Appendix 6: CAP Biorepository Accreditation Program Checklist

Every patient deserves the GOLD STANDARD ...

Master

Biorepository Checklist

CAP Accreditation Program

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04.21.2014

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Biorepository Checklist

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ON-LINE CHECKLIST AVAILABILITY

Participants of the CAP accreditation programs may download the checklists from the CAP Web site (www.cap.org) by logging into e-*LAB* Solutions. They are available in different checklist types and formatting options, including:

- Master — contains ALL of the requirements and instructions available in PDF, Word/XML or Excel formats
- Custom — customized based on the laboratory's activity (test) menu; available in PDF, Word/XML or Excel formats
- Changes Only — contains only those requirements with significant changes since the previous checklist edition in a track changes format to show the differences; in PDF version only. Requirements that have been moved or merged appear in a table at the end of the file.

SUMMARY OF CHECKLIST EDITION CHANGES
Biorepository Checklist
04/21/2014 Edition

The information below includes a listing of checklist requirements with significant changes in the current edition and previous edition of this checklist. The list is separated into three categories:

1. New
2. Revised:
   - Modifications that may require a change in policy, procedure, or process for continued compliance; or
   - A change to the Phase
3. Deleted/Moved/Merged:
   - Deleted
   - Moved — Relocation of a requirement into a different checklist (requirements that have been resequenced within the same checklist are not listed)
   - Merged — The combining of similar requirements

NOTE: The listing of requirements below is from the Master version of the checklist. The customized checklist version created for on-site inspections and self-evaluations may not list all of these requirements.

NEW Checklist Requirements

Requirement	Effective Date
BAP.01525	07/29/2013
BAP.06802	07/29/2013
BAP.06804	07/29/2013
BAP.06806	07/29/2013
BAP.06808	07/29/2013
BAP.06810	07/29/2013
BAP.06812	07/29/2013
BAP.06816	07/29/2013
BAP.06818	07/29/2013
BAP.06819	04/21/2014
BAP.06820	07/29/2013
BAP.06824	07/29/2013
BAP.06826	07/29/2013

BAP.06828	07/29/2013
BAP.06830	07/29/2013
BAP.06832	07/29/2013
BAP.06834	07/29/2013
BAP.06836	07/29/2013
BAP.06838	07/29/2013
BAP.06840	07/29/2013
BAP.06844	07/29/2013
BAP.06846	07/29/2013
BAP.06848	07/29/2013
BAP.06850	07/29/2013
BAP.06854	07/29/2013
BAP.06856	07/29/2013
BAP.06858	07/29/2013
BAP.06860	07/29/2013
BAP.06880	04/21/2014
BAP.07110	04/21/2014
BAP.07120	07/29/2013
BAP.07210	04/21/2014
BAP.07220	04/21/2014
BAP.13740	04/21/2014

REVISED Checklist Requirements

Requirement	Effective Date
BAP.01700	07/29/2013
BAP.02500	07/29/2013
BAP.06900	04/21/2014
BAP.08000	07/29/2013
BAP.08700	07/29/2013
BAP.09300	07/29/2013
BAP.09600	07/29/2013
BAP.09700	07/29/2013
BAP.12800	07/29/2013

DELETED/MOVED/MERGED Checklist Requirements

Requirement	Effective Date
BAP.04600	07/28/2013
BAP.07000	04/20/2014
BAP.07700	07/28/2013

INTRODUCTION

A biorepository is defined as an entity that receives, stores, processes, and/or disseminates biospecimens, their derivatives and relevant data, as needed. It encompasses the physical location as well as the full range of activities associated with its operation. This checklist covers a broad range of activities that occur in biorepositories. Not all checklist requirements will apply to every biorepository.*

The scope of services of the biorepository must be clearly documented.

*References used in the development of this checklist were the CAP Accreditation Checklists, 2012 Best Practices for Repositories (ISBER**), and the NCI Best Practices for Biospecimen Resources.*

*Biorepository — For the sake of consistency, biorepository will be used throughout this checklist and may be considered synonymous with biobank and repository.
**ISBER — International Society for Biological and Environmental Repositories is an international forum that addresses the technical, legal, ethical, and managerial issues relevant to repositories of biological and environmental specimens.

DEFINITION OF TERMS

Aliquot - 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.

Anonymization - The process of removing particulars from samples, test results, or records to prevent traceability to the original patient

Blinding - An action taken to prevent access to information that might affect the outcome of an observation

Coded specimen - Identifying information (such as name or social security number) that would enable the investigator to ascertain the identity of the individual to whom the private information or specimens pertain has been replaced with a number, letter, symbol, or combination thereof (*i.e.* the code); and a key to decipher the code exists, enabling linkage of the identifying information to the private information of specimens

De-identify - The removal from a specimen of all 18 elements that could be used to identify the individual or the individual's relatives, employers, or household members; these elements are enumerated in the HIPAA Privacy Rule

Derivative - A substance that can be made from another substance

Equipment - Single apparatus or set of devices or apparatuses needed to perform a specific task

Function check - The set of routines that show an instrument to be ready for operation

Instrument - An analytical unit that uses samples to perform chemical or physical assays

Legacy specimen - Biospecimens available for research once all protocol-specified endpoints, including clinical and biorepository studies, have been completed. These remaining biospecimens could be made

available by the biorepository for correlative studies (subject to application, scientific review, and approval).

Maintenance - Those activities that prolong the life of an instrument or minimize breakdowns or mechanical malfunctions. Examples include cleaning, changing parts, fluids, tubing, lubrication, electronic checks, etc.

Material Transfer Agreement (MTA) - An agreement that governs the transfer of tangible research material and associated clinical data between two organizations, when the recipient intends to use it for his/her own research purposes

Performance verification - The set of processes that demonstrate an instrument to run according to expectations

Quality assurance - The systematic monitoring and evaluation of the various aspects of a project, process, service or facility to maximize the probability that minimum standards of quality are being attained

Quality control - An integral component of *quality management* composed of the aggregate of processes and techniques used to detect, reduce, and correct deficiencies in an analytical process

Quality control (QC) is a surveillance process in which the actions of people and performance of equipment and materials are observed in some systematic, periodic way that provides a record of consistency of performance and action taken when performance does not conform to standards set by the biorepository. QC is a set of procedures designed to monitor the test method and the results to assure test system performance; QC includes testing control materials, charting the results and analyzing them to identify sources of error, and determining, performing and documenting any remedial action taken as a result of this analysis.

Remnant specimens - Remaining portion of a specimen obtained for clinical purposes that is no longer needed for its original purpose and that would otherwise be discarded

Sample - A single unit containing material derived from one specimen

Specimen - A specific tissue, blood sample, *etc.* taken from a single subject or donor at a specific time

Source Facility - Those sites that contribute specimens to the biobank. The source facility may be a clinic, hospital or individual investigator, and, in some instances, the biorepository may be the source facility, (e.g. when the biorepository does blood or specimen collections for normal controls).

BIOREPOSITORY

QUALITY MANAGEMENT

PROCEDURE MANUAL

Inspector Instructions:

	• Representative sample of procedures for completeness and laboratory director review. Current practice must match contents of procedures/policies. • Privacy and confidentiality policies and procedures

	
	• How do you access procedures? • What procedure has most recently been implemented or modified? • How do you ensure all copies of procedures are up to date? • How are changes in procedures documented and communicated to staff? • How does the facility protect patient information?
	• Identify a newly implemented procedure in the prior two years and follow the steps through authoring, director review and staff training

BAP.01000 Procedure Manual **Phase II**

A complete procedure manual is available at the workbench or in the work area.

NOTE 1: The use of inserts provided by manufacturers is not acceptable in place of a procedure manual. However, such inserts may be used as part of a procedure description, if the insert accurately and precisely describes the procedure as performed in the biorepository. Any variation from this printed or electronic procedure must be detailed in the procedure manual. In all cases, appropriate reviews must occur.

NOTE 2: A manufacturer's procedure manual for an instrument/reagent system may be acceptable as a component of the overall departmental procedures. Any modification to or deviation from the procedure manual must be clearly documented.

NOTE 3: Card files or similar systems that summarize key information are acceptable for use as quick reference at the workbench provided that:

- *A complete manual is available for reference*
- *The card file or similar system corresponds to the complete manual and is subject to document control*

NOTE 4: Electronic (computerized) manuals are fully acceptable. There is no requirement for paper copies to be available for the routine operation of the biorepository so long as the electronic versions are readily available to all personnel. However, procedures must be available to biorepository personnel when the electronic versions are inaccessible (e.g. during biorepository information system or network downtime); thus, the biorepository must maintain either paper copies or electronic copies on CD or other media that can be accessed via designated computers. <u>All procedures, in either electronic or paper form, must be readily available for review by the inspector at the time of the CAP inspection.</u>

Electronic versions of procedures must be subjected to proper document control (i.e., only authorized persons may make changes, changes are dated/signed (manual or electronic), and there is documentation of review). Documentation of review of electronic procedures may be accomplished by including statements such as "reviewed by [name of reviewer] on [date of review]" in the electronic record. Alternatively, paper review sheets may be used to document review of electronic procedures. Documentation of review by a secure electronic signature is NOT required.

REFERENCES

1) Clinical and Laboratory Standards Institute (CLSI). Quality Management System: Development and Management of Laboratory Documents; Approved Guideline - Sixth Edition. CLSI document QMS02-A6 (ISBN 1-56238-869-X). Clinical and Laboratory Standards Institute, 940 West Valley Road, Suite 1400, Wayne, Pennsylvania 19087 USA, 2013.

BAP.01100 Policy/Procedure - Confidentiality **Phase II**

Policies and procedures are in place to minimize the risk to individuals from whom the specimens and data were obtained and to protect their privacy and confidentiality.

BAP.01200 Policy/Procedure Review **Phase II**

There is documentation of review of all policies and procedures every two years by the current director or designee.

NOTE: The director must ensure that the collection of policies and technical protocols is complete, current, and has been thoroughly reviewed by a knowledgeable person. Technical approaches must be scientifically valid and clinically relevant. To minimize the burden on the biorepository and reviewer(s), it is suggested that a schedule be developed whereby roughly 1/24 of all procedures are reviewed monthly. Paper/electronic signature review must be at the level of each procedure, or as multiple signatures on a listing of named procedures. A single signature on a Title Page or Index of all procedures is not sufficient documentation that each procedure has been carefully reviewed. Signature or initials on each page of a procedure is not required.

Only policies and procedures are addressed in this requirement. Biennial review is not required for other controlled documents.

BAP.01300 New Procedure Review **Phase II**

The director reviews and approves all new policies and procedures, as well as substantial changes to existing documents, before implementation.

NOTE: Current practice must match the policy and procedure documents.

BAP.01400 New Director Procedure Review **Phase II**

If there is a change in directorship of the biorepository, the new director ensures (over a reasonable period of time) that biorepository procedures are well documented and undergo an appropriate review.

BAP.01500 Knowledge of Procedures **Phase II**

The biorepository has a system documenting that all personnel are knowledgeable about the contents of procedure manuals (including changes) relevant to the scope of their biorepository activities.

NOTE: This does not specifically require annual procedure sign-off by testing personnel. The form of this system is at the discretion of the director.

Evidence of Compliance:

- ✓ Relevant quizzes and results **OR** documentation of competency **AND**
- ✓ Systems to document policy/procedure changes **AND**
- ✓ Documentation of receipt/training in either paper or electronic format

NEW* *07/29/2013*

BAP.01525 Discontinued Procedure **Phase II**

When a procedure is discontinued or replaced, a paper or electronic copy is maintained for at least 2 years, recording initial date of use, and retirement date.

SPECIMEN HANDLING

The collection, processing, embedding, and quality check for all biospecimens is critical to the overall quality and diversity of the sample inventory.

Inspector Instructions:

	• Sampling of policies and procedures for sample handling, including sample types, samples with potentially infectious materials, aliquoting, relabeling, de-identifying or anonymizing, and specimen retrieval • Policy for the type of samples suitable for submission to the biorepository • Sampling of records for the assessment of the quality of stored specimens • Specimen rejection criteria policy and records of rejection • Records of informed consent and IRB releases
	• Specimen processing area for clean environment • Aliquot sizes of specimens • Specimen identifiers • Specimen storage conditions during sample receipt and processing • Tracking of samples as they move from one station to another
	• How does your biorepository maintain and track temperature excursion information? • Explain your quality assessment process for stored specimens • How is the risk of specimen misidentification monitored and the process improved? • What is your specimen coding system for sample identification? • How do you confirm patient consent prior to processing and banking? • What do you do if the sample size is too small relative to the requirements or it does not meet researchers' needs?
	• Follow a tissue sample released for research from the pathologist to storage, verifying specimen identification throughout the process. • Select several specimens and follow their tracking throughout the life of the specimen, including from parent to child, etc.

BAP.01600 Specimen Types Submission Criteria **Phase II**

There is a clearly defined policy defining types of specimens submitted to the biorepository that is based on:

1. **Purpose - intended use of specimen**
2. **Required specimen data**
3. **Safety - laboratories are suitable for the type of specimen/pathogen requiring processing (biosafety/risk level)**
4. **Duration of storage (may be indefinite)**

NOTE: The policy may be an overarching statement that defines the criteria required for all collections held in the biorepository. This may include the receipt or transfer of an entire collection.

REFERENCES
1) Biosafety in Microbiological and Biomedical Laboratories, 5th Edition, HHS Publication No. (CDC) 21-1112 Revised December 2009 (http://www.cdc.gov/biosafety/publications/bmbl5/BMBL.pdf

*****REVISED**** ***07/29/2013***

BAP.01700 Collection/Processing Oversight **Phase II**

A pathologist or designee assigned to the management of the biospecimens must ensure that the documented collection processes and policies reflect published best practices.

NOTE: Blood and other body fluids not required for the diagnosis or prognosis must be collected with approved protocols and may not require pathologist review. To determine remnant tissue at the site of the collection, the appropriate medical/legal designee must be involved in the decision. This does not apply to downstream processing.

If samples are acquired according to sponsor-driven protocols, the sponsor makes all decisions about sample usability. The biorepository carries out the instructions provided by the sponsor. In this instance BAP.01700 is not applicable.

REFERENCES
1) 2012 Best Practices for Repositories, Cell Preservation Technology, Vol. 10, Num 2, http://www.isber.org/bp/documents/ISBERBestPractices3rdedition.pdf

BAP.01800 Quality Control/Quality Assurance for Stored Specimens **Phase II**

A mechanism for periodic assessment of the quality of stored specimens is in place for each class of biospecimens in the biorepository.

NOTE: The frequency of the checks may be determined by the
1. *Type of specimens being stored*
2. *Preservation method*
3. *Turnover of the material*

This may take a variety of forms including direct observation of materials, sampling, integrity of records, etc. The form and frequency that this takes is to be defined by the biorepository.

Quality assurance may be assessed at the time of disbursement.

Evidence of Compliance:
- ✓ Documentation of inventory sampling **OR**
- ✓ Documentation of unsuitable specimens by collection, as applicable **OR**
- ✓ Documentation of inventory QA/QC processes **OR**
- ✓ Assessment from researchers using the specimens

BAP.01900 Aliquot Size **Phase II**

Aliquot sizes are appropriate for the intended use of the specimen.

NOTE: Freeze/thaw cycles may be deleterious to the macromolecules intended for analysis; therefore, it is important to provide some aliquots that have a suitable volume for single-use. Storage and cost logistics may require that some larger volume aliquots are maintained.

Evidence of Compliance:

✓ Documentation of sample size stated in protocols

BAP.02000 Temperature Excursions **Phase II**

Temperature excursions beyond recommended storage requirements are tracked during routine processing and distribution.

NOTE: The biorepository has all known relevant annotations on a given biospecimen that may be made available to the researcher.

BAP.02100 Clean Environment **Phase II**

Specimens are processed in a clean environment, when required.

NOTE: RNA is particularly sensitive to RNases that may be present on tools and surfaces that have not been sterilized.

BAP.02200 Biological Safety Cabinet **Phase II**

Aliquots are made using sterile pipettes within a biological safety cabinet, when required.

BAP.02300 Policy for Handling Specimens for Infectious Diseases **Phase II**

There is a policy for receipt and management of potentially infectious material that includes application of universal precautions.

NOTE: Elements of the policy must include proper handling of specimens for biohazard protection. The policy may include information about prior testing for infectious hazards.

REFERENCES
1) OSHA regulation 29CFR1910.1020.

BAP.02400 Surgical Pathology Specimens Release for Research **Phase II**

A sample of a surgical pathology gross specimen may be submitted for research only if all of the following criteria are met.

1. **The pathologist determines that the sample(s) is not necessary for diagnostic purposes.**
2. **For laboratories subject to US regulations, formal written authorization is obtained in accordance with the requirements of HIPAA if identifiable patient information is released.**
3. **The biorepository meets other relevant requirements, including but not limited to, the requirements of the institution, the directives of any applicable institutional review board (IRB) or similar entity, and state and**

local laws and regulations.

4. **De-identified/anonymized sample of a surgical pathology gross specimen may be submitted for research if a waiver of consent has been obtained.**

*****REVISED**** ***07/29/2013***

BAP.02500 Histological Characteristic Review **Phase II**

A pathologist reviews all solid tissue specimens to determine the histological characteristics of the specimens that are submitted to the biorepository.

NOTE: Characteristics may vary depending on the tissue type and the nature of any pathological changes (when present). For example, solid tissue specimens from the colon of a patient with ulcerative colitis and colonic adenocarcinoma may include a section of normal colon, a section of colon involved by the chronic active inflammatory process, and a section from the colonic adenocarcinoma. Solid tissue samples can be banked and/or processed according to the previously established protocol for handling normal, disease involved, and neoplastic colonic tissue. Pathology review may occur prior to banking or distribution.

BAP.02600 Specimen Identity **Phase II**

The identity of every specimen is maintained through each step of processing and slide preparation.

NOTE: An unambiguous system of unique specimen identification coupled with a legible, sequential container labeling system that withstands exposure to anticipated reagents and temperature extremes are essential to fulfill this requirement. Containers can be various shapes and sizes and constructed from multiple materials (plastic, glass, cardboard). It is important to ensure that the container is suitable for the type of specimen and how it will be used/stored.

BAP.02700 Misidentification Risk **Phase II**

The biorepository has a documented procedure to ensure that the risk of misidentification is monitored and subjected to continual process improvement.

NOTE: The biorepository must actively monitor the key elements of all sample types throughout the entire process. The program may include, but is not limited to: 1) maintaining identification of nucleic acids and protein derivatives from a biospecimen, 2) QC and application of a barcode or other identifier, and 3) record of the number of sample derivatives prepared.

BAP.02800 Unique Identifier **Phase II**

Each specimen received into the biorepository receives a unique identifier.

BAP.02900 Specimen Tracking Mechanism **Phase II**

The identity of every specimen is maintained and tracked throughout the life of the specimen and its derivatives, *e.g.* parent to children to grandchildren, *etc.*

NOTE: An effective tracking system must be in place to ensure that biospecimens can be tracked accurately from the collection site through biospecimen arrival and subsequent

shipment from the biorepository.

BAP.03000 Specimen Rejection Criteria **Phase II**

There are documented criteria for the condition exceptions that should be recorded and communicated to researchers regarding items that could impact research results.

NOTE: This requirement is not intended to imply that all "unacceptable" specimens be discarded or not analyzed. For example, if an unacceptable specimen is received, there must be a mechanism to notify the requesting researcher, and to note the condition of the sample on the report. For example, many semen samples are sub-optimal; all samples should be evaluated and unusual properties noted. The biorepository may wish to record that a dialogue was held with the requesting researcher.

BAP.03100 Relabeling **Phase II**

There is a procedure in place for relabeling of a biospecimen and/or aliquots.

NOTE: Circumstances under which relabeling may occur may include, but are not limited to: a) inadvertent duplication of ID from internal or external sources; b) for full de-identification; c) replacement of a label (e.g. original label has fallen off).

Evidence of Compliance:

✓ Documentation of reason for relabeling

BAP.03200 De-identification for Research **Phase II**

For specimens that are released for research, there is a procedure for de-identifying/blinding or anonymizing specimens without compromise to research-related demographic information, when required.

BAP.03300 Coding **Phase II**

There is a defined coding system for sample identification.

BAP.03400 Participation/Donor Informed Consent **Phase II**

For specimens that are released to a biorepository, appropriate participant/donor informed consent is secured.

NOTE: This is not applicable when specimens are obtained under waiver of consent.

BAP.03500 IRB Release **Phase II**

For specimens that are released to a biorepository, an appropriate IRB release is in place.

BAP.03600 Specimen Collection/Handling Protocol **Phase II**

Collection, processing, and storage times are documented as required by the

biorepository protocol in place at the time of biospecimen procurement.

NOTE: Time is kept to a minimum between when a specimen is removed from its site of origin and when it is preserved (e.g. fixed, cooled, or frozen).

BAP.03700 Retrieval Procedures **Phase II**

All specimen retrieval procedures ensure specimen integrity.

NOTE: The integrity of the biospecimen must be maintained throughout the retrieval process.

Evidence of Compliance:

✓ Procedure defining the process

BAP.03800 Paraffin Embedding and/or Fixation QC **Phase II**

The biorepository has a procedure for paraffin embedding and/or fixation and quality checks to include the frequency requirements for quality checks (*e.g.* 24 hours/48 hours).

NOTE: This requirement applies only to biorepositories that perform their own fixation and embedding and are not a part of a CAP-accredited laboratory.

STORAGE

Inspector Instructions:

	• Sampling of policies and procedures for specimen storage conditions • Storage temperature records
	• Sampling of stored specimens for temperatures required by protocols

BAP.03900 Tissue Storage Conditions **Phase II**

The procedure manual defines the necessary storage conditions of the different specimens handled, all required records and policies, and a protocol for return of each specimen type to storage after issuance for use, as appropriate.

BAP.04000 Tissue Storage Temperature **Phase II**

The records show that specimens were stored at the protocol-required temperature.

NOTE: Storage of specimens must be appropriate for the type of specimens and its means of preservation. Failure to adhere to requirements could result in a specimen not being suitable for the purpose for which it was intended.

PRESERVATION

Inspector Instructions:

	• Sampling of biospecimen QA reports for key elements of processing and preservation of solid and fluid specimens
	• If collection occurs on-site, observe the processing/preservation procedure
	• How does your biorepository capture variables that could impact biospecimen usage? • How/when would the biorepository communicate pre-analytic variables to researchers? • How do you ensure accuracy of pre-analytic data capture?

BAP.04100 Pre-Analytic Variables **Phase II**

There is a mechanism to capture pre-analytical variables that could impact potential uses of the specimens.

NOTE: While intended use of specimens is not always known, the specimens are typically stored for anticipated types of analysis (i.e. serology, molecular, proteomic) and should be fit for purpose for the anticipated applications. Preservation procedures are optimized for the greatest number of molecular analytes/analysis platforms.

REFERENCES
1) Standard Preanalytical Coding for Biospecimens: Defining the Sample PREanalytical Code, Betsou, *et al*, *Cancer Epidemiol Biomarkers Prev* April 2010 19; 1004.

BAP.04200 Processing/Preservation - Solid Specimens **Phase II**

The key elements related to the processing and preservation of solid specimens are documented in the biospecimen QA report, when available.

NOTE: These elements may include, but are not limited to:

1. *Chilling/heating/drying of tissue during handling*
2. *Size and number of tissue pieces*
3. *Percentage of tumor/necrosis/stroma in the tissue*
4. *Liquid collection media*
5. *Use of gauze wrapping, additives, and embedding compounds*
6. *Variation in fixation (e.g. temperature, buffer, pH of formalin, start/end time in fixative)*
7. *Freezing protocols*
8. *Time in fixative*
9. *Time to preserve*

The biorepository has all known relevant annotations on a given biospecimen that may be

made available to the researcher. Information regarding some of these elements may not be available to the biorepository for all biospecimen collections, especially those that were procured before recent best practices for biorepositories were published.

BAP.04300 Processing/Preservation - Fluid Biospecimens **Phase II**

The key elements related to the processing and preservation of fluid biospecimens are documented.

NOTE: Key elements may include, but are not limited to:

1. *Collection preservative*
2. *Original volume received*
3. *Temperature and duration of specimen prior to processing*
4. *Temperature and speed of first centrifugation step*
5. *Temperature and speed of subsequent separation steps*
6. *Method used for separation*
7. *Derivative(s) preserved and their volume*
8. *Quality control results for derivatives (i.e. cell viability, purity, hemolysis status, human versus non-human content)*
9. *Tumor content (%), if applicable*

The biorepository has all known relevant annotations on a given biospecimen that may be made available to the researcher. Under some circumstances some of this information may be "unknown" depending on the site and age of specimen. It is recommended that the biorepository encourage their source sites to gather/provide as much information as possible.

REFERENCES
1) Standard Preanalytical Coding for Biospecimens: Defining the Sample PREanalytical Code, Betsou, *et al*, *Cancer Epidemiol Biomarkers Prev* April 2010 19; 1004.

SPECIMEN PROCESSING

DNA/RNA EXTRACTION/AMPLIFICATION

Inspector Instructions:

	• Sampling of DNA/RNA extraction and amplification policies and procedures • Records of DNA quantity measurement • Records of nucleic acid integrity and purity assessment • Records of internal controls
	• Nucleic acid amplification procedures for proper physical containment and procedural controls to prevent carryover • Observe quantitation and quality control assessments
	• How is adequacy of nucleic acid isolation and preparation evaluated? How often is this done?

	• Follow a sample from extraction through storage

BAP.04500 Specimen Identification **Phase II**

There is a system to positively identify all participant specimens, specimen types, and aliquots through all phases of the analysis, including specimen receipt, nucleic acid extraction, nucleic acid quantification, hybridization, detection, documentation, and storage.

BAP.04700 Extraction/Purification Methods **Phase II**

Nucleic acids are extracted and purified by methods reported in the literature, by an established commercially available kit or instrument, or by a validation of a method developed in-house.

NOTE: The method should be assessed for its suitability for each source type that requires extraction. Any modification to established procedures must be documented, as well as variations to procedures depending on anatomic site and biospecimen preservation format (e.g. fresh frozen vs. OCT-embedded).

Evidence of Compliance:

✓ Written procedure for each extraction process

BAP.04800 Nucleic Acid Quantity **Phase II**

The quantity of nucleic acid is measured.

NOTE: The quantity of nucleic acid must be measured prior to use by a standard procedure that allows for the accurate determination of the concentration/quantity of the nucleic acid.

Evidence of Compliance:

✓ Records detailing the concentration and yield of nucleic acid per specimen, per extraction

BAP.04900 Human/Non-Human DNA **Phase I**

When the downstream application requires an estimation of the ratio of human versus non-human genomic DNA in the specimen, the human/non-human DNA quantity is measured.

BAP.05000 Integrity/Purity Assessment - Nucleic Acids **Phase II**

The integrity and purity of nucleic acid is assessed, when appropriate for downstream use.

NOTE: Standard measure for DNA purity is A260/280 ratio of 1.6 to 2.0. Values less than 1.6 are indicative of protein contamination and values of >2.0 are indicative of RNA

contamination. RNA should have A260/280 ratio of greater than 2.0. Analytical measures of nucleic acids include, but are not limited to: A260/280 spectrophotometric ratio, RNA-specific measures, double-stranded DNA (dsDNA), or integrity by agaroses gel-electrophoresis. RNA integrity assessments should be determined if such a quality indicator would exclude samples from specific downstream methodologies.

RNA in specimens is highly labile because RNase is ubiquitous and difficult to inhibit. For human RNA targets, RNA quality must be assessed. However, depending on the target, it may not be necessary for all specimens to be assessed for RNA quality. RNA quality is not assessed, for example, for many types of viral RNA targets; however, the false negative rate must be documented.

BAP.05100 Neoplastic Cell Content Assessment **Phase II**

There is documentation of histological assessment of neoplastic cell content for tumor specimens from which DNA or RNA is extracted for analysis.

NOTE: In addition to confirming the presence or absence of neoplastic cells by a pathologist, it may be necessary for some assays to assess neoplastic cellularity for some downstream assay to ensure that the percentage of neoplastic cells exceeds the limit of detection for the assay.

A corresponding H&E section from the same tissue block used for DNA or RNA extraction may be used to assess sample adequacy. In the case of a frozen tissue block, a validation formalin-fixed paraffin-embedded mirrored to the frozen tissue specimen may be used for histological examination of sample adequacy. Alternatively, a stain such as toluidine blue may be used to stain the slide that is being used for DNA extraction. When assessment of sample adequacy is performed outside of the testing facility, documentation of such assessment should accompany the sample.

BAP.05200 Carryover **Phase II**

Nucleic acid amplification procedures (*e.g.* PCR) are designed to minimize carryover (false positive results) using appropriate physical containment and procedural controls.

NOTE: This item is primarily directed at ensuring adequate physical separation of pre- and post-amplification samples to avoid amplicon contamination. The extreme sensitivity of amplification systems requires that special precautions are taken. For example, pre- and post-amplification samples should be manipulated in physically separate areas; gloves must be worn and frequently changed during processing; dedicated pipettes (positive displacement type or with aerosol barrier tips) must be used; and manipulations must minimize aerosolization. In a given run, specimens should be ordered in the following sequence: participant samples, positive controls, negative controls (including "no template" controls in which target DNA is omitted and therefore no product is expected). Enzymatic destruction of amplification products is often helpful, as is real-time measurement of products to avoid manual manipulation of amplification products.

BAP.05300 Internal Controls Nucleic Acid Amplification **Phase II**

In all nucleic acid amplification procedures, internal controls are run to detect a false negative reaction secondary to extraction failure or the presence of an inhibitor, when appropriate.

NOTE: The facility should be able to distinguish a true negative result from a false negative due to failure of extraction or amplification. Demonstration that another sequence can be

successfully amplified in the same specimen should be sufficient to resolve this issue. For quantitative amplification assays, the effect of partial inhibition must also be addressed.

The internal control should not be smaller than the target amplicon. There are some rare exceptions to this rule due to sequence length and design. In this situation the internal control should not be more than 10% smaller than the target amplicon and the use of a smaller internal control should be justified.

DIGITAL IMAGE CAPTURE

Inspector Instructions:

	• Sampling of qualification data
	• If significant differences in slide/staining characteristics are expected, how has the qualification taken this into account? • If clear digital images cannot be obtained, what is the process for determining the cause and correcting any potential problems with the scanning system? • What is done if tumor content is insufficient?

BAP.05400 System Qualification **Phase II**

If digital whole slide imaging is used as an integral part of the biorepository operation, there is documentation that the system has been qualified for the intended use.

TISSUE MICROARRAY (TMA)

TMA technology helps expedite discovery of the novel targets important in disease treatment by providing a tool for high-throughput screening of multiple tissues using immunohistochemical, in situ hybridization, and fluorescent in situ hybridization (FISH) analyses. (Reference: https://ccrod.cancer.gov/confluence/display/CCRTARP/About)

Inspector Instructions:

	• Sampling of tissue microarray policies and procedures • Records of methods selected for region of interest of tissue and communication with the microarray technologist
	• System to positively identify specimens, specimen types and aliquots throughout the process

	• Who is responsible for selecting tissues and performing analysis for tissue microarray? • How are the selection and number of cores determined?
	• Follow a tissue specimen for TMA from processing to final analysis. Observe specimen identification, core selection and analysis.

BAP.05500 Specimen Identification **Phase II**

There is a system to positively identify all participant specimens, specimen types, and aliquots through all phases of the analysis.

NOTE: The phases include, but are not limited to:

1. *Specimen receipt*
2. *Specimen ID key*
3. *Tissue core selection from parent paraffin block*
4. *Location and identification within the new tissue microarray recipient tissue block*
5. *Documentation*
6. *Utilization (number of times sectioned)*
7. *Storage*

BAP.05600 Preparation Procedures **Phase II**

There is documentation describing the tissue types and purpose for the TMA, including the size and placement of the tissue cores as well as control tissue cores.

NOTE: Criteria for selection and documentation of the tissue cases are required. The usefulness and analysis of tissue microarray cores can be affected by the location (edges versus center) and loss of tissue cores as the tissue microarray block is thin sectioned. Consideration is of size, frequency, and location of cores therefore, should be considered and documented to match the intended use of the tissue microarray. Examples of the intended purpose of the TMA include, but are not limited to, disease-specific TMA, disease-progression TMA, tissue staining control TMA, cell line TMA, etc.

BAP.05700 Original Paraffin Tissue Block **Phase II**

Policies are in place to determine to what extent the original paraffin tissue block lesion can be removed.

BAP.05800 Tissue Core Selection **Phase II**

Tissues selected (paraffin block and tissue region of interest) to make a TMA must be selected by a qualified anatomic pathologist.

BAP.05900 Method of Core Selection **Phase II**

Methods of the selection of the regions of interest of tissue and clear documentation to transfer the correct information to a tissue microarray technologist must be documented.

BAP.06000 Number of Cores **Phase II**

Methods for determining the relevant number of cores to accurately represent the parent tissue block must be documented.

NOTE: A procedure is in place to determine the optimum number of cores required per TMA as dictated by each study protocol.

BAP.06100 Tissue Microarray Procedure **Phase II**

There is a procedure to ensure that the correct tissue is placed in the correct location of the TMA, for example, a TMA map (tissue type, key ID, and location in the TMA).

NOTE: This would include the placement and location of tissue controls and orientation markers.

There is software available to manage the map of a TMA. This resource is very useful in helping the pathologist evaluate and read results from the TMA after it has been stained.

BAP.06200 TMA Evaluation **Phase I**

Analysis of TMAs are performed by an anatomic pathologist and documented.

NOTE: The analysis may include software-assisted analysis or manual reading by a pathologist.

LASER CAPTURE MICRODISSECTION (LCM)

LCM "captured" cells can be used in a wide range of downstream assays such as loss of heterozygosity (LOH) studies, gene expression analysis at the mRNA level or in a wide range of proteomic assays such as 2D gel analysis, Western blotting, reverse phase protein array, and surface-enhanced laser desorption ionization (SELDI) protein profiling. Commercial kits for the isolation of RNA and DNA are available and adaptable to the micro samples obtained by LCM. (Reference: http://home.ccr.cancer.gov/LOP/Research/lcm/Default.asp)

Inspector Instructions:

	• Sampling of LCM policies and procedures • Records of LCM laser focus and alignment
	• System to positively identify specimens, specimen types and aliquots throughout the process

	
	• How is the quality of LCM tissue material ensured?

BAP.06300 Specimen Identification **Phase II**

There is a system to positively identify all participant specimens, specimen types, and aliquots through all phases of the microdissection and processing procedures to the point of storage or use.

BAP.06400 LCM Procedures **Phase II**

There is a procedure in place to monitor and document the LCM process.

NOTE: LCM tissues are derivative of a parent block and condition of tissue management is important for the quality outcome of tissue components. This is especially important if the collection is from frozen tissue.

BAP.06500 LCM Equipment **Phase II**

The LCM Laser focus and alignment is maintained and documented to ensure optimal performance.

NOTE: Documentation related to the critical components of the LCM as noted by the manufacturer is required.

CELL FRACTIONATION

The purpose of cell fractionation is to obtain a pure sample of part of the original whole, such as mitochondria, plasma membranes, DNA, RNA, soluble proteins or even specific macromolecules. There are many procedures defined for each target material, such as tissue, plant cells, animal cells, cell membranes and molecular components. Fractionation can simply be the separation of components of a biospecimen, such as blood into white blood cells, serum, and red blood cells.

Inspector Instructions:

	• Sampling of cell fractionation policies and procedures
	• System to maintain the identification of the derivatives to the parent biospecimen • Cell fractionation process follows the steps in the procedure

	
	• How is the quality of the cell fractionation process ensured?

BAP.06600 Specimen Identification **Phase II**

Derivatives from fractionation of biospecimens maintain the identification associated with the parent biospecimen during the fractionation process.

NOTE: Documentation of specimen type, handling conditions, and, if applicable, storage information are elements of the identification that are maintained until the process is complete. If anonymity from the parent biospecimen is required, this can be accomplished after the fractionation is complete.

BAP.06700 Procedures **Phase II**

There are written procedures for all steps in the fractionation process.

NOTE: Deviations from the manufacturer instructions must be validated and documented.

BAP.06800 Quality Control/Quality Assurance **Phase II**

Biorepositories providing cell fractionation procedures must document all quality control and quality assurance measures.

NOTE: These measures would include the establishment of validation sets performed by the laboratory to establish consistent success in quality fractionation and where possible, enrollment in proficiency testing or performance of alternative assessment to demonstrate expertise and quality fractionation.

CELL AND TISSUE CULTURE

Inspector Instructions:

	• Sampling of cell and tissue culture policies and procedures • Sampling of records of microbial contamination and other cell line testing
	• How does the biorepository ensure that the quality of cell lines is maintained?

NEW* *07/29/2013*

BAP.06802 Culturing Environment **Phase II**

Culturing is performed under aseptic conditions in a biological safety cabinet.

NEW* *07/29/2013*

BAP.06804 Cell Line Loss **Phase I**

There is a system in place to prevent loss of the cell line in case of culture failure, contamination or other problems.

NOTE: Potential systems may include the use of duplicate or independently established cultures, harvesting in duplicate or at different times, or other control processes.

NEW* *07/29/2013*

BAP.06806 Monitoring of Passage Numbers **Phase I**

The biorepository's procedures must define the maximum number of passages for each cell line by either reference or laboratory method.

NOTE: When passages have reached the maximum passage number, the cell line should be re-established using working stock with a lower passage number.

Evidence of Compliance:

- ✓ Documentation of tracking of cell line passages **OR**
- ✓ Documentation of growth curves

NEW* *07/29/2013*

BAP.06808 Testing for Microbial Contamination **Phase I**

Cell lines must be tested for microbial contamination at intervals defined by the biorepository director.

Evidence of Compliance:

- ✓ Records detailing the type(s) of tests and test outcomes

NEW* *07/29/2013*

BAP.06810 Testing for Functionality and/or Unique Characteristics **Phase I**

Cell lines are tested for functionality or unique characteristics.

NOTE: Such testing may be performed by analyzing aspects of the phenotype (e.g. expression patterns), genotype or morphology. The biorepository should have a policy that addresses the need for identity testing.

Evidence of Compliance:

- ✓ Records of cell line evaluation **AND**
- ✓ Records of (short tandem repeats) STR profiling or another method for cell lines to accomplish this goal

NEW* *07/29/2013*

BAP.06812 **Recording of Failures** **Phase I**

Culture failures are recorded.

NOTE: Records must indicate corrective actions.

Evidence of Compliance:

✓ Documentation indicating the results of testing and indication when a cell line has failed to pass the criteria established for successful passage of the quality tests

HISTOLOGY SECTION

General Quality Control

Inspector Instructions:

	• Sampling of specimen preparation records • Sampling of histology QC policies and procedures • Sampling of QC records (histochemical)
	• Sampling of tissue blocks (identification) • Sampling of slides (labeling, quality) • Sampling of reagents (expiration date)
	• How does the histology section ensure specimen identity throughout processing?
	• If problems are identified during the review of histology procedures, further evaluate the responses, corrective actions and resolutions • Select a representative specimen and follow from receipt in the department through accessioning, grossing, processing, time reported and availability in the LIS

*****NEW**** ***07/29/2013***

BAP.06816 **Specimen Preparation Records** **Phase I**

The histology section maintains records of the number of blocks, slides, and stains prepared and appropriately denotes the block from which the slide was prepared.

*****NEW**** ***07/29/2013***

BAP.06818 **Reagent Expiration Date** **Phase II**

All reagents are used within their indicated expiration dates.

NOTE: The biorepository must assign an expiration date to any reagents that do not have a manufacturer-provided expiration date. The assigned expiration date should be based on

known stability, frequency of use, storage conditions, and risk of contamination.

This checklist requirement applies to all reagents used in the biorepository (histochemical, immunohistochemical, and immunofluorescent reagents, and reagents used for molecular tests).

The acceptable performance of histochemical stains is determined by technical assessment on actual case material, use of suitable control sections, and as part of the specimen evaluations as determined by the protocol.

Exception to the above is that some histochemical reagents used in histology are not subject to outdating, so that assignment of expiration dates may have no meaning. The acceptable performance of such reagents should be confirmed at least annually by technical assessment, as described above. (If the manufacturer assigns an expiration date, it must be observed.)

Expired reagents may be used only under the following circumstances, as long as they will not have a negative impact on downstream studies: 1. The reagents are unique, rare or difficult to obtain; or 2. Delivery of new shipments of reagents is delayed through causes not under control of the biorepository. The biorepository must document verification of the performance of expired reagents in accordance with written policy.

If expired reagents are stored in histology, there must be a policy to describe the intended use. The reagents must be stored separately and clearly labeled for the intended purpose (e.g. for training purposes, not for diagnostic use).

Evidence of Compliance:

✓ Written policy for evaluating reagents lacking manufacturer's expiration date

REFERENCES
1) Department of Health and Human Services, Centers for Medicare and Medicaid Services. Clinical laboratory improvement amendments of 1988; final rule. *Fed Register.* 2003(Jan 24):7164 [42CFR493.1252(c)]

*****NEW**** ***04/21/2014***

BAP.06819 Special Stain Quality **Phase II**

All histochemical stains are of adequate quality, and daily controls are demonstrated on each day of use for the tissue components or organisms for which they were designed.

NOTE: Positive tissue controls assess the performance of the special stain. Special stains are performed on sections of control tissue known to contain components specific to each special stain. Verification of tissue used as a positive control must be performed and documented before being used with clinical specimens.

Evidence of Compliance:

✓ Written procedure for special stains **AND**

✓ Records of special stain QC **AND**

✓ Documented results of verified special stain control tissue block

REFERENCES
1) Department of Health and Human Services, Centers for Medicare and Medicaid Services. Clinical laboratory improvement amendments of 1988; final rule. *Fed Register.* 2003(Jan 24):7166 [42CFR493.1256(e)(2)] and [42CFR493.1273(a)]

*****NEW**** ***07/29/2013***

BAP.06820 Special Stains/Studies **Phase II**

For special stains and studies using immunologic and FISH/ISH methods, results of controls are documented to be acceptable before reporting results, when applicable.

REFERENCES
1) Department of Health and Human Services, Centers for Medicare and Medicaid Services. Clinical laboratory improvement amendments of 1988; final rule. *Fed Register.* 2003(Jan 24):7166 [42CFR493.1256(f)]
2) Department of Health and Human Services, Centers for Medicare and Medicaid Services. Clinical laboratory improvement amendments of 1988; final rule. *Fed Register.* 2003(Jan 24):3708 [42CFR493.1256(d)(6)]
3) ASCO/CAP ER/PgR guidelines

Immunohistochemistry

Inspector Instructions:

	• Sampling of IHC policies and procedures • Sampling of new antibody validation records • Sampling of new reagent/shipment confirmation of acceptability records • Sampling of antibody QC records • Sampling of buffer pH records • Sampling of batch control records
	• Sampling of slides (quality)
	• How does your biorepository validate new antibodies? • How does your biorepository confirm the acceptability of new reagent lots? • How does your biorepository distinguish non-specific false-positive staining from endogenous biotin?

BAP.06824 Specimen Modification **Phase II**

If the biorepository performs immunohistochemical staining on specimens other than formalin-fixed, paraffin-embedded tissue, the written procedure describes appropriate modifications for specimen types.

NOTE: Such specimens include frozen sections, air-dried imprints, cytocentrifuge or other liquid-based preparations, decalcified tissue, and tissues fixed in alcohol blends or other fixatives.

REFERENCES
1) Perkins SL, Kjeldsberg CR. Immunophenotyping of lymphomas and leukemias in paraffin-embedded tissues. *Am J Clin Pathol* 1993:99(4):362-373

*****NEW***** ***07/29/2013***
BAP.06826 Buffer pH **Phase II**

The pH of the buffers used in immunohistochemistry is routinely monitored.

NOTE: pH must be tested when a new batch is prepared or received.

Evidence of Compliance:
✓ Written procedure defining pH range for each buffer in use **AND**
✓ Records of initial and subsequent QC on each buffer

NEW* *07/29/2013*

BAP.06828 QC - Antibodies **Phase II**

Positive tissue controls are used for each antibody.

NOTE: Positive controls assess the performance of the primary antibody. They are performed on sections of tissue known to contain the target antigen, using the same epitope retrieval and immunostaining protocols as the donor tissue. Results of controls must be documented, either in internal biorepository records, or in the donor report. A statement in the report such as, "All controls show appropriate reactivity" is sufficient.

Ideally, the positive control tissue would be the same specimen type as the donor test specimen (e.g. small biopsy, large tissue section, cell block), and would be processed and fixed in the same manner (e.g. formalin-fixed, alcohol-fixed, decalcified) as the donor specimen. However, for most biorepositories, it is not practical to maintain separate positive control samples to cover every possible combination of fixation, processing and specimen type. Thus, it is reasonable for a biorepository to maintain a bank of formalin-fixed tissue samples as its positive controls; these controls can be used for donor specimens that are of different type, or fixed/processed differently, providing that the biorepository can show that these donor specimens exhibit equivalent immunoreactivity. This can be accomplished by parallel testing a small panel of common markers to show that specimens of different type, or processed in a different way (e.g. alcohol-fixed cytology specimens, decalcified tissue) have equivalent immunoreactivity to routinely processed, formalin-fixed tissue.

A separate tissue section may be used as a positive control, but test sections often contain normal elements that express the antigen of interest (internal controls). Internal positive controls are acceptable for these antigens, but the biorepository manual must clearly state the manner in which internal positive controls are used.

A positive control section included on the same slide as the donor tissue is optimal practice because it helps identify failure to apply primary antibody or other critical reagent to the donor test slide; however, one separate positive control per staining run for each antibody in the run (batch control) may be sufficient provided that the control slide is closely scrutinized by a qualified reviewer.

Ideally, positive control tissues possess low levels of antigen expression, as is often seen in neoplasms. Exclusive use of normal tissues that have high levels of antigen expression may result in antibody titers of insufficient sensitivity, leading to false-negative results.

Evidence of Compliance:

- ✓ Written procedure for the selection and use of positive tissue controls for each antibody **AND**
- ✓ Donor reports or worksheet with control results

REFERENCES
1) O'Leary TJ. Standardization in immunohistochemistry. *Appl Immunohistochem Molecul Morphol* 2001;9:3-8
2) Clinical Laboratory Standards Institute. *Quality Assurance for Design Control and Implementation of Immunohistochemistry Assays; Approved Guideline - Second Edition*. CLSI document I/LA28-A2. Clinical and Laboratory Standards Institute, 940 West Valley Road, Suite 1400, Wayne, Pennsylvania 19087-1898 USA; 2011.

NEW* *07/29/2013*

BAP.06830 QC - Antibodies **Phase II**

Appropriate negative controls are used.

NOTE: Negative controls must assess the presence of nonspecific staining in donor tissue as well as the specificity of each antibody with the exception listed below. Results of controls must be documented, either in internal biorepository records, or in the donor report. A statement in the report such as, "All controls show appropriate reactivity" is

sufficient.

For biorepositories using older biotin-based detection systems, it is important to use a negative reagent control to assess nonspecific or aberrant staining in donor tissue related to the antigen retrieval conditions and/or detection system used. A separate section of donor tissue is processed using the same reagent and epitope retrieval protocol as the donor test slide, except that the primary antibody is omitted, and replaced by any one of the following:

- *An unrelated antibody of the same isotype as the primary antibody (for monoclonal primary antibodies)*
- *An unrelated antibody from the same animal species as the primary antibody (for polyclonal primary antibodies)*
- *The negative control reagent included in the staining kit*
- *The diluent/buffer solution in which the primary antibody is diluted*

In general, a separate negative reagent control should be run for each block of donor tissue being immunostained; however, for cases in which there is simultaneous staining of multiple blocks from the same specimen with the same antibody (e.g. cytokeratin staining of multiple axillary sentinel lymph nodes), performing a single negative control on one of the blocks may be sufficient provided that all such blocks are fixed and processed identically. This exception does not apply to stains on different types of tissues or those using different antigen retrieval protocols or antibody detection systems. The biorepository director must determine which cases will have only one negative reagent control, and this must be specified in the department's procedure manual.

The negative reagent control would ideally control for each reagent protocol and antibody retrieval condition; however, large antibody panels often employ multiple antigen retrieval procedures. In such cases, a reasonable minimum control would be to perform the negative reagent control using the most aggressive retrieval procedure in the particular antibody panel. Aggressiveness of antigen retrieval (in decreasing order) is as follows: pressure cooker; enzyme digestion; boiling; microwave; steamer; water bath. High pH retrieval should be considered more aggressive than comparable retrieval in citrate buffer at pH 6.0.

Immunohistochemical tests using polymer-based detection systems (biotin-free) are sufficiently free of background reactivity to obviate the need for a negative reagent control and such controls may be omitted at the discretion of the biorepository director, following appropriate validation.

It is also important to assess the specificity of each antibody by a negative tissue control, which must show no staining of tissues known to lack the antigen. The negative tissue control is processed using the same fixation, epitope retrieval and immunostaining protocols as the donor tissue. Unexpected positive staining of such tissues indicates that the test has lost specificity, perhaps because of improper antibody concentration or excessive antigen retrieval. Intrinsic properties of the test tissue may also be the cause of "non-specific" staining. For example, tissues with high endogenous biotin activity such as liver or renal tubules may simulate positive staining when using a detection method based on biotin labeling.

A negative tissue control must be processed for each antibody in a given run. Any of the following can serve as a negative tissue control:

1. *Multitissue blocks. These can provide simultaneous positive and negative tissue controls, and are considered “best practice” (see below).*
2. *The positive control slide or donor test slides, if these slides contain tissue elements that should not react with the antibody.*

3. *A separate negative tissue control slide.*

The type of negative tissue control used (i.e. separate sections, internal controls or multitissue blocks) must be specified in the biorepository manual.

Multitissue blocks may be considered best practice and can have a major role in maintaining quality. When used as a combined positive and negative tissue control as mentioned above, they can serve as a permanent record documenting the sensitivity and specificity of every stain, particularly when mounted on the same slide as the donor tissue. When the components are chosen appropriately, multitissue blocks may be used for many different primary antibodies, decreasing the number of different control blocks needed by the biorepository. Multitissue blocks are also ideal for determining optimal titers of primary antibodies since they allow simultaneous evaluation of many different pieces of tissue. Finally, they are a useful and efficient means to screen new antibodies for sensitivity and specificity or new lots of antibody for consistency, which should be done before putting any antibody into diagnostic use.

Evidence of Compliance:

✓ Written procedure for the selection and use of negative reagent (as appropriate) and tissue controls for IHC **AND**

✓ Donor reports or worksheet with control results

REFERENCES

1) Leong AS-Y, Cooper K, Leong FJW-M. Manual of Diagnostic Antibodies for Immunohistology. 2nd ed. London: Greenwich Medical Media; 2003
2) Dabbs DJ, ed. Diagnostic Immunohistochemistry: Theranostic and Genomic Applications. Philadelphia: Saunders/Elsevier; 2010
3) Burry RW. Specificity controls for immunocytochemical methods. *J Histochem Cytochem* 2000;48:163-166
4) Weirauch M. Multitissue control block for immunohistochemistry. *Lab Med.* 1999;30:448-449
5) Miller RT. Multitumor "sandwich" blocks in immunohistochemistry. Simplified method and preparation and practical uses. *Appl Immunohistochem* 1993;1: 156-159
6) Chan JKC, Wong CSC, Ku WT, Kwan MY. Reflections on the use of controls in immunohistochemistry and proposal for application of a multitissue spring-roll control block. *Ann Diagn Pathol* 2000;4: 329-336
7) Clinical Laboratory Standards Institute. *Quality Assurance for Design Control and Implementation of Immunohistochemistry Assays; Approved Guideline - Second Edition*. CLSI document I/LA28-A2. Clinical and Laboratory Standards Institute, 940 West Valley Road, Suite 1400, Wayne, Pennsylvania 19087-1898 USA; 2011.

*****NEW***** ***07/29/2013***

BAP.06832 Endogenous Biotin **Phase I**

If the biorepository uses an avidin-biotin complex (ABC) detection system (or a related system such as streptavidin-biotin or neutravidin-biotin), there is a policy that addresses nonspecific false-positive staining from endogenous biotin.

NOTE: Biotin is a coenzyme present in mitochondria, and cells that have abundant mitochondria such as hepatocytes, kidney tubules and many tumors (particularly carcinomas) are rich in endogenous biotin. Biotin-rich intranuclear inclusions are also seen in gestational endometrium and in some tumors that form morules. If steps are not included in the immunostaining method to block endogenous biotin before applying the ABC detection complex, nonspecific false-positive staining may occur, particularly when using heat-induced epitope retrieval (which markedly increases the detectability of endogenous biotin). This artifact is often exquisitely localized to tumor cells and may be easily misinterpreted as true immunoreactivity.

Blocking endogenous biotin involves incubating the slides with a solution of free avidin (which binds to endogenous biotin), followed by incubation with a biotin solution (which saturates any empty biotin-binding sites remaining on the avidin). Biotin-blocking steps should be performed immediately after epitope retrieval and before incubation with primary antibody.

REFERENCES

1) Miller RT, Kubier P. Blocking of endogenous avidin-binding activity in immunohistochemistry: the use of egg whites. *Appl Immunohistochem* 1997; 5: 63-66

2) Miller RT, Kubier P, Reynolds B, Henry T. Blocking of endogenous avidin-binding activity in immunohistochemistry: the use of skim milk as an economical and effective substitute for commercial biotin solutions. *Appl Immunohistochem & Molec Morphol* 1999;7:63-65

*****NEW**** ***07/29/2013***

BAP.06834 Control Slide Review **Phase II**

The biorepository director or designee reviews all control slides each day specimens are stained.

NOTE: Records of this review must be maintained and should clearly document that positive and negative controls for all antibodies stain appropriately. Control records must be retained for one inspection cycle (every 3 years).

The control slides must be readily available upon request. The location of the slides should be stated in the procedure manual.

REFERENCES
1) Shellhorn N. IHC troubleshooting tips. Advance/Lab. 2000;9(1):33-37

*****NEW**** ***07/29/2013***

BAP.06836 Antibody Validation **Phase II**

The biorepository has documented validation of new antibodies, prior to sample characterization, including appropriate positive and negative controls.

NOTE: The performance characteristics of each assay in the immunohistochemistry biorepository must be appropriately validated before being made available as characterization data for the specimen type. The initial goal is to establish the optimal antibody titration, incubation time, temperature, detection system, and antigen retrieval protocol. Once optimized, a panel of tissues must be tested to determine the assay's sensitivity and specificity. The scope of the validation is at the discretion of the biorepository director and will vary with the antibody. For a well-characterized antibody with a limited spectrum of antigenic targets, like chromogranin or prostate specific antigen, the validation can be limited. A panel of 10 positive and 10 negative cases would be sufficient in this setting. For an antibody that is not well characterized and/or has a wide range of reported reactivity, a more extensive validation is necessary. The number of tissues tested should, in this circumstance, be large enough to determine whether the staining profile matches that previously described.

For most antibodies, normal controls are available for use in validation. In the exceptional case where only limited control tissue is available (fewer than 10 cases), the biorepository director should alert the investigator of this limitation.

Evidence of Compliance:

✓ Written procedure for the evaluation/validation of new antibodies

REFERENCES
1) Hsi ED. A practical approach for evaluating new antibodies in the clinical immunohistochemistry laboratory. *Arch Pathol Lab Med.* 2001;125:289-294
2) Clinical Laboratory Standards Institute. *Quality Assurance for Design Control and Implementation of Immunohistochemistry Assays; Approved Guideline - Second Edition*. CLSI document I/LA28-A2. Clinical and Laboratory Standards Institute, 940 West Valley Road, Suite 1400, Wayne, Pennsylvania 19087-1898 USA; 2011.

*****NEW**** ***07/29/2013***

BAP.06838 New Reagent Lot Confirmation of Acceptability **Phase II**

The performance of new lots of antibody and detection system reagents is compared with old lots before or concurrently with being placed into service.

NOTE: Parallel staining is important to control for variables such as disparity in the lots of detection reagents or instrument function. New lots of primary antibody and detection system reagents must be compared to the previous lot using an appropriate panel of control tissues. This comparison must be made on slides cut from the same control block.

Evidence of Compliance:

✓ Written procedure for the confirmation of acceptability of new reagent lots prior to use **AND**

✓ Records of confirmation of new reagent lots

NEW* *07/29/2013*

BAP.06840 Slide Quality **Phase II**

The immunohistochemical stains produced are of acceptable technical quality.

NOTE: The biorepository director or designee reviews slides and determines if they are of acceptable technical quality. The inspector must examine examples of the immunohistochemical preparations offered by the biorepository. A reasonable sample might include 5-10 diagnostic antibody panels.

REFERENCES
1) Shellhorn N. IHC troubleshooting tips. *Advance/Lab*. 2000;9(1):33-37

Histology Section Safety

NOTE TO THE INSPECTOR: The inspector should review relevant requirements from the Safety section of the General checklist, to assure that the histology section is in compliance.

The following requirements pertain specifically to the histology section.

Inspector Instructions:

	• Sampling of histology safety policies and procedures • Sampling of microwave reproducibility and ventilation checks • Sampling of formaldehyde vapor monitoring records
	• Location of automated tissue processor • Storage cabinets • Biohazard disposal bins

NEW* *07/29/2013*

BAP.06844 Automated Tissue Processor **Phase II**

Each open (*i.e.* generative of flammable vapors into the ambient workspace) automated tissue processor is operated at least 5 feet from the storage of combustible materials and from the paraffin dispenser.

NOTE: Each open (i.e. generative of flammable vapors into the ambient workspace) automated tissue processor must be located at least 5 feet from the storage of combustible materials unless separated by one-hour fire-resistive construction. Flammable and

combustible liquids must not be positioned near sources of heat or ignition. At least 5 feet must separate each open system tissue processor from the paraffin dispenser.

Tissue processors that operate as a closed system confine ignitable vapor hazards within the processor and thus do not pose a hazard requiring a 1.52 m (5 ft.) separation.

*****NEW**** ***07/29/2013***
BAP.06846 Microtome Storage **Phase II**

Microtome knives are stored in original containers or by some other means to avoid personnel injury or equipment damage.

*****NEW**** ***07/29/2013***
BAP.06848 Waste Disposal **Phase II**

Infectious tissues and other contaminated materials are disposed of with minimum danger to professional, technical, and custodial personnel.

NOTE: Waste disposal must be in accord with all regulations and disposed of with minimum danger to professional, technical, and custodial personnel.

Evidence of Compliance:

✓ Written procedure for waste disposal in accordance with local regulations

*****NEW**** ***07/29/2013***
BAP.06850 Creutzfeldt-Jakob Disease (CJD) Special Handling **Phase II**

There are documented procedures for the special handling of tissues in the biorepository from cases in which Creutzfeldt-Jakob disease is suspected.

NOTE: In addition to specimen handling, the policy should include guidelines for appropriate intralaboratory communication.

Neuropathology tissues from suspected cases of Creutzfeldt-Jakob disease should be treated with formic acid. Paraffin blocks and slides prepared from formic-acid-treated tissue may be handled routinely.

If tissue has not been treated with formic acid, it must be hand-processed and treated as containing potentially transmissible prions. Double gloves must be worn at all times when handling such tissue. All solutions, including water washes, must be collected and treated with equal volumes of fresh undiluted household bleach for 60 minutes before disposal. All scraps of paraffin and unused sections should be collected on a disposable sheet. The microtome may be wiped with bleach or NaOH solution. No special precautions are needed in handling intact glass slides once they have been coverslipped. Broken slides should be decontaminated and discarded. Paraffin blocks should be stored in a bag or box and labeled as infectious. Alternatively, the biorepository may reseal the cut surface of the blocks with paraffin.

NOTE: The following three requirements apply to microwave devices used in the histology section.

*****NEW**** ***07/29/2013***
BAP.06854 Microwave Usage **Phase I**

Microwave devices are used in accordance with manufacturer's instructions.

NOTE: Microwave devices should be used in accordance with manufacturer's instructions,

unless CAP requirements are more stringent.

Evidence of Compliance:

✓ Written procedure for microwave usage

*****NEW***** ***07/29/2013***

BAP.06856 Microwave Monitoring **Phase I**

Microwave devices are at least annually monitored for reproducibility.

NOTE: "Reproducibility" is defined as consistency in diagnostic quality obtained from microwave equipment and procedures. For some devices, reproducibility may be evaluated by monitoring the temperatures of identical samples after microwave processing. For those microwave devices (particularly those incorporated into histology processing equipment) that use temperature-independent methods to evaluate reproducibility, the biorepository should have a written procedure for monitoring reproducibility that follows instrument manufacturer's instructions. Information on such procedures is given in the reference to this checklist requirement (see below).

The microwave device should be tested for radiation leakage if there is visible damage to the device.

Evidence of Compliance:

✓ Written procedure for monitoring the diagnostic quality of specimens processed using microwaves

REFERENCES

1) Clinical and Laboratory Standards Institute. *Microwave Device Use in the Histology Laboratory; Approved Guideline.* CLSI document GP28-A [ISBN 1-56238-563-1]. Clinical and Laboratory Standards Institute, 940 West Valley Road, Suite 1400, Wayne, Pennsylvania 19087-1898 USA, 2005

*****NEW***** ***07/29/2013***

BAP.06858 Microwave Container Venting **Phase I**

All containers used in microwave devices are vented.

NOTE: This checklist item does not apply to microwave devices that are designed by the manufacturer to operate without venting.

Microwave devices should be placed in an appropriate ventilation hood to contain airborne chemical contaminants and potentially infectious agents. Before operation of the microwave device, flammable and corrosive reagents should be removed from the hood, to prevent fire or chemical damage to the electronic components of the device. Microwave devices used outside a fume hood should have an integral fume extractor that is certified by the manufacturer for use in a clinical laboratory.

The effectiveness of ventilation should be monitored at least annually.

This checklist requirement does not apply if only non-hazardous reagents (and non-infectious specimens) are used in the device (e.g. water, certain biological stains, paraffin sections). The biorepository should consult the safety data sheets (formerly MSDS) received with reagents and stains to assist in determining proper handling requirements and safe use.

Venting of containers is necessary so that processing occurs at atmospheric pressure, to prevent explosion. For procedures using pressure above that of the atmosphere, specialized containers must be used, with strict adherence to manufacturer instructions.

Evidence of Compliance:

✓ Written procedure for the use of appropriately vented containers **AND**

✓ Records of annual evaluation of ventilation effectiveness

NEW* *07/29/2013*

BAP.06860 Formaldehyde/Xylene Safety **Phase II**

Formaldehyde and xylene vapor concentrations are maintained below the following maxima, expressed as parts per million, in all areas of the biorepository where formaldehyde or xylene are used.

NOTE: Formaldehyde and xylene vapor concentrations must be monitored in all areas where these reagents are used: e.g. surgical pathology gross dissection room, histology laboratory, etc. Initial monitoring involves identifying all employees who may be exposed at or above the action level or at or above the STEL and accurately determining the exposure of each employee identified. Further formaldehyde monitoring is mandated at least every 6 months if results of the initial monitoring equal or exceed 0.5 ppm (8 hr time-weighted exposure, the "action level") or at least once per year if the results exceed the short term exposure limit (STEL) 2.0 ppm. The laboratory may discontinue periodic formaldehyde monitoring if results from 2 consecutive sampling periods taken at least 7 days apart show that employee exposure is below the action level and the short-term exposure limit, and 1) no change has occurred in production, equipment, process or personnel or control measures that may result in new or additional exposure to formaldehyde, and 2) there have been no reports of conditions that may be associated with formaldehyde exposure.

Formaldehyde monitoring must be repeated any time there is a change in production, equipment, process, personnel, or control measures which may result in new or additional exposure to formaldehyde for any employee involved in the activity. If any personnel report signs or symptoms of respiratory or dermal conditions associated with formaldehyde exposure, the laboratory must promptly monitor the affected person's exposure.

Xylene must be monitored initially, but there is no requirement for periodic monitoring of xylene.

Repeat monitoring should be considered when there is a change in production, equipment, process, personnel, or control measures likely to increase exposure levels.

	8 hr Time-Weighted Exposure Limit	Action Level (8 hr Time-Weighted Exposure)	15 min Short-Term Average Exposure Limit (STEL)
Formaldehyde	**0.75**	**0.5**	**2.0**
Xylene	**100**		**150**

Evidence of Compliance:

✓ Written procedure for formalin/xylene safety including action limits, criteria for discontinuation of monitoring and criteria for resumption of monitoring **AND**

✓ Record of initial formalin/xylene monitoring and repeat monitoring when indicated **AND**

✓ Records of corrective action when exposure limits are exceeded

REFERENCES
1) Montanaro A. Formaldehyde in the workplace and in the home. Exploring its clinical toxicology. *Lab Med.* 1996;27:752-757
2) Goris JA. Minimizing the toxic effects of formaldehyde. *Lab Med.* 1997;29:39-42
3) Wenk PA. Disposal of histology stains. *Lab Med.* 1998;29:337-338
4) Occupational Safety and Health Administration. 29CFR1910.1048 and 1450, revised July 1, 1998

INSTRUMENTS AND EQUIPMENT

A variety of instruments and equipment are used to support the biorepository. All instruments and equipment should be properly operated, maintained, serviced, and monitored to ensure proper performance. The procedures and schedules for instrument maintenance and function checks must be as thorough and as frequent as specified by the manufacturer. Examples of equipment include, but are not limited to centrifuges, microscopes, incubators, heat blocks, biological safety cabinets, fume hoods, etc.

Inspector Instructions:

	• Sampling of instrument policies and procedures • Sampling of instrument maintenance logs and repair records
	• Instrument records (promptly retrievable) • Instruments (clean and well-maintained)
	• How frequently do you change solutions in the tissue processor? How is the timeframe for changing solutions determined? • How does your laboratory prevent cross-contamination of paraffin sections in the flotation bath? • What do you do when you receive notification of a freezer out of range? • How often do you decontaminate your cryostat?

*****NEW**** ***04/21/2014***

BAP.06880 Instrument/Equipment Function Verification **Phase II**

The operation of all instruments and equipment is verified upon installation and after major maintenance and repairs to ensure that they function as intended.

Evidence of Compliance:

✓ Written procedure for function verification **AND**

✓ Records of function verification

*****REVISED**** ***04/21/2014***

BAP.06900 Maintenance/Function Check Performance **Phase II**

Appropriate maintenance and function checks are performed and documented for all instruments (e.g. analyzers) and equipment (e.g. centrifuges) following a defined schedule, at least as frequent as specified by the manufacturer, prior to operation.

NOTE: There must be a schedule and procedure at the instrument/equipment for appropriate function checks and maintenance. These may include (but are not limited to) cleaning, electronic, mechanical and operational checks. The procedure and schedule must be at least as thorough and as frequent as specified by the manufacturer.

Function checks should be designed to detect drift, instability, or malfunction, before the problem is allowed to affect test results.

Since some equipment have no standard frequency or extent for maintenance and function checks, each biorepository should establish a schedule that reasonably reflects the

workload and specifications of its equipment.

BAP.07100 Availability of Instrument and Equipment Service Records **Phase II**

Instrument and equipment maintenance, function checks, service, and repair records (or copies) are available in a timely manner to, and usable by, the staff operating the equipment.

NOTE: Effective utilization of instruments and equipment by the technical staff depends upon the prompt availability of maintenance, repair, and service documentation (copies are acceptable). Biorepository personnel are responsible for the reliability and proper function of their instruments and must have access to this information. Off-site storage, such as with centralized medical maintenance or computer files, is not precluded if the inspector is satisfied that the records can be promptly retrieved.

*****NEW**** ***04/21/2014***
BAP.07110 Automated Stainer **Phase II**

There is a schedule to change the solutions in automated stainers.

NOTE: Solutions must be changed at intervals appropriate for the biorepository's workload. Cleaning of the stainers should be documented when performed.

Evidence of Compliance:
- ✓ Written procedure defining frequency of changing staining solutions **AND**
- ✓ QC records that document compliance with the procedure

*****NEW**** ***07/29/2013***
BAP.07120 Incubator QC **Phase II**

Incubators are monitored for temperature, CO_2 level, and humidity on each day of use.

NOTE: The procedure manual must specify the allowable limits for each type of culture. Readings must be recorded each day that cultures are incubated. There must be documentation of corrective action if the allowable limits are exceeded.

Evidence of Compliance:
- ✓ Instrument QC records

BAP.07200 Tissue Processor Solutions **Phase II**

Solutions are changed as needed.

NOTE: Tissue processor solutions must be changed at intervals appropriate for workload. The settings and solutions of shared processors must be checked before each use.

Evidence of Compliance:
- ✓ Written procedures for a change of solutions based on usage **AND**
- ✓ QC records documented at defined frequency

*****NEW***** ***04/21/2014***
BAP.07210 Tissue Processing Programs **Phase II**

Tissue processing programs are validated.

NOTE: To validate new processing programs, the biorepository should run tissue samples of the same size, thickness and fixation in duplicate Reagents on the processor(s) should be comparable, e.g. all fresh reagents. Process, embed, cut, and stain slides at the same time and evaluate the quality of the blocks, e.g. firmness, ease of cutting. The slides should be evaluated by the pathologist without knowledge of which processing program was used and graded on quality of section and staining. The new processing program must be of equal or better quality before being put into use.

This method may also be used to verify a routine processing program before putting a new processor into production.

Evidence of Compliance:

✓ Written procedure for validation of new tissue processing programs **AND**
✓ QC records documenting validation

*****NEW**** ***04/21/2014***

BAP.07220 Tissue Processing Programs **Phase I**

Specific tissue processing programs are available for different types and sizes of specimens.

NOTE: To achieve acceptable results for diagnostic purposes, processing programs may be needed for different sizes and types of specimens. Biopsy specimens may be processed on a shorter schedule than larger specimens; large, dense or fatty specimens and brain specimens will not process adequately on a shorter schedule. A variety of processing programs should be used to achieve good processing results.

Evidence of Compliance:

✓ Written procedure defining processing programs for various types and sizes of specimen tissues

BAP.07300 Paraffin Bath and Dispenser Temperature **Phase II**

Paraffin baths and dispensers are controlled and maintained.

NOTE:

1. *Instruments must be clean and well-maintained*
2. *The temperature of the dispenser must be correct for the type of paraffin used*
3. *Temperatures are checked regularly and recorded*

The frequency of checks must be determined by the director/designee.

Evidence of Compliance:

✓ Documentation of frequency requirements **AND**
✓ Records of temperature checks

BAP.07400 Flotation Baths **Phase II**

Flotation baths are clean and well-maintained, and there is a procedure for preventing cross-contamination of paraffin sections in the bath.

NOTE: Of particular importance are periodic water changes or blotting of the water surface so that sections from one biospecimen block are not inadvertently carried over to another (so-called "floaters" or "extraneous tissue").

BAP.07500 Microtome Maintenance **Phase I**

Microtomes are clean, well-maintained, properly lubricated, and without excessive play in the advance mechanism.

BAP.07600 Cryostat Decontamination **Phase II**

There is a documented procedure for the decontamination of the cryostat at defined intervals and under defined circumstances, and decontamination records are evident.

NOTE: The cryostat must be defrosted and decontaminated by wiping all exposed surfaces with tuberculocidal disinfectant. The cryostat should be at room temperature during decontamination unless otherwise specified by the manufacturer. This should be done at an interval appropriate for the institution; this must be weekly for instruments used daily. Trimmings and sections for tissue that accumulate inside the cryostat must be removed during decontamination. Although not a requirement, steel mesh gloves should be worn when changing knife blades.

REFERENCES

1) Clinical and Laboratory Standards Institute (CLSI). *Protection of Laboratory Workers From Occupationally Acquired Infections; Approved Guideline—Third Edition.* CLSI document M29-A3 (ISBN 1-56238-567-4). Clinical and Laboratory Standards Institute, 940 West Valley Road, Suite 1400, Wayne, Pennsylvania 19087-1898 USA, 2005.
2) http://www.well.ox.ac.uk/_asset/file/leica-disinifection-2.pdf
3) http://www.epa.gov/oppad001/list_b_tuberculocide.pdf

STORAGE EQUIPMENT

This section of storage equipment for a biorepository should be based on the type of specimen(s) to be stored, the length of time in storage, and the intended use of the specimen(s).

Inspector Instructions:

	• Sampling of specimen storage policies and procedures • Sampling of preventative and reactive maintenance procedures • Records of storage container calibrations • Sampling of temperature monitoring records
	• Adequate space for storage containers • Active alarm systems in place • Walk-in storage environment • Liquid Nitrogen tanks, if applicable
	• What do you do in the event of freezer breakdown? • How do you prevent overflow of storage containers?
	• Have you ever suffered a significant loss of samples? How did you address this and what were the corrective/preventative actions that became policy as a result?

BAP.07800 Storage Equipment Calibration/Calibration Verification **Phase II**

There is a procedure for calibration and calibration verification for all applicable storage equipment.

NOTE: The documentation of calibration and calibration verification includes:

1. *Date calibration was performed*
2. *Identity of person who ran the calibration*
3. *Documentation of results*
4. *Name of the device used against which instrument was calibrated*

Evidence of Compliance:

✓ Documentation of calibration/calibration verification **OR** manufacturers' certification of calibration

BAP.07900 Temperature Set Points **Phase I**

High and low temperature set-points have been established and documented that are appropriate for each storage environment.

NOTE: A best practice is to perform and record temperature mapping for each new freezer prior to being placed in service and periodically for freezers currently in service. The frequency of mapping is determined by the director/designee as well as the review of the data generated.

*****REVISED** 07/29/2013***

BAP.08000 Consistent Temperature **Phase I**

There is evidence that all temperature-controlled storage units maintain the proper temperature throughout the unit.

NOTE: On all temperature-controlled storage units, multiple point temperature readings should be taken on a periodic basis to ensure that a required temperature is maintained throughout. There must be documentation that such readings have been taken. Unrestricted air circulation within the unit reduces the potential for warmer or colder areas that may have detrimental effects on blood/component units without detection by the monitoring system. This requirement also applies to liquid nitrogen (LN2) storage units.

A best practice is to perform and record temperature mapping for each new temperature controlled storage unit prior to being placed in service and periodically for freezers currently in service. The frequency of mapping is determined by the director/designee as well as the review of the data generated.

BAP.08100 Refrigerator/Freezer Temperature QC **Phase II**

Refrigerator/freezer temperatures are checked and recorded daily.

NOTE: Storage temperature of biospecimens must be appropriate for the type of tissue and its means of preservation. Failure to adhere to requirements could result in a unit not being suitable for the purpose for which it was intended.

This checklist requirement applies to refrigerators/freezers containing reagents or biological specimens. "Daily" means every day (seven days per week, 52 weeks per year). The biorepository must define the acceptable temperature ranges for these units. If temperature(s) are found to be outside of the acceptable range, the biorepository must document appropriate corrective action, which may include evaluation of contents for adverse effects.

The two acceptable ways of recording temperatures are: 1) recording the numerical temperature, or 2) placing a mark on a graph that corresponds to a numerical temperature (either manually, or using a graphical recording device). If the records are manually obtained, the identity of the individual recording the temperature(s) must be documented (recording the initials of the individual is adequate).

The use of automated (including remote) temperature monitoring systems is acceptable, providing that biorepository personnel have ongoing immediate access to the temperature data, so that appropriate corrective action can be taken if a temperature is out of the acceptable range. The functionality of the system must be documented daily.

BAP.08200 Walk-in Storage Criteria **Phase II**

Walk-in storage systems should have:

1. **Dual compressors**
2. **Internal safety release**
3. **Non-slip floor covering**
4. **Interior oxygen and CO_2 monitoring system, when required**

BAP.08300 Freezer Preventative Maintenance **Phase II**

There is a procedure for freezer preventative maintenance.

NOTE: Regular preventive maintenance is required to keep units functioning properly. Routine cleaning and maintenance should be done by assigned employees according to a Preventive Maintenance Schedule. Actions should be targeted at elimination of the causes of equipment failure and unscheduled interruptions. This activity involves regular, routine cleaning, lubricating, testing, calibrating and adjusting, checking for wear and tear and eventually replacing components to avoid breakdown.

Evidence of Compliance:

✓ Record of employees trained to perform preventive maintenance **AND**

✓ Results of all preventive maintenance will be recorded

BAP.08400 Emergency Response Plan **Phase II**

There is an emergency response plan if acceptable temperature ranges for refrigerators and/or freezers are exceeded.

BAP.08500 Specimen Transfer Procedure **Phase II**

There is a procedure for maintaining appropriate temperatures in the event of a system failure.

NOTE: There is a plan in place for transfer and back-up storage. For example, having 10% back-up storage containers would be considered best practices for each type of temperature-controlled unit should any one unit suffer an unrecoverable failure. Failure

mode analysis should be performed to identify possible root causes of failure. Corrective actions should include service calls to providers for system repair, as applicable. Duration of failure should also be recorded, as well as any potential adverse effects to specimens.

Evidence of Compliance:

- ✓ Temperature and alarm records **AND**
- ✓ Updated specimen location records **AND**
- ✓ Corrective action/preventative action documentation

If nitrogen in the liquid phase is used, the following requirements apply.

BAP.08600 Liquid Nitrogen Supplies **Phase II**

Adequate liquid nitrogen (LN2) supplies are maintained onsite if LN2 is used as refrigerant or coolant for a storage environment.

NOTE: In general, vapor phase storage is the preferred method over storage in the liquid phase of nitrogen because vapor phase provides sufficiently low temperatures to maintain temperatures below the Tg (glass transition temperature). Storage in the vapor stage also avoids safety hazards inherent in liquid phase storage.

*****REVISED**** ***07/29/2013***

BAP.08700 LN2 Monitoring **Phase II**

LN2 daily usage and LN2 levels are monitored and documented for each storage container.

NOTE: The interval for monitoring of usage must be based on the requirements of the instruments.

Evidence of Compliance:

- ✓ Documentation of usage monitoring, as applicable

BAP.08800 Storage Containers Approval **Phase II**

All specimen storage containers have been approved for use under intended storage conditions.

NOTE: Refer to contact supplier specification sheet for valid use conditions.

TEMPERATURE MONITORING AND ALARMS

Inspector Instructions:

- Records of traceability to NIST standards
- Sampling of temperature logs
- Sampling of records of alarm trigger response
- Sampling of alarm system testing records

	• Active alarm systems in place • Availability of emergency power supply
	• What do you do when a storage container alarm triggers? • What is the biorepository's contingency plan if the alarm system fails? • What do you do if a unit cannot maintain appropriate temperature?
	• Select a storage container that has had a temperature failure and follow the process from notification to response and final corrective action

BAP.08900 NIST Thermometer **Phase II**

An appropriate thermometric standard device of known accuracy (*e.g.* guaranteed by manufacturer to meet the standards of the National Institute for Standards and Technology) is available.

NOTE: Thermometers should be present on all temperature-controlled instruments and environments and checked daily. Thermometric standard devices should be recalibrated or recertified prior to the date of expiration of the guarantee of calibration; documentation of recalibration/certification should be maintained for review.

BAP.09000 Non-Certified Thermometers **Phase II**

All non-certified thermometers in use are checked against an appropriate thermometric standard device before initial use.

BAP.09100 Temperature Checks **Phase II**

Temperatures are checked and recorded on each day of use, specifying the unit and location for all temperature dependent instruments and equipment.

NOTE: Controlled-temperature devices used must have temperatures recorded at least daily for units that are within the prescribed temperature range, and at least every 15 minutes if outside of that range.

The two acceptable ways of recording temperatures are: 1) recording the numerical temperature, or 2) placing a mark on a graph that corresponds to a numerical temperature (either manually, or using a graphical recording device). The identity of the individual recording the temperature(s) must be documented (recording the initials of the individual is adequate).

The use of automated (including remote) temperature monitoring systems is acceptable, providing that biorepository personnel have ongoing immediate access to the temperature data, so that appropriate corrective action can be taken if a temperature is out of the acceptable range. The functionality of the system must be documented daily.

BAP.09200 Alarm Response Time **Phase I**

Temperature limits for the alarm are established with consideration for anticipated response time.

*****REVISED**** ***07/29/2013***

BAP.09300 Storage Temperature Deviation Procedure **Phase II**

There are documented procedures to follow if there are deviations in the storage temperature limits, with an impact assessment when required.

NOTE: Specific procedures must be documented and understood by personnel regarding handling biological specimens if storage temperature limits cannot be maintained. The primary concern is the preservation of specimen. If there is a failure, arrangements must be made for service, and for alternative storage.

BAP.09400 Emergency Power Supply **Phase II**

Temperature controlled storage equipment have an emergency power supply.

BAP.09500 Storage Unit Alarms **Phase II**

There is an audible alarm for each component storage unit, the alarm is continuously monitored 24 hours per day (in biorepository or remote), and the response system to an alarm has been validated.

NOTE: The biorepository should be able to demonstrate how this system works, and that there is a process to ensure a timely response to an alarm.

Evidence of Compliance:

- ✓ Written procedure defining criteria for monitoring alarms **AND**
- ✓ Records of response time to the alarm

*****REVISED**** ***07/29/2013***

BAP.09600 Alarm System Checks **Phase II**

Alarm systems functionality is tested (e.g. alarm triggers, ability to communicate, etc.) at specified periodic intervals (no less frequently than quarterly) and results recorded.

NOTE: Freezer alarms should be tested without taking specimens outside their acceptable range. Some ways to perform this testing may include: 1) electronic manipulation of freezer set points to trigger the alarm system, 2) warming or cooling the probe using external measures that do not affect the operating temperature at which the specimens are held, and other acceptable processes.

*****REVISED**** ***07/29/2013***

BAP.09700 Alarm Sensors To Trigger Action Needed **Phase II**

Alarms are adjusted to be triggered before the temperature falls outside the acceptable temperature range.

NOTE: The biorepository defines the acceptable range for specimen storage.

Evidence of Compliance:

✓ Records of trigger temperatures during alarm checks **AND**
✓ Records of corrective action, when appropriate

BAP.09800 Power Failure Back-Up **Phase II**

The alarms will continue to function if the power is interrupted.

NOTE: Alarm systems must continue to function during a power failure. This may be accomplished by having the alarm on a separate circuit, installing battery power back-up, or having a power failure alarm.

BAP.09900 Off-Site Notification Process **Phase II**

If the monitoring system allows for off-site notification, there is a

1. **Trained person on-call (24/7) to respond to alarm conditions**
2. **List of phone numbers or alternate means of contact for trained personnel in case the on-call person fails to respond**

BAP.10000 Back-Up Alarm QC **Phase II**

There is a back-up alarm system in place with documentation of regular testing.

BAP.10100 Alarm System Monitoring **Phase II**

There is a mechanism for monitoring the alarm system.

BAP.10200 Alarm System Contingency Plan **Phase II**

There is a contingency plan in place for monitoring if the alarm system fails.

NOTE: Downtime procedures should exist and staff should be trained on these procedures. This contingency procedure should be periodically tested.

INFORMATION TECHNOLOGY SYSTEMS

If the computer system(s) is located in a remote site, the biorepository should have a service level agreement with the site(s) that states the requirements of the biorepository for data transmission as well as stating the exceptions related to security and other criteria determined necessary by the biorepository.

HARDWARE AND SOFTWARE

Inspector Instructions:

	• Sampling of hardware and software policies and procedures • Sampling of application training records

	• Sampling of documentation for system modifications • Records of bug-fixes
	• How does your biorepository verify the IT system following a hardware or software failure? • Who do you notify when there is a computer malfunction? • Where is the server located? • What are the safety features of the facility or rating where the server is located?

BAP.10300 IT System Testing **Phase II**

There is documentation that programs are adequately tested for proper functioning after installation of new systems or changes or modification of the existing systems, with documentation of approval for use by the biorepository director or designee.

NOTE: Computer programs must be checked for proper performance after installation of new systems or modifications of existing systems. Any changes or modifications to the system must be documented, and the director or designee must approve all changes, additions and deletions in programs, the test library, and major computer functions before they are released. Documentation must be retained for at least two years beyond the service life of the system.

BAP.10400 Custom IT System **Phase II**

Customized programs are appropriately documented.

NOTE: The purpose of the computer program, the way it functions, and its interaction with other programs must be clearly stated. The level of detail should be adequate to support trouble-shooting, system modifications, or additional programming.

BAP.10500 Software Bug or Issue Tracking **Phase II**

There is an adequate tracking system to identify and report all malfunctions or issues with biorepository software.

NOTE: The tracking system should also include responses to reports of software bugs.

Evidence of Compliance:

✓ Records of software bugs and issues

BAP.10600 Software Bug or Issue Resolution and Tracking **Phase II**

There is a written policy for correcting software malfunctions or issues, as well as an audit log of all changes to the software application.

Evidence of Compliance:

✓ Audit log of software bugs and issues and corrections made to the system

BAP.10700 Software Modification Tracking **Phase II**

There is an adequate tracking system to identify all persons who have added or modified software.

Evidence of Compliance:

✓ Records of individuals adding or modifying software

BAP.10800 IT System Training **Phase II**

There is documentation that all users of the computer system receive adequate training initially, after system modification, and after installation of a new system.

BAP.10900 Computer Malfunction Notification **Phase II**

There is a written policy with instructions for contacting a responsible person (*e.g.* Computer System Manager) in case of computer malfunction.

Evidence of Compliance:

✓ Written policy with instructions for contacting a responsible person in case of system malfunction

BAP.11000 IT System Integrity **Phase II**

There is a documented process to verify the integrity of the system (operating system, applications, and database) after restoration of data files.

NOTE: The computer system must be checked after restoration of data files to ensure that no inadvertent alterations have occurred that might affect clinical result reporting. The integrity of the system may be verified, for example, by review of a representative number of computer-generated participant reports, or by generating test ("dummy") participant reports for review. The IT director is responsible for determining verification procedure(s) appropriate to the biorepository. Whether or not the data center is located on site, all facilities served by the data center must participate in the verification of the system(s) integrity following a hardware or software failure.

Evidence of Compliance:

✓ Records of verification after a hardware or software failure

SYSTEM SECURITY

The following requirements concern unauthorized users. If a system is vulnerable, steps should be taken to prevent unauthorized access.

Inspector Instructions:

	• Sampling of computer security policies and procedures • Records of system vulnerability tests
	• Ask a non-IT individual if they have/can install external software on their workstation

	
	• Access privileges and restrictions in applications/databases

BAP.11100 Access Data **Phase II**

There are explicit documented policies that specify who may use the computer system to enter or access data, change data or alter programs.

NOTE: Policies must define those who may only access data and users, who are authorized to enter data, change data, change billing, or alter computer tables or programs.

BAP.11200 Computer Access Codes **Phase I**

Computer access codes (security codes, user codes) are in place to limit individuals' access to those functions they are authorized to use and the security of access codes is maintained (*e.g.* inactivated when employees leave, not posted on terminals).

NOTE: The biorepository should establish security (user) codes to permit only specifically authorized individuals to access patient data or alter programs. A system that allows different levels of user access to the system based on the user's authorization is desirable and usually provides effective security. Examples of best practices include these requirements: periodic alteration of passwords by users; minimum character length for passwords; password complexity requirements (e.g. a combination of alphanumeric characters); recording of failed log-on attempts with user lock-out after a defined number of unsuccessful log-on attempts.

BAP.11300 Time-out/Lock-out **Phase I**

The computer systems have an appropriate security feature such as a mandatory time-out and a password lock-out mechanism.

BAP.11400 System Testing **Phase I**

Systems are tested in a privileged and non-privileged manner to identify vulnerabilities that may lead to unintentional or unauthorized disclosure and/or modification of data.

Evidence of Compliance:

✓ Records and results of vulnerability tests
✓ Documented corrective actions if a vulnerability is identified

BAP.11500 Unauthorized Software Installation **Phase I**

Policies and procedures are in place that govern installation of software on any computer used by the biorepository.

NOTE: Biorepository computers often serve multiple functions. Many of these computers are connected in a network. The security of the system should be sufficient to prevent the casual user from installing software. Such unauthorized installation may cause instability of the operating system or introduce other unwanted consequences. Many operating systems allow procedures to restrict certain users from installing software.

BAP.11600 Public Network Security **Phase II**

If the facility uses a public network, such as the Internet (including email) as a data exchange medium, there are adequate network security measures in place to ensure confidentiality of patient data.

NOTE: Information sent over a public domain such as the Internet is considered in the public domain. Thus it is potentially accessible to all parties on that network. Systems must be in place to protect network traffic, such as "fire walls" and data encryption schemes.

Evidence of Compliance:

✓ Written policy defining mechanism for data protection

DATA RETRIEVAL AND PRESERVATION

Inspector Instructions:

- Data preservation policies and procedures
- Audit logs detailing users and system changes

BAP.11700 Data/Services Protection **Phase II**

Data and services are protected from loss.

NOTE: Policies and procedures must:

1. *Be adequate to address scheduled and unscheduled interruptions of power or function*
2. *Be tested periodically for effectiveness*
3. *Include systems to backup programs and data*
4. *Include a written plan.*

The performance of the data protection can be performed by in-house staff or by a subcontractor, e.g. documented by a paid invoice.

BAP.11800 Data Input ID **Phase II**

There is an adequate system to identify all individuals who have entered and/or modified data or control files.

NOTE: When data is entered, the system must provide an audit trail to document each

person involved.

REFERENCES
1) Jones JB. The importance of integrating POCT data into an organized database. *Advance/Laboratory*. 1999;8(9):8-10
2) Halpern NA, Brentjens T. Point of care testing informatics. The critical care-hospital interface. *Crit Care Med.* 1999;15:577-591

BAP.11900 Archived Data **Phase II**

Access to archived data, including all data relevant to the biospecimens through the original reports is readily available.

NOTE: Stored data and archival information must be easily and readily retrievable within a time frame consistent with research needs.

BAP.12000 Data Preservation/Destructive Event **Phase II**

There are documented procedures for the preservation of data and equipment in case of an unexpected destructive event (*e.g.* fire, flood), software failure and/or hardware failure, and these procedures allow for the timely restoration of service.

NOTE: These procedures can 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 participant information. Changes to hardware and software commonly require review and re-evaluation of these documented procedures. These procedures must specifically address the physical environment and equipment. This checklist requirement is often addressed by the organization's disaster plan.

REFERENCES
1) Valenstein P, *et al*. Laboratory computer availability. A College of American Pathologists Q-Probes study of computer downtime in 422 institutions. *Arch Pathol Lab Med.* 1996;120:626-632

INTERFACES

Inspector Instructions:

	• Interface systems policies and procedures • Sampling of reports transmitted to each interfaced system
	• How does your facility verify the accuracy of data transmission to interfaced systems?

BAP.12100 Interface Security **Phase II**

If data in other computer systems can be accessed through the biorepository system, there are documented policies to prevent unauthorized access to that data.

BAP.12200 Interface Result Integrity **Phase II**

There is a procedure to verify that data are accurately transmitted from the point of data entry to reports (whether paper or electronic).

NOTE: Verification must be performed prior to implementation of an interface (i.e. pre go-live), and every two years thereafter. This includes evaluation of data transmitted to other computer systems and their output devices.

Verification of accurate data transmission to other systems must be performed by reviewing data in the first downstream (or interfaced) system. This requirement can be met by printing screen shots or by other methods that document that a verification procedure has been performed. At implementation of a new interface, or change to an existing interface, validation of at least two examples of reports satisfies the intent of this checklist requirement.

Evidence of Compliance:

✓ Records of verification

REFERENCES
1) Cowan DF, *et al*. Validation of the laboratory information system. *Arch Pathol Lab Med.* 1998;122:239-244

BAP.12300 Interface Shutdown/Recovery **Phase II**

There are procedures for changes in processes necessary during partial or complete shutdown and recovery of systems that interface with the information system.

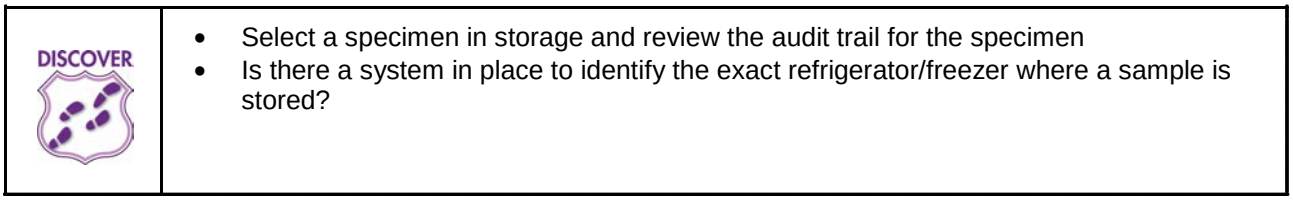
NOTE: These procedures must ensure integrity of data. Procedures must include verifying recovery of interfaced systems, and replacement or updating of data files, as necessary.

REFERENCES
1) Valenstein P, *et al.* Laboratory computer availability. A College of American Pathologists Q-Probes study of computer downtime in 422 institutions. *Arch Pathol Lab Med.* 1996;120:626-632

INVENTORY SYSTEM

Inspector Instructions:

	• Records of system privilege levels for employees • Records of inventory system audits • Inventory tracking criteria • Sampling of sample distribution records
	• Sample being removed from inventory • Use of inventory tracking criteria • Sample being placed into inventory • Labeling of specimens with a unique identifier/code
	• How are privilege levels assigned for the inventory system? • What is the process if a sample entered into the inventory system cannot be located? • What are you looking for when performing a sample pre-distribution quality check?



BAP.12500 Inventory Process **Phase II**

There is a documented inventory management process.

NOTE: Privilege levels should be set for performing specific functions in the system and for access to specific data.

Evidence of Compliance:

✓ Documentation of each person's level of access

BAP.12600 Computer-Based Inventory System Privileges **Phase II**

If the inventory system is computer-based, the system is controlled by assigning privilege levels to the biorepository staff.

BAP.12700 Computer-Based Inventory System Verification/Audits **Phase II**

If a computer-based inventory system is used, it has been verified and is subject to regular quality assurance audits.

NOTE: Frequency of the audits is determined by the director.

*****REVISED**** ***07/29/2013***

BAP.12800 Inventory System Tracking Criteria **Phase II**

The inventory system tracks, as applicable:

1. **Unique identifier**
2. **Study and study participant identifier**
3. **Visit identifier, if applicable**
4. **Specimen material type**
5. **Preservatives/additives/preservation methods**
6. **Specimen *parent/child* relationship, if applicable**
7. **Specimen vial type**
8. **Specimen volume**
9. **Date/time of collection**
10. **Date/time of receipt into inventory**
11. **Date/time of processing**
12. **Date/time and location of distribution**
13. **Number of thaws**
14. **Number of times sent previously for testing, if applicable**
15. **Condition warnings (e.g. partially frozen upon receipt, micro-clots present, frozen sideways, or any other relevant exceptions to the SOP)**
16. **Clinical data, as applicable**
17. **Biospecimen status (*e.g.* reserved or available)**
18. **Clinical collection site identifier, if applicable**

NOTE: If clinical data is not stored at the biorepository in the inventory tracking system,

there is a method for linking the physical spec with the clinical information, as needed.

Information regarding some of these elements may not be available to the biorepository for all biospecimen collections, especially those that were procured before recent best practices for biorepositories were published or for legacy collections.

BAP.12900 Inventory System Audit Trail Criteria **Phase II**

The inventory system includes a full audit trail of changes made to the database to include:

1. **Original date**
2. **Changed date**
3. **Identity of who made the change**
4. **Reason for change**
5. **What was changed**
6. **How the change was made**

BAP.12950 Specimen Quantity Warnings **Phase II**

If required by the sponsor, there is a mechanism in place to ensure minimum vial and minimum volume warnings are triggered before quantities fall below collection specified quantities.

NOTE: The warning mechanism may be either manual or automated. The intent of the requirement is inventory based.

BAP.13000 Inventory System Distribution Records **Phase II**

The inventory system keeps full records for specimens after distribution.

BAP.13100 Environmental Storage Areas Identifiers **Phase II**

Environmental storage areas (*e.g.* freezers and refrigerators) have their own unique identifier that includes a defined convention for numbering shelves, racks, boxes, and the location within each container.

BAP.13200 Shipment Acceptance Confirmation **Phase II**

Recipients are notified before shipping to ensure that appropriate personnel are available to receive the shipment.

BAP.13300 Shipping Tracking Criteria **Phase II**

Tracking information for shipment of specimens includes the following, as applicable.

1. **Invoice/tracking number**
2. **Recipient/source**
3. **Date of shipment or receipt**
4. **Courier name and ID# for each package**
5. **Sample description**

6. **Number of samples shipped/received**
7. **Study name/number**
8. **Shipping conditions (*e.g.* dry ice, ambient temperature)**
9. **Key investigators identification**
10. **Confirmation of receipt**
11. **Any discrepancies from manifest and actual shipment**
12. **Specimen damage**

BAP.13400 Specimen/Shipping Manifest Linkage **Phase II**

Specimens are labeled with a unique identifier and/or code.

NOTE: The intent of this requirement is to ensure that specimens arrive with accurate manifest of the contents of the shipping container.

BAP.13500 Reconciliation of Discrepancies **Phase II**

When specimens are retrieved from storage, any discrepancies found are documented and reconciled prior to distribution.

BAP.13600 Pre-Distribution QC **Phase II**

A quality check is performed prior to distribution.

NOTE: Quality checks may include, but are not limited to, gross observations, labeling accuracy, condition of specimens, weight, and verification that storage temperature is appropriate for the shipping temperature.

BAP.13700 Missing Specimen - Inventory Update **Phase II**

If a specimen is missing, inventory is updated to reflect that the specimen cannot be located.

RECORDS AND DISPOSITION

Inspector Instructions:

- Policy for record retention
- Policy for disposition of specimen and data
- Sampling of disposition records from the last 2 year period

NEW *04/21/2014*

BAP.13740 Record Retention **Phase II**

The biorepository must have a policy that specifies the length of time in which all records, paper and/or electronic, are retained.

NOTE: The length of time will depend on the nature of the record and is determined by the biorepository. The records include, but are not limited to, equipment maintenance and

repair records, clinical and patient information, and records pertaining to closed collections.

BAP.13750 Disposition of Specimens, Data and Regulatory Documents **Phase II**

There is a policy consistent with the regulations that govern the biorepository for the disposition of specimens, data, and related regulatory documents.

NOTE: Reasons for disposition may include, but are not limited to:

1. *Transfer or termination of collection*
2. *End of funding period*
3. *Depletion of the biospecimen*
4. *Research participant's request for discontinuation*
5. *Informed consent issues*
6. *IRB issues*
7. *Discrepancies between any clinical data and specimens*
8. *Quality of the physical specimen (e.g. insufficient fixation or processing, hemolysis)*

SOURCE FACILITY

If the biorepository is not the source, the requirements under the Source Facility section are not applicable.

Inspector Instructions:

	• Sampling of protocol procedures • Sampling of record content when the biorepository is the sponsor • Sampling of source facility procedures • Sampling of collection site audits, when the biorepository is the sponsor
	• The QC process for specimens received from collection sites not under the control of the biorepository
	• How do you ensure the quality of specimens from collection sites not under the control of the biorepository? • When the biorepository is the collection sponsor, who conducts the audits, how are the audits documented and who ensures corrective action is appropriate when needed?

BAP.13800 Biorepository/Source Facility Responsibilities **Phase II**

The responsibilities between the biorepository and the source facility(ies) are clearly documented and available during the inspection, and reviewed by the biorepository within the last 24 months.

BAP.13900 Protocols **Phase II**

There is/are documented protocol(s) describing methods for participant identification, participant education, specimen collection and labeling, specimen preservation, and conditions for transportation, and storage before testing, consistent with good clinical practice and good laboratory practice, when applicable.

NOTE: All specimens must be labeled with a unique identifier and sufficient quality control practices must be in place to ensure appropriate linkage of that identifier to the participant. Protocols may be separate documents or included in the procedure manual.

BAP.13950 Source Facility Procedure Manual **Phase II**

The procedure manual is comprehensive and includes information on the following elements, as applicable to the scope of the biorepository.

1. **Informed consent**
2. **Equipment monitoring, calibration, maintenance, and repair**
3. **Control of biospecimen collection supplies (disposable and reagents)**
4. **Biospecimen identification and labeling conventions**
5. **Biospecimen collection and processing methods**
6. **Storage and retrieval**
7. **Shipping and receiving**
8. **Laboratory tests performed in-house including biospecimen QC**
9. **Biospecimen data collection and management (informatics)**
10. **Biosafety**
11. **Training**
12. **Security**

NOTE: A copy of the procedure manual would enable the sponsor to ensure that best practices are being followed.

BAP.14100 Remote/Collection Sites QC **Phase I**

There is a documented system to monitor the quality of specimens and associated documentation received from remote sites and collection sites not under the control of the biorepository.

BAP.14200 Remote Site Contact Information **Phase I**

Contact information for remote sites should be readily available to personnel at all times to resolve discrepancies or other issues that may arise.

NOTE: This may include active phone numbers, email, etc.

SPONSOR FACILITY

If the biorepository is not the sponsor, the requirements under the Sponsor Facility section are not applicable.

BAP.14220 Registration/License **Phase I**

If the biorepository is the primary requestor/sponsor for the specimen collection, the biorepository ensures that all source facilities are registered, licensed, and accredited as required by state, and federal regulations, and appropriate for the study.

BAP.14230 Record Content for Sponsor Facility **Phase II**

If the biorepository is the sponsor for collections, the biorepository keeps a record of the following for each contributing site, as applicable.

1. **Principal investigator (PI)**
2. **Protocol number**
3. **Protocol title**
4. **Protocol version date**
5. **Informed consent**
6. **Informed consent version date**
7. **Study expiration date**
8. **Approval of the above by Institutional Review Board**
9. **Principal investigator signature for Protocol and version against approval letter**
10. **Signature and delegation list for employees responsible of consenting patients, sample transport, clinical data, sample processing, manifesting of samples, and coordination of shipments**
11. **Curriculum vitae of principle investigator**
12. **License or diploma (for non-US sites) of PI**
13. **Governmental approval as required for each participating site**

BAP.14240 Contributing Sites Audits **Phase II**

If the biorepository is the sponsor for collections, the regulatory staff at the biorepository performs scheduled audits of contributing sites.

NOTE: The scope of the audit is defined by the activities of the contributing facility. The type of audit (onsite, paper, etc.) and the timeframe are determined by the biorepository.

Evidence of Compliance:

✓ Written procedures for auditing eternal collection sites **AND**
✓ Written results of each audit **AND**
✓ Corrective action plans for issues of non-compliance and follow up on each plan

INFORMED CONSENT AND INSTITUTIONAL REVIEW BOARD

This section applies to human subjects research only.

Inspector Instructions:

	• Privacy and confidentiality policies and procedures • Informed consent criteria

	
	• What action is taken if a sample is received without the proper informed consent documentation? • How do you ensure that the proposed use of human tissue is consistent with the informed consent?
	• Select a specimen in storage and review that the proper informed consent documentation is complete

BAP.14600 Informed Consent Criteria **Phase II**

Mechanisms are in place to ensure that the proposed uses of human tissue with or without data shared for research purposes are consistent with the informed consent and scope of services, when applicable.

NOTE: There are some instances when informed consent and/or waiver of consent are not applicable (e.g. non-human specimens).

Evidence of Compliance:

✓ Document outlining the mechanism

BAP.14700 Required Approval(s) Documentation **Phase II**

When human specimens are to be collected, all of the required approvals (*e.g.* IRB or other ethics committees) have been documented and appropriate patient consent processes are complete.

NOTE: The only exception to this is when there has been a waiver of consent.

BAP.14800 Informed Consent Documentation **Phase II**

Informed consent documentation is obtained for the collection, storage, distribution, and use of identifiable human specimens and data.

NOTE: The only exception to this is when there has been a waiver of consent.

BAP.14900 Waiver of Consent **Phase II**

A waiver of consent, in accordance with applicable laws and/or requirement and approved by the institution's ethics review committee, is obtained when informed consent documentation is not obtained/required.

BAP.15000 **Biospecimen/Data Usage** **Phase II**

Processes are in place to ensure that the proposed use of the biospecimen/data is within the guidelines of the project and of the informed consent, when applicable.

BAP.15100 **Privacy/Confidentiality** **Phase II**

Policies and procedures are in place to ensure the privacy and confidentiality of the patient/donor.

BAP.15200 **Procedures Available for Review** **Phase II**

The biorepository's procedures for human specimen collection, processing, storage, and dissemination are available for ethics committee and/or IRB review, as needed.

DISTRIBUTION POLICIES AND AGREEMENTS

Inspector Instructions:

	• Sampling of material transfer agreements (MTAs) • End-user distribution policy
	• Who ensures that the MTA includes all the required information? • Describe the MTA process

BAP.15300 **Material Transfer Agreements Criteria** **Phase II**

Material transfer agreements (MTAs) define the rights and obligations of the provider (biorepository) and recipient (researcher), including allowable uses for the specimen and/or data once transferred.

BAP.15400 **MTA Areas Covered** **Phase II**

The MTA addresses each of the following areas as applicable.

1. **Future distribution of modifications and derivations made by the recipient**
2. **Documentation of each participant's role in the modifications or derivations**
3. **Terms of confidentiality**

BAP.15500 End-User Distribution Policy Criteria **Phase II**

The distribution policy includes confirmation that the end-user has IRB approval or there is an MTA in place that provides relevant assurance for the appropriate use of the specimen according to appropriate ethical and legal requirements.

Evidence of Compliance:

✓ Copies of IRB approvals from end-users **OR** copies of MTA agreements