ATCC®

Storing Biological Materials for Pharmaceutical R&D

BIOREPOSITORIES SEE BROADER ROLES AND LARGER SAMPLE VOLUMES

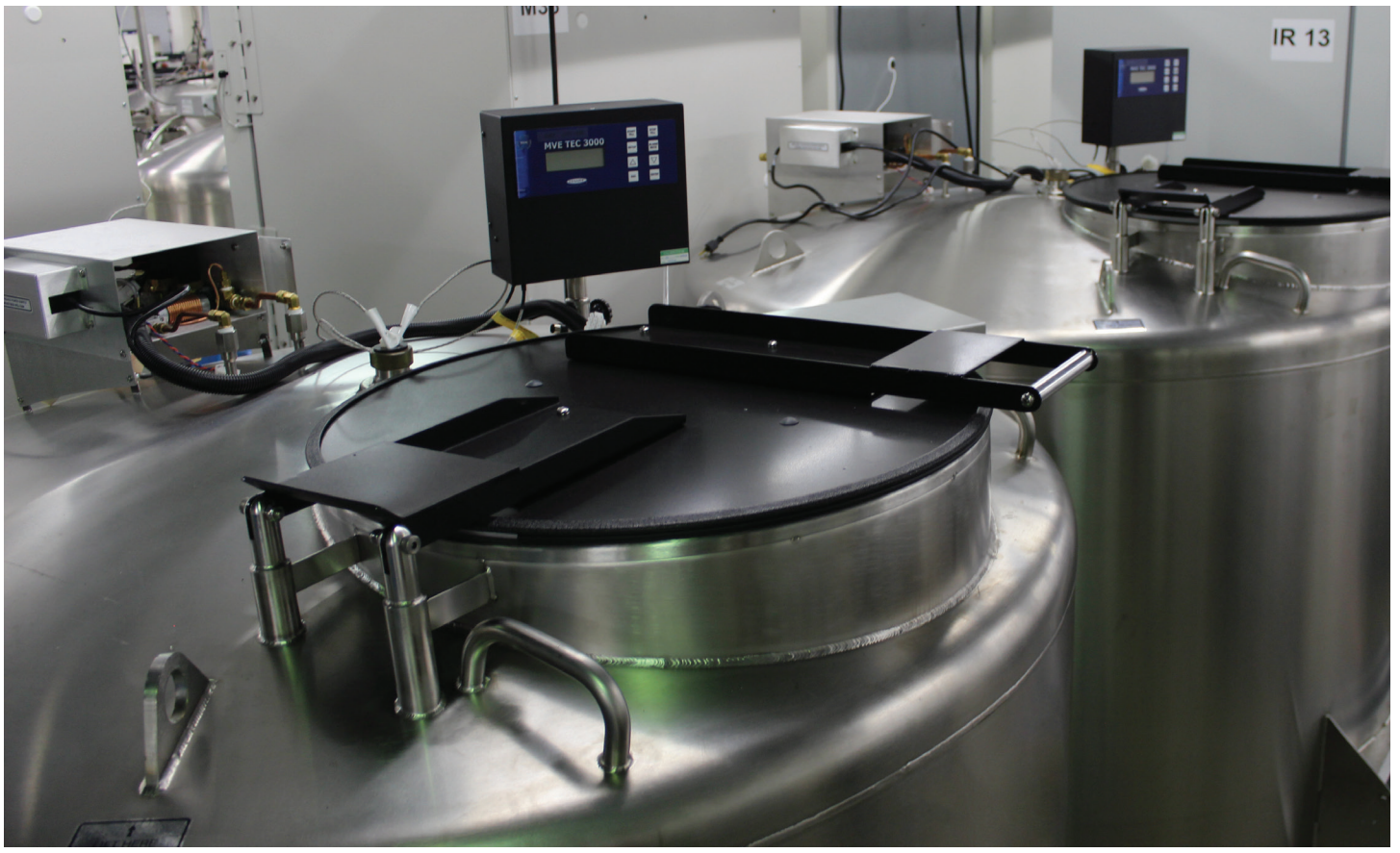
INTRODUCTION

High-quality biological samples have become essential tools for supporting research and development (R&D) in the pharmaceutical industry. Pharmaceutical R&D remains a broad field of study, but several areas of particular focus and interest have arisen recently. These include personalized medicine, translational (laboratory-to-clinical) research, studies of the human microbiome, population-based genetic testing, infectious disease research, and studies of antimicrobial resistance. R&D efforts in these and other areas often require specific biological materials, such as cell lines, microorganisms, and other biological tools. Biorepository facilities, which are dedicated to the collection, handling, storage, and distribution of biological materials for use in research, are the places of choice for maintaining these biomaterials. This article is designed to provide an overview of the relationship between the evolving practices of modern biorepositories and the current trends in pharmaceutical R&D.

A GROWING VOLUME OF BIOMATERIALS

The current pharmaceutical research environment is driven by the desire to improve quality of life and health outcomes while reducing the costs of healthcare. R&D efforts are being carried out in an environment in which the costs of DNA sequencing and synthesis are decreasing quickly and gene profiling methods are improving through the analysis of rapidly expanding data sets. Treatment approaches are becoming more individualized as personalized medicine becomes a clinical reality. In addition, research tools—from analysis to automation—are improving as well.

The increased level of R&D involving biomarkers, personalized medicine, clinical genomics, translational research, infectious diseases, and others, has led to a need to handle and store a large proliferation of biological samples. The increase in samples requires more storage and an increased need for sample processing, as well as mechanisms and systems for packing and distribution of samples. Biorepositories offer a specialized set of expertise surrounding the collection, processing, authentication, storage, and distribution of a large volume of biological samples. For the purposes of this white paper, the terms biological storage facility, biobank, biorepository, and biological resource center are used interchangeably; although, there may be some subtle distinctions among those terms by those involved in the industry. The differences are outside the scope of the current article.



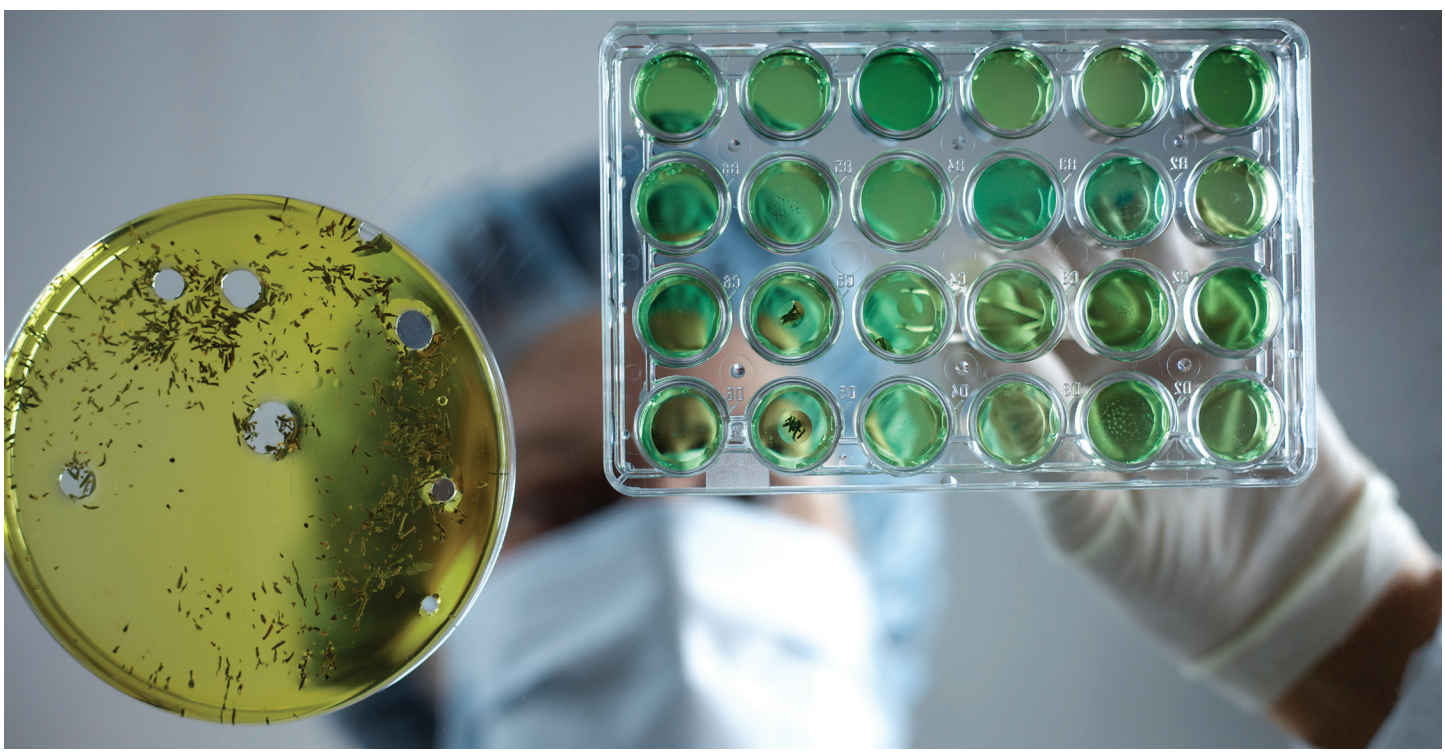
SHIFTING ROLES FOR BIOREPOSITORIES

There is a long history of collecting biological specimens for use in diagnosing diseases (for example, in biopsies and post-mortem pathology), but the collection, storage, and use of biological samples in drug development and basic research is a somewhat newer phenomenon. Many early bio-storage collections were based in academic laboratories and were designed to support specific research projects. Over time, the collections evolved and expanded to include institutional and government-supported repositories that supported multiple research efforts, as well as commercial (for-profit) biorepositories, population-based biobanks, and others.

Specialized biorepositories have arisen to store and provide access to a wide range of biological materials, including cell lines, tissues, microbes, and others, in support of studies on disease etiology or the development of new therapies, drugs, biomarkers, prognostic and diagnostic tests, and clinical trials for FDA approval. The current R&D environment has driven a dramatic increase in the number of samples requiring competent storage, testing, and traceability. Paralleling the expansion in samples is an effort on the part of the biological storage industry toward standardization and harmonized best practices.

Currently, a comprehensive, verifiable biobank inventory is not currently available, making it difficult to reliably determine the total number of repositories worldwide. This has also slowed efforts aimed at facilitating cooperation and standardization within the industry. However, a significant amount of information on the network of biological storage facilities does exist. A recent (2016) market report from BCC Research forecasts that the biobank industry will grow to $240.2 billion between 2016 and 2021, with a 3.9% corporate average growth rate (CAGR).[1] The sector projected to experience the most growth in the market is the Population Biobanks at a CAGR of 5.8%, growing to a level of $76.7 billion. The growth in the Population Biobanks sector is attributed to the fact that many countries across the globe are witnessing the emergence of new population-based biobanks. Private Sector Biobanks will grow at a CAGR of 3.6% and rise to a level of $93.7 billion by 2021. Disease-based biobanks will grow at a CAGR of 2.4% from 2016 to 2021 and increase to a size of $69.8 billion by 2021. Disease-based biobank activity is projected to grow significantly within the biotechnology/pharmaceutical and Private Sector Companies market segment; this growth is accounted for in the segment's overall growth.

As the needs of industrial pharmaceutical R&D change and the capabilities of bio-storage facilities expand and improve, the relationships between biorepositories and private companies continue to evolve. But, there are several trends worth noting. While many current collections are still owned by individual institutions for specialized purposes, biorepository facilities that are dedicated exclusively to the centralized storage of important biomaterials for general research purposes have emerged in the past two decades. These facilities have also become key players in drug development—they are used by the pharmaceutical industry as sources of archived biospecimens on which to perform a wide range of molecular analyses. Further, samples from biobanks can aid investigations into disease biomarkers. The validity of research using archived biospecimens and cell lines depends greatly on the methods, protocols, and conditions under which the materials are collected, processed, and stored. This includes not only storage temperatures, but also detailed information on the sample storage history.



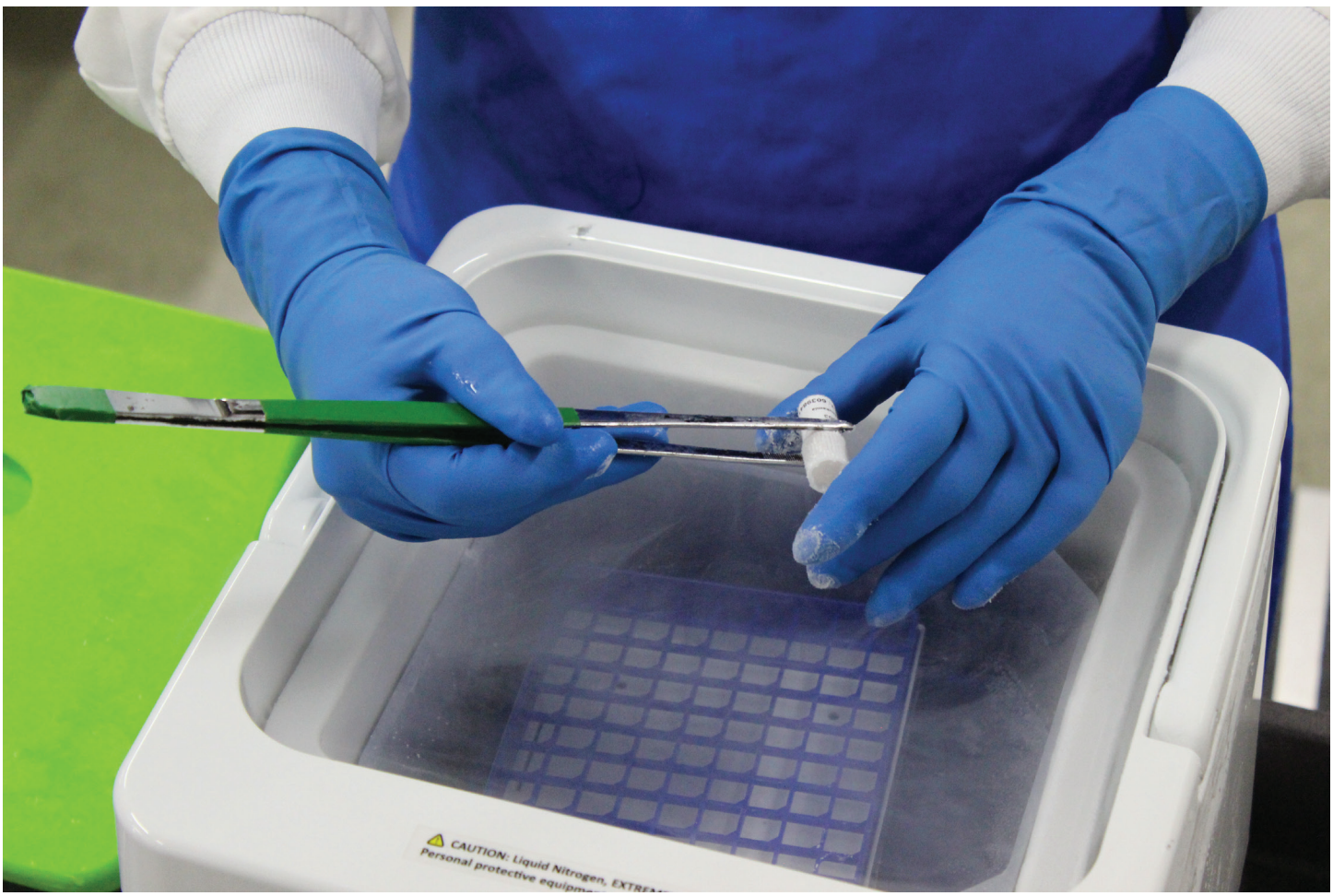
DEDICATED EXPERTISE

Due to the importance of preserved biological samples in the research and development of pharmaceutical products, the collection, handling, and long-term storage of biomaterials has become a specialized scientific discipline unto itself, and centralized, dedicated facilities for storage have emerged. Many pharmaceutical companies are currently weighing the costs and benefits of maintaining their own in-house biorepositories and cell banks versus outsourcing the bio-storage services to a dedicated bioresource center that can offer specialized expertise, detailed knowledge of privacy concerns and ethical standards for de-identification, and distribution of materials to laboratories globally.

In many cases, centralized biorepositories are capable of providing a number of services more efficiently than a single pharmaceutical company could achieve by building its own collection in-house. Also, building a world-class biorepository facility requires a significant outlay of capital for buildings, equipment, instrumentation, personnel, security, and transportation infrastructure. Therefore, in many cases, it has made sense to outsource the operations to such biorepositories and to use established facilities for R&D projects.

Modern biorepositories offer professional and support staff with specialized expertise and experience in handling biomaterials that benefit drug discovery and development research. Bio-storage facilities are highly complex operations that employ individuals with a wide range of specialized expertise in the storage and handling of biomaterials. These areas include tissue handling, cryogenics, pathology, genetics, molecular biology, microbiology, and clinical data management. In addition, dedicated biorepositories are set up for distribution of materials. These kinds of multi-disciplinary teams are required to run the storage facilities and operate the laboratories in a modern biorepository. In addition, knowledge housed at dedicated biorepositories lies in the areas of biospecimen authentication, regulatory compliance related to collection and privacy, and adherence to standards related to storage and labeling.

Physical biomaterials are not the only items stored—for the effective use of biomaterials in pharmaceutical product development, information and data associated with the biospecimen are also critical. Today's biological storage facilities also possess associated data and information associated with each sample. As such, they require secure information management systems and a keen awareness of applicable legal and ethical requirements for biological samples, including privacy and cybersecurity issues.

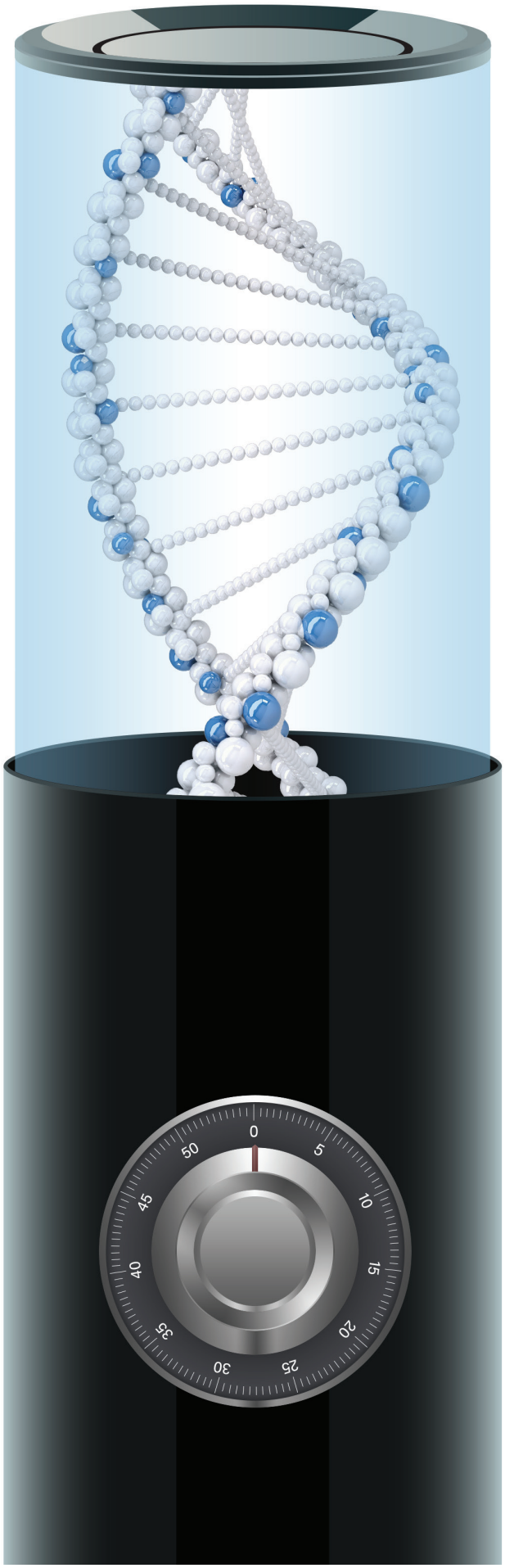


PRIVACY AND SECURITY ISSUES

Collecting, processing, storing, and distributing biological specimens are activities fraught with legal and ethical issues, especially when human tissues and cells are involved. In situations where biological samples are collected directly from humans in the context of a specific research project, and the sample donor's personal information is identifiable to the researchers, then the sample is considered part of human subject research and is governed by U.S. Department of Health and Human Services regulations (Title 45 Code of Federal Regulations part 46; also known as the "Common Rule"). The same is true of microbiological strains that are isolated from clinical sources. The Common Rule requires that researchers obtain informed consent from sample donors prior to collecting, storing, and using their tissues for research purposes. In addition to the Common Rule, the U.S. FDA also has regulations (Title 21 Code of Federal Regulations Part 50) on informed consent and protection of human subjects. Finally, biological storage facilities, when handling protected health information associated with biological samples, are also bound by the Health Insurance Portability and Accountability Act, also known as the HIPAA Privacy Rule. Federal law and regulations leaves doubts and uncertainty, which has been addressed to some extent by case law.

The Indiana University Center for Bioethics (Bloomington, Ind.; bioethics.medicine.iu.edu) has outlined a number of issues with regard to biorepositories and the ethics of collecting and storing human tissues. These questions explore the balance between advancing medicine and improving health, which requires the broad collection of specimens and information while simultaneously recognizing and protecting individuals' rights not to donate specimens. Among the questions cited by IU are the following:

- Should the application of the Common Rule be contingent upon whether or not specimens are directly identifiable to the researcher?
- Should an institutional review board (IRB) be allowed to waive application of the Common Rule for biobanking research because individuals may not be aware their specimens are being used for research, or does this conflict with the IRB's function?
- Can (or should) an individual provide "blanket consent," giving permission to an institution and its research partners the ability to use one's specimen for future unspecified use, or does this undermine the purpose of informed consent?
- Does respecting an individual's autonomy give one the ability to limit how one's specimen is used (such as authorizing use for a particular study only and not for other studies)?
- How (if at all) should biobanks address the principle of benefit sharing with donors?
- The current assumption of current jurisprudence is that an individual no longer owns one's tissues once they have been excised from one's body by consent or waiver. Is this desirable?
- Does an individual have a right to prevent one's specimen from being used in for-profit research intended to develop commercial products such as gene patents or genetic diagnostic tests?
- How should we address the potential for information leaks in genome wide association studies? Does this change when research falls under the Common Rule and Privacy Rule because the donor can be identifiable?



ACCREDITATION AND STANDARDS

Historically, there have not been established standards for biorepositories. The lack of standards complicates data sharing and transfer of samples between laboratories, which can hinder research progress. Conversely, compliance with a common set of standards across all biomaterial storage facilities would facilitate research collaboration and study comparisons by different laboratories and at different times by ensuring a common set of handling and storage protocols. Now, a network of modern biorepositories is at the forefront of developing harmonized best practices. Efforts are now ongoing toward standardizing best practices for storage, processing samples, handling, and so on.

Biobanks become more complex and expensive when they comply with standards and best practice guidelines, but the positive aspects of standardization far outweigh the negatives. With the important goal of global harmonization of standards and protocols for bio-storage and handling in mind, consortia and agencies are working on developing such standards. Among the most important organizations involved in issuing relevant standards and regulations for biological storage facilities are the International Organization for Standardization (ISO), the College of American Pathologists (CAP), and the U.S. Food and Drug Administration (FDA).

ISO. The International Organization for Standardization (ISO; Geneva, Switzerland; www.iso.org) publishes international standards across many industries and sectors. Among its most popular standards is ISO 9001, an international standard that specifies the requirements for an organization's quality management system (QMS). Originally published in 1987, the ISO 9001 standard is currently on its 2015 version. The standard is based on a number of quality management principles, according to ISO, including a strong customer focus, the motivation and implication of top management, the process approach, and continual improvement. Some of the leading biorepository facilities have patterned their own QMS to adhere to the ISO 9001 standard. For example, according to the National Cancer Institute (Bethesda, Md.; www.cancer.gov), "Biospecimen collection, processing, management, and distribution should be carried out within a quality management system (QMS) that contains documented quality assurance/quality control (QA/QC) policies and written SOPs [standard operating procedures]."[4] NCI adds that where feasible, the QMS should be managed by individuals who are not involved in repository operations; although, the institute acknowledges that this is not always possible.

In a best practices document, the International Society of Biological and Environmental Repositories (ISBER)[5] states the need for biorepositories to meet the requirements of the ISO 9001 standard. A biorepository's purpose is to "supply biological materials and their associated data in form that meets specific quality criteria and is provided in compliance with all necessary regulatory and statutory obligations," the ISBER document says, adding that therefore, a QMS that includes both quality assurance and quality control programs "should cover the full spectrum of a repository's operations." Among other items, ISBER recommends that repositories be able to carefully track all specimens that are received and distributed by the facility and that repositories have a set of standard operating procedures that governs all handling and processing activities.

CAP. Another credential relevant to biorepository operations is the Laboratory Accreditation Program administered by the College of American Pathologists (CAP; Northfield, Ill.; www.cap.org), which is a professional organization that fosters improved practices in pathology and laboratory medicine. According to CAP, the laboratory accreditation program helps a wide range of laboratories to meet Clinical Laboratory Improvement Amendment (CLIA) regulatory requirements (for U.S.-based laboratories). Using the most highly scientifically endorsed laboratory standards, the program is designed to maintain the accuracy of test results and ensure accurate patient diagnosis. For biorepository facilities, the CAP accreditation requirements guide the testing of biomaterials derived from both humans and animals.

FDA. Biorepositories that are involved with pharmaceutical product R&D may also adhere to current good manufacturing practice (cGMP) regulations, which are enforced by the U.S. Food and Drug Administration (FDA; Silver Spring, Md.; www.fda.gov). The cGMPs outline requirements for the proper design, monitoring, and control of manufacturing processes and facilities for pharmaceutical products. According to FDA, this includes establishing strong quality management systems, ensuring high-quality raw materials, using robust operating procedures and detecting and investigating product quality deviations. For facilities that handle biomaterials, compliance with cGMPs is an expensive and difficult proposition, but it allows greater involvement in a wider range of drug development and clinical research.

CONCLUDING REMARKS

Biorepositories are dedicated to serving the scientific community by maintaining valuable biological materials. By providing access to a wide range of highly characterized biomaterials, biorepositories play an important role in advancing life science research in the public and private sectors. They have become an indispensable part of the research enterprise in life sciences and beyond for both academic researchers and private companies. Technology and practices related to collecting, storing, processing, and distributing biomaterials will continue to advance within biorepositories alongside the research community.

For more information on products and services offered by ATCC, visit www.atcc.org/biorepository.

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ATCC: OVER A CENTURY OF BIOMATERIALS MANAGEMENT

Among the world's leading facilities for the storage and distribution of biomaterials for life science research is ATCC, a not-for-profit organization with a history of more than 100 years in the handling of biological resources. The organization serves as a prime example of a dedicated biorepository that supports research in a range of scientific disciplines, including cell biology, microbiology, medicine, and others. In its mission statement, ATCC states that it focuses on "the acquisition, authentication, production, preservation, development, and distribution of standard reference microorganisms, cell lines, and other materials." ATCC serves U.S.-based and international researchers by "characterizing cell lines, bacteria, viruses, fungi, and protozoa; developing and evaluating assays and techniques for validating research resources; and preserving and distributing biological materials to global public, private industry, and government research and scientific communities."

Initially established in 1925 as a central collection of microorganisms that would serve scientists across the globe, ATCC has grown its holdings substantially since then, and now occupies a 126,000-square-foot facility in Manassas, Va., not far from Washington, D.C., as well as a new 36,000-square-foot facility in Gaithersburg, MD.

ATCC currently holds a number of biological materials collections in several major categories. The organization's cell biology collections include more than 3,600 cell lines from 140 different species, including a range of hTERT-immortalized primary cells (those that can be expanded for more passages by introduced expression of the human telomerase reverse transcriptase [hTERT] gene). ATCC also maintains the world's largest collection of bacteria, viruses, protozoa, fungi, and yeast, including materials for infectious disease research, antimicrobial resistance studies, and bioenergy research. Further, ATCC offers a range of specialized products for life science research, including culture reagents, testing and characterization tools, and quality control strains. In addition to biorepository activities, which include order fulfillment and distribution, ATCC also conducts independent research and development in pursuit of its mission, develops biological standards and national consensus standards, and provides a variety of services to the scientific community.

Paralleling its biomaterials, ATCC offers a full slate of services to meet the needs of a specific project. ATCC partners with research teams to conduct small- and large-scale manufacture of cell lines from several vials to thousands of vials, including the creation of master and working cell banks. ATCC also provides cell authentication services, including human cell line STR profiling, mycoplasma detection, and CO1 testing for species identification. Project managers and ATCC subject matter experts work with research teams throughout all stages of the project, including the design of the project, the production and authentication of the biological materials, and the ultimate distribution of the materials. These services leverage the collective specialized expertise in biomaterial management within ATCC, allowing customers to focus on their own core competencies.

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