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Biorepositories for Long-Term Preservation and Future Analysis

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Given the increasingly important role of biospecimens in pharmaceutical development, it is essential for researchers to ensure the long-term viability of biospecimens collected during clinical research. Effective biospecimen preservation requires a comprehensive strategy for the collection, transport, protection and tracking of these temperature-sensitive materials. The specifics of the strategy may vary depending on the nature and intended use of these assets and the size and complexity of the collection, but common principles apply.[1]

The FDA and international regulatory agencies that enforce Good Laboratory Practices, Good Manufacturing Practices, and Good Clinical Practice have laws, regulations and guidances that affect various aspects of biosample collection, processing, storage, transportation and electronic documentation. These laws and regulations include FDA 21 CFR Part 11 and the Health Insurance Portability and Accountability Act (HIPAA).[2,3] New regulations are certain to emerge in the future; they may restrict or prohibit the use of biosamples that have not been maintained under the most stringent conditions.

Biospecimen Sample Collection and Preparation

Biospecimen collection involves three components: collection of the sample, processing of the sample, and recording of information about the sample. Information about the sample is of three types: its source (e.g., study subject), its characteristics (e.g., skin tissue plug biopsy), and its post-collection processing and storage (e.g., placement in freezer 10 minutes after collection). For example, the time elapsed in each step from collection through storage should be recorded and tracked to ensure a consistent process and possibly explain anomalies. Unrecorded information is lost forever, potentially a big problem since future uses of a sample often cannot be anticipated. Privacy issues, of course, must be considered.

Research protocols should therefore include clear and detailed instructions for collecting, processing and storing biosamples, e.g., temperature, centrifuge time, and shipping materials. Since most biorepositories deep-freeze the samples, this article will focus on this method of storage.

Sample preparation methods may affect the results or interpretation of biological studies. Inexact sample preparation can lead to sample loss, reprocessing or complicated data interpretation. For example, tissue sample slices are best obtained immediately after removal from the freezer, as thawing can produces a sub-optimal sample that evades slicing.[4]

To prevent degradation of RNA and DNA, stabilize the matrix (e.g., with alcohol) immediately upon collection. After the matrix has been stabilized, store it at the proper temperature without temperature excursions. Compartmentalized storage equipment, 24/7 temperature monitoring, and back-up power sources are essential.

If possible, aliquot only once. Modern assay technology requires very small volumes for most tests. Divide the sample into as many controlled-volume vessels as might be useful. Document any freeze/thaw cycles to support submission documentation.

Considerations for Long-Term Sample Storage

Sample preservation is essential for both prospective and retrospective analyses. A sample that has maintained the appropriate storage temperature will yield better results than a sample that has undergone fluctuations in temperature due to poor handling or storage practices.[5] Organizations can both protect their financial investment and streamline their research with a strategic sample management plan that takes into account best practices for temperature-controlled storage and logistics, regulatory guidelines, and audit trails.

The U.S. Food & Drug Administration (FDA), the U.S. Centers for Disease Control (CDC), and professional organizations, such as the American Association of Tissue Banks, the National Cancer Institute, and the International Society for Biological and Environmental Repositories, provide guidelines for biorepositories.[6-10] Examples of Good Storage Practices (GSP) include the following:

- Secure facilities and robust quality assurance measures to ensure specimens are stored in compliant conditions at all times
- Qualified staff that has been trained, for example, in global sample transportation procedures, including regulatory and customs issues
- Temperature monitoring of samples around the clock with a comprehensive audit trail and automatic notification system
- Business continuity plans, back-up power, and redundant systems to protect sample integrity during emergencies

Information Management and Audit Trails

The database in which biorepository information is recorded is often called the "biospecimen informatics system." For analysis to be meaningful and accurate, the system should record and report processes through all stages of a sample's shipping, handling and storage lifecycle. The documentation must include an auditable record of who performed what work at what time and on what date.[11] The system must also identify aliquots (subsamples) of the stock sample and exact locations of inventory. Because sample inventories can grow exponentially over time, systems should be scalable and robust enough to quickly locate a physical sample and retrieve its data for an approved user located anywhere in the world. Finally, the system needs to auto-store temperature records without human intervention.

To prove that a sample has been maintained in adequate conditions, three sets of data are required: storage temperature(s), a lifecycle audit trail of the sample from entry into the system through retrieval or disposal, and a complete chain of custody of actions taken on the sample during storage. An audit trail that complies with FDA 21 CFR Part 11 requires documentation of the action taken on the sample along with the date, time and handler's signature.

Biorepository Capabilities

Some central laboratories that test blood and tissue samples offer sample storage as an ancillary service. However, it is essential that long-term storage facilities be optimized for reliability and information management. Specialized biorepository vendors may provide services like automated sample tracking and reporting through barcode capture; fully verifiable audit trails; extraction of nucleic acid; verification of DNA purity, yield and concentration; and volumetric and normalized aliquoting. These services allow researchers to customize various quantities of samples from a given subset of subjects into the sample sizes and tubes required for testing.

Cold Chain Logistics

Cold chain management is necessary for the packaging, transport and storage of temperature-sensitive biomaterials. Biorepository logistics personnel must be familiar with cold-chain logistics best practices and global customs and regulatory requirements. Study sponsors should provide clear and detailed instructions on sample collection and delivery to support cold-chain logistics decisions. For example, shipping a biosample over the weekend may require extra dry ice and a larger package. Managing the cold chain, especially as clinical research globalizes, requires meticulous application of best practices.

Conclusion

Preservation of the integrity of scientific sample assets is becoming increasingly important to research companies as prospective biomarker testing and the need for retrospective sample analysis grows. Proper protection of sample assets for research purposes requires a comprehensive biorepository strategy, including compliant collection processes, reliable cold chain transport, Good Storage Practices, and comprehensive audit trails.

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