countries (*e.g.*, India) only allow specimens to leave the country for research purposes if a collaborating investigator from the country accompanies them and participates in the research. This practice may promote technology transfer and development of local research infrastructure.

Best Practice: The repository procedures for *collection*, storage, distribution, use and disposal of specimens should respect the perspectives and traditions of donors from whom the specimens were obtained and minimize the risks to communities, populations, and groups.

Best Practice: Repositories that import specimens and data from other countries should respect the autonomy of the providing country and ensure that fair and equitable benefits are made available to the providing country.

M2.500 Publishing and Provision of Data to Repositories

In publications that result from the use of specimens, the repository should be acknowledged as the source of the specimens. Prior to providing the specimens, authorship guidelines should be established, so that it is clearly delineated between those cases when the repository is merely serving as a source of specimens and those cases when repository staff members actively participate in the research project itself, and therefore should be considered co-authors (*e.g.*, by providing substantial intellectual input beyond the routine role of the repository, which may include data analysis or manuscript preparation).

Many repositories are required to provide an annual report to funding agencies that describes the outcome of the studies that recipient researchers have performed with biospecimens. For this reason, recipient researchers may be requested to provide the repository with a listing of abstracts, presentations, publications, patent applications, and funding that has been the direct result of using specimens from the repository.

Some repositories may ask specimen recipients to provide research data on individual specimens to the repository (either aggregate findings or individual-level data). The desired data format can range from the abstract of any publication based on analysis of the materials to the publication itself, a data summary, or the complete experimental data set. Repositories may also request a description of analytical methods used to generate or process the data, including *quality control* measures. The provision of such data may enhance the value of repositories, depending upon their purpose and nature. Consideration of a data provision policy is recommended, particularly when significant specimen-specific data is available. Repository administrators should consider whether the repository's purpose would be served by retrieving data generated through analysis of shared materials.

The repository's intended use of data will influence other aspects of its data acquisition practices. Repositories may ask researchers to provide the repository with data derived from individual samples or aggregate research results for a variety of reasons including:

- To document repository value and accomplishments.
- To share data with future researchers who will use aliquots from the same specimen, case or donor.
- To conduct further analyses of the data to generate new findings.

Repositories may specify a date by which sample recipients should or must provide data. A standard date may be set (*e.g.*, 12 months after publication or completion of the research), or a date may be set by project. Sample recipients often require time following the completion of research activity for publication of results or for securing intellectual property rights before data can be provided to a repository.

Best Practice: When biospecimens are used in research publications, care must be taken to ensure donor confidentiality. In most cases, de-identified biospecimens are provided to recipient investigators such that coded numbers fully protect the privacy of the donors.

M2.600 Material Transfer Agreement

A *Material Transfer Agreement* (MTA) is a contract that governs the transfer of tangible research materials between two organizations, a provider and a recipient, when the recipient intends to use it for his or her own research purposes. The MTA defines the rights of the provider and the recipient with respect to the materials and any derivatives. Biological materials such as specimens, reagents, cell lines, plasmids and vectors, are the most frequently transferred materials, but MTAs may also be used for other types of materials, such as chemical compounds and even some types of software.

Other types of agreements without the title of MTA may be used, but generally would serve the same purpose and have the same components as an MTA.

M2.610 MTA for Specimens

An MTA (or other document) for transfer of specimens to a recipient should address:

- Purpose of the transfer.
- Restrictions on the use of the specimens (e.g. specimens may not be banked, sold or redistributed to third parties).
- Requirements for maintaining privacy and confidentiality.
- Restrictions on re-identification (where de-identified specimens are provided).
- Requirements for appropriate biosafety training.
- Intellectual property rights.
- Publication rights.
- Provision of research data.
- Any other factors that may govern the transfer.

Best Practice: An MTA or similar agreement should be executed to document the obligations and responsibilities of parties involved in the transfer of materials from a repository prior to shipment. The agreement should be initiated as soon as possible, as additional time may be required for legal or regulatory approval prior to transfer.

M2.620 Data Transfer

Repositories should execute an agreement with recipients prior to data transfer. This agreement may constitute a stand-alone Data Transfer Agreement, or the necessary terms may be included in the MTA. Content of such agreements may include:

- Description of the data to be distributed.
- Purpose for which the data will be used.
- Whether redistribution or forwarding of the data to others is permitted and under what circumstances.
- Protection of data against unauthorized access.
- Protection of donor privacy and anonymity upon transfer (prohibiting attempts to learn a subject's identity and publishing identifying information).
- Requirements for human subjects/ethics committee or applicable animal use approval or other approvals concerning data use.
- Ownership, access and control of transferred data.
- *Disposition* of data (destruction) upon research completion or agreement termination.
- Terms of agreement, indemnification, payment of fees and rights and title to the research performed.

Best Practice: Repositories should execute an MTA or similar agreement with recipients who receive specimen-associated data from the repository.

M3.000 CULLING OF COLLECTIONS

Culling is the process of reviewing and eliminating selected specimens or an entire collection either by destruction or by transfer to a new *custodian*. This action may be needed periodically due to storage space constraints and/or the need to control costs.

Other reasons for culling may include consent issues, regulatory changes, protocol modifications and/or compromised specimen integrity.

Policies should be established for culling or transfer of collections when specimen resources have fulfilled their original purpose, are no longer suitable for their intended purpose or if participants request the withdrawal of their specimens. These policies should be clearly described and openly available, as appropriate, to users and potential users of the specimen collections. Repositories should remember that there are costs for culling associated with retrieving specimens from their environmental storage *containers* as well as costs involved with the destruction or transfer to a new custodian.

Best Practice: The best time to plan for the culling of a collection is prior to the acquisition of any specimens.

Best Practice: The value of specimen collections should be reviewed on a regular basis.

Best Practice: Repositories should have a system in place to track the elimination of collections either through sample destruction or transfer to a new custodian. The system should include documentation of the history of the collection, what records may accompany the collection and the reason for the culling of the collection. Administrative review may be helpful to see if there are others within the institution affiliated with the repository that may be able to make use of the collection, providing this is allowed by the consent documentation. Records regarding culling should be included with other archival records for the repository (see Section G, Records Management).

M3.100 Specimen Destruction

There are a number of circumstances that may influence decisions as to whether or not a collection should be destroyed. Some of the reasons for destroying samples may include:

- When all identifying information has been lost.
- When samples have been compromised by equipment failure.
- When samples have experienced freeze-thaw cycles such that the molecular contents have been compromised.
- When a custodian has left the organization and key information regarding the specimens has been lost.
- When required by consent, study design or regulation.
- Lack of use.
- When there is new information about potential biohazards associated with the specimen.
- When extra specimens were collected or stored in excess of the Investigator's protocol.

- When the status of a participant changes from “eligible to ineligible” or their case/control status changes.

Best Practice: A repository should assess and document the destruction of any samples, noting when they are destroyed and for what reason. This information can be important to the repository’s quality management and may serve as an indicator for the repository of areas that need improvement.

M3.110 Safe Disposal of Specimens

As discussed in the Safety section (Section E) repositories must train their staff in matters regarding *universal precautions* (i.e., to handle all specimens as though they are potentially hazardous). Repository staff that may become exposed to human specimens should be vaccinated against possible risks. These staff members should also be regularly checked for their level of immunity.

This same level of *safety* must be extended to clients who receive biospecimens from repositories. Namely, clients must be advised of the potential hazards associated with all biospecimens, and sign-off on their agreement to handle all specimens with the necessary safety methods. In this agreement, the client also agrees that the repository will not be liable for any health risk or damage that may result from unsafe handling of the biospecimens.

M3.120 Transfer of a Collection

A repository may have a need to transfer a collection to another repository or a custodian. In this situation, the new custodian should be made aware of consent and ownership issues related to the collection and all documentation associated with the specimens should be transferred. New human subjects/ethics review will be necessary for new uses for the specimens. A Material Transfer Agreement (MTA) will need to be established to document allowable uses for the collection. The cost for retrieving and transporting the collection to the new custodian should also be taken into account.

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APPENDIX A: INTERNET RESOURCES

These internet references are made available for information only. ISBER does not warrant any of the information contained therein.

Subject	Website	Organization	Topics
Access and Benefit Sharing	http://abs.scnat.ch	Swiss National Academy of Sciences	The joint regulation of access to genetic resources and the sharing of benefits arising from their use by the researchers or companies from user countries and the representatives of the states, in which the genetic resources have been accessed.
Animal Welfare	http://homeoffice.gov.uk/science-research/animal-research/	Animal Health and Welfare Strategy for Great Britain, Home Office	The regulated use of animals for research in the development of drugs and medical technologies that help to reduce suffering among humans and animals.
Best Practices for Biological Resource Centers	http://www.oecd.org/dataoecd/7/13/38777417.pdf	Organisation for Economic Co-Operation and Development	Consensus Best Practices for Biological Resource Centers in OECD Countries
Bioethics	http://bioethics-international.org/iab-2.0/index.php?show=objectives	International Organisation of Bioethics	The IAB facilitates the exchange of information between those working in bioethics in different parts of the world
Bioethics Advisory Committee	http://www.bioethics-singapore.org/	Bioethics Advisory Committee, Singapore	Resources for the ethical, legal and social issues arising from biomedical sciences research in Singapore
Biorepository Protocols	http://www.abrn.net/protocols.htm	Australasian Biospecimen Network	Protocols and best practices for collecting and processing human biospecimens
Biosafety	http://governance.iarc.fr/ENG/Docs/safetymanual.pdf	The Division of Biosafety and Biotechnology (SBB), Scientific Institute of Public Health in Belgium.	Biosafety risk assessment tools and Biosafety manuals, laws and regulations, guidelines on containment facilities, equipment and practices, shipping and transport
Biosafety	http://www.ebsaweb.eu/Resources.html	European Biosafety Association	Conferences and other resources on European biosafety issues
Biosafety	http://www.ebsaweb.eu/ebsa_media/Downloads/Biosafety7-	World Health Organisation	Laboratory biosafety manual covering equipment and facility design and techniques

2012 ISBER BEST PRACTICES FOR REPOSITORIES

Subject	Website	Organization	Topics
	view_image-1-called_by-ebsa.pdf		
Biosafety	http://www.cjd.ed.ac.uk	UK Surveillance Unit for Creutzfeldt-Jakob Disease	Surveillance data on Creutzfeldt-Jakob Disease; technical information; links
Blood Collection Protocols	http://www.csmc.edu/5455.html	Cedars-Sinai Medical Center	Blood collection guidelines
Convention on Biological Diversity	http://www.cbd.int	United Nations Environmental Programme	Sustainable development and Intellectual Property Rights
Convention on International Trade in Endangered Species of Wild Fauna and Flora	http://www.cites.org	IUCN (The World Conservation Union)	Trade in Endangered Species of Wild Fauna and Flora
Case Studies of Human Tissue Repositories	http://www.rand.org/pubs/monographs/2004/RAND_MG120.pdf	Rand Corporation and the National Cancer Institute	Best Practices for repositories based on information collected from a defined number of U.S.-based repositories
Chemical and Laboratory Resources	http://www.neis.com/environmental_resources.html	Chemindustry.com	A variety of resources for laboratory equipment and supplies for over a hundred countries world-wide (under the tab for “lab supplies”).
Chemical Safety	http://www.cdc.gov/niosh/database.html	National Institute for Occupational Safety and Health (NIOSH), U.S.	Databases and information resource links and publications in the United States
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://www.cdc.gov/niosh/chem-inx.html	Master Index of Occupational Health Guidelines for Chemical Hazards (NIOSH), U.S.	U.S. National guidelines for chemical hazards of specific chemicals
Chemical Safety	http://www.who.int/ifcs/en/	Intergovernmental Forum for Global Chemical Safety	Policy guidance on chemical safety
Chemicals Management	http://www.environment.gov.au/settlements/chemicals/index.html	The Australian Government Department of the Environment and Water Resources	Chemicals management strategies to protect human health and the environment

2012 ISBER BEST PRACTICES FOR REPOSITORIES

Subject	Website	Organization	Topics
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
Dry Ice Safety	http://eur-lex.europa.eu/LexUriServ/LexUriServ.do?uri=CELEX:32008R1272:EN:NOT	Regulation (EC) No 1272/2008 of the European Parliament	European regulations for dry ice
Dry Ice Safety	http://www.ercweb.com/resources/viewreg.aspx?id=6779	Environmental Resource Center	Requirements for shipping dry ice
Environmental Health	http://www.environment.gov.au/approvals/index.html	The Australian Government Dept. of the Environment and Water Resources	Approvals, permits and licensing
Environmental Specimen Bank Design	http://www.ehponline.org/members/1995/Suppl-3/wise-full.html	U.S. National Institute of Standards and Technology	Paper presented at the Conference on Human Tissue Monitoring and Specimen Banking: Opportunities for Exposure Assessment, Risk Assessment, and Epidemiologic Research held 30 March-1 April 1993 in Research Triangle Park, North Carolina.
Ethics Committee	http://www.hugo-international.org/committee_ethics.htm	Human Genome Organisation	Promotes discussion and understanding of social, legal and ethical issues as they relate to the conduct of, and the use of knowledge derived from, human genome research.
Ethics Guides	http://www.moh.govt.nz/moh.govt.nz/moh.nsf/indexmh/guidelines-use-human-tissue	New Zealand Ministry of Health	Guidelines for the Use of Human Tissue for Future Unspecified Research Purposes
Exposure Prevention Program Information	http://www.healthsystem.virginia.edu/internet/epinet/subpage2.cfm	Exposure Prevention Information Network; University of Virginia, International Health Care Worker Safety Center	Provides standardized methods for recording and tracking percutaneous injuries and blood and body fluid contacts
General Safety	http://www.osha.gov/comp-links.html	Occupational Safety and Health Administration, Department of Labor, USA	Current U.S regulations and regulations under development; technical, prevention and training information; links
General Safety	http://www.lbl.gov/ehs/pub3000	Lawrence Berkeley National Laboratory; University of California, California, U.S.	U.S.-based health and safety manual

2012 ISBER BEST PRACTICES FOR REPOSITORIES

Subject	Website	Organization	Topics
Records Management	http://oma.od.nih.gov/ms/records/recdisp/index.html		
Human Subjects	https://wcd.coe.int/ViewDoc.jsp?id=977859	Council of Europe; Committee of Ministers	Recommendation Rec(2006)4 of the Committee of Ministers to member states on research on biological materials of human origin
Human Subjects	http://www.hhs.gov/ohrp/international/HSPCompilation.pdf	Office of Human Research Protections; U.S. Department of Health and Human Services	Human subjects research legislation, regulations, or guidelines for 79 countries, two confederations and two organizations
Human Subjects	http://www.hhs.gov/ohrp/humansubjects/guidance/45cfr46.htm	Office of Human Research Protections, U.S. Department of Health and Human Services	U.S. Federal Human Subjects Regulations
Human Subjects	http://www.accessdata.fda.gov/scripts/cdrh/cfdocs/cfcfr/CFRSearch.cfm	Food and Drug Administration, U.S. Department of Health and Human Services	U.S.-based human subjects regulations: 21 CFR parts 50, 56, 812
Human Subjects	http://www.hhs.gov/ohrp/policy/index.html	Office of Human Research Protections, U.S. Department of Health and Human Services	Policy documents from the Office of Human Research Protections, U.S.
Human Subjects	http://www.hhs.gov/ohrp/international/	U.S. Office of Human Research Protections, U.S. Department of Health and Human Services	International Compilation of Human Subjects Research Protections
International Statistical Classification of Diseases and Related Health Problems	http://apps.who.int/classifications/apps/icd/icd10online/	World Health Organization (WHO)	The International Classification of Diseases (ICD) is the international standard diagnostic classification for all general epidemiological, many health management purposes and clinical use.
Laboratory Automation	http://www.slas.org/	Society for Laboratory Automation and Screening	Automation in the laboratory including liquid handling, sample storage and retrieval, specimen processing.
Laboratory Standards Development	http://www.clsi.org	Clinical and Laboratory Standards Institute	U.S. based general and technical Information for the development of laboratory standards
National Cancer Institute Best Practices for	http://biospecimens.cancer.gov/NCI_Best_Practices_060507.pdf	National Cancer Institute; National Institutes of Health; U.S. Department of Health	Best Practices for biospecimen handling, processing, storage and retrieval for specimens collected

2012 ISBER BEST PRACTICES FOR REPOSITORIES

Subject	Website	Organization	Topics
Biospecimen Resources		and Human Services	through NCI-sponsored research
Natural History Museum Benefit Sharing Practices	http://www.canmexworkshop.com/documents/papers/III.5d.2.pdf	International Expert Workshop on Access to Genetic Resources and Benefit Sharing	Concepts in Benefit Sharing for Museum Collections
Occupational Health and Safety	http://governance.iarc.fr/ENG/Docs/safetymanual.pdf	International Agency for Research on Cancer	Health and safety manual
Occupational Health and Safety	http://www.ccohs.ca/	Canadian Centre for Occupational Health and Safety	Information on biological hazards, chemical and materials, health and safety programs
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://hazmat.dot.gov/hazhome.htm	U.S. Department of Transportation (DOT)	U.S.-based standards for shipping human specimens by ground
Plant Collection Protocols	http://www.uaf.edu/museum/herb/howtocoll.html	University of Alaska, U.S.	Guidance on collecting plant specimens
Privacy	http://www.hhs.gov/ocr/hipaa/	U.S. Department of Health and Human Services	Health Insurance Portability and Accountability Act of 1996 (HIPAA)
Privacy	http://privacyruleandresearch.nih.gov/	National Institutes of Health, U.S. Department of Health and Human Services	HIPAA Privacy Rule and research
Privacy	http://www.usdoj.gov/oip/04_7_1.html	U.S. Department of Justice	Privacy Act of 1974, 5 U.S.C. § 552a
Radiological Safety	http://www.jmu.edu/safetyplan/radiology/advisorycommittee.shtml	James Madison University	Example of U.S. radiation protection program
Resources for Pathology Laboratories	http://www.cap.org/apps/cap.portal?_nfpb=true&_pageLabel=reference	College of American Pathologists	General and Technical Information for lab management for U.S.-based laboratories
Tissue Procurement Protocols	http://www.tubafrost.org	European Human Frozen Tumour Tissue Bank (TuBaFrost) project	Collection and storage of human tissues
Tissue Procurement	http://www.bd.com/vacutainer/pdfs/plus_plasti	Becton-Dickenson	Wall chart on blood tube order for

2012 ISBER BEST PRACTICES FOR REPOSITORIES

Subject	Website	Organization	Topics
Protocols	c_tubes_wallchart_orderfordraw_VS5729.pdf		blood collection
Transnational Shipment of Chemicals	http://www.basel.int/	The Basel Convention.	Transnational boundary movements of hazardous wastes and their disposal
Transport of Infectious Substances	http://www.who.int/csr/resources/publications/biosafety/WHO_CDS_CSR_LYO_2004_9Final.pdf	World Health Organization	Recommendations developed by the United Nations Economic and Social Council's Committee of Experts on the transport of dangerous goods
Transportation Safety	http://www.cta-otc.gc.ca/legislation/index_e.html	Canadian Transportation Agency	Transportation related legislation and other related matters can be found here, along with details of the Statutes and Regulations enforced by the Canadian Transportation Agency.
Wildlife Trade Regulations	http://ec.europa.eu/environment/cites/legis_wildlife_en.htm	European Council Regulation No. 338/97	Regulations on the protection of species of wild fauna and flora by regulating trade and to suspend the introduction into the community of certain species from certain countries.

APPENDIX B: GLOSSARY

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

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

ALIQUOT – 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.

ANALYTE – Component represented in the name of a measurable quantity. This includes any element, ion, compound, substance, factor, infectious agent, cell, organelle, activity, property, or other characteristics which are to be determined.

ANNOTATION – Additional information associated with a particular point in a document or other piece of information.

ANONYMOUS – Identifiable personal information was not collected for the specimens and associated data or, if collected, was not maintained and cannot be retrieved, such that there is no way to trace the identity of the subject from whom the specimens were obtained.

ASSENT - To agree, as to a proposal; concur.

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

AUTOPSY - Postmortem examination of the organs and tissues of a body to determine cause of death or pathological conditions.

AXENIC STATE - state of non-contamination by or non-association with any other living organisms.

BANKING – The process of storing material or specimens for future use (see also BIOBANKING).

BATCH – A specific quantity of specimens 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).

BIOBANK – See REPOSITORY.

BIOHAZARD – An organism, or substance derived from an organism that poses a threat to (primarily) human health. This can include medical waste, samples of a microorganism, virus or toxin (from a biological source) that can impact human health. It can also include substances harmful to animals.

BIOLOGICAL SAFETY HOOD - Cabinet designed to provide microbe-free work free work environment which enables workers to perform work on samples in an isolated area.

BIOREPOSITORY – See REPOSITORY.

BIOSPECIMEN RESOURCE – A collection of biological specimens that is acquired for a defined purpose. Management responsibility of the biospecimen resource is led by the custodian for the collection. Biospecimen resources may be stored in a repository or laboratory, depending on the numbers of specimens contained therein.

CALIBRATION – The process of adjusting the output or indication on a measurement instrument to agree with value of the applied standard, within a specified accuracy.

COLD CHAIN – A temperature-controlled supply chain.

COLLECTION – May refer to the practice or technique of collecting a specimen (See RETRIEVAL) or to a specific sample or group of samples that has been isolated for future research purposes.

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

CRYOPROTECTANT – An additive or mixture of additives that allow living cells, tissues, organs and organisms to survive exposure to cryogenic temperatures, of which the main type is a colligative cryoprotectant. This is a protective additive that must be able to penetrate the cell, applied to prevent damage caused by excessive cell volume changes and the toxic concentration of solutes (*i.e.*, colligative injury). An osmotic cryoprotectant is an additive that does not penetrate the cell. It confers additional protection by osmotically withdrawing water from the cell (osmotic dehydration), consequently reducing the amount of water that is available to form ice. Mixtures of colligative and osmotic cryoprotectants are often used in plant, algal and microbial cryoprotective solutions, as well as in cryoprotective solutions for some mammalian cells. **CULLING** – Reviewing and eliminating specimens in a collection or an entire collection either by destruction or transfer to a new custodian.

CUSTODIAN – The individual responsible for the management of a biospecimen resource. The custodian works with other key stakeholders in the management of the resource including the tracking of all relevant documentation for the resource and for ensuring that policies regarding access to the resource are in place and implemented according to appropriate guidelines.

DATABASE – A structured collection of records or data that is stored in a computer system so that a computer program or person using a query language can consult it to answer queries.

DEHYDRATION – Removal of water from a tissue.

DESICCATION – Excessive loss of moisture; the process of drying up.

DEVIATION – An intentional or unintentional event that is a departure from a procedure or a normal practice.

DEWAR – A specialized container to hold liquefied gases. A Dewar may also be referred to as a Dewar flask or Dewar vessel.

DISINFECTANT – An agent that reduces the number of viable microorganisms.

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. In some countries the term SUBJECT or “individual” may be used in the same context as donor, especially as the context relates to human specimens.

DRY ICE – Solid phase carbon dioxide (CO₂). CO₂ solidifies at -78.5 °C.

END-USER – A health care practitioner, scientist, or laboratory staff member who performs an appropriate procedure, test or archival function.

ENVIRONMENTAL MONITORING SYSTEM – An automated, centralized monitoring system that monitors environmental conditions and alarms in conjunction with remote access, security features and electronic data storage.

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.

FREEZE-DRIED – Dehydrated for storage by conversion of the water content of a frozen specimen to a gaseous state under vacuum. Also called lyophilized.

GLASS TRANSITION – see **VITRIFICATION**.

ICE NUCLEATION –also termed “seeding” is the point at which ice crystals are first initiated in a cryopreserved sample; usually applied in the context of controlled rate cooling.

IDENTIFIER/IDENTIFYING INFORMATION – Information (*e.g.*, name, social security number, medical record or pathology accession number, *etc.*) that would enable the identification of the subject. For some specimens this information might include the taxon name and collection number.

INCIDENT – Any unplanned 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.

INFORMED CONSENT – A decision to participate in research, taken by a competent individual who has received the necessary information; who has adequately understood the information; and who, after considering the information, has arrived at a decision without having been subjected to coercion, undue influence, inducement, or intimidation.

INSTITUTIONAL REVIEW BOARD (IRB) - Any board, committee, or other group formally designated by an institution to review biomedical research involving humans as subjects, to approve the initiation of the research and conduct periodic review of such research.

LABEL – Any written, printed or graphic material on or affixed to a specimen container or package.

LIQUID NITROGEN – Coolant used to cool and store samples. Nitrogen becomes liquid at -196 °C. Samples stored in the vapor phase of liquid nitrogen are -190 °C and warmer, depending on the distance from the liquid phase.

LIQUID NITROGEN DRY SHIPPER – A container used for sending samples in the vapor phase of liquid nitrogen.

LOT – A quantity of reagents, supplies or containers that is processed or manufactured at one time and identified by a unique identification number (see BATCH).

LYOPHILIZED - Dehydrated for storage by conversion of the water content of a frozen specimen to a gaseous state under vacuum. Also called freeze-dried.

MATERIAL TRANSFER AGREEMENT – An agreement that governs the transfer of tangible research materials and data between two organizations, when the recipient intends to use it for his or her own research purposes. It defines the rights and obligations of the provider and the recipient with respect to the use of the materials.

MORPHOGENETIC COMPETENCE (OR POTENTIAL): terms used to describe the state of cells that are able to respond to stimuli and in vitro manipulations and undergo morphogenesis, usually to produce differentiated structures comprising, shoots, roots and embryos.

NECROPSY – See AUTOPSY.

POLICIES AND PROCEDURES MANUAL – See STANDARD OPERATING PROCEDURES (SOP) MANUAL.

PRESERVATION – Use of chemical agents, alterations in environmental conditions or other means during processing and storage 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 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.

PROSPECTIVE- A study or collection maintained for expected or likely use in the future.

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).

REMOVAL – See RETRIEVAL.

REPOSITORY – An entity that receives, stores, processes and/or distributes specimens, as needed. It encompasses the physical location as well as the full range of activities associated with its operation. It may also be referred to as a BIOREPOSITORY or BIOBANK.

RETRIEVAL – The removal, acquisition, recovery, harvesting, or collection of specimens.

RETROSPECTIVE – Relating to or being a study or collection (as of a disease) that looks back on or deals with past events or situations.

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 subject or donor at a specific time. For some biological collections “specimen” may have the same meaning as “individual.”

STERILITY – Absence of detectable, viable, contaminating microorganisms.

STORAGE – Maintenance of specimens under specified conditions for future use.

SUBJECT – See DONOR.

TAXON – Any recognized category in the taxonomic hierarchy. For many purposes, the category “species” is the most important.

TELEMETRY SYSTEM – A system that allows for measurements to be taken from a distance, usually via radio wave transmission and reception of the information.

T_g – The glass transition temperature marks the temperature at which a fluid becomes so viscous it appears solid. The extreme viscosity reduces diffusion and molecular restructuring, slowing reactions that might otherwise cause samples to deteriorate. The *T_g* for pure water is -132 °C.

TOTIPOTENCY - in the context of plants, means that a single somatic (non-germ line) cell has the ability to differentiate along a developmental pathway and regenerate a plant. More generally, the potential for an undifferentiated cell to regenerate into a complete new plant.

VITRIFICATION (see also *GLASS TRANSITION*) - refers to the transformation of a glass-forming liquid into a glass, which usually occurs upon rapid cooling. It is a dynamic phenomenon occurring between two distinct states of matter (liquid and glass), each with different physical properties.

APPENDIX C: ABBREVIATIONS

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

1D – One dimensional

2D – Two dimensional

cGCP – Current Good Clinical Practices

cGLP – Current Good Laboratory Practices

cGMP – Current Good Manufacturing Practices

cGP – Current Good Practices

CO₂ – Carbon dioxide

DNA – Deoxyribonucleic Acid

ESB – Environmental specimen bank

EDTA – Ethylenediaminetetraacetic Acid

H&E - Hematoxylin-Eosin

IATA – International Air Transport Association

ICAO - International Civil Aviation Organization

ID – Identification Reference

IRB – Institutional Review Board

ISO – International Organization for Standardization

LN₂ – Liquid Nitrogen

MSDS – Material Safety Data Sheet

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

SOP – Standard Operating Procedures

Tg – Glass Transition Temperature