From Collection To Destruction

Managing the lifecycle of a biological sample during a clinical trial is a strenuous task, to say the least. Meticulous record maintenance of each sample for each trial is required for successful results

Eric Hayashi
at LabConnect

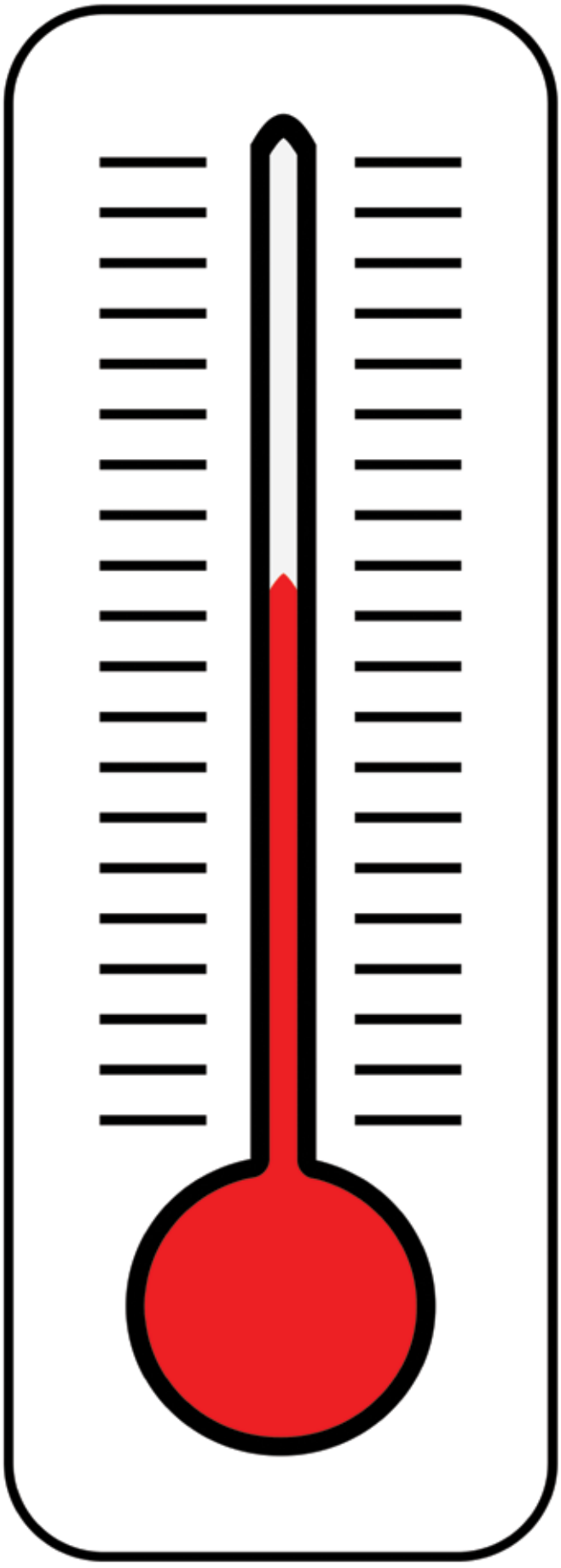
Biological samples are supremely delicate and exceptionally valuable. Samples that were once tested and discarded are today carefully preserved in biorepositories – as insurance against future regulatory enquiries, as well as to potentially serve as vital keys to biomarker studies to come, or to some yet-unknown branch of research. With such valuable assets at stake, the entire research community must work together to ensure that each and every sample from every clinical trial – untold billions in all – is uniquely known, and that its entire history can be verified from the moment it is collected until it is deemed no longer needed.

Best Practices

Today's best practices in sample management have changed and continue to evolve as new lines of cellular and other research avenues are developed. Nowadays, to be research-viable, samples must be much more tightly controlled and surrounded by additional data, with further careful planning going into each step of their existence.

Chief among the best practices to preserve sample integrity is the development of a comprehensive strategic sample management plan, to help control pre-analytic variables that could compromise sample integrity, or otherwise alter research outcomes. The planning procedure looks at every detail, including what samples should be collected, how they should be handled and how they will be accessioned into a sample tracking system – as well as how they will be transported, analysed and prepared for long-term storage.

To safeguard integrity, every step in a sample's lifecycle must be monitored, recorded and carried out through meticulous adherence to uniform standard operating procedures (SOPs) that are harmonised throughout the study. From collection through cold chain transport, to central laboratory testing and



biorepositories, everything must be standardised, including collection tubes, shipping containers, laboratory equipment and cryogenic freezers.

Developing Countries

The growth of clinical trials in developing countries and in rural areas introduces a new level of complexity to ensure trial-wide adherence to SOPs. One trend that is facilitating the whole process of conducting trials in China, Eastern Europe and other regions is that central laboratories – offering state-of-the-art testing and biorepository services – are building facilities, and/or establishing strategic partnerships to respond to the demands of large, global CROs.

In many cases, the location of these buildings dramatically shortens the distance between investigative sites and appropriate testing and storage facilities – thereby lowering the cost of logistics, as well as reducing opportunities for unexpected temperature excursions. Having facilities relatively close by also enables specialised processing for some procedures that may have to be completed within 24 hours or less. In addition to new testing sites, many well-known international shipping companies are establishing cold chain logistics systems and capabilities in these rural regions, which are comparable to those found in more developed countries.

Cellular and Gene-based Research

Additional care should be taken in the sample management of new cellular and gene-based research and studies on immunology or cancer immunotherapies. With each sample collected from a participant at different intervals during the study, the biorepository may be required to extract DNA and RNA, and make aliquots of each sample. Additionally, the biorepository may need to isolate peripheral blood mononuclear cells (PBMCs) and cryopreserve them in liquid nitrogen.

When preparing a comprehensive sample management plan, several of these facilities and carriers may need to be investigated to ensure they have the regional capability and capacity to carry out the programme in the intended way. This process should be conducted carefully and methodically – not only because the integrity of individual samples is affected by this, but also because various regulatory agencies may demand the researcher's due diligence in selecting resources. Prior to first patient, first visit, the investigator site list should likewise be evaluated to determine if specific locations should be subject to a logistics dry run. This process provides an opportunity to develop alternative solutions before problems occur.

Standard Tools

Another key aspect of unified sample management is to provide investigative sites with appropriate tools. If protocol

calls for collecting blood and isolating PBMCs, each of the sites must have kits containing the right kind of collection tubes, labelling and barcoding equipment, as well as validated shipping containers that have been certified for a variety of conditions, including crush resistance and temperature maintenance. Shippers may also be equipped with a temperature monitoring device, as it is necessary to be able to monitor and document temperatures of these samples for later reference. Typically, sites do not maintain the kinds of resources in their own inventory, so it is up to the CRO or central laboratory and biorepository to provide suitable shippers, monitors and air bills.

As clinical trials are conducted in more and more places around the world, the regulatory and customs requirements of individual countries – and even of some cities – take on increasing importance. Having a sample held up in customs can adversely affect a study. In preparing a sample management plan, it is mandatory that the legal requirements of each destination to which the samples will be sent is understood – as well as the regulations and requirements of the International Air Transport Association, the US Department of Transportation and individual carriers such as FedEx, DHL, World Courier and so forth.

Sample Tracking

In contemporary clinical trials, data collection and sample management go hand in hand; each must be meticulously maintained and data must be carefully annotated to each sample and corresponding aliquot. To document the fact that samples have been held under correct conditions from the time they are collected until they enter long-term storage, a comprehensive system to digitally track and monitor each individual sample in real time is needed.

Because researchers today are looking for the best ways to leverage individual specimens to drive clinical research, as well as translational and personalised medicine, they want complete datasets surrounding each specific sample. The increasing size and complexity of sample collections underscore the necessity of standardised procedures and a comprehensive sample management system (1). What is needed is a system that applies a unique identifier to each sample that will be maintained throughout its lifecycle. This allows individual samples to be tracked and monitored at every step from collection through testing and during long-term storage, while also providing an unalterable, 21 Code of Federal Regulations (CFR) Part 11 compliant audit trail for later reference.

Entering the Biorepository

Primary sample testing is only one aspect of sample management. How development teams preserve the sample for downstream testing becomes increasingly important, due to the move of translational medicine and the facilitation of drug discovery for personal medicine and companion diagnostics utilising biomarkers. As a facet of sample management planning, teams must imagine every possible use for samples as a part of the protocol development discussion.

When pharmaceutical sponsors, CROs or academic researchers select a biorepository today, they require the facility and its team to support their long-term goals. Furthermore, not only do they expect the biorepository to do more than merely ensure sample integrity, they also want to be reassured that it is able to provide on demand well-annotated biospecimens that have been maintained according to a predefined set of controlled environmental conditions. This helps to guarantee validity of downstream analytics – whether histological,

biomarker or molecular in nature. In addition, clients need to be certain that biospecimens are safe and secure, that risk of damage or loss is minimised, and that there are processes in place to provide business continuity.

Biorepository features should include:

- Ambient (room temperature) storage
- Cold storage (-20°C)
- Ultra-low temperature storage (-70°C to -80°C)
- Liquid nitrogen vapour phase storage (-190°C)
- Fully validated and mapped backup freezers
- Backup generator and redundant heating, ventilation and air conditioning systems
- Temperature monitoring system for all freezers and refrigerators with 21 CFR Part 11 compliant unalterable audit trail
- Redundant whole building and biorepository security systems

For a Better Future

Clinical trials have evolved in ways and in locations that would have been difficult to imagine even a few years ago. It is only relatively recently, however, that the importance of implementing a standardised approach to meticulously manage samples – from collection to destruction – has been recognised as a critical criterion for success in clinical research. Standardising SOPs study-wide includes minimising the effects of pre-analytical variables, while the annotation of biospecimens with comprehensive data optimises the value of the sample – and facilitates research outcomes that may be years in the future.

Reference

1. May M, Better features for biobanks, *Bioscience Technology*, January 2013. Visit: www.biosciencetechnology.com/articles/2013/01/better-features-biobanks#.UoPIV_nNW-M

About the author

Eric Hayashi's experience includes more than 22 years in the clinical trials industry. He currently serves as President and Chief Executive Officer of LabConnect, a leading provider of global central laboratory services, including routine and esoteric laboratory testing, kit building, sample management, biorepository and scientific support services for biopharmaceutical, medical device and CROs. Email: ehayashi@labconnectllc.com