



## Biorepository Checklist

CAP Accreditation Program



**Disclaimer and Copyright Notice**

CAP inspections are performed with the edition of the Checklists mailed to a facility at the completion of the application or reapplication process, not necessarily those currently posted on the website. The checklists undergo regular revision and a new edition may be published after the inspection materials are sent.

For questions about the use of the Checklists or Checklist interpretation, email [accred@cap.org](mailto:accred@cap.org) or call 800-323-4040 or 847-832-7000 (international customers, use country code 001).

The Checklists used for inspection by the College of American Pathologists' Accreditation Programs have been created by the CAP and are copyrighted works of the CAP. The CAP has authorized copying and use of the checklists by CAP inspectors in conducting laboratory inspections for the Council on Accreditation and by laboratories that are preparing for such inspections. Except as permitted by section 107 of the Copyright Act, 17 U.S.C. sec. 107, any other use of the Checklists constitutes infringement of the CAP's copyrights in the Checklists. The CAP will take appropriate legal action to protect these copyrights.

All Checklists are ©2024. College of American Pathologists. All rights reserved.

# Biorepository Checklist



## TABLE OF CONTENTS

<b>SUMMARY OF CHANGES.....</b>	<b>4</b>
<b>INTRODUCTION.....</b>	<b>6</b>
<b>DEFINITION OF TERMS.....</b>	<b>6</b>
<b>BIOSPECIMEN COLLECTION AND HANDLING.....</b>	<b>8</b>
SPECIMEN COLLECTION AND HANDLING.....	8
INFORMED CONSENT AND INSTITUTIONAL REVIEW BOARD.....	13
SOURCE FACILITY.....	14
SPONSOR FACILITY.....	15
<b>BIOSPECIMEN PROCESSING AND QUALITY.....</b>	<b>17</b>
BIOSPECIMEN QUALITY.....	17
DNA/RNA EXTRACTION/AMPLIFICATION.....	20
CELL FRACTIONATION.....	23
CELL AND TISSUE CULTURE.....	25
HISTOLOGY.....	27
<b>SPECIALIZED TECHNIQUES.....</b>	<b>36</b>
WHOLE SLIDE IMAGING.....	36
DIGITAL IMAGE ANALYSIS (DIA).....	36
VALIDATION AND CALIBRATION (DIA).....	37
QUALITY CONTROL.....	37
SPECIMEN ANALYSIS.....	39
PERSONNEL.....	39
TISSUE MICROARRAY (TMA).....	40
LASER CAPTURE MICRODISSECTION (LCM).....	42
MOLECULAR METHODS.....	43
ELECTROPHORESIS.....	43
TARGET AMPLIFICATION/POLYMERASE CHAIN REACTION (PCR).....	44
IN SITU HYBRIDIZATION (ISH).....	45
<b>INSTRUMENTS AND EQUIPMENT.....</b>	<b>47</b>
<b>STORAGE.....</b>	<b>52</b>
TEMPERATURE DEPENDENT STORAGE EQUIPMENT.....	52
TEMPERATURE MONITORING AND ALARMS.....	55
<b>INVENTORY MANAGEMENT SYSTEM.....</b>	<b>58</b>
INVENTORY.....	58
SAMPLE MANAGEMENT.....	60
RECORDS.....	61
DISTRIBUTION POLICIES AND AGREEMENTS.....	62

## ON-LINE CHECKLIST DOWNLOAD OPTIONS

Participants of the CAP accreditation programs may download the checklists by logging into cap.org and going to e-LAB Solutions Suite - Accreditation Checklists. 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.

## CHECKLIST ACCREDITATION RESOURCES

CAP accredited laboratories have access to additional checklist accreditation tools and resources found on the CAP website (cap.org) by logging into e-LAB Solutions Suite - Accreditation Resources. Content found in Accreditation Resources includes:

- A library of past Focus on Compliance webinars and laboratory inspection preparation videos
- Answers to the most common checklist questions
- Customizable templates and forms (eg, competency assessment, personnel, validation/verification, quality management)
- Proficiency testing (PT) frequently asked questions, forms, and troubleshooting guides
- IQCP eligibility, frequently asked questions, forms, templates, and examples
- Laboratory director education and resources
- Quality management resources
- Inspector training and inspection tip sheets
- Self and post inspection toolbox

## SUMMARY OF CHECKLIST EDITION CHANGES

### Biorepository Checklist

### 12/26/2024 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 requirements listed below are from the Master version of the checklist. The customized checklist version created for inspections and self-evaluations may not list all of these requirements.*

### Previously Cited Checklist Requirements

- The **inspector's version** of the checklist contains a listing of previously cited checklist requirements. Specific information on those citations, including the inspection date and inspector comments, is included following each related requirement within the checklist.
- Laboratories can access data on previously cited deficiencies by logging into e-LAB Solutions Suite on cap.org and going to Accreditation Reports - Inspection Summation Report.

NEW Checklist Requirements

<u>Requirement</u>	<u>Effective Date</u>
BAP.05350	12/26/2024

REVISED Checklist Requirements

<u>Requirement</u>	<u>Effective Date</u>
BAP.05324	12/26/2024
BAP.05348	12/26/2024
BAP.05360	12/26/2024
BAP.06780	12/26/2024
BAP.06856	12/26/2024
BAP.08600	08/24/2023
BAP.09600	08/24/2023

DELETED/MOVED/MERGED Checklist Requirements

<u>Requirement</u>	<u>Effective Date</u>
BAP.07610	08/23/2023
BAP.07620	08/23/2023

## INTRODUCTION

*A biorepository is defined as an entity that collects, processes, stores, manages, and/or distributes biospecimens, their derivatives and relevant data, as needed, for research purposes. It encompasses the physical location as well as the full range of activities associated with its operation. The term biorepository used within the checklist may be considered synonymous with biobank and repository.*

*The term laboratory may also be used to describe a biorepository. When the term "patient" is used within the checklist, it may also refer to donors, clients, and study participants.*

*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 recorded.*



*Policy/Procedure icon - The placement of this icon next to a checklist requirement indicates that a written policy or procedure is required to demonstrate compliance with the requirement. The icon is not intended to imply that a separate policy or procedure is required to address individual requirements. A single policy or procedure may cover multiple checklist requirements.*

**Laboratories not subject to US regulations:** *Checklist requirements apply to all laboratories unless a specific disclaimer of exclusion is stated in the checklist. When the phrase "FDA-cleared/approved test (or assay)" is used within the checklist, it also applies to tests approved by an internationally recognized regulatory authority (eg, CE-marking).*

*References used in the development of this checklist were the CAP Accreditation Checklists, 2023 ISBER \* Best Practices for Repositories, and the NCI Best Practices for Biospecimen Resources.*

*\*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 (ie, 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.

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

**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).

**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.

**Pathologist** - A physician who has successfully completed an approved graduate medical education program in pathology.

In the US, a physician is defined as a doctor of medicine, doctor of osteopathy, or doctor of podiatric medicine who is licensed by the state to practice medicine, osteopathy, or podiatry within the state in which the laboratory is located. In jurisdictions not subject to US regulations, a physician is defined as an individual who has a primary medical school degree (eg, MBBS, MBChB, MD, DO) in keeping with the standards of that particular jurisdiction.

**Qualified pathologist** - A pathologist who has training in the specific functions to be performed (eg, an anatomic pathologist for anatomic pathology functions, a clinical pathologist for clinical pathology functions, or an anatomic pathologist or dermatopathologist for skin biopsies).

**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 recording any corrective 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.

**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, (eg, when the biorepository does blood or specimen collections for normal controls).

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

**Sponsor** - The person, organization or biorepository that seeks and is responsible for the initiation, maintenance, and governance of the biospecimen collection. The sponsor typically provides the financial support to create and maintain the collection.





NOTE: This could include: 1) a sponsor-investigator (such as a pharmaceutical company seeking samples for an internal research project or as part of a multi-site clinical trial); 2) a biobank seeking biosamples to fulfill the needs of its research clients; 3) a cooperative oncology group that sets criteria (such as disease type, specific samples required, accompanying medical data, informed consent specifications) for inclusion into a biobank and that cooperative oncology group confirms all criteria have been met (directly or through a contracted biobank) before submitted samples are accepted into the biobank.

## BIOSPECIMEN COLLECTION AND HANDLING

### SPECIMEN COLLECTION AND HANDLING

*The collection and handling for all biospecimens is critical to the overall quality and diversity of the sample inventory.*

#### Inspector Instructions:

	<ul style="list-style-type: none"> <li>• Sampling of policies and procedures for sample collection and handling, including sample types, samples with potentially infectious materials, preservation, de-identifying or anonymizing, aliquoting, specimen storage conditions, and chain-of-custody</li> <li>• Policy for the type of samples suitable for submission to the biorepository</li> <li>• Storage temperature records</li> <li>• Sampling of biospecimen QA reports for key elements of processing and preservation of solid and fluid specimens</li> <li>• Records of informed consent and IRB releases</li> </ul>
	<ul style="list-style-type: none"> <li>• Sampling of stored specimens for temperatures required by protocols</li> <li>• If collection occurs on-site, observe the processing/preservation procedure</li> <li>• Specimen storage conditions during sample receipt</li> </ul>
	<ul style="list-style-type: none"> <li>• How does your biorepository capture variables that could impact biospecimen usage?</li> <li>• How/when would the biorepository communicate pre-analytic variables to researchers?</li> <li>• How do you ensure accuracy of pre-analytic data capture?</li> <li>• What is your specimen coding system for sample identification?</li> <li>• How do you confirm patient consent prior to processing and banking?</li> <li>• What do you do if the sample size is too small relative to the requirements or it does not meet researchers' needs?</li> <li>• Do you receive specimens considered infectious biological agents from outside the United States?</li> </ul>
	<ul style="list-style-type: none"> <li>• Follow a tissue sample released for research from the pathologist to storage</li> </ul>





**The biorepository defines the types of specimens submitted based on the following:**

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

*NOTE: This 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) Department of Health and Human Services. Biosafety in Microbiological and Biomedical Laboratories, 6th ed. June 2020.

### **BAP.01700 Collection/Processing Oversight**

**Phase II**

**A pathologist or designee assigned to the management of the biospecimens ensures that collection policies and processes 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) International Society for Biological and Environmental Repositories (ISBER). ISBER best practices recommendations for repositories. 5th ed. ISBER; 2023.

### **BAP.01703 Disease Control Import Permit**

**Phase II**

**If the biorepository receives specimens that are considered infectious biological agents imported from outside of the United States and its territories, the biorepository has obtained the Centers for Disease Control Import Permit.**

*NOTE: The Office of Public Health Preparedness and Response CDC Import Permit Program regulates the importation of the following into the United States:*

- *Naturally occurring or bioengineered infectious biological agents capable of causing disease in a human;*
- *Any material that is known or reasonably expected to contain an infectious biological agent;*
- *Vectors, including animals/animal products that are known to transfer or are capable of transferring an infectious biological agent to a human.*

*If the material being imported is rendered sterile (eg, thermal, chemical or irradiation treatment) or it has been confirmed not to contain infectious agents for humans, a CDC-issued import permit is not required for importation. Information, guidance documents, and resource materials may be found on the following website: <http://www.cdc.gov/import-permit-program/php/index.html>. The application may be obtained from <http://www.cdc.gov/import-permit-program/php/eipp/index.html>.*

### **BAP.01704 Chain-of-Custody Procedures**

**Phase II**



**The biorepository follows a defined process for chain-of-custody specimen collection, accessioning, and handling.**

*NOTE: If specimens are referred to another laboratory, the collection site must follow chain-of-custody instructions provided by the referral laboratory.*

## REFERENCES

- 1) Clinical and Laboratory Standards Institute (CLSI). *Toxicology and Drug Testing in the Medical Laboratory*. 3rd ed. CLSI guideline C52. Clinical and Laboratory Standards Institute, Wayne, PA; 2017.

**BAP.01706 Biospecimen Chain of Custody****Phase II**

**The biorepository has a system to track biospecimen chain of custody.**

*NOTE: Chain of custody is used to maintain the integrity of the biospecimen by providing records of the control, transfer, and analysis of biospecimens.*

*The intent of this requirement is to have a system in place to ensure adequate records of the "life history" of the biospecimen. Chain of custody provides a traceable record that guarantees unbroken control over biospecimens and its containers from initial collection to final disposition. This is achieved with accurate and effective labeling, tracking and reporting.*

*Chain of custody requires that from the moment the biospecimen is received every transfer between departments be recorded.*

**Evidence of Compliance:**

- ✓ Logs or message boards showing specimen movement through biorepository **AND**
- ✓ Work flow diagrams

**BAP.01709 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 national, federal, state (or provincial), 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.

**BAP.01712 De-identification for Research****Phase II**

**For specimens that are released for research, the biorepository follows a defined process for de-identifying/blinding or anonymizing specimens without compromise to research-related demographic information, when required.**

**BAP.01715 Coding****Phase II**

**There is a defined coding system for sample identification.**

**BAP.01718 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.01721 IRB Release Phase II**

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

**BAP.01722 Specimen Handling Phase II**

**Specimens are handled in a manner that prevents specimen loss, alteration, or contamination.**

*NOTE: Because of the high sensitivity and potential for contamination in molecular testing involving amplification of DNA, the biorepository must be alert to the possibility of commingled specimens. An example of a potentially commingled specimen is one that is received after the specimen container was entered by a sampling device that enters multiple samples, albeit with rinses in between specimens. If such samples must be tested by molecular methods, the results should be interpreted with caution, considering the potential for contamination.*

**REFERENCES**

- 1) Clinical and Laboratory Standards Institute (CLSI). *Establishing Molecular Testing in Clinical Laboratory Environments*: CLSI document MM19-A (ISBN 1-56238-773-1). Clinical and Laboratory Standards Institute, 940 West Valley Road, Suite 1400, Wayne, Pennsylvania 19087-1898 USA, 2011.
- 2) Compton CC, Robb JA, Anderson MW, et al. Preanalytics and Precision Pathology: Pathology Practices to Ensure Molecular Integrity of Cancer Patient Biospecimens for Precision Medicine. *Arch Pathol Lab Med*. 2019;143(11):1346-63.

**BAP.01724 Specimen Collection/Handling Protocol Phase II**

**Collection, processing, and storage times are recorded, 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 (eg, fixed, cooled, or frozen).*

**BAP.01727 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 (ie, 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.01730 Processing/Preservation - Solid Specimens Phase II**

**The key elements related to the processing and preservation of solid specimens are recorded 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 (eg, 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.01733 Processing/Preservation - Fluid Biospecimens

Phase II

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

*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 (ie, 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.

### BAP.01734 Specimen Processing/Storage

Phase II



**Specimens are processed promptly or stored appropriately to minimize degradation of nucleic acids.**

#### REFERENCES

- 1) Farkas DH, Kaul KL, Wiedbrauk DL, *et al*. Specimen Collection and Storage for Diagnostic Molecular Pathology Investigation. *Arch Pathol Lab Med*. 1996;120:591-596
- 2) Kiechle FL, Kaul KL, Farkas DH. Mitochondrial Disorders: Methods and Specimen Selection for Diagnostic Molecular Pathology. *Arch Pathol Lab Med*. 1996;120:597-603
- 3) Farkas DH, Drevon AM, Kiechle FL, *et al*. Specimen Stability for DNA-based Diagnostic Testing. *Diag Molec Pathol*. 1996;5(4):227-235
- 4) Rainen L, *et al*. Stabilization of mRNA expression in whole blood samples. *Clin Chem*. 2002;48:1883-1890
- 5) Pahl A, Brune K. Stabilization of gene expression profiles in blood after phlebotomy. *Clin Chem*. 2002;48:2251-2253
- 6) Clinical and Laboratory Standards Institute (CLSI). *Collection, Transport, Preparation, and Storage of Specimens for Molecular Methods*. 2nd ed. CLSI guideline MM13. Clinical and Laboratory Standards Institute, Wayne, PA; 2020.
- 7) Compton CC, Robb JA, Anderson MW, *et al*. Preanalytics and Precision Pathology: Pathology Practices to Ensure Molecular Integrity of Cancer Patient Biospecimens for Precision Medicine. *Arch Pathol Lab Med*. 2019;143(11):1346-63.

### BAP.01736 Specimen Storage Conditions

Phase II



**The biorepository has defined storage conditions for the different specimens handled and a protocol for the return of each specimen type to storage after issuance for use, as appropriate.**

#### Evidence of Compliance:

- ✓ Records of storage conditions **AND**
- ✓ Records of return of specimens to storage

### BAP.01739 Specimen Storage Temperature

Phase II




**Records show that specimens were stored at the protocol-required temperatures.**

*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.*

## INFORMED CONSENT AND INSTITUTIONAL REVIEW BOARD

*This section applies to human subjects research only.*

### Inspector Instructions:

	<ul style="list-style-type: none"> <li>• Privacy and confidentiality policies and procedures</li> <li>• Informed consent criteria</li> <li>• Waiver of Consent criteria</li> </ul>
	<ul style="list-style-type: none"> <li>• What action is taken if a sample is received without the records of proper informed consent?</li> <li>• How do you ensure that the proposed use of human tissue is consistent with the informed consent?</li> </ul>
	<ul style="list-style-type: none"> <li>• Select a specimen in storage and review that the proper informed consent records are complete</li> </ul>

#### BAP.01742 Informed Consent Criteria

Phase II



**The biorepository ensures 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 (eg, non-human specimens).*

#### BAP.01745 Required Approval(s) Records

Phase II

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

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

#### BAP.01748 Informed Consent Records

Phase II



**Informed consent records are 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.01751 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 is not obtained/required.**

**BAP.01754 Biospecimen/Data Usage Phase II**



**The biorepository ensures that the proposed use of the biospecimen/data is within the guidelines of the project and of the informed consent, when applicable.**

**BAP.01757 Privacy/Confidentiality Phase II**



**The biorepository ensures the privacy and confidentiality of patients/donors and their data.**

**BAP.01760 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.**

## SOURCE FACILITY

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

### Inspector Instructions:

	<ul style="list-style-type: none"> <li>• Sampling of protocol procedures</li> <li>• Sampling of record content when the biorepository is the sponsor</li> <li>• Sampling of source facility procedures</li> <li>• Sampling of collection site audits when the biorepository is the sponsor</li> </ul>
	<ul style="list-style-type: none"> <li>• The QC process for specimens received from collection sites not under the control of the biorepository</li> </ul>
	<ul style="list-style-type: none"> <li>• How do you ensure the quality of specimens from collection sites not under the control of the biorepository?</li> <li>• When the biorepository is the collection sponsor, who conducts the audits, how are the audits recorded, and who ensures corrective action is appropriate when needed?</li> </ul>

**BAP.01763 Biorepository/Source Facility Responsibilities Phase II**

**The responsibilities between the facility(ies) and its sponsor are clearly defined in writing, reviewed by the biorepository within the last 24 months, and available during the inspection.**

**BAP.01766 Protocols****Phase II**

**The biorepository follows protocols 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.01769 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.01772 Off-site Contact Information****Phase I**

**Contact information for off-site collection sites is 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**

*The requirements under the Sponsor Facility section are applicable only if the biorepository is the sponsor.*

*If the biorepository initiated the collection, the biorepository is the sponsor and the following requirements are applicable. If an entity other than the biorepository initiated the collection, the biorepository is not the sponsor and the requirements below do not apply to those collections. It is possible that the biorepository will be the sponsor for some collections, but not others.*

**BAP.01775 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 national, federal, state (or provincial), and local regulations, and appropriate for the study.**



**BAP.01778 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 for obtaining consent from 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.01781 Off-site Collection Sites QC****Phase I**

The biorepository monitors the quality of specimens and associated records received from off-site collection sites not under the direct control of the sponsor facility following a defined process approved by the biorepository director.

*NOTE: The sponsor facility should perform an annual review of off-site collection QA/QC data as part of their quality management system.*

**BAP.01784 Contributing Sites Audits****Phase II**

If the biorepository is the sponsor for collections, the biorepository performs audits of contributing sites at defined frequencies.

*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.*

*The audit is part of the sponsor facility's QC procedures to ensure contributing/collection sites are following protocols and procedures appropriately. Records required to ensure protocols and procedures are being followed should be checked and those checks recorded as part of the audit. CAP inspectors should be able to understand from audit records that policies and procedures are being followed by the contributing/collection site and monitored by the sponsor biorepository. If the contributing/collection sites are located outside of the United States, audit records should be in English and also in the official native language(s) of the contributing/collection site country.*

**Evidence of Compliance:**

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







# BIOSPECIMEN PROCESSING AND QUALITY

## BIOSPECIMEN QUALITY

*The biorepository must have a written quality assessment process applicable to the scope of activities performed. This quality process should be capable of detecting, reducing and correcting any deviation from acceptable standards set by the biorepository. Examples may include enrollment in a proficiency testing program or using sets of testing control materials to check the biorepository samples over time.*

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

### Inspector Instructions:

	<ul style="list-style-type: none"> <li>• Sampling of policies and procedures for specimen processing including aliquoting, relabeling, and specimen retrieval</li> <li>• Sampling of records for the assessment of the quality of stored specimens</li> <li>• Specimen rejection criteria policy and records of rejection</li> </ul>
	<ul style="list-style-type: none"> <li>• Specimen processing area for clean environment</li> <li>• Aliquot sizes of specimens</li> <li>• Specimen identifiers</li> <li>• Specimen storage conditions during sample processing</li> <li>• Tracking of samples as they move from one station to another</li> <li>• Sampling of reagents (expiration date)</li> </ul>
	<ul style="list-style-type: none"> <li>• How does your biorepository maintain and track temperature excursion information?</li> <li>• Explain your quality assessment process for stored specimens</li> <li>• How is the risk of specimen misidentification monitored and the process improved?</li> <li>• What do you do if the sample size is too small relative to the requirements or it does not meet researchers' needs?</li> </ul>
	<ul style="list-style-type: none"> <li>• Follow a tissue sample released for research from the pathologist to storage, verifying specimen identification throughout the process</li> <li>• Select several specimens and follow their tracking throughout the life of the specimen, including from parent to child, etc.</li> </ul>

### BAP.01800 Quality Assessment of Stored Specimens

### Phase II



**The biorepository periodically assesses the quality of stored specimens for each class of biospecimens in the biorepository.**

*NOTE: The frequency of the checks may be determined by the following:*

1. Type of specimens being stored
2. Preservation method
3. Turnover of the material

*The form and frequency for the periodic assessment is to be defined by the biorepository. The assessment may take a variety of forms including direct observation of materials, sampling, integrity of records, enrollment in proficiency testing, or other alternate performance assessment.*

*The quality of stored specimens may be assessed at the time of disbursement.*

**Evidence of Compliance:**

- ✓ Records of inventory sampling **OR**
- ✓ Records of unsuitable specimens by collection, as applicable **OR**
- ✓ Records 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:**

- ✓ Records 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 Safe Handling of Specimens for Infectious Diseases**

**Phase II**



**The biorepository follows a defined process for receipt and management of potentially infectious material that includes application of standard precautions.**

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

**REFERENCES**

- 1) OSHA regulation 29CFR1910.1020.
- 2) Clinical and Laboratory Standards Institute. *Protection of Laboratory Workers From Occupationally Acquired Infections; Approved Guideline*. 4<sup>th</sup> ed. CLSI document M29-A4. Clinical and Laboratory Standards Institute, Wayne, PA; 2014.

**BAP.02500 Histological Characteristic Review**

**Phase II**



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

*NOTE: Histologic review of banked solid tissue biospecimens is important for the following reasons: 1) the review of banked solid tissue biospecimens ensures that well-annotated, high quality biospecimens will be utilized in downstream testing; and 2) the review of banked solid tissue biospecimens may be used to confirm diagnostic findings. The timing of the pathologists' histologic review is at the discretion of the biorepository director. There may be situations where the sponsor of the collection or the user arranges for pathology review outside of the biorepository. This should be recorded by the biorepository.*

#### **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 monitors the risk of misidentification and subjects the related processes 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.*

##### **Evidence of Compliance:**

- ✓ Occurrence records/error logs demonstrating appropriate review and follow-up of significant errors and patterns of errors in identification and other processes

#### **BAP.02800 Unique Identifier**

**Phase II**



**Each specimen received into the biorepository receives a unique identifier.**

#### **BAP.02900 Specimen Tracking Mechanism**

**Phase II**



**The biorepository maintains and tracks the identity of every specimen throughout the life of the specimen and its derivatives (eg, 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, processing, storage, and subsequent shipment from the biorepository.*

#### **BAP.03000 Specimen Rejection Criteria**

**Phase II**



**The biorepository follows defined criteria for specimen condition exceptions to be recorded and communicated to researchers regarding conditions that may 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 specimen on the report. For example, many semen specimens are sub-optimal; all specimens 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**

**The biorepository has a defined process 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) full de-identification; c) replacement of a label (eg, original label has fallen off).*

**Evidence of Compliance:**

- ✓ Records, including reason for relabeling

**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.*

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

**The biorepository has a process for paraffin embedding and/or fixation that includes quality checks at a defined frequency (eg, 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.*



**Evidence of Compliance:**

- ✓ Records of quality checks

## DNA/RNA EXTRACTION/AMPLIFICATION

### Inspector Instructions:

	<ul style="list-style-type: none"> <li>• Sampling of nucleic acid extraction and amplification policies and procedures</li> <li>• Sampling of nucleic acid measurement records</li> <li>• Records of nucleic acid integrity and purity assessment</li> <li>• Records of internal controls</li> <li>• Sampling of specimen processing, handling, aliquoting, and storage policies and procedures</li> </ul>
	<ul style="list-style-type: none"> <li>• Nucleic acid amplification procedures for proper physical containment and procedural controls to prevent carryover</li> <li>• Observe quantitation and quality control assessments</li> </ul>

	<ul style="list-style-type: none"> <li>• How is adequacy of nucleic acid isolation and preparation evaluated? How often is this done?</li> <li>• How does your laboratory ensure RNase-free conditions are maintained?</li> </ul>
	<ul style="list-style-type: none"> <li>• Follow a sample from extraction through storage</li> </ul>

**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, preparation of records, and storage.**

**BAP.04525 Extracted Nucleic Acid Specimens****Phase II**

**If extracted nucleic acid is accepted as a specimen type, the biorepository ensures that isolation of nucleic acids for clinical testing occurs in a CLIA-certified laboratory or a laboratory meeting equivalent requirements as determined by the CAP and/or the CMS. This policy is clearly displayed to ordering clients.**

*NOTE: All clinical testing must be performed in CLIA-certified laboratories or laboratories meeting equivalent requirements (refer to GEN.41350). This includes all components of testing that may impact the quality of the test result, including isolation or extraction of nucleic acids. Laboratories may choose to have referring clients formally attest that extracted nucleic acid submitted for testing has been isolated or extracted in an appropriately qualified laboratory.*

**Evidence of Compliance:**

- ✓ Written statement on the test requisition, test catalog, or policy available to referring clients stating that the laboratory only accepts isolated or extracted nucleic acids for which extraction or isolation is performed in an appropriately qualified laboratory

**BAP.04700 Nucleic Acid Extraction/Isolation/Purification****Phase II**

**Nucleic acids are extracted, isolated, and purified by methods reported in the literature, by an established commercially available kit or instrument, or by a validated method developed by the laboratory.**

*NOTE: The method should be assessed for its suitability for each source type that requires extraction. Any modification to established procedures must be recorded, as well as variations to procedures depending on anatomic site and biospecimen preservation format (eg, fresh frozen vs. OCT-embedded). Extraction procedures may combine purification or isolation of nucleic acids according to the level of purity needed for downstream applications.*

**Evidence of Compliance:**

- ✓ Records to support nucleic acid extraction/isolation/purification is performed by a validated method

**REFERENCES**

- 1) Clinical and Laboratory Standards Institute. *Establishing Molecular Testing in Clinical Laboratory Environments*: CLSI Document MM19-A. Clinical and Laboratory Standards Institute, Wayne, PA; 2011.
- 2) Clinical and Laboratory Standards Institute. *Genomic Copy Number Microarrays for Constitutional Genetic and Oncology Applications*. 1st ed. CLSI guideline MM21-ED1. Clinical and Laboratory Standards Institute, Wayne, PA, 2015.

**BAP.04800 Nucleic Acid Quantity and Quality Determination****Phase II**

**The quantity and quality of nucleic acids are determined, when appropriate.**

*NOTE: The quantity and quality of nucleic acids (DNA or RNA) must be measured prior to use in a procedure whose success depends on accurately determining the quantity, concentration, integrity, and/or purity of the nucleic acids. Techniques commonly used to assess nucleic acid quantity and/or quality include electrophoresis, UV/VIS spectrophotometry, and fluorescence spectroscopy.*

*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 agarose 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 recorded.*

**Evidence of Compliance:**

- ✓ Records of nucleic acid quantity and/or quality determination

**REFERENCES**

- 1) Tsui NBY, Ng EKO, Lo YMD. Stability of Endogenous and Added RNA in Blood Specimens, Serum and Plasma. *Clin Chem* 48:1647-1653, 2002
- 2) Farrell R. Gel electrophoresis based assessment of cellular RNA quality may also be used (RNA Isolation Strategies). In: RNA Methodologies: A Laboratory Guide for Isolation and Characterization. Academic Press, 1998
- 3) Clinical and Laboratory Standards Institute. *Diagnostic Nucleic Acid Microarrays: Approved Guideline*; CLSI Document MM12-A. Clinical and Laboratory Standards Institute, Wayne, PA; 2006.

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

**For paraffin-embedded tumor specimens from which DNA or RNA is extracted for analysis (eg, microsatellite instability, *KRAS* or *KIT* analysis), there is a record of histological assessment of neoplastic cell content.**

*NOTE: In addition to confirming the presence or absence of neoplastic cells by a qualified pathologist, it may be necessary for some assays to estimate and consider neoplastic cellularity in relation to the lower limit of detection of the assay.*

*A corresponding H&E section from the same tissue block used for nucleic acid extraction may be used to assess sample adequacy. Alternatively, a stain such as toluidine blue may be used to stain the slide that is being used for nucleic acid extraction. When assessment of sample adequacy is performed outside of the testing laboratory, a record of such assessment must accompany the sample.*

*This requirement is applicable to all molecular methods for the detection of sequence variants (eg, Sanger sequencing, NGS, PCR).*

**BAP.05125 Ribonuclease-Free Conditions****Phase I**





### Ribonuclease-free conditions are maintained for all assays that detect RNA or use an RNA probe.

*NOTE: RNA is extremely susceptible to degradation by ribonucleases that are ubiquitous in the environment. To ensure preservation of target RNA or RNA probes, special precautions are needed.*

#### Evidence of Compliance:

- ✓ Records that RNase-free conditions are maintained (ie, wipe test in event of contamination incident) with corrective action if conditions are not met

#### REFERENCES

- 1) Gulley ML, *et al.* Guidelines for interpreting EBER *in situ* hybridization and LMPI immunohistochemical tests for detecting Epstein-Barr virus in Hodgkin lymphoma. *Am J Clin Pathol.* 2002;117:259-267

## BAP.05200 Carryover - Nucleic Acid Amplification

Phase II



### Nucleic acid amplification procedures (eg, PCR) use appropriate physical containment and procedural controls to minimize carryover (false positive results).

*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. Enzymatic destruction of amplification products is often helpful, as is real-time measurement of products to avoid manual manipulation of amplification products.*

#### REFERENCES

- 1) Clinical and Laboratory Standards Institute (CLSI). *Establishing Molecular Testing in Clinical Laboratory Environments: CLSI document MM19-A.* Clinical and Laboratory Standards Institute, Wayne, PA, 2011.

## BAP.05300 Internal Controls Nucleic Acid Amplification

Phase II



### In 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.*

#### Evidence of Compliance:




- ✓ Records of assay validation and monitoring statistics for test result trends

## 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:

	<ul style="list-style-type: none"> <li>• Sampling of cell fractionation policies and procedures</li> </ul>
	<ul style="list-style-type: none"> <li>• System to maintain the identification of the derivatives to the parent biospecimen</li> <li>• Cell fractionation process follows the steps in the procedure</li> </ul>
	<ul style="list-style-type: none"> <li>• How is the quality of the cell fractionation process ensured?</li> </ul>

### BAP.05303 Specimen Identification

Phase II



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

*NOTE: Records 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.05306 Cell Fractionation

Phase II



**The biorepository follows a defined process for all steps in the cell fractionation process.**

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

### BAP.05309 Quality Control/Quality Assurance

Phase II



**Biorepositories performing cell fractionation record 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:

	<ul style="list-style-type: none"> <li>• Sampling of cell and tissue culture policies and procedures</li> <li>• Sampling of records of microbial contamination and other cell line testing</li> </ul>
	<ul style="list-style-type: none"> <li>• How does the biorepository ensure that the quality of cell lines is maintained?</li> <li>• How do you define and monitor maximum cell line passage?</li> </ul>

#### BAP.05312 Culturing Environment

Phase II



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

#### BAP.05315 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 include duplicate or independently established cultures, harvesting in duplicate or at different times, or other control processes.*

#### BAP.05318 Monitoring of Passage Numbers

Phase I



**The biorepository defines 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:**

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

#### BAP.05321 Testing for Microbial Contamination

Phase I



**The biorepository tests cell lines for microbial contamination at intervals defined by the biorepository director.**

##### **Evidence of Compliance:**

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

**\*\*REVISED\*\* 12/26/2024**

#### BAP.05324 Testing for Functionality and/or Unique Characteristics

Phase I



**Cell lines, organoids, and patient-derived xenografts that are created by the biorepository are tested for functionality or unique characteristics and to ensure that they are fit for purpose.**

*NOTE: Such testing may be performed by analyzing aspects of the phenotype (eg, 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/OR**
- ✓ Records of (short tandem repeats) STR profiling or another method such as histologic staining or immunohistochemistry for cell lines to accomplish this goal

**BAP.05327 Recording of Failures**

**Phase I**

**Culture failures are recorded.**





*NOTE: Records must indicate corrective actions.*

**Evidence of Compliance:**

- ✓ Records of 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

### Inspector Instructions:

	<ul style="list-style-type: none"> <li>• Sampling of histology policies and procedures</li> <li>• Sampling of specimen preparation records</li> <li>• Sampling of histology QC policies and procedures</li> <li>• Sampling of QC records (histochemical)</li> <li>• Sampling of records of daily review of histologic slide quality</li> <li>• Sampling of immunofluorescence QC records</li> <li>• Sampling of IHC policies and procedures</li> <li>• Sampling of new antibody validation/verification records</li> <li>• Sampling of new reagent/shipment confirmation of acceptability records</li> <li>• Sampling of antibody QC records</li> <li>• Sampling of buffer pH records</li> <li>• Sampling of batch control records</li> </ul>
	<ul style="list-style-type: none"> <li>• Sampling of tissue blocks (identification)</li> <li>• Sampling of slides (labeling, quality)</li> </ul>
	<ul style="list-style-type: none"> <li>• How does the histology section ensure specimen identity throughout processing?</li> <li>• How does your biorepository validate/verify new antibodies?</li> <li>• How does your biorepository confirm the acceptability of new reagent lots?</li> <li>• How does your biorepository distinguish non-specific false-positive staining from endogenous biotin?</li> </ul>
	<ul style="list-style-type: none"> <li>• If problems are identified during the review of histology procedures, further evaluate the responses, corrective actions and resolutions</li> <li>• Select a representative specimen and follow from receipt in the department through accessioning, grossing, processing, time reported and availability in the LIS</li> </ul>

#### BAP.05330 Specimen Preparation Records

Phase I

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

#### BAP.05332 Cross-Contamination - Histology

Phase II



**The biorepository prevents cross-contamination of specimens in the histology section.**

*NOTE: The process must address steps to prevent cross-contamination during the various phases of tissue handling including: processing, embedding, microtomy, and slide preparation. Problems with cross-contamination must be addressed in the biorepository quality management system.*

*Instruments must be clean and well-maintained (eg, tissue processors, embedding centers, dispensers, floatation baths, staining and coverslipping equipment).*

*At the embedding station, cleaning or wiping of forceps between cases is required. Only one cassette should be handled at a time.*

*For microtomy, there must be a clear process for handling of blocks and labeling of slides to prevent specimen mix-ups. Floatation baths require periodic water changes or blotting of the water surface so that sections from one patient block are not inadvertently carried over to another case or block (so-called "floaters" or "extraneous tissue").*

#### REFERENCES

- 1) Lott R, Tunncliffe J, Sheppard E, et al. *Practical Guide to Specimen Handling in Surgical Pathology*. Northfield, IL: College of American Pathologists; 2023. 11.0. <https://documents.cap.org/documents/practical-guide-specimen-handling.pdf>. Published September 2023. Accessed December 21, 2023.
- 2) Gephardt GN, Zarbo RJ. Extraneous tissue in surgical pathology: A College of American Pathologists study of 275 laboratories. *Arch Pathol Lab Med*. 1996; 120:1009-14.

### BAP.05336 Special Stains/Studies

#### Phase II



**For special stains, including histochemical stains, and studies using immunologic and ISH methodology, positive and negative controls are verified and recorded as acceptable prior to or concurrent with the reporting of patient results and records retained.**

*NOTE: Controls must be verified and recorded as acceptable by a pathologist or designee (provided the designee meets high complexity testing qualifications).*

*Positive tissue controls must contain the component specific to the special stain that is being applied to the specimen.*

*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 laboratory director following appropriate validation.*

*If interpretation of the special stain or study is performed by a different laboratory, there must be a procedure for the laboratory performing the stain or study to verify the acceptability of the controls before transfer, if the controls are not sent with the patient slides (regardless of the outside laboratory's accrediting organization). Records of this verification must be readily available to the laboratory performing the interpretation.*

#### Evidence of Compliance:

- ✓ Records for verification of control acceptability (prior to completion of associated cases)

#### 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);[42CFR493.1256(e)(2)].
- 2) Department of Health and Human Services, Centers for Medicare and Medicaid Services. Clinical laboratory improvement amendments of 1988; final rule. *Fed Register*. 2023(Dec 28);[42CFR493.1273(a)]

### BAP.05337 Paraffin Microtomy

#### Phase II



**The appropriate thickness of paraffin embedded tissue for various tissue types and procedures is defined.**

*NOTE: Paraffin embedded sections are routinely sectioned at 4-5 microns. Some tissues (eg, renal biopsy) may require thinner sections, while some special stain techniques (eg, Congo red stain) may require thicker sections. Use of the recommendations in the table below is at the discretion of the laboratory director.*

Tissue	Thickness
Routine Paraffin	4 to 5 microns
Renal Sections	1 to 3 microns
Bone Marrow	2 to 3 microns
Nerve histochemical staining	6 to 15 microns
Amyloid demonstration	6 to 12 microns

**BAP.05338 Slide Quality****Phase II**

**Slides are of sufficient quality for diagnosis.**

*NOTE: Histopathology slides must be of adequate technical quality to be diagnostically useful. Criteria to evaluate include adequate tissue fixation, processing, thickness of sections, absence of interfering tissue folds and tears, and good staining technique and coverslipping. For hematoxylin and eosin and other routine stains, the patient slide serves as the internal control to ensure adequate staining technique. The sections must be cut from sufficient depth in the block to include the entire tissue plane.*

**BAP.05342 Specimen Modification****Phase II**

**If the biorepository performs immunohistochemical staining on specimens other than formalin-fixed, paraffin-embedded tissue, the written procedure defines appropriate modifications, if any, 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
- 2) Clinical and Laboratory Standards Institute. *Quality Assurance for Design Control and Implementation of Immunohistochemistry Assays; Approved Guideline*. 2<sup>nd</sup> ed. CLSI Document I/LA28-A2. Clinical and Laboratory Standards Institute, Wayne, PA; 2011.

**BAP.05345 Buffer pH****Phase II**

**The pH of the buffers used in immunohistochemistry is monitored at defined intervals.**

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

**Evidence of Compliance:**

- ✓ Records of initial and subsequent QC on each buffer

**\*\*REVISED\*\* 12/26/2024****BAP.05348 QC - Antibodies****Phase II**

**Positive controls are used for each antibody.**

*NOTE: Positive controls assess the performance of the immunohistochemistry assay (including impact of fixation and antigen retrieval) and can assess the sensitivity of the assay. They should, whenever possible, be subjected to the same processing, antigen retrieval, and immunostaining protocol as donor tissue.*

*Results of controls must be recorded, 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 tissue-based positive controls, the ideal control is of the same specimen type as the donor test specimen (eg, small biopsy, large tissue section, cell block), and is processed and fixed in the same manner (eg, 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 (eg, 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 included on the same slide as the donor tissue is optimal practice because it helps identify failure to apply primary antibody or other critical reagents to the donor test slide; however, one separate positive control per staining run for each antibody in the run (ie, batch control) may be sufficient provided that the control slide is closely scrutinized by a qualified reviewer.*

*Ideally, positive controls have low levels of antigen expression, as is often seen in neoplasms. Different expression level controls are suggested if related to companion diagnostic clinical decision points (ie, HER2; 0, 1+, 2+, 3+). Exclusive use of normal tissues that have high levels of antigen expression may result in failure to identify assays of insufficient sensitivity, leading to false-negative results.*

*Synthetic materials (eg, microbeads) and cell lines containing IHC analytes of interest may be run as controls in addition to positive tissue controls. Synthetic controls and cell lines should contain the target epitope of the IHC assay. Controls that assess the IHC protocol should be sensitive to the antigen retrieval step.*

*Synthetic and cell line-based controls can be particularly useful to assess assay performance at low expression levels, such as detecting low levels of expression in breast cancer. Synthetic and cell line-based controls are not ideal for optimizing digital pathology algorithms, which are optimally tuned to IHC expression in human tumors.*

#### **Evidence of Compliance:**

- ✓ Donor reports or worksheet with control results **AND**
- ✓ Immunohistochemical-stained slides with positive controls

#### **REFERENCES**

- 1) Clinical and 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.
- 2) Allen M. Gown, MD. Diagnostic Immunohistochemistry: What Can Go Wrong and How to Prevent it. *Arch Pathol Lab Med*. 2016;140(9):893-898.
- 3) Cheung CC, D'Arrigo C, Dietel M, et al; From the International Society for Immunohistochemistry and Molecular Morphology (ISIMM) and International Quality Network for Pathology (IQN Path). Evolution of Quality Assurance for Clinical Immunohistochemistry in the Era of Precision Medicine: Part 4: Tissue Tools for Quality Assurance in Immunohistochemistry. *Appl Immunohistochem Mol Morphol*. 2017;25(4):227-230.
- 4) Cheung CC, Taylor CR, Torlakovic EE. An Audit of Failed Immunohistochemical Slides in a Clinical Laboratory: The Role of On-Slide Controls. *Appl Immunohistochem Mol Morphol*. 2017;25(5):308-312.
- 5) Torlakovic EE, Nielsen S, Francis G, et al. Standardization of positive controls in diagnostic immunohistochemistry: recommendations from the International Ad Hoc Expert Committee. *Appl Immunohistochem Mol Morphol*. 2015;23(1):1-18.
- 6) ISO 20166-4:2020 Molecular in vitro diagnostic examinations. Specifications for pre-examination processes for formalin-fixed and paraffin-embedded (FFPE) tissue. Part 4: in situ detection techniques. International Organization for Standardization. 2020.

**\*\*NEW\*\* 12/26/2024**

**BAP.05350 Synthetic and Commercial Control Range Establishment or Verification**

**Phase II**



**If synthetic or commercial controls are used for quantitative testing, the biorepository establishes or verifies an acceptable control range for each lot of synthetic or commercial control material.**

*NOTE: The biorepository must verify control ranges supplied by the manufacturer if provided and establish an acceptable range by repetitive analysis if control ranges are not provided by the manufacturer.*

*Control values supplied by the manufacturer may be used without verification for qualitative (eg, positive or negative) testing.*



**Evidence of Compliance:**

- ✓ Records for control range establishment or verification of each lot, as applicable

**REFERENCES**

- 1) Clinical and Laboratory Standards Institute (CLSI). *Evaluation of Precision Performance of Quantitative Measurement Methods. Approved Guideline*. 3rd ed. CLSI document EP05-A3. Clinical and Laboratory Standards Institute, Wayne, PA; 2014.
- 2) Clinical and Laboratory Standards Institute (CLSI). *Statistical Quality Control for Quantitative Measurement Procedures, Principles and Definitions*. 4th ed. CLSI guideline C24. Clinical and Laboratory Standards Institute, Wayne, PA; 2016.

**BAP.05351 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 recorded, 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 (eg, 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 "good 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 (ie, separate sections, internal controls or multitissue blocks) must be specified in the biorepository manual.*

*Multitissue blocks or tissue microarray (TMA) 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 of 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:**

- ✓ Donor reports or worksheet with control results **AND**
- ✓ Immunohistochemical-stained slides with appropriate negative controls

#### **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 and 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.
- 8) Torlakovic EE, Francis G, Garratt J, et al. International Ad Hoc Expert Panel. Standardization of negative controls in diagnostic immunohistochemistry: recommendations from the international ad hoc expert panel. *Appl Immunohistochem Mol Morphol*. 2014;22(4):241-52.

## **BAP.05354 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), nonspecific false-positive staining from endogenous biotin is addressed.**

*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 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
- 3) Clinical and Laboratory Standards Institute. *Quality Assurance for Design Control and Implementation of Immunohistochemistry Assays: Approved Guideline*. 2<sup>nd</sup> ed. CLSI Document I/LA28-A2. Clinical and Laboratory Standards Institute, Wayne, PA; 2011.
- 4) Allen M. Gown, MD. Diagnostic Immunohistochemistry: What Can Go Wrong and How to Prevent it. *Arch Pathol Lab Med*. 2016;140(9):893-898.

**BAP.05357 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 retained and clearly show that positive and negative controls for all antibodies stain appropriately. Control records must be retained for two years.*

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

**Evidence of Compliance:**

- ✓ Records of worksheets with control results

**REFERENCES**

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

**\*\*REVISED\*\* 12/26/2024**

**BAP.05360 Validation/Verification - IHC Antibody Testing****Phase II**

**The biorepository has records of validation/verification of new antibodies, including introduction of a new clone, prior to sample characterization.**

*NOTE: The performance characteristics of each assay must be appropriately validated/verified before being made available as characterization data for the specimen type. The initial goal is to establish the optimal antibody titration, 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/verification is at the discretion of the biorepository director and will vary with the antibody.*

*Means of validation/verification may include, but are not limited to: 1) correlating the results using the new antibody with the morphology and expected results; 2) comparing the results using the new antibody with the results of prior testing of the same tissues with a validated/verified assay in the same laboratory; 3) comparing the results using the new antibody with the results of testing the same tissue in another laboratory with a validated/verified assay; or 4) comparing the results using the new antibody with previously validated/verified non-IHC tests or testing previously graded tissue challenges from a formal proficiency testing program.*

*For an initial validation/verification, biorepositories should receive at least 90% overall concordance between the new test and the comparator test or expected results.*

*For validation of **laboratory-developed or modified FDA-cleared/approved assays**, the validation must be performed on a minimum of 10 positive and 10 negative tissues.*

*For verification of **unmodified FDA-cleared/approved assays**, the biorepository must follow the instructions provided by the manufacturer. If the instructions do not list a minimum number of samples for assay verification, the verification must be performed on a minimum of 10 positive and 10 negative tissues.*

*If the biorepository director determines that fewer validation/verification cases are sufficient for a specific marker (eg, a rare antigen or tissue), the rationale for that decision needs to be recorded. Positive cases in the validation/verification set should span the expected range of clinical results (expression level), especially for those markers that are reported quantitatively.*

*When possible, biorepositories should use tissues that have been processed using the same fixative and processing methods as cases that will be tested clinically. If IHC is regularly done on specimens that are not fixed or processed in the same manner as the tissues used for validation/verification (eg, alcohol fixed cell blocks, cytologic smears, formalin post fixed tissue, or decalcified tissue), the biorepository should test a sufficient number of such tissues to ensure that assays consistently achieve expected results. The biorepository director is responsible for determining the number of positive and negative cases and the number of markers to test.*

#### **Evidence of Compliance:**

- ✓ Records of validation/verification, if applicable

#### **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 and 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.
- 3) Allen M. Gown, MD. Diagnostic Immunohistochemistry: What Can Go Wrong and How to Prevent it. *Arch Pathol Lab Med.* 2016;140(9):893-898.
- 4) Uhlen M, Bandrowski A, Carr S, et al. A proposal for validation of antibodies. *Nat Methods.* 2016; 13(10):838-7.
- 5) Goldsmith JD, Troxell M, Roy-Chowdhuri S, et al. Principles of analytic validation of immunohistochemical assays: guideline update. *Arch Pathol Lab Med.* 2024. <https://doi.org/10.5858/arpa.2023-0483-CP>

### **BAP.05361 IHC Assay Performance**

### **Phase I**

**Biorepositories confirm assay performance when conditions change that may affect performance.**

*NOTE: A change in antibody clone requires full revalidation/verification of the assay (equivalent to initial analytic validation/verification - see BAP.05360).*

*Biorepositories must confirm assay performance with at least two known positive and two known negative cases when an existing validated/verified assay has changed in any of the following ways: antibody dilution, antibody vendor (same clone), or the incubation or retrieval times (same method).*

*A more extensive study to confirm acceptable assay performance in accordance with published guidelines must be performed when any of the following have changed: fixative type, antigen retrieval protocol (eg, change in pH, different buffer, different heat platform), antigen detection system, tissue processing or testing equipment, environmental conditions of testing (eg, biorepository relocation), or biorepository water supply. This study must include a representative sampling of the assays affected by the change and an appropriate number of positive and negative cases per assay, sufficient to confirm acceptable assay performance. The biorepository director is responsible for determining the extent of the study. The rationale for the assays selected and number of positive and negative cases checked per assay must be recorded.*

#### **REFERENCES**

- 1) Goldsmith JD, Troxell M, Roy-Chowdhuri S, et al. Principles of analytic validation of immunohistochemical assays: guideline update. *Arch Pathol Lab Med.* 2024. <https://doi.org/10.5858/arpa.2023-0483-CP>

### **BAP.05363 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:**

- ✓ Records of confirmation of new reagent lots

**BAP.05366 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

**BAP.05367 QC - Immunofluorescence****Phase II**

**For immunofluorescence microscopy, appropriate positive and negative controls are performed.**

*NOTE: Internal antigens serve as positive controls (eg, IgA in tubular casts, IgG in protein droplets and C3 in blood vessels). When internal positive controls are absent, daily external positive controls are required. Non-reactive elements in the patient specimen may serve as a negative tissue control. A negative reagent control in which the patient tissue is processed in an identical manner to the test specimen, but with the primary antibody omitted, should be performed for each patient test specimen at the discretion of the biorepository director.*

**Evidence of Compliance:**

- ✓ Records of immunofluorescence QC

**REFERENCES**

- 1) Walker PD, et al. Practice guidelines for the renal biopsy. *Mod. Pathol*. 2004;17:1555-1563
- 2) Department of Health and Human Services, Centers for Medicare and Medicaid Services. Clinical laboratory improvement amendments of 1988; final rule. *Fed Register*. 2023(Dec 28):[42CFR493.1273(a)]

**BAP.05369 Special Handling of Creutzfeldt-Jakob Disease (CJD)****Phase II**

**The biorepository handles tissues from cases of suspected transmissible spongiform encephalopathies (TSE), including Creutzfeldt-Jakob disease (CJD), using procedures that minimize the risk of transmission.**

*NOTE: Specialized handling instructions and an appropriate process for intra-laboratory communication must be addressed in the written procedure.*

*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.*

**REFERENCES**



- 1) Brown W, et al. A simple and effective method for inactivating virus activity in formalin-fixed tissue samples from patients with Creutzfeldt-Jakob disease. *Neurology*. 1990; 40:887-890.
- 2) Brown P. Guidelines for high risk autopsy cases: special precautions for Creutzfeldt-Jakob disease. In: Hutchins G, ed. *Autopsy performance and reporting*. Northfield, IL: College of American Pathologists. 1990:68-74.
- 3) Greenblatt M. Q&A. Northfield, IL: College of American Pathologists. *CAP Today*. 1993(March); 7(3):69-70.
- 4) Crain BJ. Safety tips for anatomic studies of possible CJD. Northfield, IL: College of American Pathologists. *CAP Today*. 1996(Jan); 10(1):56.

- 5) Rank JP. How can histotechnologists protect themselves from Creutzfeldt-Jakob disease. *Lab Med.* 1999; 30:305.
- 6) Nixon RR. Prions and prion diseases. *Lab Med.* 1999; 30:335-338.
- 7) Collins KA, ed. *Autopsy Performance & Reporting*. 3rd ed. Northfield, IL: CAP Press; 2017.

## SPECIALIZED TECHNIQUES

### WHOLE SLIDE IMAGING

#### Inspector Instructions:

	<ul style="list-style-type: none"> <li>• Sampling of training records</li> <li>• System validation records</li> </ul>
	<ul style="list-style-type: none"> <li>• How are the images generated used?</li> </ul>

#### BAP.05375 Whole Slide Imaging User Training

Phase I

**There are records showing that all users of the whole slide imaging system have been trained.**

*NOTE: Users of the whole slide imaging system include individuals responsible for slide scanning and digital slide quality assessment, as well as pathologists. The training procedure should include role-specific training, as defined in the approved laboratory procedures. Retraining may be required when significant system changes are made.*

##### **Evidence of Compliance:**

- ✓ Records for whole slide image training in personnel files

#### BAP.05400 System Qualification - Whole Slide Imaging

Phase II



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

## DIGITAL IMAGE ANALYSIS (DIA)

*This section applies to laboratories using digital image analysis to evaluate specific features in a tissue section image following enhancement and processing of that image, including but not limited to, IHC, morphometric analysis, and ISH. This checklist section does not apply to laboratories that are imaging slides for manual scoring or review by an individual.*

## VALIDATION AND CALIBRATION (DIA)

### Inspector Instructions:

	<ul style="list-style-type: none"> <li>• Sampling of validation and calibration policies and procedures</li> <li>• Sampling of validation/calibration records</li> </ul>
	<ul style="list-style-type: none"> <li>• What is your course of action if calibration is unacceptable?</li> </ul>

#### BAP.05410 Preanalytic Testing Phase Validation

Phase II

**There are records showing that the preanalytic phase of the test system has been validated for each assay, including fixation and processing.**

*NOTE: Applicable requirements under the "Test Method Validation and Verification-Nonwaived Tests" of the All Common Checklist must be followed.*

#### REFERENCES

- 1) Hipp J, Bauer TW, Bui MM, et al. *CAP Pathology Resource Guide: Digital Pathology*. Version 7.0(2). Northfield, IL: College of American Pathologists; 2017.

#### BAP.05415 Calibration

Phase II





**Each instrument is calibrated in accordance with the specifications of the instrument.**

#### REFERENCES

- 1) Hipp J, Bauer TW, Bui MM, et al. *CAP Pathology Resource Guide: Digital Pathology*. Version 7.0(2). Northfield, IL: College of American Pathologists; 2017.

## QUALITY CONTROL

### Inspector Instructions:

	<ul style="list-style-type: none"> <li>• Sampling of QC policies and procedures</li> <li>• Sampling of QC records</li> </ul>
	<ul style="list-style-type: none"> <li>• How do you determine when QC is unacceptable and corrective actions are needed?</li> </ul>

#### BAP.05420 Quality Control - Digital Image Analysis

Phase II



**Control materials are run concurrently with patient specimens to ensure appropriate functionality of the digital image system.**

*NOTE: Controls are samples that act as surrogates for patient/client specimens. They are periodically processed like a patient/client sample to monitor the ongoing performance of the analytic process. Controls should check test performance at relevant decision points for the digital image analysis system.*

*For qualitative tests, a positive and a negative control may be sufficient. For quantitative or semiquantitative tests, controls at more than one level should be used.*

**Evidence of Compliance:**

- ✓ Records of QC results

**REFERENCES**

- 1) Department of Health and Human Services, Centers for Medicare and Medicaid Services. Medicare, Medicaid and CLIA programs; CLIA fee collection; correction and final rule. *Fed Register*. 2003(Jan 24):5232 [42CFR493.1256(d)(3)(i)]
- 2) Clinical and Laboratory Standards Institute (CLSI). *Statistical Quality Control for Quantitative Measurement Procedures: Principles and Definitions*. 4th ed. CLSI guideline C24. Clinical and Laboratory Standards Institute, Wayne, PA, 2016.

**BAP.05425 QC Handling**

**Phase II**



**The biorepository tests control specimens in the same manner and by the same personnel as patient/client samples.**

*NOTE: Personnel who routinely perform patient/client testing must analyze QC specimens; however, this does not imply that each operator must perform QC daily. Personnel must participate in QC on a regular basis. To the extent possible, all steps of the testing process must be controlled.*

**Evidence of Compliance:**

- ✓ Records reflecting that QC is run by the same personnel performing patient testing

**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(d)(8)]; 2) *ibid*, 2003(Jan 24):3708[42CFR493.1256(d)(7-8)]

**BAP.05430 QC Confirmation of Acceptability**

**Phase II**

**Personnel review control results for acceptability before reporting results.**

*NOTE: Control results must be reviewed before reporting patient/client results.*

**Evidence of Compliance:**

- ✓ Records of control result approval

**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)]

**BAP.05435 Monthly QC Review**

**Phase II**

**The biorepository director or designee reviews and assesses quality control data at least monthly.**

*NOTE: The reviewer must record follow-up for outliers, trends, or omissions that were not previously addressed.*

*The QC data for tests performed less frequently than once per month may be reviewed when the tests are performed.*



**Evidence of Compliance:**

- ✓ Records of QC review **AND**
- ✓ Records of corrective action taken when acceptability criteria are not met

## SPECIMEN ANALYSIS

### Inspector Instructions:



- Sampling of specimen analysis policies and procedures

#### BAP.05440 Area of Analysis

Phase II



**A qualified pathologist selects or confirms the appropriate areas for analysis prior to reporting the results, as applicable.**

*NOTE: Specimens that do not represent "in situ" samples embedded in paraffin may not require pathologist review. Examples include cultured preparations and direct preparations of liquid specimens including blood, urine, pleural fluid, etc.*

#### BAP.05445 Analysis Guidelines

Phase II



**There are written guidelines for identification of appropriate areas and cells for analysis.**

*NOTE: Evaluation of heterogeneous cell populations requires use of specific guidelines and procedures to ensure analysis of the appropriate areas and/or cells, particularly if there is background or nonspecific staining, or if there is cell debris, endogenous pigment, and/or artifacts of aging, sectioning or preparation.*

*Test results may be affected by fixation parameters, including time of fixation, type of fixative used, hemorrhage, necrosis, and autolysis of tissue.*

## PERSONNEL

### Inspector Instructions:



- Records of personnel education and experience

#### BAP.05450 Testing Personnel Qualifications

Phase II

**Personnel who are responsible for evaluating the imaging system data are qualified as high-complexity testing personnel.**

*NOTE: Refer to the Laboratory General Checklist for high complexity testing personnel (GEN.54750) and general supervisor (GEN.53600) qualifications. Detailed information on*

personnel qualifications can be found in the CAP Personnel Guidance Document located in e-LAB Solutions Suite on cap.org (log-in required) under Accreditation Resources - Accreditation Checklists.

#### Evidence of Compliance:

- ✓ Records of qualifications including diploma, transcript(s), primary source verification report, equivalency evaluation, or current license (if required) **AND**
- ✓ Work history in related field





#### REFERENCES

- 1) Department of Health and Human Services, Centers for Medicare and Medicaid Services. Clinical laboratory improvement amendments of 1988; final rule. *Fed Register*. 2023(Dec 28):[42CFR493.1489].

## 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:

	<ul style="list-style-type: none"> <li>• Sampling of tissue microarray policies and procedures</li> <li>• Records of methods selected for region of interest of tissue and communication with the microarray technologist</li> </ul>
	<ul style="list-style-type: none"> <li>• System to positively identify specimens, specimen types and aliquots throughout the process</li> </ul>
	<ul style="list-style-type: none"> <li>• Who is responsible for selecting tissues and performing analysis for tissue microarray?</li> <li>• How are the selection and number of cores determined?</li> </ul>
	<ul style="list-style-type: none"> <li>• Follow a tissue specimen for TMA from processing to final analysis. Observe specimen identification, core selection and analysis.</li> </ul>

#### BAP.05500 Specimen Identification - Tissue Microarray

#### 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. Preparation of records
6. Utilization (number of times sectioned)
7. Storage

**BAP.05600 Preparation - Tissue Microarray****Phase II**

**There are records describing the tissue types and purpose for the tissue microarray (TMA), including the size and placement of the tissue cores as well as control tissue cores.**

*NOTE: Criteria for selection and records 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 of size, frequency, and location of cores therefore, should be considered and recorded 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 - Tissue Microarray****Phase II**

**The biorepository has criteria for determining the extent to which the original paraffin tissue block lesion can be removed.**

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

**A qualified anatomic pathologist selects the appropriate tissues (paraffin block and tissue region of interest) to make a tissue microarray.**

**BAP.05900 Core Selection - Tissue Microarray****Phase II**

**There is a defined process for selecting the regions of interest in the tissue and clearly communicating the instructions to the tissue microarray technologist.**

**BAP.06000 Number of Cores - Tissue Microarray****Phase II**

**The methods for determining the relevant number of cores to accurately represent the parent tissue block are recorded.**

*NOTE: The biorepository must follow a written procedure to determine the optimum number of cores required per tissue microarray, as dictated by each study protocol.*

**BAP.06100 Tissue Placement - Tissue Microarray****Phase II**

**Personnel follow a defined process for ensuring that the correct tissue is placed in the correct location of the tissue microarray (TMA) (eg, a TMA map identifying tissue type, key ID, and location in the TMA).**

*NOTE: This includes 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.*

**REFERENCES**

- 1) Clinical and Laboratory Standards Institute. *Fluorescence in Situ Hybridization Methods for Clinical Laboratories; Approved Guideline*. 2<sup>nd</sup> ed. CLSI Document MM07-A2. Clinical and Laboratory Standards Institute, Wayne, PA; 2013.

**BAP.06200 Analysis - Tissue Microarray****Phase I**

**Analysis of tissue microarrays is performed by an anatomic pathologist.**

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




**Evidence of Compliance:**

- ✓ Records of tissue microarray analysis

## 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.

### Inspector Instructions:

	<ul style="list-style-type: none"> <li>• Sampling of LCM policies and procedures</li> <li>• Records of LCM laser focus and alignment</li> </ul>
	<ul style="list-style-type: none"> <li>• System to positively identify specimens, specimen types and aliquots throughout the process</li> </ul>
	<ul style="list-style-type: none"> <li>• How is the quality of LCM tissue material ensured?</li> </ul>

**BAP.06300 Specimen Identification - LCM****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 Process****Phase II**

**The biorepository monitors and records laser capture microdissection (LCM) following a defined 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.*

**REFERENCES**




- 1) Clinical and Laboratory Standards Institute (CLSI). *Collection, Transport, Preparation, and Storage of Specimens for Molecular Methods*. 2nd ed. CLSI guideline MM13. Clinical and Laboratory Standards Institute, Wayne, PA; 2020.

**BAP.06500 LCM Equipment****Phase II**

**The laser capture microdissection (LCM) laser focus and alignment is maintained and recorded to ensure optimal performance.**

*NOTE: Maintenance records related to the critical components of the LCM as noted by the manufacturer are required.*

**MOLECULAR METHODS****ELECTROPHORESIS****Inspector Instructions:**

	<ul style="list-style-type: none"> <li>Sampling of electrophoresis policies and procedures</li> </ul>
	<ul style="list-style-type: none"> <li>Autoradiographs/gel photographs (sufficient resolution/quality)</li> </ul>
	<ul style="list-style-type: none"> <li>How does your laboratory prevent degradation of the nucleic acid sample used for electrophoresis?</li> </ul>

**BAP.06510 Loading Analytical Gels****Phase I**

**Standard amounts of nucleic acid are loaded on analytical gels, when possible.**

**BAP.06520 Molecular Weight Markers****Phase II**

**Known molecular weight markers that span the range of expected bands are used for each electrophoretic run.**

**Evidence of Compliance:**




- ✓ Records of appropriate markers with each run

**BAP.06530 Visual/Fluorescent Markers****Phase II**

**Visual or fluorescent markers are used to determine the endpoint of gel electrophoresis.**

## TARGET AMPLIFICATION/POLYMERASE CHAIN REACTION (PCR)

### Inspector Instructions:

	<ul style="list-style-type: none"> <li>Sampling of amplification/PCR policies and procedures</li> </ul>
	<ul style="list-style-type: none"> <li>Physical containment practices (frequent glove change, separate manipulation of pre- and post-specimens, dedicated pipettes)</li> </ul>
	<ul style="list-style-type: none"> <li>How does your laboratory distinguish a true negative from a false negative result?</li> </ul>

#### BAP.06610 Carryover - Nucleic Acid Amplification

Phase II



**Nucleic acid amplification procedures (eg, PCR) use appropriate physical containment and procedural controls to minimize carryover (false positive results).**

*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 the laboratory take special precautions. 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. Enzymatic destruction of amplification products is often helpful, as is real-time measurement of products to avoid manual manipulation of amplification products.*

#### REFERENCES

- 1) Kwok S, Higuchi R. Avoiding false positives with PCR. *Nature* 1989;339:237-238
- 2) Clinical and Laboratory Standards Institute (CLSI). *Establishing Molecular Testing in Clinical Laboratory Environments*: CLSI document MM19-A (ISBN 1-56238-773-1). Clinical and Laboratory Standards Institute, 940 West Valley Road, Suite 1400, Wayne, Pennsylvania 19087-1898 USA, 2011.

#### BAP.06620 Internal Controls - Nucleic Acid Amplification

Phase II



**In 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 biorepository 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.

## BAP.06630 Melting Temperature

Phase I



**For tests that generate a result based on a  $T_m$ , appropriately narrow temperature ranges (+/- 2.5 °C) are defined and recorded each day of use.**

## IN SITU HYBRIDIZATION (ISH)

The use of the term *in situ hybridization (ISH)* in this section applies to all ISH methods, including fluorescence (FISH), chromogenic (CISH), silver (SISH), and brightfield (BRISH) *in situ hybridization*.

Please refer to the Definition of Terms section in the All Common (COM) Checklist for definitions of analytical validation and analytical verification.

### Inspector Instructions:

	<ul style="list-style-type: none"> <li>• Sampling of ISH policies and procedures</li> <li>• Sampling of probe validation/verification records</li> <li>• Sampling of QC records</li> <li>• Sampling of patient test reports</li> </ul>
	<ul style="list-style-type: none"> <li>• How are ISH cut-off values established?</li> <li>• How does your laboratory validate/verify assay performance prior to test implementation?</li> <li>• What is your course of action when a probe does not produce an internal control signal?</li> </ul>

## BAP.06710 ISH Probe Validation/Verification

Phase II

**All in situ hybridization (ISH) probes are validated/verified.**

*NOTE: Additional requirements for test method validation/verification are in the All Common Checklist.*

### Evidence of Compliance:

- ✓ Records of ISH probe validation/verification

### REFERENCES

- 1) American College of Medical Genetics, Standards and Guidelines for Clinical Genetics Laboratories, 2021 edition.
- 2) Clinical and Laboratory Standards Institute (CLSI). *Fluorescence In Situ Hybridization Methods for Clinical Laboratories; Approved Guideline—Second Edition*. CLSI document MM07-A2 (ISBN 1-56238-885-1) Clinical and Laboratory Standards Institute, 940 West Valley Road, Suite 2500, Wayne, Pennsylvania 19087-1898 USA, 2013.
- 3) Lawrence Jennings, Vivian M. Van Deerlin, Margaret L. Gulley (2009) Recommended Principles and Practices for Validating Clinical Molecular Pathology Tests. *Archives of Pathology & Laboratory Medicine*: Vol. 133, No. 5, pp. 743-755
- 4) Wiktor AE, Van Dyke DL, Stupca PJ, et al. Preclinical validation of fluorescence in situ hybridization assays for clinical practice. *Genetics in Medicine* 8:16-23, 2006.
- 5) Weremowicz S, Sandstrom DJ, Morton CC, Miron PM. Validation of DNA probes for preimplantation genetic diagnosis (PGD) by fluorescence in situ hybridization (FISH) R1. *Prenat Diagn.* 2006 Nov;26(11):1042-50.
- 6) Saxe DF, Persons DL, Wolff DJ, Theil, KS; Cytogenetics Resource Committee of the College of American Pathologists. Validation of fluorescence in situ hybridization using an analyte-specific reagent for detection of abnormalities involving the mixed lineage leukemia gene. *Arch Pathol Lab Med.* 2012; 138(1):47-52.

## BAP.06720 Interphase ISH - Cut-off Value

Phase II

**For interphase in situ hybridization (ISH), the biorepository establishes a normal cut-off value for results for each probe used, when applicable.**

*NOTE: Refer to the All Common Checklist for specific test method validation/verification requirements. Cut-off values are usually required when ISH testing uses locus-specific probes against nuclear DNA.*

**Evidence of Compliance:**

- ✓ Records from cut-off value studies

**REFERENCES**

- 1) American College of Medical Genetics, Standards and Guidelines for Clinical Genetics Laboratories, 2021 edition.
- 2) Clinical and Laboratory Standards Institute. *Fluorescence In Situ Hybridization Methods for Clinical Laboratories; Approved Guideline*. 2<sup>nd</sup> ed. CLSI Document MM07-A2. Clinical and Laboratory Standards Institute, Wayne, PA; 2013.

**BAP.06740 ISH Assay Performance**

**Phase I**

**There are records of in situ hybridization (ISH) performance for each assay.**

*NOTE: Assay performance should include monitoring hybridization efficiency, probe signal intensity and overall assay results, including controls, as applicable.*

**Evidence of Compliance:**

- ✓ Records of QC monitoring of ISH assay performance at defined frequency

**BAP.06750 ISH Probe Intended Target**

**Phase I**



**A system is used to ensure that the in situ hybridization (ISH) probe used is for the intended target.**

*NOTE: Examples can include (but may not be limited to): 1) concurrent analysis of any available metaphase cells in an interphase cell analysis; 2) inclusion of an internal or external target that results in a positive signal for each hybridization; 3) written protocols that ensure the respective probe is applied to the intended specimen.*

**Evidence of Compliance:**

- ✓ Records confirming intended target

**BAP.06760 ISH Scoring**

**Phase II**



**Scoring of in situ hybridization (ISH) assays, including the number of cells scored, is performed as defined in a written procedure.**

**REFERENCES**

- 1) American College of Medical Genetics, Standards and Guidelines for Clinical Genetics Laboratories, 2021 edition.
- 2) Clinical and Laboratory Standards Institute (CLSI). *Fluorescence In Situ Hybridization Methods for Clinical Laboratories; Approved Guideline—Second Edition*. CLSI document MM07-A2 (ISBN 1-56238-885-1) Clinical and Laboratory Standards Institute, 940 West Valley Road, Suite 2500, Wayne, Pennsylvania 19087-1898 USA, 2013.

**BAP.06770 ISH Controls**

**Phase II**



**The biorepository performs and records controls (internal and/or external) for each in situ hybridization (ISH) analysis.**

*NOTE: What functions as a control depends on the specific assay, signal pattern present, and sample type. For example, assays designed to detect deletions may use internal controls that include both the probe of interest and a control locus probe, both of which map to the same chromosome. In this situation, there are two internal controls, the signal for the probe of interest on the normal homolog and the control locus signals on both the normal and deleted homolog. For a dual fusion assay, the probe signals on each of the normal homologs function as internal controls. If a probe is used that does not produce an internal control signal (eg, a Y chromosome probe in a female), another sample that is known to have the probe target must be run in parallel as an external control with the patient sample. In addition, many ISH assays use an external*

control(s). For FDA-cleared or approved ISH assays, biorepositories must follow manufacturer's instructions for quality control at minimum.

#### Evidence of Compliance:

- ✓ Records of QC results

#### REFERENCES

- 1) American College of Medical Genetics, Standards and Guidelines for Clinical Genetics Laboratories, 2021 edition.
- 2) Clinical and Laboratory Standards Institute (CLSI). *Fluorescence In Situ Hybridization Methods for Clinical Laboratories; Approved Guideline—Second Edition*. CLSI document MM07-A2 (ISBN 1-56238-885-1) Clinical and Laboratory Standards Institute, 940 West Valley Road, Suite 2500, Wayne, Pennsylvania 19087-1898 USA, 2013.
- 3) Stupca P, Meyer RG, Dewald GW. Using controls for molecular cytogenetic testing in clinical practice. *J Assoc Genet Tech*. 2005;31:4-8.

**\*\*REVISED\*\* 12/26/2024**

**BAP.06780 Image and Slide Retention - ISH**

**Phase II**



**Photographic or digitized images or permanent slides are retained of all in situ hybridization (ISH) assays for an appropriate period.**

*NOTE: Images or permanent slides of ISH assays for neoplastic disorders must be retained for 10 years; images or permanent slides of ISH assays for constitutional disorders must be retained for 20 years. For an ISH assay with a normal result, retain an image of at least one cell illustrating the normal probe signal pattern. For an ISH assay with an abnormal result, retain images of at least two cells illustrating each relevant abnormal probe signal pattern.*

*There is no retention requirement for retaining images of slide preparations when the source slides remain readable for the required retention period. If slides are expected to become unreadable before the end of the required retention period (for example, FISH slides), then images of the slides must be retained.*

*If representative images of chromosome ISH slides are retained, those with a normal result must include an image of at least one cell illustrating the normal probe signal pattern, and those with an abnormal result must include images of at least two cells illustrating each relevant abnormal probe signal pattern.*

#### REFERENCES

- 1) American College of Medical Genetics, Standards and guidelines for clinical genetics laboratories, 2021 edition.

**BAP.06790 ISH Interpretation**

**Phase II**

**If an in situ hybridization (ISH) study requires consultation with a qualified pathologist and/or a cytogeneticist for an accurate interpretation, the appropriate expert is consulted and their involvement is recorded.**

#### REFERENCES

- 1) Clinical and Laboratory Standards Institute (CLSI). *Fluorescence In Situ Hybridization Methods for Clinical Laboratories; Approved Guideline*. 2nd ed. CLSI document MM07-A2. Clinical and Laboratory Standards Institute, Wayne, PA, 2013.




## 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, microwaves, etc.*

*The checklist requirements in this section should be used in conjunction with the requirements in the All Common Checklist relating to instruments and equipment.*



## Inspector Instructions:

	<ul style="list-style-type: none"> <li>• Sampling of histology safety policies and procedures</li> <li>• Sampling of microwave reproducibility and ventilation checks</li> <li>• Sampling of thermocycler monitoring records</li> </ul>
	<ul style="list-style-type: none"> <li>• Location of automated tissue processor</li> <li>• Storage cabinets</li> </ul>
	<ul style="list-style-type: none"> <li>• How frequently do you change solutions in the tissue processor? How is the timeframe for changing solutions determined?</li> <li>• How does your laboratory prevent cross-contamination of paraffin sections in the flotation bath?</li> <li>• How often do you decontaminate your cryostat?</li> <li>• How does your laboratory ensure the individual wells of the thermocycler are maintaining accurate temperature?</li> </ul>

### BAP.06844 Automated Tissue Processor

Phase II

**Each open (ie, generative of flammable vapors into the ambient workspace) automated tissue processor is operated at least five feet (1.5 m) from the storage of combustible materials and from the paraffin dispenser.**

*NOTE: Tissue processors that operate as a closed system confine ignitable vapor hazards within the processor and thus do not pose a hazard requiring five feet of separation.*

*Each open (ie, generative of flammable vapors into the ambient workspace) automated tissue processor must be located at least five 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 five feet must separate each open system tissue processor from the paraffin dispenser.*

### BAP.06846 Microtome Knife Storage

Phase II

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

### BAP.06851 Microtome Maintenance

Phase I

**Microtomes and microtome knives are clean and well-maintained.**

*NOTE:*

1. Microtomes must be clean, properly lubricated, and without excessive play in the advance mechanism
2. Knives must be sharp and free of nicks

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

### BAP.06854 Microwave Usage

Phase I

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

**\*\*REVISED\*\* 12/26/2024**

**BAP.06856 Microwave Monitoring**

**Phase I**

**Microwave devices (used for any purpose) are monitored for reproducibility at least annually.**

*NOTE: 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 reproducibility must be assessed following instrument manufacturer's instructions.*

*The microwave device must be tested for radiation leakage if there is visible damage to the device. A description of the specific damage along with the result of the test must be recorded.*

**Evidence of Compliance:**

- ✓ Records of monitoring the diagnostic quality of specimens processed using microwaves **AND**
- ✓ Records of reproducibility testing for microwave use

**BAP.06858 Microwave Container Venting**

**Phase I**



**All containers used in microwave devices are vented or are used in compliance with manufacturer's instructions for the microwave instrumentation used.**

*NOTE: 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's instructions.*

**BAP.06865 Microwave Venting**

**Phase I**

**Microwave devices are properly vented and the effectiveness of ventilation is monitored at least annually.**

*NOTE: Some types of microwave devices need to be operated in an appropriate ventilation hood to contain airborne chemical contaminants and potentially infectious agents. Before operation of the microwave device, flammable and corrosive reagents must 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 must have an integral fume extractor certified by the manufacturer for use in a clinical laboratory.*

*This checklist item does not apply to microwave devices that are designed by the manufacturer to operate without venting. It also does not apply if non-hazardous reagents (as defined in the safety data sheets) and non-infectious specimens (eg, paraffin specimens) are used in the device.*

**Evidence of Compliance:**

- ✓ Records of annual evaluation of ventilation effectiveness

**BAP.07110 Automated Stainer**

**Phase II**



**The biorepository changes the solutions in automated stainers following a defined schedule.**

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

**Evidence of Compliance:**

- ✓ Records for solution changes

**BAP.07120 Incubator QC****Phase II**

**Incubators are monitored for temperature, CO<sub>2</sub> 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 records of corrective action if the allowable limits are exceeded.*

**Evidence of Compliance:**

- ✓ Instrument QC records

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

**Tissue processor solutions are changed at intervals appropriate for the workload.**

*NOTE: When solutions are changed, they must be entirely replaced with new solution and not just "topped off."*

**Evidence of Compliance:**

- ✓ Records of solution changes at the defined frequency

**REFERENCES**

- 1) Compton CC, Robb JA, Anderson MW, et al. Preanalytics and Precision Pathology: Pathology Practices to Ensure Molecular Integrity of Cancer Patient Biospecimens for Precision Medicine. *Arch Pathol Lab Med*. 2019;143(11):1346-63.

**BAP.07210 Tissue Processing Programs - Validation****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, eg, all fresh reagents. Process, embed, cut, and stain slides at the same time and evaluate the quality of the blocks, eg, 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:**

- ✓ Records of validation

**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 defined and used to achieve good processing results.*

**Evidence of Compliance:**

- ✓ Defined processing programs for various types and sizes of specimen tissues

**BAP.07400 Paraffin Baths, Flotation Baths, and Embedding Stations****Phase II**

**Paraffin baths, flotation baths, and embedding stations are clean, controlled and well-maintained.**

*NOTE: Instruments must be clean and well-maintained (eg, tissue processors, embedding centers, dispensers, flotation baths, stain lines, coverslipping equipment).*

*The temperature of the paraffin dispenser and paraffin baths must be correct for the type of paraffin used. At a minimum, the equipment must be maintained according to the manufacturer's instructions and paraffin temperatures recorded.*

*The CAP recommends the use of high-quality paraffin with a melting point of <60°C. The benefit of low-melt paraffin is that it is removed more efficiently during de-paraffinization and/or antigen retrieval. Efficient paraffin removal is essential for all molecular analyses.*

*Written procedures must include required water type, fill volume, and optimal temperature range for the type of paraffin used for tissue blocks. Inappropriate temperatures may affect the downstream use of the biospecimen.*

**Evidence of Compliance:**

- ✓ Records of maintenance **AND**
- ✓ Records of temperature checks

**REFERENCES**

- 1) Compton CC, Robb JA, Anderson MW, et al. Preanalytics and Precision Pathology: Pathology Practices to Ensure Molecular Integrity of Cancer Patient Biospecimens for Precision Medicine. *Arch Pathol Lab Med.* 2019;143(11):1346-63.

**BAP.07600 Cryostat Decontamination****Phase II**

**The cryostat is decontaminated at defined intervals and under defined circumstances.**

*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.*

*Decontamination must 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, cut-resistant gloves should be worn when changing knife blades.*

**Evidence of Compliance:**

- ✓ Records of cryostat decontamination

**REFERENCES**

- 1) Clinical and Laboratory Standards Institute. *Protection of Laboratory Workers From Occupationally Acquired Infections; Approved Guideline.* 4<sup>th</sup> ed. CLSI Document M29-A4. Clinical and Laboratory Standards Institute, Wayne, PA; 2014.
- 2) US Environmental Protection Agency: Antimicrobials Products Tested or Pending Testing. <https://www.epa.gov/pesticide-registration/antimicrobials-products-tested-or-pending-testing> Accessed April 19, 2018.

**BAP.07630 Thermocycler Temperature Checks****Phase II**

**Individual wells (or a representative sample thereof) of thermocyclers are checked for temperature accuracy before being placed in service and at least annually thereafter.**

*NOTE: A downstream measure of well-temperature accuracy (such as productivity of amplification) may be substituted to functionally meet this requirement. For closed systems, this function should be performed as a component of the manufacturer-provided preventive maintenance.*

**Evidence of Compliance:**

- ✓ Records of thermocycler verification

**REFERENCES**





- 1) Saunders GC, *et al.* Interlaboratory study on thermal cycler performance in controlled PCR and random amplified polymorphic DNA analyses. *Clin Chem.* 2001;47:47-55

## STORAGE

*This section of storage for a biorepository should be based on the type of equipment, the type of specimen(s) to be stored, the length of time in storage, and the intended use of the specimen(s). Performing visual audits of refrigerators/freezers to assess for clutter, water damage, and mold, along with daily refrigerator/freezer temperature and humidity monitoring would be considered best practice.*

### TEMPERATURE DEPENDENT STORAGE EQUIPMENT

#### Inspector Instructions:

	<ul style="list-style-type: none"> <li>• Sampling of specimen storage policies and procedures</li> <li>• Sampling of preventive and corrective maintenance procedures</li> <li>• Records of storage container calibrations and calibration verifications</li> <li>• Sampling of temperature monitoring records</li> <li>• Sampling of temperature set points</li> </ul>
	<ul style="list-style-type: none"> <li>• Adequate space for storage containers</li> <li>• Active alarm systems in place</li> <li>• Walk-in storage environment</li> <li>• Liquid nitrogen tanks usage monitoring and storage, if applicable</li> </ul>
	<ul style="list-style-type: none"> <li>• What do you do in the event of freezer breakdown?</li> <li>• How do you prevent overflow of storage containers?</li> </ul>
	<ul style="list-style-type: none"> <li>• Have you ever suffered a significant loss of samples? How did you address this and what were the corrective actions that became policy as a result?</li> </ul>

#### BAP.07800 Storage Equipment Calibration/Calibration Verification

#### Phase II



**The biorepository performs calibration and calibration verification for all applicable storage equipment.**

*NOTE: The records of calibration and calibration verification include:*

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

#### Evidence of Compliance:

- ✓ Records 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 that are appropriate for each storage environment.**

**BAP.08000 Proper 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, temperature mapping must be performed on a periodic basis to ensure that the proper temperature is maintained throughout. There must be records 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 (vapor phase only).*

*Temperature mapping must be performed and recorded 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****Phase II**

**The biorepository monitors and records refrigerator/freezer temperatures daily, as defined in written procedure.**

*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 record 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 recorded (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. There must be records showing daily functionality of the system.*

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

**Walk-in storage systems have the following:**

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

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



### The biorepository performs regular freezer preventive 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 Process

Phase II



**The biorepository has a defined process 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 and preventive action records

**\*\*REVISED\*\* 08/24/2023**

### BAP.08600 Liquid Nitrogen Supplies

Phase II

**Adequate liquid nitrogen (LN2) supplies are maintained securely 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), while avoiding safety hazards inherent in liquid phase storage.*

*The biorepository must have sufficient LN2 supply to fill a spare storage vessel and/or to allow for freezing of specimens in an emergency.*

*Access to supply tanks stored outside of the laboratory must be limited to trained personnel and authorized individuals (eg, vendors).*

#### Evidence of Compliance:

- ✓ LN2 supply storage within the restricted area of the laboratory **OR** locked supply storage area outside of the laboratory with limited key access

### BAP.08700 LN2 Monitoring

Phase II





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

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

**Evidence of Compliance:**

- ✓ Records 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:

	<ul style="list-style-type: none"> <li>• Sampling of temperature logs</li> <li>• Sampling of records of alarm trigger response</li> <li>• Sampling of alarm system testing records</li> </ul>
	<ul style="list-style-type: none"> <li>• Active alarm systems in place</li> <li>• Availability of emergency power supply</li> </ul>
	<ul style="list-style-type: none"> <li>• What do you do when a storage container alarm triggers?</li> <li>• What is the biorepository's contingency plan if the alarm system fails?</li> <li>• What do you do if a unit cannot maintain appropriate temperature?</li> </ul>
	<ul style="list-style-type: none"> <li>• Select a storage container that has had a temperature failure and follow the process from notification to response and final corrective action</li> </ul>

**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 recorded (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. There must be records showing daily functionality of the system.

**Evidence of Compliance:**

- ✓ QC records for continuous temperature monitoring **OR** records of checks at defined frequency

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

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

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



**The biorepository follows a defined process for deviations in the storage temperature limits, with an impact assessment when required.**

*NOTE: Procedures for the handling of biological specimens if storage temperature limits cannot be maintained must be written and included in personnel training. 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:**

- ✓ Records of response time to the alarm

**\*\*REVISED\*\* 08/24/2023**

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



**Alarm system functionality is tested at least semiannually (eg, alarm triggers, ability to communicate, etc.).**

*NOTE: The Biorepository Director may define policies for more frequent alarm system testing based on the level of risk associated with an alarm system and/or communication failure. Temperature controlled storage unit alarms should be tested without taking specimens outside of 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. This includes both individual alarms and central monitoring systems.*

*Records of appropriate alarm triggering and notification of personnel during normal operations may also be used as evidence of functionality.*

**Evidence of Compliance:**

- ✓ Records of alarm system testing

**BAP.09700 Alarm Adjustment**

**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 records of testing at defined intervals.**

**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.*

# INVENTORY MANAGEMENT SYSTEM

## INVENTORY

### Inspector Instructions:

	<ul style="list-style-type: none"> <li>Records of inventory system privilege levels for employees</li> <li>Records of inventory system audits</li> <li>Inventory tracking criteria</li> </ul>
	<ul style="list-style-type: none"> <li>Use of inventory tracking criteria</li> <li>Sample being placed into inventory</li> <li>Labeling of specimens with a unique identifier/code</li> </ul>
	<ul style="list-style-type: none"> <li>How are privilege levels assigned for the inventory system?</li> </ul>
	<ul style="list-style-type: none"> <li>Select a specimen in storage and review the audit trail for the specimen</li> <li>Is there a system in place to identify the exact refrigerator/freezer where a sample is stored?</li> </ul>

### BAP.12500 Inventory Process

Phase II



**The biorepository follows a defined 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:

- ✓ Records 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 quality assurance audits at intervals defined by the director.**

**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 (eg, 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 (eg, 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 (eg, 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.13150 Missing Specimen - Inventory Update





Phase II



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

## SAMPLE MANAGEMENT

### Inspector Instructions:

	<ul style="list-style-type: none"> <li>Sampling of sample distribution records</li> </ul>
	<ul style="list-style-type: none"> <li>Sample being removed from inventory</li> </ul>
	<ul style="list-style-type: none"> <li>What is the process if a sample entered into the inventory system cannot be located?</li> <li>What are you looking for when performing a sample pre-distribution quality check?</li> <li>How do you ensure personnel are available to receive shipments?</li> </ul>
	<ul style="list-style-type: none"> <li>Select a specimen that was shipped and review the audit trail for the specimen</li> </ul>

#### 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 (eg, 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 recorded 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.*

## RECORDS

### Inspector Instructions:



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

**BAP.13740 Record Retention - Biorepository****Phase II**

**The biorepository 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**

**The biorepository complies 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 (eg, insufficient fixation or processing, hemolysis)*

## DISTRIBUTION POLICIES AND AGREEMENTS

### Inspector Instructions:

	<ul style="list-style-type: none"> <li>• Sampling of material transfer agreements (MTAs)</li> <li>• End-user distribution policy</li> </ul>
	<ul style="list-style-type: none"> <li>• Who ensures that the MTA includes all the required information?</li> <li>• Describe the MTA process</li> </ul>

#### 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 material transfer agreement (MTA) addresses each of the following areas as applicable.**

1. **Future distribution of modifications and derivations made by the recipient**
2. **Records 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 a material transfer agreement (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