Towards Norms for Accreditation of Biobanks for Human Health and Medical Research: Compilation of Existing Guidelines into an ISO Certification/Accreditation Norm-compatible Format

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Summary

In recent years, biobanks have evolved into professional infrastructures that acquire, validate, process, store, manage and distribute biological material of human origin to public or private end-users/researchers. This article (a) highlights the importance of quality assurance for both the biobank basic processes and sample annotation in order to ensure reliable results of research based on these samples, (b) suggests that certification according to international standards can contribute to the organization of the biobanking processes while accreditation can contribute to the organization of sample characterization/validation, and (c) provides a compilation of all existing

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guidelines against an International Organization for Standardization (ISO) format.

Key Words: biobank; norm; human samples; medical research; standards

Introduction

Research biobanks[1] (biobanks) facilities are organized to collect, store, annotate and distribute human biological specimens from a large number of patients and healthy persons. By providing materials to basic, translational and epidemiological researchers undertaking ethically approved scientific research, biobanks play a critical role in the science of improving both our understanding and capability of improving the human health condition. In many instances, biobanks enable meaningful scientific discovery that would not otherwise be possible.

Biobanking has witnessed significant changes in the recent past with an increased emphasis on donor interests, rights and privacy and an explosion of new technologies and research knowledge. Biobanks, as operating units, have worked diligently to ensure their operations meet or exceed standards in the community in which the bank operates. Overall the growth in biobanking has led to community standards in the form of published guidelines. The challenge for individual biobanks is to meet the various guidelines.

This paper examines the major guidelines available at the time of the study for comparison and possible inclusion in an ISO certification/accreditation format.

Background

Once considered an individual research initiative, the rise in the scientific importance and contribution of biobanks, along with an increased awareness of privacy and ethical responsibilities, has resulted in a global understanding of the need to create stable and well managed operations to oversee the critical resource of human biological materials. Biobanks are evolving from a cottage operation to a mature operation.

Human tissues that are currently being used in such research studies are collected, either in conjunction with a specific research project (*project-driven biobanks*) or systematically, before elaboration of any specific project (*systematic biobanks*). However, human biological material sampled for diagnostic and treatment purposes in the public and private health-care system (*diagnostic biobanks*) constitutes the vast majority of samples. Such samples are being stored and could be used for research (at least for genetic research, based on DNA, which is the most robust macromolecule), after appropriate 're-qualification' procedures. 'Re-qualification' is the procedure that allows samples collected for medical purposes to be used in research. For example, tens of millions of samples are being stored every year from each European population, in blood donor bank settings. Finally, there are some initiatives aiming at compilation of large population cohorts for large-scale prospective epidemiological genetic studies (*epidemiological biobanks*) [1].

In 1999, the Organisation for Economic Cooperation and Development (OECD) suggested that national governments 'should support the development of an accreditation system for biobanks based upon scientifically acceptable objective international criteria for quality, expertise and financial stability' [2]. Since then, guidelines have been published by the International Society for Biological and Environmental Repositories (ISBER) [3], the National Cancer Institute (NCI) [4] and the OECD itself [5]. However, none of the above organizations has

[1]For evolutionary reasons, research biobanks are frequently referred to as 'tissue banks'. The term 'tissue' in this instance refers to all human solid tissue, biological fluids, and their derivatives, such as cell lines, DNA or RNA.

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the production and promulgation of such standards as its primary purpose.

So, despite the availability of several guidelines, no relevant international norm exists that can be applied to biobanks. Nowadays, multicentre (often international) medical studies based on human samples are increasing and have become of major importance for future patient care. Therefore, biobanks need to guarantee exchangeability of samples, without institute-dependent intrinsic bias. Sample validation is the only way to guarantee that samples distributed to industry/academia researchers meet the required specifications, and corresponds to an activity that can be accredited by an external body. An international norm is essential in this situation.

This paper looks at the available guidelines for biobanks and compares them with the requirements of those currently available international standards that could be applied. In addition, a critical compilation of existing guidelines for medical research biobanks has been created following the structure of ISO standards. This can form the basis of a future norm for certification/accreditation of biobanks for health and medical research.[2]

Methods

Current ISO standards that might be applied to biobanks were examined and the best ISO format for biobanking was determined. International reference documents which could apply to biobanks are ISO 9001:2000 [6], ISO 17025:2005 [7] and ISO Guide 34:2000 [8]. All existing and previously published guidelines/best practices intended for biobanks were assembled into this ISO norm-compatible format. To enable proper comparison of all these documents the vocabulary needed to be adapted to ensure language uniformity as outlined in Inset 1.

Some parts of the original texts were far more detailed than others. Detailed implementation guidelines/best practices in original documents became 'notes' in the final compilation document in order to ensure scope uniformity. The following implementation guidelines were characterized as notes (the organizations responsible for publication of the original texts are shown in parentheses):

- training (ISBER);
- working environment (ISBER);
- safety (biological, chemical, electrical, fire, physical, radiological) (ISBER);
- equipment (refrigerators, liquid nitrogen freezers, supply, back-up storage capacity, alarm systems …) (ISBER);
- specimen types (ISBER);
- the NCI Center for Bioinformatics (NCI);
- locating specimens in storage (ISBER);
- packing instructions (ISBER);
- bar coding (ISBER);
- labels (ISBER);
- code of Federal regulations (ISBER);
- Health Insurance Portability and Accountability Act (ISBER);
- release of de identified datasets (ISBER);
- release of limited datasets (ISBER).

Results

Table 4 shows the final results of the compilation; numbers of chapters are shown. This table summarizes the integral compilation text that was devised. The text is published in this issue of the QAJ and can be downloaded as colour-coded version from http://www.marblearchgroup.org/guidelines.compilation.htm or http://www.biobanque-picardie.com/compilation.pdf.

Despite the availability of several guidelines, no relevant international norm covering all of the activities of a biobank exists. One international and flexible norm that could apply to biobanks is ISO 9001:2000, but this remains a generic norm for the implementation of quality

[2]Certification is a procedure by which a third party gives written assurance that a product, a process or a service conforms to specific requirements. Accreditation is a procedure by which an authoritative body gives formal recognition that a body or a person is competent to carry out specific tasks. Accreditation is the proof of the competence, the impartiality and the independence of a certification body in view of existing norms.

Table 1. Interpretation of terms used in the compilation of Table 4 and vocabulary changes made in the compiled text

(Bio)Repository (ISBER)	Biobank
BRC (OECD)	Biobank
Laboratory (17025)	Biobank
Interlaboratory (17025)	Interbiobank
Testing and calibration (17025)	Acquisition, maintenance and provision of biological materials and/or validation/authentication
Item, material, product or substance (17025, Guide 34)	Sample or biospecimen
Test (17025), test or calibration item	Sample
Guidance (OECD)	Standard
Measurement (17025)	Sample or sample quality
Measurement (Guide 34)	Validation/authentication
Test results (17025)	Sample quality or sample-associated data
Testing (17025)	Validation/authentication
Calibration (17025)	End usage
Governmental (NCI)	National
Sampling, measurement and test equipment (17025)	Reception, preparation and maintenance and validation/authentication equipment
Handling of test/calibration items (17025)	Handling of biological samples
Reporting of results (17025)	Reporting of data
Results or test/calibration results (17025)	Sample-associated data or data
Test/calibration certificate (17025)	Validation/authentication certificate
Test report or test/calibration report/certificate (17025)	Sample report
Substance, material or product sampled (17025)	Aliquots
Viable strain (OECD)	Available sample
Access (17025)	Access to samples and data

management systems, client satisfaction and continuous improvement [6]. ISO 9001:2000 remains geared towards management. Other international reference documents, focused on competence, include ISO 17025:2005, which applies to assays and calibration [7] and ISO Guide 34:2000, which concerns general requirements for reference material producers [8]. ISO Guide 34 applies to those biological materials that may be submitted to extensive characterization and therefore be considered as reference materials. Moreover, the Council of Europe has published recommendations on biological material of human origin [9].

Some biobanks fall within the definition of reference material producers as 'technically competent bodies that are fully responsible for assigning the certified or other property values of the reference materials they produce and supply which have been produced in accordance with ISO Guide 34' [8]. ISO Guide 34, in combination with ISO 17025, meets the need of these biobanks for a technical standard as envisaged by the International Laboratory Accreditation Cooperation (ILAC) General Assembly in October 2004 [10]. This General Assembly resolved that accreditation of technically competent bodies producing reference materials with assigned values will be conducted against harmonized criteria based on ISO Guide 34 and ISO/IEC 17025. Examples of biobanks as reference material producers are those banks that provide well characterized microorganisms or established cell lines (Figure 1). However, most biobanks do not act as reference material producers. For example, banks providing human tissue to researchers contain only a few samples from each donor and a researcher will use material from multiple donors based on disease diagnosis or other donor characteristics. The characteristics of interest may not be known at the time samples are collected and an individual sample may be of value to many researchers with different research interests, but supply is limited.

This type of biobank may carry out some testing such as safety testing by looking for blood-borne viruses, but most banks are not

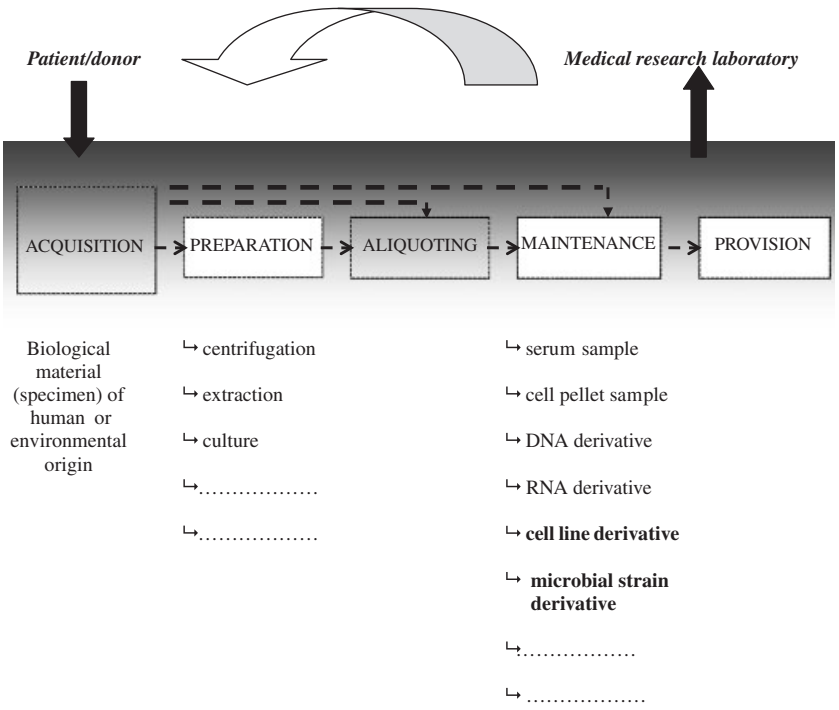

Figure 1. Global Schema of Biobank Processes. The scope of biobanking activities is shadowed. Biological material, may be a 'specimen' (what is collected), a 'sample' (what is stored) or a 'derivative' (what is produced after laboratory processing of a sample). Derivatives in bold are those potentially considered as 'reference materials'

trying to characterize the samples fully. Thus, they are not producing well-characterized material in the same sense as a reference material producer; the key technical challenge is the preservation of the characteristics of the samples as closely as possible to their *in vivo* state. Some biobanks do not carry out any testing on the samples collected because of the limited nature of the material. Use of ISO 17025 and ISO Guide 34 is not appropriate for these biobanks.

Results of research using human biological samples often depend on the 'events' that samples have undergone during their 'lifetimes' from sampling through to processing, freezing, and thawing prior to usage (the so-called 'pre-analytical variations'). Therefore, biobanks must guarantee traceability of all such events and ideally perform quality-control testing for sample validation/authentication prior to release of materials to researchers [11].

These characteristics made ISO 17025 (Table 2) and ISO Guide 34 (Table 3) most suitable to use for the compilation of standards for accreditation. Care has been taken to incorporate all those requirements of ISO 17025 and ISO Guide 34 that are relevant to the scope of acquisition, preparation, maintenance and provision of biological materials and of validation/authentication services that can be covered by the biobank's quality system.

Compilation

The following elements were not included:

- EU-specific terms (Member States): REC (2006) 4;
- US-specific terms (HIPAA, OSHA): ISBER;
- 5.6.2.1. Calibration: ISO 17025 (not applicable);
- 5.10.4. Calibration certificates: ISO 17025 (not applicable).

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Table 2. ISO 17025 Overview

1	Scope
2	Normative References
3	Terms and Definitions
4	Management Requirements
4.1	Organization
4.2	Management System
4.3	Document Control
4.3.1	General
4.3.2	Document Approval and Issue
4.3.3	Document Changes
4.4	Review of Requests, Tenders and Contracts
4.5	Subcontracting of Tests and Calibrations
4.6	Purchasing Services and Supplies
4.7	Service to the Customer
4.8	Complaints
4.9	Control of Non-conformity Testing and/or Calibration Work
4.10	Improvement
4.11	Corrective Action
4.11.1	General
4.11.2	Cause Analysis
4.11.3	Selection and Implementation of Corrective Actions
4.11.4	Monitoring of Corrective Actions
4.11.5	Additional Audits
4.12	Preventive Action
4.13	Control of Records
4.13.1	General
4.13.2	Technical Records
4.14	Internal Audits
4.15	Management Reviews
5	Technical Requirements
5.1	General
5.2	Personnel
5.3	Accommodation and Environmental Conditions
5.4	Test and Calibration Methods and Method Validation
5.4.1	General
5.4.2	Selection of Methods
5.4.3	Laboratory-developed Methods
5.4.4	Non-standard Methods
5.4.5	Validation of Methods
5.4.6	Estimation of Uncertainty of Measurement
5.4.7	Control of Data
5.5	Equipment
5.6	Measurement Traceability
5.6.1	General
5.6.2	Specific Requirements
5.6.3	Reference Standards and Reference Materials
5.7	Sampling
5.8	Handling of Test and Calibration Items
5.9	Assuring the Quality of Test and Calibration Results
5.10	Reporting the Results
5.10.1	General
5.10.2	Test Reports and Calibration Certificates
5.10.3	Test Reports
5.10.4	Calibration Certificates

Table 3. ISO Guide 34 Overview

1	Scope
2	Normative references
3	Terms and definitions
4	Organization and management requirements
4.1	Quality system requirements
4.2	Organization and management
4.3	Document and information control
4.4	Request, tender and contract reviews
4.5	Use of collaborators
4.6	Procurement of services and supplies
4.7	Client feedback
4.8	Control of non-conforming (poor quality) reference materials
4.9	Corrective action
4.10	Preventive action
4.11	Records
4.12	Internal audits
4.13	Management reviews
5	Technical and production requirements
5.1	Management, staffing and training
5.2	Collaborators
5.3	Production planning
5.4	Production control
5.5	Environment
5.6	Material handling and storage
5.7	Post-distribution service
5.8	Material preparation
5.9	Assessment of homogeneity and stability
5.10	Measurement methods
5.11	Measuring equipment
5.12	Traceability and validation
5.13	Data evaluation
5.14	Characterization
5.15	Assignment of property values and their uncertainties
5.16	Certificates and information for users

The following elements were added to the original ISO 17025 text, as paragraphs 6 and 7 respectively:

- Supply of biological material (retrieval, order placement, regulatory recommendations), as addressed in the OECD, the NCI and the ISBER guidelines.
- Ethical aspects (privacy, informed consent, access to samples and data, custodianship, intellectual property), as addressed in the NCI, the ISBER and the European recommendation documents. Intellectual property issues are solely addressed in the NCI recommendations.

Table 4 contains the results of the compilation; numbers of the chapters containing comparable requirements or recommendations are shown. Interestingly, several management requirements of ISO 17025 are not addressed in any of the existing guidelines for biobanks. These requirements include review of requests, tenders and contracts, subcontracting, control of non-conforming testing, improvement, preventive actions and management reviews. All

Table 4. Compilation against ISO 17025

ISO 17025	OECD	REC 2006(4)	ISBER	NCI	Guide 34
1 Scope	5-6	Art 1 Art 2:1-2-3-4			
1.1, 1.2, 1.3, 1.4					
1.5			F2.200 F2.210		
1.6					
2 Normative References					
3 Terms and Definitions	7-8-9	Art 3 Art 17:1	A3.000 A4.000		3.1
4 Management Requirements					
4.1 Organization		Art 4 Art 19:1-3			
4.1.1		Art 14:1			
4.1.2	10				4.1.1 4.1.2 4.1.3
4.1.3					
4.1.4					
4.1.5 a, e, h	14-15-16				
4.1.5 b, c, d, j					
4.1.5 l					
4.1.5 k	20				
4.1.5 f					
4.1.6					
4.2	11-12	Art 14:2 Art 19:4			
4.2.1	13				
4.2.2	21				
4.2.3					
4.2.4	18		H2.400 H2.500 H2.600 H2.700		
4.2.5, 4.2.6, 4.2.7					
4.3			E1.000 E1.100 E1.200 E1.300 E1.400 E1.500		
4.3.1			C1.200	1A3 1A4 1A11	
4.3.2	7				
4.3.2.1			E1.600		
4.3.2.2					
4.3.3. Document Changes	36-37-38		C1.500		
4.3.3.1, 4.3.3.2, 4.3.3.3					
4.4 Review of Requests, Tenders and Contracts					
4.4.1, 4.4.2, 4.4.3, 4.4.4, 4.4.5					
4.5 Subcontracting of Tests and Calibrations					5.2.1.

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Table 4. Continued.

ISO 17025	OECD	REC 2006(4)	ISBER	NCI	Guide 34
4.5.1, 4.5.2, 4.5.3, 4.5.4					
4.6 Purchasing Services and Supplies					
4.6.1	34				
4.6.2	56				
4.6.3, 4.6.4					
4.7 Service to the Customer					
4.7.1					
4.7.2	95-96-97				
4.8 Complaints	86-88				
4.9 Control of Non-conforming Testing and/or Calibration Work					
4.9.1, 4.9.2					
4.10 Improvement					
4.11 Corrective Action					
4.11.1 General	87				
4.11.2, 4.11.3, 4.11.4, 4.11.5					
4.12 Preventive Action					
4.12.1, 4.12.2					
4.13 Control of Records		Art 14:3			
4.13.1 General					
4.13.2 Technical records				1A12	
4.13.2.1, 4.13.2.2, 4.13.2.3					
4.14 Internal Audits					
4.14.1	92				
4.14.2, 4.1.4.3					
4.14.4	93-94				
4.15 Management Reviews					
5 Technical Requirements					5.1.1
5.1 General					5.3.3
5.1.1.					
5.1.2					
5.2 Personnel					
5.2.1			B2.100		
			B2.110		
			B2.120		
			B2.130		
5.2.2	17		G5.000		
5.2.3					
5.2.4					
5.2.5	19				
5.3 Accommodation and environmental conditions					
5.3.1	22-23-24-25-26-27		D1.000	1D1	
			D2.000	1C7	
			D2.100	1D9	
			D2.200	1D8	
			D3.000	1D3	
			D3.100		
			D3.200		
			D4.000		
			D4.100		
			D4.200		
			D4.210		
			D4.220		
			D5.100		
			D5.200		
			G1.000		
			G2.000		
			G3.000		
			G4.000		

Table 4. Continued.

ISO 17025	OECD	REC 2006(4)	ISBER	NCI	Guide 34
5.3.2	33			1C4	
				1D5	
5.3.3	28-29-30		G6.100	1D11	
			G6.200	1D7	
			G6.300	1D2	
			G6.400	1D10	
			G6.500		
			G6.600		
			G7.000		
5.3.4.	32		D4.300		
5.3.5			E4.000	1C6	
5.4.					
5.4.1	55				5.10.1
	63				
5.4.2	67-68-69		K1.000	1A8	
5.4.3 Laboratory-developed methods					
5.4.4 Non-standard methods					
5.4.5 Validation of methods	76-77-98				
5.4.5.1, 5.4.5.2, 5.4.5.3					
5.4.6 Estimation of uncertainty of measurement					
5.4.6.1, 5.4.6.2, 5.4.6.3.					
5.4.7 Control of data		Art 16		IE3	
5.4.7.1				1E2	
5.4.7.2	47-48		K4.200		
5.5.Equipment			E2.000		
5.5.1			E5.100		
			E5.200		
			E5.210		
			E5.220		
			E5.230		
			E5.240		
			E5.250		
			E5.260		
			E5.270		
			E5.300		
			E5.400		
			E5.500		
			E5.510		
			E5.520		
			E5.530		
			E5.600		
5.5.2	35		E6.200		5.11.1
5.5.3					
5.5.4					
5.5.5.	31				
5.5.6			E6.100		
5.5.7			E6.300		
5.5.8					
5.5.9					
5.5.10					
5.5.11					
5.5.12					
5.6. Measurement traceability					
5.6.1. General					
5.6.2 Specific requirements					
5.6.2.1 Calibration					
5.6.2.2. Validation/authentication					
5.6.2.2.1					5.10.2
5.14					
5.15					
5.15.1					

Table 4. Continued.

ISO 17025	OECD	REC 2006(4)	ISBER	NCI	Guide 34
5.15.2					
5.6.2.2.2.					
5.6.3 Reference standards and reference materials					
5.6.3.1 Reference standards					
5.6.3.2 Reference materials					
5.6.3.3 Intermediate checks					
5.6.3.4. Transport and storage					
5.7 Sampling	62-70 71-72				
5.7.1					5.10.3
5.7.2					
5.7.3					
5.8 Handling of biological samples	58-60 64				
5.8.1	57		K2.000 K3.110 K3.200 K3.300 K3.400 K3.500 K3.600 K3.700 K3.800 K4.100 K4.200	1A2 1A1 1A7 1A10 1A13	5.8.1
5.8.2	59			1E1	
5.8.3	61				
5.8.4	65-73-74-75				5.6.3 5.6.4 5.9.2 5.9.4
5.9 Assuring the quality of validation/ authentication results					
5.9.1					
5.9.2					
5.10 Reporting the data					
5.10.1 General	39-41-42 43-44-49		C1.400 C1.300 I3.100 I3.200 I3.300 I3.400 E3.000	1B1 1B2 1E5 1C5.	5.16
5.10.2 Validation/authentication reports and validation/authentication certificates					
5.10.3 Sample reports	46				
5.10.3.1					
5.10.3.2					
5.10.4 Calibration certificates					
Not applicable					
5.10.5 Opinions and interpretations					
5.10.6 Validation/authentication results obtained from subcontractors					
5.10.7 Electronic transmission of data	40-45 50-51- 52-53-54				
5.10.8 Format of reports and certificates					
5.10.9 Amendments to validation/authentication reports and sample reports					
6.Supply	78-79-80-81-82		K5.100	1A9	5.7.2

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Table 4. Continued.

ISO 17025	OECD	REC 2006(4)	ISBER	NCI	Guide 34
	83-84-85		K5.200	1A15	
	89-90-91		K5.300	1A16	
			I4.000	1A17	
			J1.000	1A18	
			J2.100	1D6	
			J2.200	1A14	
			J2.300		
			J2.400		
			J2.500		
			J2.600		
			J3.100		
			J3.200		
			J3.300		
			J3.400		
			J4.100		
			J4.200		
			J4.300		
			J4.400		
			I1.000		
			I2.100		
			I2.200		
7.1 Ethics – Privacy		Art 5:1	L2.100	1E4	
		Art 5:2	L2.200	2C1	
		Art 6	L2.210	2C2	
		Art 8:1	L2.220	2C3	
		Art 8:2			
		Art 9			
		Art 25			
7.2 Ethics – Informed consent		Art 15:1-2-3	L2.120	2A1	
		Art 22:1-2		2A2	
		Art 23:1-2		2A3	
				2A4	
				2A5	
				2A6	
				2A7	
7.3 Ethics – Access				2B1	
				2B2	
				2B3	
				2B4	
				2B5	
				2B6	
				2B7	
7.4 Ethics – Custodianship		Art 24	L1.000	2D1	
			L2.110	2D2	
				2D3	
				2D4	
7.5 Ethics – Intellectual Property				2E1	
				2E2	
				3E3	
				4E4	

technical requirements of ISO 17025 are addressed in at least two of the four existing biobank guidelines that were examined, with the exception of measurement traceability and assuring the quality of validation/authentication results.

The integral compilation text is published in this issue. The interested reader can download the text at http://www.biobanque-picardie.com/compilation.pdf or http://www.marblearchgroup.org/guidelines.compilation.htm where a colour code is used allowing distinctions to be

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made between the original texts. This compilation will allow the possibility of implementing an ISO certification/accreditation schema to biobanks to be studied.

Discussion

ISO 17025, as an ISO 9001-derived norm, is theoretically suitable for a biobank setting because biobanks are providers of services and products, and therefore are amenable to improvement of their services and products, and to satisfaction of their clients'/end-users' needs. We showed that the scope of biobanking activities – acquisition, preparation, maintenance and provision of biological materials, and their validation/authentication – is compatible with the structure of ISO 17025.

Certification against ISO 9001 does not *per se* demonstrate the competence of the biobank to provide technically valid samples and associated data. Biobanks complying with the ISO-compatible standard described here would, therefore, also operate in accordance with relevant aspects of ISO 17025 and ISO Guide 34. Each biobank would have to define its processes and scope of activities carefully. The generic standard ISO 9001:2000 applies to all types of biobanks. ISO 17025 only applies to biobanks including preparation and/or quality control laboratory activities which are able to perform validation/authentication of samples and produce results that can be assessed as technically valid. ISO Guide 34 in combination with ISO 17025 applies to those biobanks dealing with samples such as microbiological strains and established cell lines; these biobanks can be considered as reference material producers.

The acceptance of biological samples and associated data between countries will be facilitated if biobanks comply with an International Standard and if they obtain certification/accreditation from bodies which have entered into mutual recognition agreements with equivalent bodies in other countries using an International Standard. The use of an International Standard, like the one shown in our study, will facilitate cooperation between biobanks and other bodies, will assist in the exchange of information and experience and will result in the harmonization of standards and procedures.

The ultimate goal for a biobank certification/accreditation system is to provide researchers with documented collections of biological samples of known quality, including traceability of the samples collection, preparation, aliquoting, storage and retrieval procedures, in order to guarantee the accuracy, reproducibility and comparability of research results. Assessment of technical competence and granting of accreditation, will help set standards, give confidence to biobanks users and facilitate the increasing international use of research materials from biobanks.

This document contains all of the previously published requirements that biobanks should meet if they wish to demonstrate that they operate a quality system and are able to provide biological samples that conform to specified requirements.

Furthermore, this document is a proof-of-concept and could serve as a basis for further *de novo* development of a biobank-specific international certification/accreditation standard, corresponding to the research 'market' requirements. Such a standard could be developed and promoted by national standardization agencies and applied by accredited certification bodies recognized by governments.

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Appendix

Compiled Standard Model for Biobanks, based on ISO/IEC 17025, OECD, REC(2006), ISBER, NCI, ISO Guide 34[3]

1. Scope

These best practice guidelines give general best practice for the acquisition, maintenance and provision of biological materials and on the management of Biological Resource Centres (BRCs) as defined by the Organisation for Economic Co-operation and Development (OECD) (see definition below, section 3).

NOTE The expressions 'Biological Resource Centre' (BRC) and 'biobank' are used interchangeably in this document.

The purpose of these best practice guidelines is to help ensure that biological materials are of the highest standard and authentic. The preservation techniques used should retain the key features of the biological material and ensure its consistency between centres supplying it. This will help provide a reliable basis for research and development in different laboratories and contribute towards protection of the health of biobank personnel, the public and the environment.

Countries should protect the dignity and identity of all human beings and guarantee everyone, without discrimination, respect for their integrity, right to private life and other rights and fundamental freedoms with regard to any research governed by this recommendation.

This recommendation applies to the full range of research activities in the health field involving the removal of biological materials of human origin to be stored for research use. It also applies to the full range of research activities in the health field involving the use of biological materials of human origin that were removed for a purpose other than that mentioned in the previous paragraph; this includes material removed for a previous research project. This recommendation does not apply to embryonic and foetal tissues.

The use of biological material of human origin may be accompanied by the use of associated personal data.

1.1

This International Standard specifies the general requirements for the competence to carry out acquisition, maintenance and provision of biological materials and validation/authentication. It covers validation/authentication performed using standard methods, non-standard methods, and biobank-developed methods.

1.2

This International Standard is applicable to all organizations performing acquisition, maintenance and provision of biological materials and validation/authentication of biological samples. These include, for example, biobank *in situ* or external laboratories, performing where validation/authentication forms part of inspection and product certification.

This International Standard is applicable to all biobanks regardless of the number of personnel or the extent of the scope of validation/authentication activities. When a biobank does not undertake one or more of the activities covered by this International Standard, such as the design/development of new methods, the requirements of those clauses do not apply.

[3]The procedures for establishing this draft guideline are described in the main text of this article.

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1.3

The notes given provide clarification of the text, examples and guidance. They do not contain requirements and do not form an integral part of this International Standard.

1.4

This International Standard is for use by biobanks in developing their management system for quality, administrative and technical operations. Biobank customers, regulatory authorities and accreditation bodies may also use it in confirming or recognizing the competence of biobanks. This International Standard is intended to be used as the basis for certification of biobanks.

NOTE 1 The term 'management system' in this International Standard means the quality, administrative and technical systems that govern the operations of a biobank.

NOTE 2 Certification of a management system is sometimes also called registration.

1.5

Compliance with regulatory and safety requirements on the operation of biobanks is not covered by this International Standard.

Quality Standards

Current Good Biobank Laboratory Practice (GBLP)

Good biobank laboratory practice is regulatory guidelines that should be interpreted by the repository to fit its particular circumstances. Good biobank laboratory practice may be more relevant to larger, corporate repositories, but academic and other smaller repositories may wish to aim towards GBLP guidelines. Generally, these standards are interpreted as follows:

- the facility is in a secure, locked area with limited access;
- personnel must be trained in all procedures and such training is documented;
- the facility is subject to internal Quality Assurance (QA) audits by external clients and agencies as appropriate;
- policies and procedures are documented in SOPs that are approved by appropriate personnel and changed or updated only under strict document control rules;
- an extensive paper trail for all materials and equipment is maintained;
- equipment maintenance procedures are performed as required and document.

1.6

If biobanks comply with the requirements of this International Standard, they will operate a quality management system for their acquisition, maintenance and provision of biological materials and validation/authentication activities that also meets the principles of ISO 9001. This International Standard covers technical competence requirements that are not covered by ISO 9001.

NOTE 1 It might be necessary to explain or interpret certain requirements in this International Standard to ensure that the requirements are applied in a consistent manner.

NOTE 2 If a biobank wishes accreditation for part or all of its validation/authentication activities, it should select an accreditation body that operates in accordance with ISO/IEC 17011.

2. Normative References

ISO 17025
ISO Guide 34

3. Terms and Definitions

For the purposes of this document, the relevant terms and definitions given in ISO/IEC 17000 and VIM (*Vocabulaire International de Métrologie*) apply.

NOTE General definitions related to quality are given in ISO 9000, whereas ISO/IEC 17000 gives definitions specifically related to certification and laboratory accreditation. Where different definitions are given in ISO 9000, the definitions in ISO/IEC 17000 and VIM are preferred.

The term 'biological material' as used in this document covers all materials listed in the OECD definition of BRCs given below.

'Biological Resource Centres are an essential part of the infrastructure underpinning

biotechnology. They consist of service providers and repositories of the living cells, genomes of organisms, and information relating to heredity and the functions of biological systems. BRCs contain collections of culturable organisms (e.g. microorganisms, plant, animal and human cells), replicable parts of these (e.g. genomes, plasmids, viruses, cDNAs), viable but not yet culturable organisms cells and tissues, as well as data bases containing molecular, physiological and structural information relevant to these collections and related bioinformatics. BRC must meet the high standards of quality and expertise demanded by the international community of scientists and industry for the delivery of biological information and materials. They must provide access to biological resources on which R&D in the life sciences and the advancement of biotechnology depends.'

Authentication

Authentication is the process by which biological materials are characterized up to a defined level using appropriate technology to establish a conclusive basis for accepting the material as genuine.

Identifiability of Biological Materials

Biological materials may be identifiable or non-identifiable:

Identifiable biological materials are those biological materials which, alone or in combination with associated data, allow the identification of the persons concerned either directly or through the use of a code. In the latter case, the user of the biological materials may either:

(a) Have access to the code: the materials are hereafter referred to as 'coded materials'; or
(b) Not have access to the code, which is under the control of a third party: the material are hereafter referred to as 'linked anonymized materials'.

Non-identifiable biological materials, hereafter referred to as 'unlinked anonymized materials', are those biological materials which, alone or in combination with associated data, do not allow, with reasonable efforts, the identification of the persons concerned.

A population biobank is a collection of biological materials that has the following characteristics: the collection has a population basis; it is established, or has been converted, to supply biological materials or data derived therefrom for multiple future research projects; it contains biological materials and associated personal data, which may include or be linked to genealogical, medical and lifestyle data and which may be regularly updated; and it receives and supplies materials in an organized manner.

Definition of Terms

ACCIDENT – Any occurrence that deviates from Standard Operating Procedures (SOPs) or applicable government laws and regulations during specimen retrieval, processing, labelling, storage or distribution that may affect subsequent use of those specimens.

ADVERSE OUTCOME – An undesirable effect or untoward complication consequent to or reasonably related to specimen integrity.

ALIQUOT – A 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.

ASEPTIC PROCESSING – Processing of specimens using methods to restrict or minimize the potential contamination with microorganisms from the environment, processing personnel and equipment.

AUDIT – A documented review of procedures, records, personnel functions, equipment materials, facilities, and/or vendors in order to evaluate adherence to written SOPs or government laws and regulations.

BATCH – A specific quantity of specimen that is intended to have a uniform character and quality, within specific limits, and is produced or processed according to a single processing protocol during the same processing cycle. (See LOT below.)

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CLEAN ROOM – A room in which the concentration of air-borne particles is monitored and controlled to defined specification limits.

COLLECTION – See RETRIEVAL.

CONSIGNEE – Any individual, agency, institution, or organization that receives specimens and assumes responsibility for storage, dispensing, and tracking the disposition of specimens.

CONTAINER – Enclosure for one unit or units of specimen(s).

CONTROLLED AREAS – Restricted work areas of low microbial and particulate content in which non-sterile materials are prepared.

CRITICAL AREAS – Restricted work areas where containers and closures are exposed to the environment.

CROSS CONTAMINATION – The transfer of any part of one specimen to another specimen (e.g. microorganisms, blood, DNA, RNA, protein).

CRYOPROTECTANT – An additive that serves to minimize osmotic imbalances that occur with the progression of freezing fronts through a substance, and is intended to limit the amount of cell damage due to cell shrinkage and intracellular ice formation.

DEHYDRATION – Removal of water from a tissue.

DEVIATION – An intentional or unintentional event that is a departure from a procedure or a normal practice.

DISINFECTANT – An agent that reduces the number of viable microorganisms.

DISINFECTION – A process that reduces the number of viable cellular microorganisms, but does not necessarily destroy all microbial forms, such as spores and viruses.

DISPOSITION – Final destination of specimens.

DISTRIBUTION – A process that includes receipt of request for specimens, selection of appropriate specimens, and final inspection, in conjunction with subsequent shipment and delivery of specimens to another repository, specimen collection centre, or laboratory.

DONOR – Living or deceased individual who is the source of the specimen in accordance with established medical criteria, procedures and privacy regulations.

DRY ICE – Solid-phase carbon dioxide.

END-USER – A health care practitioner, scientist, or laboratory personnel who performs an appropriate procedure, test or archival function for the specimen.

EQUIPMENT QUALIFICATION STUDIES – Protocols designed to adequately evaluate, prior to use, whether equipment will perform to expectations, and normally function within tolerance limits.

ERGONOMICS – The science that explores human abilities and limitations, and applies that knowledge to improve a person's interactions with their environment, tools, products, and practice.

ERROR – A departure from SOPs or applicable government laws and regulations during specimen retrieval, processing, testing, quarantining, labelling, storage or distribution that might adversely affect the specimen.

FREEZE DRIED/LYOPHILIZED – Dehydrated for storage by conversion of the water content of a frozen specimen to a gaseous state under vacuum.

INFORMED CONSENT – A process by which information concerning the donation process is presented to the donor or donor's next-of-kin with an opportunity for them to ask questions, after which specific approval is documented.

IN-PROCESS CONTROLS – Any tests, samples, evaluations, monitoring, or measurements performed during processing or preservation that are designed to evaluate the processing or preservation procedure or the specimens subjected to processing or preservation for conformance to specifications in SOPs.

IN-PROCESS MATERIAL – Any material that is used in the processing of specimens, including but not limited to, incoming specimens, water, alcohol, acid, containers and closures.

LABEL – Any written, printed or graphic material on or affixed to a specimen container or package.

LIQUID NITROGEN DRY SHIPPER – A container used for sending samples in the vapour phase of liquid nitrogen.

LOT – Specimens produced from one donor at one time using one set of instruments and supplies. Also refers to a quantity of reagents, supplies or containers that is processed or manufactured at one time and identified by a unique identification number. (See BATCH above.)

NEXT-OF-KIN – Person(s) most closely related to a deceased individual as designated by applicable law such as under the Uniform Anatomical Gift Act.

PACKAGE – A labelled carton, receptacle, or wrapper containing one or more containers and accompanying labelling material.

PACKAGE INSERT – Written material accompanying a specimen bearing further information about the specimen, directions for use, and any applicable warnings.

POLICIES AND PROCEDURES MANUAL – See STANDARD OPERATING PROCEDURES MANUAL.

POOLING – Intentional physical contact or mixing of specimens from two or more sources into a single receptacle.

PRESERVATION – Use of chemical agents, alterations in environmental conditions or other means during processing to prevent or retard biological or physical deterioration of a specimen.

PROCEDURE – A series of steps designed to result in a specific outcome when followed in order.

PROCESS CONTROLS – A system of checks and balances incorporated into SOPs involving critical operations to prevent errors.

PROCESS VALIDATION STUDIES – The process of demonstrating that a specific procedure will consistently produce expected results within predetermined specifications.

PROCESSING – Any procedure employed after specimen collection but prior to its distribution, including preparation, testing, and releasing the specimen to inventory and labelling.

PROCUREMENT – See RETRIEVAL.

QUALITY – Conformance of a specimen or process with pre-established specifications or standards.

QUALITY CONTROL (QC) – Specific tests defined by the QA or Quality Management System (QMS) programme to be performed to monitor procurement, processing, preservation and storage; specimen quality; and test accuracy. These may include but are not limited to: performance evaluations, testing, and controls used to determine accuracy and reliability of the repository's equipment and operational procedures as well as monitoring of the supplies, reagents, equipment and facilities.

REFERENCE MATERIAL PRODUCER – Technically competent body (organization or firm, public or private) that is fully responsible for assigning the certified or other property values of the reference materials it produces and supplies which have been produced in accordance with ISO Guides 31 and 35.

REMOVAL – See RETRIEVAL.

RETRIEVAL – The removal, acquisition, recovery, harvesting, or collection of specimens.

SAFETY – Processes, procedures and technologies to ensure freedom from danger or harm.

SAMPLE – A single unit containing material derived from one specimen.

SHIPPING MANIFEST – A written description of the contents of the shipped package.

SPECIMEN – A specific tissue, blood sample, etc. taken from a single donor at a specific time.

STANDARD OPERATING PROCEDURES (SOP) MANUAL – A group of SOPs detailing specific policies of a repository and the procedures used by the staff/personnel.

STERILITY – Absence of detectable, viable, contaminating microorganisms, as defined in the USP.

STERILIZATION – A physical or chemical process validated to destroy, inactivate, or reduce microorganisms to a sterility assurance level of 10-6.

STORAGE – Maintenance of specimens for future use.

Tg – The Glass Transition Temperature. For cellular material, it is the temperature at which a cell is dehydrated to the degree that the

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remaining liquid within it is so viscous that molecules have insufficient energy to order themselves into a crystalline structure. Below this temperature (generally regarded as −132°C) no diffusion can take place within the cell and its surroundings. Without this diffusion, the biological 'clock' stops.

TOLERANCE LIMITS – Limits that define a range of acceptable values that are established for each testing procedure, which, when exceeded, require the implementation of corrective actions designed to produce results within the acceptable range in future tests.

TRACEABILITY – The ability to locate a specimen during any step of its donation, collection, processing, testing, storage and disposition.

Abbreviations

Below is a list of abbreviations that are used throughout this document

2D – Two-dimensional

ART – Administrator Responsible for Training

CO2 – Carbon dioxide

DNA – Deoxyribonucleic Acid

DOT – Department of Transportation

EDTA – Ethylenediaminetetraacetic Acid

GBLP – Current Good Biobank Laboratory Practices

GCP – Good Clinical Practices

GLP – Good Laboratory Practices

H&E – Hematoxylin-Eosin

IATA – International Air Transport Association

ICAO – International Civil Aviation Organization

IRB – Institutional Review Board

ISO – International Organization for Standardization

LN2 – Liquid Nitrogen

MSDS – Material Safety Data Sheet

PEL – Permissible Exposure Limit

PHI – Protected Health Information

QA – Quality Assurance

QC – Quality Control

QMS – Quality Management System

RBC – Red Blood Cell

RNA – Ribonucleic Acid

SCBA – Self Contained Breathing Apparatus

SOP – Standard Operating Procedure

Tg – Glass Transition Temperature

UPS – Uninterruptible Power Supply

4 Management Requirements

4.1 Organization

Countries should promote the establishment of codes of good practice to ensure compliance with the provisions of this recommendation.

Each population biobank should be subject to independent oversight, in particular to safeguard the interests and rights of the persons concerned in the context of the activities of the biobank.

Procedures should be developed for the transfer and for the closure of a population biobank.

4.1.1

The biobank or the organization of which it is part shall be an entity that can be held legally responsible. The person and/or institution responsible for the collection should be designated

4.1.2

It is the responsibility of the biobank to carry out its acquisition, maintenance and provision of biological materials and validation/authentication activities in such a way as to meet the requirements of this International Standard and to satisfy the needs of the customer, the regulatory authorities or organizations providing recognition.

The BRC should meet the OECD definition and must be compliant with appropriate national law and regulations. A BRC should describe and document the nature of the biological resources it holds. It should define the biological domain and therefore the domain specific criteria that apply, e.g. microorganisms or human-derived materials.

It should be recognized that a reference material needs to be characterized mainly to the level of accuracy required for its intended purpose (i.e. appropriate measurement uncertainly). The reference material producer shall describe the procedure for establishing the

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quality of materials as a component of the quality system. Reference material producers shall define their scope in terms of the application, the validation/authentication methods used in the stability and characterization studies, and any limitations due to the material matrix. The reference material producer shall define and document its policy, objectives and commitment to ensuring and maintaining the quality of all aspects of reference material production, including material quality (e.g. stability), characterization (e.g. use of appropriate statistical procedures) and material handling, storage and transport procedures.

The reference material producer shall establish and maintain documentation and a quality system that covers the following:

- arrangements for ensuring the suitable choice (e.g. concentration range, etc.) of the candidate reference materials;
- preparation procedures;
- procedures for undertaking characterization;
- assignment of property values, including preparation of certificates or statements in accordance with ISO Guide 31 when appropriate;
- arrangements for suitable identification, labelling and packaging facilities, packing and delivery procedures and customer service.

4.1.3

The management system shall cover work carried out in the biobank's permanent facilities, at sites away from its permanent facilities, or in associated temporary or mobile facilities.

4.1.4

If the biobank is part of an organization performing activities other than acquisition, maintenance and provision of biological materials and validation/authentication, the responsibilities of key personnel in the organization that have an involvement or influence on the acquisition, maintenance and provision of biological materials and validation/authentication activities of the biobank shall be defined in order to identify potential conflicts of interest.

NOTE 1 Where a biobank is part of a larger organization, the organizational arrangements should be such that departments having conflicting interests, such as production, commercial marketing or financing do not adversely influence the biobank's compliance with the requirements of this International Standard.

NOTE 2 If the biobank wishes to be recognized as a third-party laboratory, it should be able to demonstrate that it is impartial and that it and its personnel are free from any undue commercial, financial and other pressures which might influence their technical judgement. The third-party testing or validation/authentication laboratory should not engage in any activities that may endanger the trust in its independence of judgement and integrity in relation to its validation/authentication activities.

4.1.5

The biobank shall

(a) Have arrangements to ensure that its management and personnel are free from any undue internal and external commercial, financial and other pressures and influences that may adversely affect the quality of their work.
(b) Have policies and procedures to ensure the protection of its customers' confidential information and proprietary rights, including procedures for protecting the electronic storage and transmission of data.
(c) Have policies and procedures to avoid involvement in any activities that would diminish confidence in its competence, impartiality, judgement or operational integrity.
(d) Appoint deputies for key managerial personnel.
(e) Have managerial and technical personnel who, irrespective of other responsibilities, have the authority and resources needed to carry out their duties, including the implementation, maintenance and improvement of the management system, and to identify the occurrence of departures from the management system or from the procedures for performing acquisition, maintenance and provision of biological materials

and validation/authentication, and to initiate actions to prevent or minimize such departures (see also 5.2).

(f) Define the organization and management structure of the biobank, its place in any parent organization, and the relationships between quality management, technical operations and support services.

(g) Have technical management that has overall responsibility for the technical operations and the provision of the resources needed to ensure the required quality of biobank operations.

(h) Appoint a member of staff as quality manager (however named) who, irrespective of other duties and responsibilities, shall have defined responsibility and authority for ensuring that the management system related to quality is implemented and followed at all times; the quality manager shall have direct access to the highest level of management at which decisions are made on biobank policy or resources.

(i) Ensure that its personnel are aware of the relevance and importance of their activities and how they contribute to the achievement of the objectives of the management system.

NOTE Individuals may have more than one function and it may be impractical to appoint deputies for every function.

All staff involved in providing a product or service contribute to the achieved quality. The role of the Quality Management System is to guide and advise staff on quality matters and to provide independent assurance of quality to the senior management.

(a) Specify the responsibility, authority and interrelationships of all personnel who manage, perform or verify work affecting the quality of the tests and/or calibrations;

(b) Designate a Biosecurity Officer, at operational level within the BRC, whose responsibility is to ensure internal compliance with *Best Practice Guidelines on Biosecurity for BRCs*.

The Quality Manager's duties include:

- administering and monitoring an efficient up-to-date quality management system;
- reporting and advising on quality matters;
- representing the biobank on quality matters when dealing with users, suppliers and outside bodies.

Where possible a deputy should be appointed to serve in the absence of the Quality Manager. The Quality Manager has direct access to the senior management of the biobank on matters concerning quality.

4.1.6

Top management shall ensure that appropriate communication processes are established within the biobank and that communication takes place regarding the effectiveness of the management system.

4.2 Management System

Long-term sustainability

The biobank should develop a strategy for its long-term sustainability. Adequate and reliable sources of funding vary from government support, income from services and private support. If its future is threatened, the BRC should have a plan to ensure that its key holdings remain available.

Transparency

The purpose(s) of a collection should be specified. The principles of transparency and accountability should govern its management, including access to and use and transfer of its biological materials and disclosure of information.

Population biobanks should publish reports on their past and planned activities at least annually, or more frequently if appropriate

4.2.1

The biobank shall establish, implement and maintain a management system appropriate to the scope of its activities. The biobank shall document its policies, systems, programmes,

procedures and instructions to the extent necessary to assure the quality of the acquisition, maintenance and provision of biological materials and validation/authentication activities. The system's documentation shall be communicated to, understood by, available to, and implemented by the appropriate personnel.

Primary responsibility lies with the BRC senior management who may delegate responsibility for implementation of its policies to named and suitably qualified members of staff and provide them with defined responsibilities and authority. The list of such staff and their specific responsibilities should be available to all staff of the BRC and should particularly be made available to new staff, students and visitors.

4.2.2

The biobank's management system policies related to quality, including a quality policy statement, shall be defined in a quality manual (however named). The overall objectives shall be established, and shall be reviewed during management review. The quality policy statement shall be issued under the authority of top management. It shall include at least the following:

(a) The biobank management's commitment to good professional practice and to the quality of its acquisition, maintenance and provision of biological materials and validation/authentication in servicing its customers.
(b) The management's statement of the biobank's standard of service.
(c) The purpose of the management system related to quality.
(d) A requirement that all personnel concerned with acquisition, maintenance and provision of biological materials and validation/authentication activities within the biobank familiarize themselves with the quality documentation and implement the policies and procedures in their work.
(e) The biobank management's commitment to comply with this International Standard and to continually improve the effectiveness of the management system.

NOTE The quality policy statement should be concise and may include the requirement that acquisition, maintenance and provision of biological materials and validation/authentication shall always be carried out in accordance with stated methods and customers' requirements. When the biobank is part of a larger organization, some quality policy elements may be in other documents.

It is the responsibility of all staff to familiarize themselves with documented protocols and comply with the policies and procedures laid down in the BRC SOPs and associated documentation at all times. It is the management's responsibility to ensure that staff has access to quality manuals and that they are understood and kept informed of any amendments.

4.2.3

Top management shall provide evidence of commitment to the development and implementation of the management system and to continually improving its effectiveness.

4.2.4

Top management shall communicate to the organization the importance of meeting customer requirements as well as statutory and regulatory requirements.

Staff should be trained according to documented protocols in skills specific to the job and should receive training as new technologies or practices are introduced. Such training should be reviewed annually. All BRC staff has a responsibility towards the main objective of a BRC that is to provide high quality, biological resource services to the public.

Training Documentation

Once the training is complete, a written record should be made of the trainee's signature as well as the trainer's signature indicating that the training is complete.

NOTE 1 Periodicity of Training: Some regulations require training before the employee begins working and yearly thereafter.

NOTE 2 Cross Training: Biobanks may find it advantageous to implement a system of cross training. Cross training is the practice in which staff is trained in a variety of procedures and no individual should perform only his/her designated tasks all of the time. Cross training alleviates staff burn out and reduces the staff turnover rate. Since some tasks require repetitive motion, cross training may minimize physical strain among those performing those particular responsibilities. Cross training also allows for critical procedures to be covered when regular staff is absent from the biobank.

Training Records

A Training File should be maintained for each biobank staff member and should include, but may not be limited to the following:

- Position description that includes the job title and responsibilities, as well as the educational experience required to perform the required task.
- Resume.
- Example of the employee's signature and initials.
- Copies of any certificates documenting that the employee has had specialized training. This should include training in shipping and safety.
- Documentation that an employee has read and understood all SOPs pertinent to the employee's responsibilities.

The Training File should be kept in the biobank and be available for Quality Assurance or client review.

4.2.5

The quality manual shall include or make reference to the supporting procedures including technical procedures. It shall outline the structure of the documentation used in the management system.

4.2.6

The roles and responsibilities of technical management and the quality manager, including their responsibility for ensuring compliance with this International Standard, shall be defined in the quality manual.

4.2.7

Top management shall ensure that the integrity of the management system is maintained when changes to the management system are planned and implemented.

4.3 Document Control

Standard Operating Procedures Manual

Purpose and Design

Each biobank should develop written policies and procedures in a standardized written format that should be incorporated into a SOP manual. The SOPs should state policies and define and describe in detail, all procedures. These SOPs should be utilized to ensure that all samples are appropriately stored so that they may be effectively disseminated for subsequent research and other uses.

Contents

The SOP manual should specifically include, but should not be limited to:

- Specimen handling policies and procedures including supplies, methods and equipment.
- Biobank procedures for tests performed in-house and any specimen aliquoting or other specimen processing.
- Policies and procedures for shipping and receiving specimens.
- Records management policies. This should include policies regarding the shredding of confidential documentation at the appropriate time.
- QA and QC policies and procedures for supplies, equipment, instruments, reagents, labels, and processes employed in sample retrieval and processing.
- Policies regarding safety programmes. These would include pre- and post-employment medical evaluations and immunization records.
- Emergency and safety policies and procedures, including reporting of staff injuries and exposure to potential blood-borne pathogens.

- Policies and procedures for the investigation, documentation and reporting of accidents, errors, complaints and adverse outcomes.
- Policies, procedures and schedules for equipment inspection, maintenance, repair and calibration for the purpose of maintaining equipment.
- Procedures for disposal of medical waste and other hazardous waste.
- Policies and procedures describing requirements of training programs for technical and QA staff.

Implementation

Either the biobank Director and/or the individual responsible for the QA programme should review and approve all SOPs and associated process validation studies prior to implementation. Upon implementation, all SOPs must be followed as written.

Modifications

Each repository should have document control policies in place that govern modifications or revisions to SOPs. Prior to implementation, each modification should be approved by the Director and other appropriate individuals. Implementation dates should be recorded for all procedures.

SOP Review

All SOPs should be reviewed every two years.

4.3.1 General

The biobank shall establish and maintain procedures to control all documents that form part of its management system (internally generated or from external sources), such as regulations, standards, other normative documents, acquisition, maintenance and provision of biological materials and validation/authentication methods, as well as drawings, software, specifications, instructions and manuals.

NOTE 1 In this context 'document' could be policy statements, procedures, specifications, calibration tables, charts, text books, posters, notices, memoranda, software, drawings, plans, etc. These may be on various media, whether hard copy or electronic, and they may be digital, analogue, photographic or written.

NOTE 2 The control of data related to validation/authentication is covered in 5.4.7. The control of records is covered in 4.13.

Compliance with Internal Documentation

All staff must adhere to the prescribed policies and procedures. Any departures from documented procedures must be agreed by senior management prior to deviation. Written permission and justification must then be included in the relevant records.

In the case where a procedure is not followed a deviation report is required outlining the specific error and corrective actions that will be taken. If failure has been brought about by a misunderstanding or misdirection, the error must be investigated, rectified and retraining implemented if necessary.

Maintain a thorough and consistent level of biospecimen annotation while maintaining donor patient privacy pursuant to informed consent provisions.

Use a computerized inventory system that tracks the specific position of every stored aliquot. Each storage container should be labelled with a unique identifier. All other relevant information should be tied to this unique identifier. Inventory systems should contain security provisions sufficient to safeguard privacy and other informed consent provisions.

Establish inventory tracking systems and storage organizational methods to minimize disruption of the stable environment during sample retrieval.

Record Retention

Collection, processing, storage, distribution and QA records should be maintained for a

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minimum of ten years after the last expiration of the specimens involved.

When there is no expiration date, records should be maintained for ten years after the date of distribution.

4.3.2 Document Approval and Issue

4.3.2.1

All documents issued to personnel in the biobank as part of the management system shall be reviewed and approved for use by authorized personnel prior to issue. A master list or an equivalent document control procedure identifying the current revision status and distribution of documents in the management system shall be established and shall be readily available to preclude the use of invalid and/or obsolete documents.

Staff Access and Review

Current copies of the SOP manual should be stored in designated locations and available to the staff at all times. New and revised policies and procedures should be reviewed by the staff prior to implementation. Documentation of staff review and any associated training should be maintained in a Training Record.

4.3.2.2

The procedure(s) adopted shall ensure that:

(a) Authorized editions of appropriate documents are available at all locations where operations essential to the effective functioning of the biobank are performed.
(b) Documents are periodically reviewed and, where necessary, revised to ensure continuing suitability and compliance with applicable requirements.

4.3.3 Document Changes

The BRC Quality Manager should be responsible for ensuring that all documentation is correctly updated. Alterations to any operating documents should not be allowed unless agreed to by the Quality Manager. Amendment sheets should be issued to all holders. Short-term sanctioned alterations should be made in ink by scoring through existing wording so that it is still legible. Scribble, correction fluid or tape should not be allowed. The alterations should be signed and dated by the Quality Manager. Copies of the quality manual and, if appropriate, specific procedures should be such that they can be made available to enquirers, course participants and staff through the BRC Quality Manager. In such cases, they should be provided with copies clearly marked as uncontrolled copies and such copies should not be updated.

All staff should adhere to the prescribed policies and procedures. Any departures from documented procedures should be agreed by senior management prior to deviation. Written permission and justification should then be included in the relevant records.

In the case where a procedure is not followed a deviation report is required outlining the specific error and corrective actions that will be taken. If failure has been brought about by a misunderstanding or misdirection, the error should be investigated, rectified and retraining implemented if necessary.

4.3.3.1

Changes to documents shall be reviewed and approved by the same function that performed the original review unless specifically designated otherwise. The designated personnel shall have access to pertinent background information upon which to base their review and approval.

4.3.3.2

Where practicable, the altered or new text shall be identified in the document or the appropriate attachments.

4.3.3.3

If the biobank's document control system allows for the amendment of documents by hand pending the re-issue of the documents, the procedures and authorities for such amendments shall be defined.

Amendments shall be clearly marked, initialled and dated. A revised document

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shall be formally re-issued as soon as practicable.

Corrections and/or Changes

Corrections or changes in a record should be made with a single line drawn through the altered text. Corrections should be initialled and dated by the individual making the correction or change. Changes in electronic records should be noted and tracked.

4.4 Review of Requests, Tenders and Contracts

4.4.1

The biobank shall establish and maintain procedures for the review of requests, tenders and contracts. The policies and procedures for these reviews leading to a contract for acquisition, maintenance and provision of biological materials and validation/authentication shall ensure that:

(a) The requirements, including the methods to be used, are adequately defined, documented and understood (see 5.4.2).
(b) The biobank has the capability and resources to meet the requirements.
(c) The appropriate acquisition, maintenance and provision of biological materials and validation/authentication methods are selected and are capable of meeting the customers' requirements (see 5.4.2).

Any differences between the request or tender and the contract shall be resolved before any work commences. Each contract shall be acceptable both to the biobank and the customer.

NOTE 1 The request, tender and contract review should be conducted in a practical and efficient manner, and the effect of financial, legal and time schedule aspects should be taken into account. For internal customers, reviews of requests, tenders and contracts can be performed in a simplified way.

NOTE 2 The review of capability should establish that the biobank possesses the necessary physical, personnel and information resources, and that the biobank's personnel have the skills and expertise necessary for the performance of the acquisition, maintenance and provision of biological materials and validation/authentication in question. The review may also encompass results of earlier participation in inter-biobank comparisons or proficiency testing and/or the running of trial validation/authentication programmes using samples or items of known value in order to determine uncertainties of measurement, limits of detection, confidence limits, etc.

NOTE 3 A contract may be any written or oral agreement to provide a customer with acquisition, maintenance and provision of biological materials and validation/authentication services.

4.4.2

Records of reviews, including any significant changes, shall be maintained. Records shall also be maintained of pertinent discussions with a customer relating to the customer's requirements or the results of the work during the period of execution of the contract.

NOTE For review of routine and other simple tasks, the date and the identification (e.g. the initials) of the person in the biobank responsible for carrying out the contracted work are considered adequate. For repetitive routine tasks, the review need be made only at the initial enquiry stage or on granting of the contract for on-going routine work performed under a general agreement with the customer, provided that the customer's requirements remain unchanged. For new, complex or advanced acquisition, maintenance and provision of biological materials and validation/authentication tasks, a more comprehensive record should be maintained.

4.4.3

The review shall also cover any work that is subcontracted by the biobank.

4.4.4

The customer shall be informed of any deviation from the contract.

4.4.5

If a contract needs to be amended after work has commenced, the same contract review process shall be repeated and any amendments shall be communicated to all affected personnel.

4.5 Subcontracting of Acquisition, Maintenance and Provision of Biological Materials or Validation/ Authentication

4.5.1

When a biobank subcontracts work, whether because of unforeseen reasons (e.g. workload, need for further expertise or temporary incapacity) or on a continuing basis (e.g. through permanent subcontracting, agency or franchising arrangements), this work shall be placed with a competent subcontractor. A competent subcontractor is one that, for example, complies with this International Standard for the work in question.

4.5.2

The biobank shall advise the customer of the arrangement in writing and, when appropriate, gain the approval of the customer, preferably in writing.

4.5.3

The biobank is responsible to the customer for the subcontractor's work, except in the case where the customer or a regulatory authority specifies which subcontractor is to be used.

4.5.4

The biobank shall maintain a register of all subcontractors that it uses for acquisition, maintenance and provision of biological materials or validation/authentication and a record of the evidence of compliance with this International Standard for the work in question.

At the limit, the reference material producer may have no laboratory facilities, but shall ensure that all scientific work carried out by collaborators which may contribute to the assignment on the property values of interest is fit for that purpose and in compliance with the above requirements.

4.6 Purchasing Services and Supplies

4.6.1

The biobank shall have a policy and procedure(s) for the selection and purchasing of services and supplies it uses that affect the quality of the acquisition, maintenance and provision of biological materials and validation/authentication. Procedures shall exist for the purchase, reception and storage of reagents and laboratory consumable materials relevant for the acquisition, maintenance and provision of biological materials and validation/authentication.

Any support services used by the biobank should be of adequate quality to sustain confidence in its activities. Supplies should be sought from reputable companies with, where possible, proven quality of products. Preference should be given to services and supplies covered by certification schemes. Where no independent assurance of quality of support services is available, the BRC should be responsible for confirming the quality of vital supplies. Copies of purchase orders should be held on file and records of suppliers, standing orders etc. should be maintained for a minimum period of five years.

4.6.2

The biobank shall ensure that purchased supplies and reagents and consumable materials that affect the quality of acquisition, maintenance and provision of biological materials and validation/authentication are not used until they have been inspected or otherwise verified as complying with standard specifications or requirements defined in the methods for the acquisition, maintenance and provision of biological materials and validation/authentication concerned. These services and supplies used shall comply with specified requirements. Records of actions taken to check compliance shall be maintained.

Supplies of materials for use should be of high standard and should not be contaminated.

4.6.3

Purchasing documents for items affecting the quality of biobank output shall contain data describing the services and supplies ordered. These purchasing documents shall be reviewed and approved for technical content prior to release.

NOTE The description may include type, class, grade, precise identification, specifications,

drawings, inspection instructions, other technical data including approval of test results, the quality required and the management system standard under which they were made.

4.6.4

The biobank shall evaluate suppliers of critical consumables, supplies and services which affect the quality of acquisition, maintenance and provision of biological materials and validation/authentication, and shall maintain records of these evaluations and list those approved.

4.7 Service to the Customer

4.7.1

The biobank shall be willing to cooperate with customers or their representatives in clarifying the customer's request and in monitoring the biobank's performance in relation to the work performed, provided that the biobank ensures confidentiality to other customers.

NOTE 1 Such cooperation may include:

(a) Providing the customer or the customer's representative reasonable access to relevant areas of the biobank for the witnessing of acquisition, maintenance and provision of biological materials and validation/authentication performed for the customer.
(b) Preparation, packaging, and dispatch of validation/authentication items needed by the customer for verification purposes.

NOTE 2 Customers value the maintenance of good communication, advice and guidance in technical matters, and opinions and interpretations based on results. Communication with the customer, especially in large assignments, should be maintained throughout the work. The biobank should inform the customer of any delays or major deviations in the performance of the acquisition, maintenance and provision of biological materials and validation/authentication.

4.7.2

The biobank shall seek feedback, both positive and negative, from its customers. The feedback shall be used and analysed to improve the management system, acquisition, maintenance and provision of biological materials and validation/authentication activities and customer service.

NOTE Examples of the types of feedback include customer satisfaction surveys and review of validation/authentication reports with customers.

Staff of the BRC should undertake at least one audit each year according to the schedule described in the rolling audit programme. This programme entails the review of all BRC activities including documentation, supply, accession, database, training records, equipment and maintenance, enquiries and complaints records and external support services. In addition it should include a strain deposit trail through to storage and a supply trail from receipt of order to supply. These should be chosen at random. The day workbooks, enquiry records and database records should also be reviewed. The results of the audit and record reviews should be recorded and any fault rectified.

An external independent qualified person should carry out a third-party audit of the procedures, preferably each year. This too should include a biological material deposit trail through to storage and a supply trail from receipt of order to supply. These should be chosen at random. The day workbooks, enquiry records and database records should also be reviewed. The results of the third-party audit and record reviews should be recorded and any fault rectified.

A meeting of all audit staff, BRC staff and line management should be held annually to review the audit reports, enquiries and complaints received and discuss potential improvement in procedures and monitoring. The results of the review should be recorded and the Quality Manager is responsible for implementation of actions prescribed

4.8 Complaints

The biobank shall have a policy and procedure for the resolution of complaints received from customers or other parties. Records shall be maintained of all complaints and of the

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investigations and corrective actions taken by the biobank (see also 4.11)

The BRC should record all user queries or complaints and acknowledge as soon as possible (preferably on the same day) by fax, telephone or e-mail.

Records of responses/solutions should be stored.

4.9 Control of Non-conforming Acquisition, Maintenance and Provision of Biological Materials and Validation/Authentication Work

4.9.1

The biobank shall have a policy and procedures that shall be implemented when any aspect of acquisition, maintenance and provision of biological materials and validation/authentication work, or the results of this work, do not conform to its own procedures or the agreed requirements of the customer. The policy and procedures shall ensure that:

(a) The responsibilities and authorities for the management of non-conforming work are designated and actions (including halting of work and withholding of acquisition, maintenance and provision of biological materials and validation/authentication as necessary) are defined and taken when non-conforming work is identified.
(b) An evaluation of the significance of the non-conforming work is made.
(c) Correction is taken immediately, together with any decision about the acceptability of the non-conforming work.
(d) Where necessary, the customer is notified and work is recalled.
(e) The responsibility for authorizing the resumption of work is defined.

NOTE Identification of non-conforming work or problems with the management system or with acquisition, maintenance and provision of biological materials and validation/authentication activities can occur at various places within the management system and technical operations. Examples are customer complaints, quality control, instrument calibration, checking of consumable materials, staff observations or supervision, validation/authentication checking, management reviews and internal or external audits.

4.9.2

Where the evaluation indicates that the non-conforming work could recur or that there is doubt about the compliance of the biobank's operations with its own policies and procedures, the corrective action procedures given in 4.11 shall be promptly followed.

4.10 Improvement

The biobank shall continually improve the effectiveness of its management system through the use of the quality policy, quality objectives, audit results, analysis of data, corrective and preventive actions and management review.

4.11 Corrective Action

4.11.1 General

The biobank shall establish a policy and a procedure and shall designate appropriate authorities for implementing corrective action when non-conforming work or departures from the policies and procedures in the management system or technical operations have been identified.

NOTE A problem with the management system or with the technical operations of the biobank may be identified through a variety of activities, such as control of non-conforming work, internal or external audits, management reviews, feedback from customers and from staff observations.

The BRC should investigate the complaints as soon as received and implement the necessary corrective actions. All complaints should be included in regular trend analysis.

4.11.2 Cause Analysis

The procedure for corrective action shall start with an investigation to determine the root cause(s) of the problem.

NOTE Cause analysis is the key and sometimes the most difficult part in the corrective action

procedure. Often the root cause is not obvious and thus a careful analysis of all potential causes of the problem is required. Potential causes could include customer requirements, the samples, sample specifications, methods and procedures, staff skills and training, consumables, or equipment and its calibration.

4.11.3 Selection and Implementation of Corrective Actions

Where corrective action is needed, the biobank shall identify potential corrective actions. It shall select and implement the action(s) most likely to eliminate the problem and to prevent recurrence.

Corrective actions shall be to a degree appropriate to the magnitude and the risk of the problem.

The biobank shall document and implement any required changes resulting from corrective action investigations.

4.11.4 Monitoring of Corrective Actions

The biobank shall monitor the results to ensure that the corrective actions taken have been effective.

4.11.5 Additional Audits

Where the identification of non-conformities or departures casts doubts on the biobank's compliance with its own policies and procedures or on its compliance with this International Standard, the biobank shall ensure that the appropriate areas of activity are audited in accordance with 4.14 as soon as possible.

NOTE Such additional audits often follow the implementation of the corrective actions to confirm their effectiveness. An additional audit should be necessary only when a serious issue or risk to the business is identified.

4.12 Preventive Action

4.12.1

Needed improvements and potential sources of non-conformities, either technical or concerning the management system, shall be identified. When improvement opportunities are identified or if preventive action is required, action plans shall be developed, implemented and monitored to reduce the likelihood of the occurrence of such non-conformities and to take advantage of the opportunities for improvement.

4.12.2

Procedures for preventive actions shall include the initiation of such actions and the application of controls to ensure that they are effective.

NOTE 1 Preventive action is a pro-active process to identify opportunities for improvement rather than a reaction to the identification of problems or complaints.

NOTE 2 Apart from the review of the operational procedures, the preventive action might involve analysis of data, including trend and risk analyses and proficiency testing results.

4.13 Control of Records

Each sample of biological material in the collection should be appropriately documented, including information on any relevant consent or authorization.

4.13.1 General

4.13.1.1

The biobank shall establish and maintain procedures for identification, collection, indexing, access, filing, storage, maintenance and disposal of quality and technical records. Quality records shall include reports from internal audits and management reviews as well as records of corrective and preventive actions.

4.13.1.2

All records shall be legible and shall be stored and retained in such a way that they are readily retrievable in facilities that provide a suitable environment to prevent damage or deterioration and to prevent loss. Retention times of records shall be established.

NOTE Records may be in any media, such as hard copy or electronic media.

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4.13.1.3

All records shall be held secure and in confidence.

4.13.1.4

The biobank shall have procedures to protect and back-up records stored electronically and to prevent unauthorized access to or amendment of these records.

4.13.2 Technical Records

Regularly review the performance of all long-term storage systems and equipment using standardized protocols.

4.13.2.1

The biobank shall retain records of original observations, derived data and sufficient information to establish an audit trail, acquisition, maintenance and provision of biological materials and validation/authentication records, staff records and a copy of each validation/authentication issued, for a defined period. The records for each validation/authentication shall contain sufficient information to facilitate, if possible, identification of factors affecting the uncertainty and to enable the validation/authentication to be repeated under conditions as close as possible to the original. The records shall include the identity of personnel responsible for the sampling, performance of validation/authentication and checking of results.

NOTE Technical records are accumulations of data (see 5.4.7) and information that result from carrying out acquisition, maintenance and provision of biological materials and validation/authentication and which indicate whether specified quality or process parameters are achieved. They may include forms, contracts, work sheets, work books, check sheets, work notes, control graphs, external and internal test reports and calibration certificates, customers' notes, papers and feedback.

4.13.2.2

Observations, data and calculations shall be recorded at the time they are made and shall be identifiable to the specific task.

4.13.2.3

When mistakes occur in records, each mistake shall be crossed out, not erased, made illegible or deleted, and the correct value entered alongside. All such alterations to records shall be signed or initialled by the person making the correction. In the case of records stored electronically, equivalent measures shall be taken to avoid loss or change of original data.

4.14 Internal Audits

4.14.1

The biobank shall periodically, and in accordance with a predetermined schedule and procedure, conduct internal audits of its activities to verify that its operations continue to comply with the requirements of the management system and this International Standard. The internal audit programme shall address all elements of the management system, including the acquisition, maintenance and provision of biological materials and validation/authentication activities. It is the responsibility of the quality manager to plan and organize audits as required by the schedule and requested by management. Such audits shall be carried out by trained and qualified personnel who are, wherever resources permit, independent of the activity to be audited.

NOTE The cycle for internal auditing should normally be completed in one year.

Periodic audits should be carried out by management to ensure that the BRC policies and procedures, as set out in these best practice guidelines and the supplemental domain specific best practice guidelines, are being followed. External, independent audits should be carried out. A process should be in place to identify any potential source of non-conformity to BRC guidance.

4.14.2

When audit findings cast doubt on the effectiveness of the operations or on the correctness or validity of the biobank's acquisition, maintenance and provision of biological materials and validation/authentication results, the biobank shall take timely corrective action and shall notify customers in writing if investigations show that the biobank results may have been affected.

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4.14.3

The area of activity audited, the audit findings and corrective actions that arise from them shall be recorded.

4.14.4

Follow-up audit activities shall verify and record the implementation and effectiveness of the corrective action taken.

The BRC manager or a delegate, assisted by BRC staff if necessary, should carry out an assessment of the effectiveness of procedures and organize the audit programme.

The Quality Manager should be responsible for ensuring that reviews are recorded and that any actions are implemented.

4.15 Management Review

4.15.1

In accordance with a predetermined schedule and procedure, the biobank's top management shall periodically conduct a review of the biobank's management system and acquisition, maintenance and provision of biological materials and validation/authentication activities to ensure their continuing suitability and effectiveness, and to introduce necessary changes or improvements.

The review shall take account of:

- the suitability of policies and procedures;
- reports from managerial and supervisory personnel;
- the outcome of recent internal audits;
- corrective and preventive actions;
- assessments by external bodies;
- the results of inter-biobank comparisons or proficiency tests;
- changes in the volume and type of the work;
- customer feedback;
- complaints;
- recommendations for improvement;
- other relevant factors, such as quality control activities, resources and staff training.

NOTE 1 A typical period for conducting a management review is once every 12 months.

NOTE 2 Results should feed into the biobank planning system and should include the goals, objectives and action plans for the coming year.

NOTE 3 A management review includes consideration of related subjects at regular management meetings.

4.15.2

Findings from management reviews and the actions that arise from them shall be recorded. The management shall ensure that those actions are carried out within an appropriate and agreed timescale.

5. Technical requirements

5.1 General

5.1.1

Many factors determine the correctness and reliability of the acquisition, maintenance and provision of biological materials and validation/authentication performed by a biobank. These factors include contributions from:

- human factors (5.2);
- accommodation and environmental conditions (5.3);
- acquisition, maintenance and provision of biological materials methods, sample validation/authentication methods and method validation (5.4);
- equipment (5.5);
- measurement traceability (5.6);
- sampling (5.7);
- the handling of acquisition, maintenance and provision of biological materials and validation/authentication items (5.8).

The production of reference materials should, where possible, only be undertaken by organizations having experience in the production of the particular type of reference material (or related material), as well as having experience in the measurement of the properties being determined.

In planning the production processes, the reference material producer shall have

procedures and service facilities, where appropriate, for:

(a) Material selection (including, where appropriate, sampling).
(b) Maintaining suitable environments for all aspects of production.
(c) Material selection.
(d) Measuring/testing.
(e) Calibration/validation of equipment/measurement methods.
(f) Assessing material homogeneity.
(g) Assessing material stability.
(h) Organizing inter-biobank studies with its collaborators.
(i) Assigning property values based on the results of validation/authentication methods.
(j) Producing uncertainty budgets and uncertainty intervals to the assigned property values.
(k) Ensuring adequate storage facilities and conditions.
(l) Ensuring adequate packaging facilities.
(m) Ensuring appropriate transport arrangements.
(n) Ensuring an adequate post-distribution service.

5.1.2

The extent to which the factors contribute to the total uncertainty of sample quality differs considerably between (types of) samples and between (types of) end usages. The biobank shall take account of these factors in developing acquisition, maintenance and provision of biological materials and validation/authentication methods and procedures, in the training and qualification of personnel, and in the selection and calibration of the equipment it uses.

5.2. Technical Requirements

Personnel

5.2.1

The biobank management shall ensure the competence of all who operate specific equipment, perform acquisition, maintenance and provision of biological materials and validation/authentication, evaluate biospecimens and sign validation/authentication certificates. When using staff who are undergoing training, appropriate supervision shall be provided. Personnel performing specific tasks shall be qualified on the basis of appropriate education, training, experience and/or demonstrated skills, as required.

NOTE 1 In some technical areas (e.g. non-destructive testing) it may be required that the personnel performing certain tasks hold personnel certification. The biobank is responsible for fulfilling specified personnel certification requirements. The requirements for personnel certification might be regulatory, included in the standards for the specific technical field, or required by the customer.

NOTE 2 The personnel responsible for the opinions and interpretation included in test reports should, in addition to the appropriate qualifications, training, experience and satisfactory knowledge of the testing carried out, also have:

- Relevant knowledge of the technology used for the acquisition, maintenance and provision of biological materials and for validation/authentication of the samples tested, or the way they are used or intended to be used, and of the defects or degradations which may occur during or in service.
- Knowledge of the general requirements expressed in the legislation and standards.
- An understanding of the significance of deviations found with regard to the normal use of the samples concerned.

Director

Qualifications

The Director should be qualified by training and experience to fulfil the scope of activities conducted by the biobank.

General Operations

The Director should implement policies of the organization and should be responsible for all operations, including compliance with current and applicable regulations. This individual

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should ensure that repository activities are in compliance with national, and local authorities.

Depending upon the biobank, the Director may have other responsibilities including:

(a) Ensuring that the biobank operates within budget (at an academic institution this would entail securing funding for the biobank either by writing external grants or securing contracts with clients).
(b) Ensuring that all patient consent forms are updated annually to be in compliance with IRB regulations and serving as a liaison for the IRB.
(c) Serving as a liaison for researchers within an academic setting, this would include ensuring that tissue needs are met in a timely fashion; (serving as a liaison for hospital staff (surgeons, nurses, operating room staff, pathologists, and residents) this would include ensuring that patient issues are addressed and that biobank staff are responding in an appropriate manner.

Personnel

The Director should construct and maintain a current organizational chart that delineates the functional relationships within the biobank. Members of the supervisory and technical staff should be appointed and directed by the Director.

The Director should approve and maintain job descriptions and should document staff responsibilities. The Director should ensure that personnel responsible for performing repository activities are adequate in number, have adequate experience, and should be assigned responsibilities commensurate with their capabilities.

The Director should also be responsible for developing and reviewing employee training programmes and should ensure that there is an appropriate and acceptable safety programme.

5.2.2

The management of the biobank shall formulate the goals with respect to the education, training and skills of the biobank personnel. The biobank shall have a policy and procedures for identifying training needs and providing training of personnel. The training programme shall be relevant to the present and anticipated tasks of the biobank. The effectiveness of the training actions taken shall be evaluated.

Staff may be engaged at many levels of experience and qualifications but they should not be allocated to any piece of work without expert training, or until training appropriate to the job is completed and they are proved competent. Each member of staff should have documented job descriptions with specific delegated tasks and defined responsibilities.

Training

General requirements of training programmes include the following:

- Training in each area of safety should be given to employees before they begin their work.
- The training should be updated yearly for all employees.
- Training should be lead by knowledgeable trainers in a language that is appropriate for the employees being trained.
- The training should be at a level that is appropriate for the educational background of each employee and for the risks to which each employee may be exposed. Thus, there may be a need for different levels of training in safety based upon the needs and requirements of specific employees.
- Records of employee training should be maintained for at least three years, although this requirement may vary nationally.

NOTE Training in safety reflects the same areas of focus as the general areas of concerns in safety. Of these areas, requirements for training in biohazards (e.g. blood-borne pathogens), chemical hazards and radiological hazards are the most demanding. Biobank staff who come in contact with patients also need to be trained in bioethical regulations regarding the disclosure of confidential patient information to

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patients and others. Guidelines need to be established for interactions with patients when obtaining signed consent prior to procurement of tissues. Also, biobank staff needs to be made aware of risks associated with consenting patients such as infections and diseases that they could contract (e.g. scabies, tuberculosis, etc.) As part of the blood-borne pathogen training, staff members are encouraged to get hepatitis vaccines.

5.2.3

The biobank shall use personnel who are employed by, or under contract to, the biobank. Where contracted and additional technical and key support personnel are used, the biobank shall ensure that such personnel are supervised and competent and that they work in accordance with the biobank's management system.

5.2.4

The biobank shall maintain current job descriptions for managerial, technical and key support personnel involved in acquisition, maintenance and provision of biological materials and validation/authentication.

NOTE Job descriptions can be defined in many ways. As a minimum, the following should be defined:

- the responsibilities with respect to performing acquisition, maintenance and provision of biological materials and validation/authentication;
- the responsibilities with respect to the planning of acquisition, maintenance and provision of biological materials and validation/authentication and evaluation of results;
- the responsibilities for reporting opinions and interpretations;
- the responsibilities with respect to method modification and development and validation of new methods;
- expertise and experience required;
- qualifications and training programmes;
- managerial duties.

5.2.5

The management shall authorize specific personnel to perform particular types of acquisition, maintenance and provision of biological materials and sampling, validation/authentication, to issue validation/authentication certificates, to give opinions and interpretations and to operate particular types of equipment. The biobank shall maintain records of the relevant authorization(s), competence, educational and professional qualifications, training, skills and experience of all technical personnel, including contracted personnel. This information shall be readily available and shall include the date on which authorization and/or competence is confirmed.

Authorization to use specialist equipment should be documented in training records. For example, new staff should not be allowed to use autoclaves, centrifuges, freeze-drying equipment, cryopreservation facilities, safety cabinets until they have been trained in their use and are proved competent.

5.3 Accommodation and Environmental Conditions

5.3.1

Biobank facilities for acquisition, maintenance and provision of biological materials and validation/authentication, including but not limited to energy sources, lighting and environmental conditions, shall be such as to facilitate correct performance of the acquisition, maintenance and provision of biological materials and validation/authentication.

The biobank shall ensure that the environmental conditions do not invalidate the results or adversely affect the required quality of any sample. Particular care shall be taken when acquisition, maintenance and provision of biological materials and validation/authentication are undertaken at sites other than a permanent biobank facility. The technical requirements for accommodation and environmental conditions that can affect the results of acquisition, maintenance and provision of biological materials and validation/authentication shall be documented.

All staff should follow the procedures laid down under the appropriate level of containment for the organisms being handled to avoid

contaminating samples and risk of infection (details are provided in the domain *Specific Best Practice Guidelines for BRCs*).

An environment should be provided that is conducive to handling authenticated materials appropriate to the organism domain and to facilitate the acquisition, maintenance and provision of biological materials and its services.

It is the responsibility of the member of staff allocated to a task to check that the accommodation is clean and well lit and that usual aseptic techniques are followed. Appropriate protective clothing should be worn and safety procedures followed.

Appropriate arrangements, in accordance with national and international regulations, for site security should be made to ensure hazardous organisms cannot be released to unauthorized users.

The BRC should describe the premises and processes (including all areas under the responsibility of the BRC) used for the specific operation of the BRC. These areas, as well as the environment and equipment in the premises, should be in conformity with all relevant national and international standards and regulations.

The safe operational level or safety limit for the resources available should be justified and documented and the BRC should not operate beyond these limits.

Maintain and repair all equipment according to SOPs. Establish preventive maintenance schedules.

Establish fire emergency plans and practice them regularly.

Properly ground freezers and other electrical equipment.

Develop a safety programme and associated training procedures by identifying national and international requirements regarding biohazards and likely sources of current information concerning biobank biosafety.

Biosafety

Assume that all human biospecimens are potentially infective and biohazardous. Use universal precautions practices in biobanks similar to those used in other laboratories and clinical settings. Handle biospecimens according to, at a minimum, Biosafety Level 2 (BSL – 2).

Identify and address risks and other general issues of biosafety. Identify frequent biorepository activities and analyse safety issues involved with each activity. Take appropriate actions to ameliorate hazards.

General

An efficient biobank has many design elements to ensure the safe keeping of the material being stored, support the equipment employed, and provide a safe and efficient working environment for the biobank operators. Knowledge of the types of material being stored, the required storage conditions, the projected retention periods, and the projected use of the materials is essential to good biobank design. The biobank design should include sufficient space to accommodate the material being preserved and provide for the safe movement of people, equipment and specimens as needed.

NOTE 1 Heating, Ventilation and Air Conditioning (HVAC)

Temperature – In most biobanks ambient temperature is a major consideration. In most cases sufficient heating capacity must be provided to prevent freezing of water and drain lines. More commonly, heat is the problem. Where mechanical freezers and refrigerators are employed, sufficient air conditioning must be provided to maintain the ambient temperature equal or less than 72 °F (22 °C) at the level of the freezers/refrigerators. This is necessary to prevent excess load on the compressor systems and associated excess wear and early failure.

Air Flow and Circulation – Sufficient air circulation and control must be provided to prevent excess moisture and condensation. Left unchecked, excess humidity can lead to fungal growth, which can render a biobank great harm. Sufficient space for air circulation is required especially in areas where freezers and refrigerators are employed, to prevent excess heat accumulation that may negatively affect compressor function. Adequate ventilation is also critical in LN2 repositories and where dry ice is used

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to ensure that sufficient oxygen levels are maintained.

NOTE 2 Lighting

General Lighting – Lighting in a biobank must be sufficient to provide a safe working environment and to allow materials to be accurately put away and retrieved. Lighting levels required will depend on the type of storage conditions, the size and type of material being stored, and the labelling/identification system employed. Lighting may be both general and task, depending on the situation. General area lighting may be incandescent, florescent, metal halide, or other. Some biobanks may contain materials that are sensitive to light levels or frequencies/colour temperature. In these instances adjustments to limit levels or frequency must be made.

Task Lighting – Task lighting may be necessary to get sufficient illumination for tightly stored materials, reading small labels, or where overhead lighting is impaired. Where task lighting is employed, care must be taken that the lighting method does not adversely affect the storage conditions. For example, the heat from incandescent task lighting placed too close to stored material can cause thawing in samples.

Florescent lighting is generally recommended for task lighting of frozen materials.

NOTE 3 Security Systems

General – The purpose of any biobank is the safekeeping of the materials. To that end every biobank should employ basic security systems. The systems must be monitored and alarms responded to 24 hours per day, 7 days per week. Response systems must be in place such that a responsible individual can take the necessary action to respond to an alarm in a time frame that prevents or minimizes loss or damage to the collection materials. Systems should allow for calls to other key staff from a list of staff phone numbers when the first individual fails to acknowledge the alarm. Emergency contact numbers should be posted in prominent locations in the biobank.

NOTE 4 Fire

Sprinkler Systems – A fire-prevention system is required by building codes for new construction, and compliance with code is normally required if a facility is being converted or renovated. The most common type of fire suppression is the water sprinkler system. The standard system has water in the pipes at all times. Excess heat causes the system to activate, spraying water into the area.

When computer equipment and electrical systems are in place, a pre-action sprinkler system can be employed. In a pre-action system, the sprinkler pipes are dry until a fire is detected. This type of system prevents water damage from accidental activation of the sprinkler system.

Non-Water Based Fire Retardants – Due to the nature of certain equipment and stored materials, water is an unsuitable fire suppression mechanism. In these instances, other chemicals are employed.

The fire suppression mechanism generally smothers the fire by cutting off the supply of oxygen. These systems are very effective. However, they are costly and pose some safety hazards. Personnel must be trained to evacuate the area immediately to prevent asphyxiation. For high-value materials and those samples that would be adversely affected by exposure to water, these non-aqueous systems are necessary.

NOTE 5 Uninterruptible Power Supplies (UPSs)

Biobanks, with exception of those that house only non-temperature sensitive materials, require a constant source of electrical power. Given that all commercial power will fail at some time, a back-up power system is required.

Best Practice: Computer systems and electronic systems, such as freezer controllers, should also be protected by an uninterruptible power supply (UPS) system.

Generators – The most common type of back-up power is the motor generator. These units, typically fuelled by diesel, natural gas or propane, have automatic controls that start them when commercial power is lost. A generator must have a fuel supply to run continuously for a minimum of 48 hours and preferably a minimum of 72 hours, with an ability to re-supply fuel storage supplies. Natural gas supplied by a pipeline may serve as an unlimited source, provided supply lines are not interrupted.

NOTE 6 Safety

General – Issues related to safe operation of an organization are complex and extensive and depend in most cases on the activities of the organization. For example, if the biobank stores and handles human material, then complex national regulations related to precautions necessary to protect employees from blood-borne pathogens and tuberculosis may

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need to be followed. In contrast, if no radioactive material is stored or handled in a biobank, a safety plan dealing with radiological safety is unnecessary. Issues related to fire, electrical and physical safety affect all organizations. Thus, each organization must determine which areas of safety affect it and develop a safety programme to protect its employees.

Regulations – In developing best practices in safety, national regulations must be met in order to protect the health and safety of employees.

Considerations – Safety plans are used to prevent or to minimize injuries to employees. In order to develop an effective safety plan, the likelihood and source of specific injuries for each employee must be identified. The sources and likelihood of specific injuries depends upon the procedures/activities that employees perform as well as the rooms in which the employee is likely to spend time. Each person and their supervisor should identify potential sources of injury and how the likelihood of injury can be minimized via changes in procedures or engineering changes including the use of safety equipment or the improvement of ventilation within a specific area.

Safety Infrastructure – The Director or other designated individual (this may be the CEO in some private institutions) has total responsibility for the safe operation of all components of the institution. This individual may be subject to civil and criminal penalties depending on safety violations and the extent of any injuries resulting from safety violations/problems. While the individual with this responsibility may be legally held responsible, the responsibility for safe operation lies with each and every employee. The institution usually establishes a Safety Committee which is responsible for the overall safety plan of the institution, and for periodic monitoring and updating, of the plan. The Safety Committee usually appoints a Safety Officer to administer the programme.

The Safety Officer establishes a safety training programme and monitors and maintains compliance with the programme, evaluates incidents and injuries and recommends changes to the Safety Committee, as needed. The Safety Officer works closely with area supervisors to ensure local safety.

5.3.2

The biobank shall monitor, control and record environmental conditions as required by the relevant specifications, methods and procedures or where they influence the quality of the biospecimens. Due attention shall be paid, for example, to biological sterility, dust, electromagnetic disturbances, radiation, humidity, electrical supply, temperature and sound and vibration levels, as appropriate to the technical activities concerned.

Acquisition, maintenance and provision of biological materials and validation/authentication shall be stopped when the environmental conditions jeopardize the results of acquisition, maintenance and provision of biological materials and validation/authentication.

Maintenance and Inspection

Cleaning and decontamination procedures should be documented. Buildings should be cleaned on a regular basis. Cleaning of organism containment areas and specialist equipment should be performed by authorized and trained staff using appropriate personal protection equipment following documented.

Establish security systems, including equipment monitoring and alarm systems that are monitored both locally and remotely, with plans to respond at any time. Emergency power systems should be ready to operate all critical equipment during power outages.

Document all incidents where personnel are exposed. Response and treatment protocols should be prepared to be available in the event of potential exposure and infection.

5.3.3

There shall be effective separation between neighbouring areas in which there are incompatible activities. Measures shall be taken to prevent cross-contamination.

Appropriate areas are required for the specific operation of a biobank as appropriate to the domain of the biological materials. The activities that must be accommodated are as follows:

- receipt and storage of the initial sample;
- preparation, handling and processing of samples;

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- biological material storage area and back-up or safety duplicate collection;
- supply, delivery/sales (kept separate from incoming accessions);
- decontamination and cleaning of equipment and processing of wastes;
- duplicate collection in a remote building or alternative site (as a measure to mitigate against risk of disaster).

There are several ways to achieve the above as an alternative to having separate areas. For example:

(a) To construct the biobank on the 'no way back' principle.
(b) To carry out procedures in a sequential manner using appropriate precautions to ensure sample integrity (e.g. use of sealed containers).
(c) To segregate activities by time and space.

Other areas associated with the biobank must be structurally sound, unobstructed, clean and free from laboratory materials.

For any laboratory or biorepository that processes radioactive materials, ensure that proper training of personnel and acquisition of necessary equipment to obtain licenses are carried out.

NOTE 1 Biological Safety

All human specimens and to a lesser extent animal specimens, whether fixed, paraffin embedded, fresh frozen or freeze-dried should be considered as biohazardous. As the extent of alteration of tissue increases (e.g. fresh to frozen to fixed to paraffin embedded) the risk from various infective agents usually is reduced. However, certain agents such as prions (e.g. the cause of Creutzfeldt-Jacob Disease, Scrapie, Mad Cow Disease, Deer/Elk Wasting Disease) may still be infective even when tissues are fixed and processed to paraffin blocks. Thus, all human and animal specimens independent of their state should be treated with universal precautions, i.e. should be handled as if infected with agents that may be pathogenic to humans.

Immunize employees (e.g. for hepatitis) when appropriate vaccines are available.

NOTE 2 Chemical Safety

Employers should develop a written chemical hygiene plan. The chemical hygiene plan must be capable of protecting employees from hazardous chemicals in the laboratory and capable of keeping chemical exposures below the action level or in its absence the Permissible Exposure Limit (PEL). Organizations that fix tissues, for example for quality control, must follow applicable areas of the Formaldehyde Standard.

Biorepositories should also develop a chemical hygiene plan that protects employees from exposure to biohazardous levels of chemicals.

NOTE 3 Electrical Safety

Electrical injuries can be avoided by ensuring that all equipment is grounded; testing equipment when first purchased and yearly will accomplish this thereafter. Similarly, all electrical base plugs must be in good condition and electrical work should be done with great care ensuring that all areas are protected by removal of fuses and with written warnings at the fuse box. Surge protectors are recommended for stand-alone freezers, if this is not part of the building electrical infrastructure. Frequently personal electrical appliances such as radios, hairdryers, etc. may be ignored when testing for grounding and represent significant dangers. Also, great care should be taken with electrical appliances/equipment around water sources, especially sinks and bathrooms/showers. Again, applicable areas of national laws will govern electrical safety.

NOTE 4 Fire Safety

Fire safety can be evaluated by inviting an inspection by the local fire department.

Prior to such inspections and at least yearly, fire drills should be practised and emergency pathways should be posted at all room exits. Emergency exits should never be blocked, obstructed or locked and hallways must not be obstructed or cluttered. Flammable agents should be stored appropriately, including storage of large amounts of flammable agents in fire cabinets if more than several quarts are stored in one area. Refrigerator/freezers can be purchased that are non-combustible, specifically for the research laboratory. Smoking should be regulated carefully; similarly, furniture, rugs, and equipment should be constructed of non-flammable material. Regulations for types of doors to serve as fire barriers

should be followed as should fire requirements for construction of buildings that house specific activities (e.g. laboratories). Much of what has to be done for fire safety will be governed by national requirements.

NOTE 5 Physical Safety

The physical safety of employees must be considered in all organizations and for all employees. Physical safety ranges from preventing falls to ensuring employees are not physically injured or intimidated by other individuals – either employees or non-employees. Much of a plan for ensuring physical safety involves careful maintenance of the physical plant and facilities. Tears in rugs, broken steps and water, soap, paraffin and other slippery substances on floors, and inappropriate use of ladders or chairs as ladders, all may lead to unnecessary falls.

Similarly, unrestrained gas cylinders, unbalanced file cabinets, and inadequately secured shelves all can lead to injuries via falling or moving agents or structures.

Also included in causes of physical injuries are repetitive action injuries and back injuries resulting from inappropriate lifting and movement. For example, some liquid nitrogen freezers are designed with metal racks that contain ten storage boxes. Repository staff is required to stand on step stools and lift these huge heavy racks vertically out of the freezer in order to access specimens. In some repositories the task is compounded by the presence of liquid nitrogen (instead of vapour phase) in each box. Back injuries can be avoided by installing an automatic pulley mechanism to aid in the removal of the racks from the freezers. By analysing an employee's work environment and improving the proper placement of objects and/or provision of the proper tools, the potential for injury will be greatly reduced. When ergonomics is applied correctly in the work environment, visual and musculoskeletal discomfort and fatigue are reduced significantly.

Care should be taken with the overall security of the workplace; this includes limiting access to the workplace by unauthorized personnel. Keys should not be provided to delivery people (e.g. for the delivery of liquid nitrogen or supplies). Instead, delivery people will be afforded entry into the locked area under constant supervision by repository personnel. Physical injuries that are difficult to avoid include minor cuts (e.g. paper), bumps and strains due to inattentive actions.

However, such minor injuries should not be compounded by exposure, for example of broken skin, to biohazards. The overall safety programme should address other hazards that can be prevented or ameliorated. For instance, use of gloves to avoid thermal burns from both heat and cold (e.g. dry ice or liquid nitrogen).

Take precautions to prevent repetitive strain and back injuries and other accidents and injuries typical of the laboratory/biorepository environment.

NOTE 6 Radiological Safety

Few biobanks will store or use radioactive material. For organizations needing a radiological safety plan, the personnel who utilize or come into contact with radioactive material require training as well as specific monitoring equipment as do radiological safety personnel.

NOTE 7 Key Steps in Developing a Biosafety Program

- Identify requirements related to biohazard safety promulgated by national and accrediting organizations and likely sources of up-to-date information as to biosafety. Use this information in developing an overall safety programme and in training programmes related to biohazards.
- Develop the organizational infrastructure necessary to develop and maintain a safety programme.
- Identify risks and general issues of biosafety in the repository; this includes identification of work activities and the safety issues of each activity as well as risks in various workspaces.
- Develop written guidelines to ensure biosafety based on published information, national regulations as well as local and consultant experience. These guidelines should be reviewed and updated periodically and modified as soon as possible to correct any identified problems. Maintain records of incidents involving safety of personnel as well as corrective actions.
- Develop and implement a training programme of which a major focus is biosafety and maintain records of employee training.

5.3.4

Access to and use of areas affecting the quality of the acquisition, maintenance and

provision of biological materials and validation/authentication shall be controlled.

The biobank shall determine the extent of control based on its particular circumstances.

The minimal requirement is to restrict access to the BRC to authorized staff or those accompanied by them. Biological Resource Centres housing hazardous biological materials should pay particular attention to security and where appropriate be fitted with security devices (see *Best Practice Guidelines on Biosecurity for BRCs*).

Access

Biobanks should be equipped with a system that adequately limits access to appropriate staff and protects against physical intrusion. Doors should be locked.

Keys should be controlled, with a record maintained of each person having access to the biobank. Keys that cannot be readily duplicated are highly preferred.

Only persons assigned to the repository operations should have access to the material stored within. Freezers or environmental storage equipment that store valuable or sensitive specimens should be individually locked.

Best Practice: Magnetic locks should be placed.

5.3.5

Measures shall be taken to ensure good housekeeping in the biobank. Special procedures shall be prepared where necessary.

Develop a facility disaster plan based on a local area risk assessment.

The plan should include appropriate measures to protect personnel and equipment during a disaster.

Emergency Preparedness

The facility should have in place an emergency preparedness plan that addresses a wide variety of unlikely, but possible emergencies. This would include such natural disasters as earthquakes, hurricanes, tornadoes, flood, fire, terrorist activities or political demonstrations.

5.4 Acquisition, Maintenance and Provision of Biological Materials and Validation/Authentication Methods and Method Validation

5.4.1

The biobank shall use appropriate methods and procedures for all acquisition, maintenance and provision of biological materials and validation/authentication within its scope.

These include sampling, handling, transport, storage and preparation of samples to be validated/authenticated, and, where appropriate, an estimation of the measurement uncertainty as well as statistical techniques for analysis of validation/authentication data.

The biobank shall have instructions on the use and operation of all relevant equipment, and on the handling and preparation of samples for validation/authentication, or both, where the absence of such instructions could jeopardize the results of validation/authentication. All instructions, standards, manuals and reference data relevant to the work of the biobank shall be kept up to date and shall be made readily available to personnel (see 4.3). Deviation from acquisition, maintenance and provision of biological materials or validation/authentication methods shall occur only if the deviation has been documented, technically justified, authorized, and accepted by the customer.

NOTE International, regional or national standards or other recognized specifications that contain sufficient and concise information on how to perform the acquisition, maintenance and provision of biological materials and validation/authentication do not need to be supplemented or rewritten as internal procedures if these standards are written in a way that they can be used as published by the operating staff in a laboratory. It may be necessary to provide additional documentation for optional steps in the method or additional details.

The BRC should define standards for all preparations used in the growth and/or maintenance of the living biological materials held; these should be documented with the appropriate mechanisms in place to allow changes to procedures.

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Quality checks on the biological material

The reference material producer and its collaborators shall use appropriate documented methods or procedures, which include protocols defining approaches to be adopted for different analyses and related activities within their responsibility (including preparation of items, sampling handling, preservation, storage, packaging, transport to collaborators, estimation of validation uncertainly and analysis of validation/authentication data). These activities should be consistent with the required accuracy, where appropriate, of the reference material, and with any standard specifications relevant to the measurement concerned.

5.4.2 Selection of Methods

The biobank shall use acquisition, maintenance and provision of biological materials and validation/authentication methods, including methods for sampling, which meet the needs of the customer and which are appropriate for the validation/authentication it undertakes. Methods published in international, regional or national standards shall preferably be used. The biobank shall ensure that it uses the latest valid edition of a standard unless it is not appropriate or possible to do so. When necessary, the standard shall be supplemented with additional details to ensure consistent application.

When the customer does not specify the method to be used, the biobank shall select appropriate methods that have been published either in international, regional or national standards, or by reputable technical organizations, or in relevant scientific texts or journals, or as specified by the manufacturer of the equipment.

Laboratory-developed methods or methods adopted by the biobank may also be used if they are appropriate for the intended use and if they are validated. The customer shall be informed as to the method chosen. The biobank shall confirm that it can properly operate standard methods before introducing the validation/authentication. If the standard method changes, the confirmation shall be repeated.

The biobank shall inform the customer when the method proposed by the customer is considered to be inappropriate or out of date.

The BRC should select preservation and maintenance methods according to recommendations from the depositor and/or previous experience. The BRC should document these preservation procedures to ensure they are reproducible and that key parameters of the process are recorded and monitored.

Store biospecimens in a stabilized state. In selecting the biospecimen storage temperature, consider the biospecimen type, the anticipated length of storage, the biomolecules of interest, and whether goals include preserving viable cells. Use stabilizing agents as appropriate. Storage vessels should be durable under planned storage conditions. Follow consistent freezing and thawing protocols to ensure consistent quality for assays.

The biological material should be preserved by at least two methods (where two distinct methods are not applicable to the biological material, cryopreserved stocks should be maintained in separate locations) and as master cell banks and as stocks for distribution. The details of the preservation techniques are laid down in the domain specific criteria.

The labels should include at least the batch date or number and the BRC accession number.

Where possible an indication of expiry date should be provided to the user of the biological material.

Biological materials with specific hazards should be clearly differentiated.

General

Although specimen-processing practices vary according to the specific type of specimen being studied, collection and retrieval practices have many elements in common. Specimen type needs to be carefully considered prior to initiation of collection, based on

availability and intended analytic objectives for the study.

Many specimen collection protocols have special requirements for preservation of macromolecules (proteins, nucleic acids) and/or analytes of interest.

5.4.3 Laboratory-developed Methods

The introduction of acquisition, maintenance and provision of biological materials and validation/authentication methods developed by the laboratory for its own use shall be a planned activity and shall be assigned to qualified personnel equipped with adequate resources.

Plans shall be updated as development proceeds and effective communication amongst all personnel involved shall be ensured.

5.4.4 Non-standard Methods

When it is necessary to use methods not covered by standard methods, these shall be subject to agreement with the customer and shall include a clear specification of the customer's requirements and the purpose of acquisition, maintenance and provision of biological materials and validation/authentication. The method developed shall have been validated appropriately before use.

NOTE For new acquisition, maintenance and provision of biological materials and validation/authentication methods, procedures should be developed prior to the acquisition, maintenance and provision of biological materials and validation/authentication being performed and should contain at least the following information:

(a) Appropriate identification.
(b) Scope.
(c) Description of the type of sample to be validated/authenticated.
(d) Parameters or quantities and ranges to be determined.
(e) Apparatus and equipment, including technical performance requirements.
(f) Reference standards and reference materials required.
(g) Environmental conditions required and any stabilization period needed.
(h) Description of the procedure, including

- affixing of identification marks, handling, transporting, storing and preparation of items;
- checks to be made before the work is started;
- checks that the equipment is working properly and, where required, calibration and adjustment of the equipment before each use;
- the method of recording the observations and results;
- any safety measures to be observed.

(i) Criteria and/or requirements for approval/rejection.
(j) Data to be recorded and method of analysis and presentation.
(k) The uncertainty or the procedure for estimating uncertainty.

5.4.5 Validation of Methods

The BRC should document all methods and procedures used in validation.

The results of method and procedure validation should be recorded.

All methods and procedures should be subject to in-use quality checks. For example, the product should be checked for fitness for purpose, i.e. a sample should be selected from a preserved batch and appropriate stability checks carried out. Such checks should be included in the individual documented procedures.

5.4.5.1

Validation is the confirmation by examination and the provision of objective evidence that the particular requirements for a specific intended use are fulfilled.

5.4.5.2

The biobank shall validate non-standard methods, laboratory-designed/developed methods, standard methods used outside their intended scope, and amplifications and modifications of standard methods to confirm

that the methods are fit for the intended use. The validation shall be as extensive as is necessary to meet the needs of the given application or field of application. The biobank shall record the results obtained, the procedure used for the validation, and a statement as to whether the method is fit for the intended use.

NOTE 1 Validation may include procedures for collecting, processing, storing.

NOTE 2 The techniques used for the determination of the performance of a method should be one of, or a combination of, the following:

- calibration using reference standards or reference materials;
- comparison of results achieved with other methods;
- inter-biobank comparisons;
- systematic assessment of the factors influencing the result;
- assessment of the uncertainty of the results based on scientific understanding of the theoretical principles of the method and practical experience.

NOTE 3 When some changes are made in the validated non-standard methods, the influence of such changes should be documented and, if appropriate, a new validation should be carried out.

5.4.5.3

The range and accuracy of the values obtainable from validated methods (e.g. the uncertainty of the results, detection limit, selectivity of the method, linearity, limit of repeatability and/or reproducibility, robustness against external influences and/or cross-sensitivity against interference from the matrix of the sample/test object), as assessed for the intended use, shall be relevant to the customers' needs.

NOTE 1 Validation includes specification of the requirements, determination of the characteristics of the methods, a check that the requirements can be fulfilled by using the method and a statement on the validity.

NOTE 2 As method development proceeds, regular review should be carried out to verify that the needs of the customer are still being fulfilled. Any change in requirements requiring modifications to the development plan should be approved and authorized.

NOTE 3 Validation is always a balance between costs, risks and technical possibilities. There are many cases in which the range and uncertainty of the values (e.g. accuracy, detection limit, selectivity, linearity, repeatability, reproducibility, robustness and cross-sensitivity) can only be given in a simplified way due to lack of information.

5.4.6 Estimation of Uncertainty of Measurement

5.4.6.1

A testing biobank performing its own validation/authentication shall have and shall apply a procedure to estimate the uncertainty of measurement for all validation/authentication methods.

5.4.6.2

Testing biobanks shall have and shall apply procedures for estimating uncertainty of measurement. In certain cases the nature of the validation/authentication method may preclude rigorous, metrologically and statistically valid calculation of uncertainty of measurement. In these cases the biobank shall at least attempt to identify all the components of uncertainty and make a reasonable estimation, and shall ensure that the form of reporting of the result does not give a wrong impression of the uncertainty. Reasonable estimation shall be based on knowledge of the performance of the method and on the measurement scope and shall make use of, for example, previous experience and validation data.

NOTE 1 The degree of rigour needed in an estimation of uncertainty of measurement depends on factors such as:

- the requirements of the validation/authentication method;
- the requirements of the customer;
- the existence of narrow limits on which decisions on conformity to a specification are based.

NOTE 2 In those cases where a well-recognized validation/authentication method specifies limits to the

values of the major sources of uncertainty of measurement and specifies the form of presentation of calculated results, the biobank is considered to have satisfied this clause by following the validation/authentication method and reporting instructions (see 5.10).

5.4.6.3

When estimating the uncertainty of measurement, all uncertainty components that are of importance in the given situation shall be taken into account using appropriate methods of analysis.

NOTE 1 Sources contributing to the uncertainty include, but are not necessarily limited to, the reference standards and reference materials used, methods and equipment used, environmental conditions, properties and condition of the sample being tested, and the operator.

NOTE 2 The predicted long-term behaviour of the validated/authenticated sample is not normally taken into account when estimating the measurement uncertainty.

NOTE 3 For further information, see ISO 5725 and the Guide to the Expression of Uncertainty in Measurement.

5.4.7 Control of Data

Use informatics systems that support the linking of biospecimens with associated research data and, when available, the limits, if any, on the use of the sample. When applicable, track the levels of consent that each patient has given for the use of their biospecimens and whether that consent has been withdrawn.

Transborder Flows

Biological materials and associated personal data should only be transferred to another state if that state ensures an adequate level of protection.

5.4.7.1

Calculations and data transfers shall be subject to appropriate checks in a systematic manner.

Update the biorepository database each time a biospecimen is moved within or out of the biorepository.

5.4.7.2

When computers or automated equipment are used for the acquisition, processing, recording, reporting, storage or retrieval of sample-associated data, the biobank shall ensure that:

(a) Computer software developed by the user is documented in sufficient detail and is suitably validated as being adequate for use.
(b) Procedures are established and implemented for protecting the data; such procedures shall include, but not be limited to, integrity and confidentiality of data entry or collection, data storage, data transmission and data processing.
(c) Computers and automated equipment are maintained to ensure proper functioning and are provided with the environmental and operating conditions necessary to maintain the integrity of sample-associated data.

NOTE Commercial off-the-shelf software (e.g. word processing, database and statistical programmes) in general use within their designed application range may be considered to be sufficiently validated. However, laboratory software configuration/modifications should be validated as in 5.4.7.2 a).

The informatics system should ensure regular data back-up. Off-site storage of data is desirable.

Data archives should be maintained in accordance with the maintenance of the biological resource storage policy. The support of these archives should be regularly updated according to its physical characteristics (obsolescence) and to software compatibility.

Biological Resource Centres should introduce appropriate measures (protocols, tools and standards) in their own informatics systems to assure reasonable security of information. There are existing systems, e.g. authentication by user ID and password, encryption, encryption of messages and restriction of IP addresses that may provide the basis for such measures. Backup-files should be stored in secure cabinets.

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5.5 Equipment

5.5.1

The biobank shall be furnished with all items of acquisition, preparation and maintenance of biological samples and validation/authentication equipment required for the correct performance of these activities (including preparation, aliquoting, storage, sampling of validation/authentication items, processing and analysis of validation/authentication data). In those cases where the biobank needs to use equipment outside its permanent control, it shall ensure that the requirements of this International Standard are met.

Freezer and Refrigerator Monitoring

The operation of all freezers and refrigerators must be monitored. The function and temperature of each storage unit should be checked and recorded each workday. All storage units must have a mechanism to generate an alarm in the event established temperature ranges are exceeded.

All storage units should have a temperature-monitoring device that can be read and recorded. Dual or multiple temperature sensing devices are preferred.

Continuous monitoring systems should be in place for all low temperature storage units. Alarm conditions should be responded to in a time frame to ensure that no damage to the stored material occurs. Personnel with adequate training who can take corrective action should be on call 24 hours per day, seven days per week.

NOTE 1 Back-Up Storage Capacity

Adequate back-up capacity for low temperature units must be maintained in anticipation of possible equipment failure. Extra capacity equal at a minimum to the capacity of the largest single storage unit must be maintained at operating temperature at all times. This applies to each temperature storage condition. The total amount of back-up storage required for large biobanks must be determined empirically, but will typically be 1.5% to 3% of the total freezer capacity.

Personnel must be trained in processes and techniques for rapidly transferring material to back up units when necessary.

Best Practice: A process should be in place for updating records of the specimen transfer, documenting the event, and corrective action taken.

NOTE 2 Cryogenic Freezers – Liquid Nitrogen Supply

Where liquid nitrogen (LN2) refrigeration is employed, an adequate supply of refrigerant must be maintained. For freezers filled from Dewars or supply tanks, a minimum three-day supply of LN2 at normal usage and replenishment intervals should be maintained, with the assumption that a re-supply is readily available. The supply maintained on hand should be at least 20% more than the normal refill usage to allow for emergency situations. Bulk supply systems should maintain a minimum supply of 20% of the bulk tank capacity, or greater than three days' working capacity, assuming a ready re-supply system. When bulk storage and piping systems are used, another hazard is potentially present. These systems require relief valves to prevent rupturing of the pipe and bulk tanks in the event of over-pressure. If relief valves trip unexpectedly, a person near a valve can be sprayed with either the cold gas or the liquid. More likely, in the event of a blockage or overpressure event, a number of relief valves will vent nearly simultaneously. This can cause a 'white-out' condition in a matter of a few seconds. Visibility drops to near zero and the oxygen level in the area may become less than that necessary to sustain life. Personnel must evacuate immediately. This unlikely event, which is usually caused by an error during the filling of the bulk tank, can be mitigated by well-designed procedures and practices.

Best Practice: Self Contained Breathing Apparatus (SCBAs or 'air packs') should be available for use in the event of a 'white out' condition in the biobank. Personnel should receive training on the effective use of these units. In the event of an emergency staff should evacuate the facility immediately and not return until the environment is safe.

NOTE 3 Liquid Nitrogen Freezers

The use of liquid nitrogen freezers for long-term specimen preservation is optimal only if the operating conditions within the freezer are less than the critical storage temperature. The critical temperature

for storage of sensitive organisms and cells is generally considered to be −140°C or below. Care must be taken that the desired temperature is maintained in the vessel in which critical material is stored.

Many LN2 freezers, especially older models, cannot consistently maintain −140°C at the top of the tank. Staff should be aware that the temperature of the freezer increases slightly (some newer freezer models are more efficient with respect to temperature loss) each time the freezer is opened and specimens are either placed in storage or removed from storage. Care must be taken to minimize the number of times a freezer is opened within a given time frame.

Best Practice: Some type of temperature map of the freezer should be conducted on a periodic basis to verify the temperature at various locations within the freezer.

NOTE 4 Vapour vs Liquid Phase Storage

Vapour phase storage is preferred over liquid phase storage. Properly selected and operated freezers provide sufficiently low temperature to maintain a good safety margin below Tg, and have sufficient refrigerant storage capacity to avert any accidental warming. Use of vapour phase avoids the safety hazards inherent in liquid phase storage. Also, there is documentation of disease transfer via the liquid phase where primary storage containers were not hermetically sealed and the liquid nitrogen became contaminated. Note that storage in either vapour or liquid carry specific requirements for freezer design that must be considered when the decision for vapour vs. liquid is made.

NOTE 5 Selection of Appropriate Storage Containers

Liquid nitrogen expands to 700 times its original volume when brought to a gaseous phase at room temperature. This situation produces a form of explosion hazard. Plastic and glass containers can easily explode if liquid nitrogen is trapped when the container is removed from the freezer. Good practice dictates that any container which has potentially been in the liquid phase be allowed to equilibrate in the gaseous phase of the freezer prior to removal.

NOTE 6 Alarm Systems

Alarm systems should be set to monitor the liquid nitrogen level and temperature.

Alarm set points should be established that will permit sufficient time for corrective action before significant warming occurs.

NOTE 6 Protective Wear

Use of liquid nitrogen as a refrigerant poses special safety problems. With a liquid temperature of −196°C, flesh freezes almost instantly if it comes in direct contact with the liquid. Because it is a liquid, it can splash, and therefore requires the use of face and eye protection. Heavy gloves, a face shield, and a protective garment should always be used when handling liquid nitrogen.

NOTE 7 Oxygen Sensors

Because nitrogen displaces oxygen, care must be taken when LN2 freezers are employed. The risk is inversely correlated with the size of the room. Oxygen level sensors should always be employed when LN2 freezers are used in a repository. Both installed and mobile/personal monitors may be appropriate depending on the size of the facility. Even when installed units indicate an alarm condition, it may be useful to employ a personal monitor to enter the room carefully to validate the alarm condition if the area is not visible from the outside.

Mobile oxygen monitors may be the best to use in a secure area where liquid nitrogen freezers operate because the sensors in installed units will degrade over time and sound false alarms.

NOTE 8 Mechanical Freezers

Mechanical freezers are employed in a variety of storage temperature ranges, including −20, −40, −70 to −80°C, and occasionally −140°C. Mechanical freezers come in a wide variety of sizes, configurations, and operating electric voltages. Because mechanical freezers are devices attached to commercial power systems, a back up power plan and an emergency response plan must be in place. The length of time that results in the significant warming of the stored material will vary by the properties of the stored material, the thermal loading of the freezer, the ambient conditions, and the design and maintenance of the unit. It is incumbent on the facility operator to establish the critical temperatures and response times to alarms.

Common practice is to set the alarm point at about 10°C warmer than the nominal operating temperature of the unit. This allows for normal operating variation and some leeway for warming when the material is accessed.

NOTE 9 Refrigerators

Refrigerators are commonly employed where the life of the material being stored is enhanced by

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storage below ambient temperature. This is the preferred storage medium when the material must be kept cool, but is damaged by freezing. In refrigerator operation it is important to ensure that the temperature is maintained within the specified operating range, not just below a maximum temperature.

Some high-value materials, vaccines for example, must be maintained precisely between 2°C and 8°C. The facility operator must insure that high and low set points are monitored, and that alarm response time is adequate to prevent excessive temperature excursions.

Best Practice: For high-value materials, the refrigerators should be equipped with dual compressors that operate under an electrical alternating control system.

NOTE 10 Safety Features for Walk-in Freezers and Refrigerators

Door Release – Walk-in freezers and refrigerators entail special hazards. All building codes require that these units have safety releases to prevent a person from being trapped in a unit by accidentally closing doors (i.e. interior door release mechanism).

Floor Covering – Refrigerators can generate slipping and falling hazards if water condenses on the floor. Freezers can occasionally create ice on the floor. Both types of units should have some type of mat or grate to prevent slipping.

Dry Ice – Walk-in freezers should be kept free of dry ice (i.e. the solid phase of CO2). Carbon dioxide can rapidly build up, displace the oxygen in the room, and cause personnel working in the units to lose consciousness.

General Use of Dry Ice – Dry ice is frequently used as a refrigerant for shipping and emergency back up for mechanical freezers. Handling precautions (e.g. wearing insulated gloves) should be employed when handling this material, the temperature of which is approximately −79°C. As dry ice sublimates, the CO2 level in the surroundings can increase. In confined areas the carbon dioxide can displace oxygen, presenting an asphyxiation hazard. Where dry ice is employed, engineering controls to insure sufficient air or oxygen level monitoring are required.

5.5.2

Equipment and its software used for acquisition, maintenance and provision of biological materials and validation/authentication shall be capable of achieving the accuracy required and shall comply with specifications relevant to the sample concerned.

Calibration programmes shall be established for key quantities or values of the instruments where these properties have a significant effect on the sample quality. Before being placed into service, equipment (including that seed for storage) shall be calibrated or checked to establish that it meets the biobank's specification requirements and complies with the relevant standard specifications. It shall be checked and/or calibrated before use (see 5.6).

Equipment management procedures including use, control of performance, maintenance and calibration should be laid down in a predefined schedule. Instructions for these activities should be laid down in the manufacturer's handbooks/manuals or in the BRC procedure. Service records should be maintained and copies of key documents should be held in the BRC Equipment Maintenance and Calibration Log books in the care of the Quality Manager.

Calibration

A system for the calibration of all instruments should be in place. Any device that provides a readout, data, or has a meter movement, is considered an instrument, and requires calibration. Calibration should be done annually or per manufacturer's recommendation. Calibration should be performed against standards.

Best Practice: Calibration records should include the appropriate standard readings taken both before and after calibration

Measuring equipment used in reference material production shall be properly calibrated or verified and maintained, with all procedures being documented and the results recorded. Where appropriate, periodic performance checks should be carried out (e.g. to check the response, stability, linearity, resolution, alignment, repeatability and separating efficiency) to ensure that the measuring equipment is

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performing adequately. The frequency of such performance checks shall be determined by experience and based on the type and previous performance of the equipment intervals between checks shall be shorter than the time within which the equipment has been found to drift outside acceptable limits, in accordance with the requirements of ISO 10012-1.

5.5.3

Equipment shall be operated by authorized personnel. Up-to-date instructions on the use and maintenance of equipment (including any relevant manuals provided by the manufacturer of the equipment) shall be readily available for use by the appropriate laboratory personnel.

5.5.4

Each item of equipment and its software used for acquisition, maintenance and provision of biological materials and validation/authentication and significant to the result shall, when practicable, be uniquely identified.

5.5.5

Records shall be maintained of each item of equipment and its software significant to the acquisition, maintenance and provision of biological materials and validation/authentication performed. The records shall include at least the following:

(a) The identity of the item of equipment and its software.
(b) The manufacturer's name, type identification, and serial number or other unique identification.
(c) Checks that equipment complies with the specification (see 5.5.2).
(d) The current location, where appropriate.
(e) The manufacturer's instructions, if available, or reference to their location.
(f) Dates, results and copies of reports and certificates of all calibrations, adjustments, acceptance criteria, and the due date of next calibration.
(g) The maintenance plan, where appropriate, and maintenance carried out to date.
(h) Any damage, malfunction, modification or repair to the equipment.

Construction and Operation

Construction should meet appropriate national regulations and policies, e.g. to the containment level appropriate for the risk (hazard) group of the organisms worked with. If major building, renovation, repair or dirty work is necessary in BRC laboratories, normal activities should be suspended until the building, renovation, repair or dirty work is completed.

5.5.6

The laboratory shall have procedures for safe handling, transport, storage, use and planned maintenance of preparation, aliquoting, storage and measurement equipment to ensure proper functioning and in order to prevent contamination or deterioration.

NOTE Additional procedures may be necessary when equipment is used outside the permanent laboratory for acquisition, maintenance and provision of biological materials or validation/authentication.

General

A system for maintenance and repair of storage equipment, supporting systems, and facilities should be in place. Preventative maintenance should be in place for all operations and facility systems. System maintenance should be performed at regular, established intervals per manufacturer's recommendation.

Best Practice: Maintenance records should provide a description of work that was done, tests that were performed, and the results compared to the standards.

5.5.7

Equipment that has been subjected to overloading or mishandling, gives suspect results, or has been shown to be defective or outside specified limits, shall be taken out of service. It shall be isolated to prevent its use or clearly labelled or marked as being out of service until it has been repaired and shown by calibration or test to perform correctly. The biobank shall examine the effect of the defect or departure from specified limits on previous validation/authentication and shall institute the 'Control of Non-conforming Work' procedure (see 4.9).

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Validation

All equipment should be validated prior to use or following repairs that affect the instrument's measuring capabilities.

Best Practice: A validation procedure should be in place to verify the operation of all new or repaired equipment. Documentation of the testing should be maintained.

5.5.8

Whenever practicable, all equipment under the control of the biobank and requiring calibration shall be labelled, coded or otherwise identified to indicate the status of calibration, including the date when last calibrated and the date or expiration criteria when recalibration is due.

5.5.9

When, for whatever reason, equipment goes outside the direct control of the biobank, the biobank shall ensure that the function and calibration status of the equipment are checked and shown to be satisfactory before the equipment is returned to service.

5.5.10

When intermediate checks are needed to maintain confidence in the calibration status of the equipment, these checks shall be carried out according to a defined procedure.

5.5.11

Where calibrations give rise to a set of correction factors, the biobank shall have procedures to ensure that copies (e.g. in computer software) are correctly updated.

5.5.12

Preparation, aliquoting storage and test equipment, including both hardware and software, shall be safeguarded from adjustments which would invalidate the results.

5.6 Measurement traceability

5.6.1 General

All equipment used for acquisition, maintenance and provision of biological materials and validation/authentication, including equipment for subsidiary measurements (e.g. for environmental conditions) having a significant effect on the sample quality, calibration or sampling shall be calibrated before being put into service. The biobank shall have an established programme and procedure for the calibration of its equipment.

NOTE Such a programme should include a system for selecting, using, calibrating, checking, controlling and maintaining measurement standards, reference materials used as measurement standards, and equipment used to perform acquisition, maintenance and provision of biological materials and validation/authentication.

5.6.2 Specific requirements

5.6.2.1 Calibration

Not applicable. Participation in a suitable programme of inter-biobank comparisons is required where possible.

5.6.2.2 Validation/authentication

5.6.2.2.1

For testing biobanks, the biobank shall ensure that the equipment used can provide the uncertainty of measurement needed.

Validation/authentication methods developed in-house by the reference material producer, or by any collaborators, shall be validated and authorized (e.g. by a management/technical advisory group or appropriately defined person) before use. Such methods shall be thoroughly investigated, and shall clearly and exactly describe the necessary conditions and procedures for which the measurement of the property values of interest are valid at the level of accuracy commensurate with the intended use of the reference material.

NOTE 1 In some cases, reference materials are characterized for method-dependent properties (e.g. leachable metals, pH or flashpoint).

Characterization

The reference material producer shall use and document technically valid procedures to characterize its reference materials. Where possible, the characterization should comply with requirements of ISO Guide 35.

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There are several technically valid approaches to characterizing a reference material as described in ISO Guide 35. These include carrying out measurements using:

(a) A single primary (definitive) method, preferably in duplicate, by a single organization (which may consist of a number of separate laboratories).
(b) Two or more independent reference methods by on organization; the methods should have small measurement uncertainties relative to the intended use of the reference material; the characterization should be corroborated by additional methods or laboratories.
(c) A network of qualified organizations using methods of demonstrable accuracy and having an assessment of known and acceptable measurement uncertainty.
(d) A method-specific approach (inter-biobank study) giving only method-specific assessed property value(s).

Depending on the type of reference material, its intended use, the competence of laboratories involved and the quality of methods employed, one approach may be chosen as appropriate.

The single primary (definitive) approach should only be carried out when the equipment and expertise enable it to ensure traceability to the SI system. More usually, a property value can be reliably assessed when its value is confirmed by several collaborators working independently and using more than one method, for each of which the accuracy, repeatability and reproducibility have been well established. Generally, the reference material producer should select collaborators in such a manner as to ensure meeting the objective of the production programme, including ensuring an adequate level of quality for the reference materials being produced, as defined by the producer and, where appropriate, the user.

Assignment of Property Values and Their Uncertainties

The reference material producer shall use documented procedures based on accepted statistical principles for the assignment of property values. These procedures should include, as appropriate:

(a) Details of the experimental designs and statistical techniques used.
(b) Policies on treatment and investigation of statistical outliers and/or the use of robust statistics.
(c) Whether separate, method-dependent property values are assigned when significant differences are established using different methods.
(d) Whether weighting techniques are used for contributions to assigned property values derived from different methods with different measurement uncertainties.
(e) The methods used to assign measurement uncertainties to the property values.
(f) Any other significant factors which may affect the assignment of property values.

The reference material producer should never entirely on a statistical analysis of the characterization data when assessing the property values of interest. Outliers should not be excluded on purely statistical evidence until they have been thoroughly investigated and, where possible, the reasons for the discrepancies identified. Alternatively, the use of robust statistics may be appropriate in some cases.

When several methods have been used to characterize a reference material, difficulty may arise when the results show significant differences, in which case a property value based on the mean in inappropriate. It is essential in such cases that the reference material producer and its collaborators have considerable experience of the different methods and be able to give more or less weight to the results form the use of a particular validation/authentication method.

For example, the means from two (or more) measurement methods may differ statically, but the results from both methods may agree within the measurement uncertainly of each method. In some cases, the results may be weighted according to the inverse of the variance of each method. In some cases, measurement methods will produce irreconcilable results and it may be necessary to assign separate property values according to the methods used (i.e. a method-specific approach).

In assigning uncertainties to the property values of interest, any uncertainties resulting from between-unit variations and/or from possible instabilities (both during storage and during transportation) shall be included.

In assigning the property values of interest, the reference material producer should consider establishing a group of independent experts whose responsibility is to check that all work, data and documents are fit for their purpose. It is also necessary for the reference material producer to demonstrate the tractability of the property values in accordance with the requirements of ISO Guide 35.

The reference material producer shall carry out an assessment of the uncertainties of the assigned property values.

This should always be based on a combination of the uncertainties arising from the corrections for recognized systematic errors, the uncertainties arising from possible systematic errors and the uncertainty due to random variations of repeated observations. Ideally, the latter should constitute the smaller proportion of the uncertainty of a particular property value. In some cases, it may be necessary to make uncertainly estimates based on experience with the measurement methods and their reliability. In such cases, the justification should be described.

The most important aspect of establishing the property values of the reference material being produced is an assessment of their measurement uncertainties. Every measurement has an uncertainty associated with it. Proper assessment and correction of all recognized and correctable systematic errors should be carried out and the uncertainties associated with these corrections assessed. An educated assessment of measurement uncertainty arising from possible systematic errors should also be made, for example, based on the results of inter-comparisons.

5.6.2.2.2

Where traceability of measurements to SI units is not possible and/or not relevant, the same requirements for traceability to, for example, certified reference materials, agreed methods and/or consensus standards, are required.

5.6.3 Reference Standards and Reference Materials

5.6.3.1 Reference Standards

The biobank shall have a programme and procedure for the calibration of its reference standards. Reference standards shall be calibrated by a body that can provide traceability as described in 5.6.2.1. Such reference standards of measurement held by the biobank shall be used for calibration only and for no other purpose, unless it can be shown that their performance as reference standards would not be invalidated. Reference standards shall be calibrated before and after any adjustment.

5.6.3.2 Reference Materials

Reference materials shall, where possible, be traceable to SI units of measurement, or to certified reference materials. Internal reference materials shall be checked as far as is technically and economically practicable.

5.6.3.3 Intermediate Checks

Checks needed to maintain confidence in the calibration status of reference, primary, transfer or working standards and reference materials shall be carried out according to defined procedures and schedules.

5.6.3.4 Transport and Storage

The biobank shall have procedures for safe handling, transport, storage and use of reference standards and reference materials in order to prevent contamination or deterioration and in order to protect their integrity.

NOTE Additional procedures may be necessary when reference standards and reference materials are used outside the permanent biobank for validation/authentication.

5.7 Sampling

The biological material received should have the following information:

(a) Name (where one can be applied), other identifier or cell culture description.

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(b) Depositor's name and address.
(c) Source, substrate or host from which the biological material was isolated or derived (where identified) and date of isolation.
(d) Geographical origin of material (the minimum requirement is the country of origin or the furnisher of the source, substrate or host).
(e) Depositor's biological material number or other collection number(s), if deposited elsewhere.
(f) Growth media and conditions, cell preservation or storage conditions where known.
(g) Hazard information, e.g. in the form of a safety data sheet.

To ensure a minimum number of transfers or generations from the original biological material, where this is appropriate, the BRC should use master (or seed) and distribution stocks.

The BRC should produce the master stock from the original biological material. This master stock should be used to generate the distribution stock. The BRC should use the distribution stock to supply biological materials.

The BRC should adapt the size of these masters and distribution stocks to the anticipated distribution rate.

5.7.1

The biobank shall have a sampling plan and procedures for sampling when it carries out sampling of biospecimens for subsequent validation/authentication. The sampling plan as well as the sampling procedure shall be available at the location where sampling is undertaken. Sampling plans shall, whenever reasonable, be based on appropriate statistical methods. The sampling process shall address the factors to be controlled to ensure the validity of the validation/authentication results.

NOTE 1 Sampling is a defined procedure whereby a part of a substance, material or product is taken to provide for validation/authentication of a representative sample of the whole. Sampling may also be required by the appropriate specification for which the substance, material or product is to be validated/authenticated. In certain cases (e.g. forensic analysis), the sample may not be representative but is determined by availability.

NOTE 2 Sampling procedures should describe the selection, sampling plan, withdrawal and preparation of a sample or samples from a substance, material or product to yield the required information.

Where sampling is carried out as part the valorization/authentication method (e.g. subsampling a representative quantity from a batch of material), the reference material producer shall use documented procedures and appropriate statistical techniques to take test portions.

5.7.2

Where the customer requires deviations, additions or exclusions from the documented sampling procedure, these shall be recorded in detail with the appropriate sampling data and shall be included in all documents containing validation/authentication results, and shall be communicated to the appropriate personnel.

5.7.3

The biobank shall have procedures for recording relevant data and operations relating to sampling that forms part of the validation/authentication that is undertaken. These records shall include the sampling procedure used, the identification of the sampler, environmental conditions (if relevant) and diagrams or other equivalent means to identify the sampling location as necessary and, if appropriate, the statistics the sampling procedures are based upon.

5.8 Handling of Biological Samples

A risk assessment should be carried out on the biological material and the methods recorded to determine, as far as possible, the potential of harm to personnel, the public and the environment. The risk assessment should be reviewed and updated regularly.

The BRC should document its acquisition policy defining the biological material to be maintained and the criteria on which the acceptance of new biological material offered to the collection is based. This policy should

balance capability, capacity with scientific and users needs.

The BRC should perform authentication tests as well as determining the stability of some key features, growth requirements, and methods of maintenance and/or preservation as appropriate to the biological material maintained, using appropriate technology. This information should be recorded. These records should be retained and can be used as a baseline when in-storage maintenance checks are performed or for validation after preservation restocking.

Where possible the identity of the biological material should be confirmed after receipt by a competent person (employed or contracted by the BRC or its parental organization). The biological material should be checked again by these competent persons before (if there are additional transfers of the biological material before it is preserved) and after preservation. This step may include identity, purity or property check of the biological material performed by the depositor.

5.8.1

The biobank shall have procedures for the transportation, receipt, handling, preparation, protection, storage, retention and/or disposal and validation/authentication of samples, including all provisions necessary to protect the integrity of the samples, and to protect the interests of the biobank and the customer.

The BRC should document and implement procedures for the receipt and storage appropriate of the type of biological materials handled.

Base all protocols on SOPs that are established using authoritative best practices or solid research data, when available.

Biospecimen Collection, Processing, Storage, Retrieval, and Dissemination

Collect and process biospecimens under conditions appropriate for each biospecimen type and for the intended analyses, using collection protocols that are based on authoritative best practices or solid research data, when available.

Ensure that proper informed consent protocols are followed.

Ensure that a pathologist directs the collecting and processing of surgical and autopsy biospecimens to ensure that clinically important issues related to the biospecimens are adequately and accurately addressed and that patient care is not compromised.

For tissue biospecimens, minimize the time for collection and processing as much as possible (unless inadequate processing time is known to interfere with the analysis method); reduce biospecimen temperature as soon as possible after collection. Optimal processing times may vary for other types of biospecimens depending on the analysis method for which they are used.

Choose biospecimen containers with analytical goals in mind. This may require, for example, screening of containers for trace metals that may interfere with laboratory analyses.

NOTE 1 Specimen Types

A variety of specimen types may be collected for storage:

- blood and blood fractions (plasma, serum, buffy coat, red blood cells);
- urine;
- buccal cells/saliva;
- hair;
- nail clippings;
- breast milk;
- faeces;
- exhaled air;
- tissues – surgical, autopsy, frozen, paraffin-embedded;
- cell lines;
- products of conception;
- cord blood;
- bone marrow;
- fluids from cytology (ascites, pleural fluid, synovial fluid, etc.).

Timing of Specimen Collection – Biological marker levels may vary according to the time of day; however, a much greater effect may be the time and conditions associated with specimen processing.

Blood – One of the primary decisions is whether to collect anticoagulated (plasma/buffy coat/RBC) or coagulated (serum/clot) blood. When multiple blood collection devices are involved there is a proscribed order of draw. Depending on the amount of blood needed, collection of blood spots on treated or untreated cards is adequate or even preferable to collecting as above.

Urine – Urine collections should be maintained on ice or refrigerated for the duration of the collection. Plastic or glass containers should be clean and dry, and have a 50–3,000 ml capacity, a wide mouth and leak-proof cap. Depending on the analyte to be measured, a preservative may be needed. The type of preservative may differ according to test methodologies, time delay and transport conditions. EDTA and sodium metabisulfite are examples of preservatives commonly used in urine collections.

Tissues – Specimen protocols for collecting human tissues vary greatly.

Nail Clippings – Nail clippings are used for trace metal analysis. These samples are simple to collect, store and ship but present special washing, hydrolysis and matrix problems for the analytic laboratory.

Saliva – Collection devices include non-covered cotton roll, polypropylene-covered polyether roll and paraffin wax chewing stimulation. Some researchers may request patients to provide saliva samples directly into a container; make sure that the opening is adequately large to facilitate this collection.

Breast Milk – Breast milk can be initiated when breast-feeding starts. It can be collected by manual expression or vacuum pump and should be collected in autoclaved bottles.

Additional Specimen Types – Various protocols for collection and processing exist for rare or difficult to collect specimens such as bone marrow, cord blood, products of conception, and fluids from cytology (ascites, pleural fluid, synovial fluid, etc.).

Best Practice: Collection of specimens for research must under no circumstances interfere with appropriate patient diagnosis.

Best Practice: A pathologist must review all patient tissue specimens to determine what material can be made available for research. Blood and other body fluids not required for diagnosis can be collected in accordance with approved protocols and do not require pathologic review.

Plasma, Serum and Urine

- All staff should wear protective equipment, as appropriate, such as lab coats, disposable gloves, freezer gloves, face shields, goggles (mandatory when working with liquid nitrogen).
- Assure that correct specimens are located; retrieve requisitioned specimens from the freezer using established QC procedures.
- Specimens in plastic cryovials should be thawed at room temperature.
- Specimens in glass vials should be thawed slowly overnight in a refrigerator to prevent cracking.
- Open and aliquot specimens in a biological safety hood. Sterile vials and pipettes are used to avoid contaminating samples.
- Determine the proper pipette and tip to use depending on required volumes.
- Use different pipette tip for each specimen and rinse pipette tip with 10% bleach solution before discarding.

NOTE 2 Freezing and Thawing Considerations

The rate and method of freezing and thawing specimens can have serious effects on the viability of cells. The following must be taken into consideration when freezing and thawing specimens for which cellular viability is important. Exact freezing and thawing protocols should be developed to ensure that the method used supports the known or anticipated use for the specimens.

Rate of cooling – The rate of cooling controls the size of ice crystals and how fast they are formed, which may affect cell recovery. A uniform cooling rate of -1°C per minute from ambient temperature is effective for a wide variety of cells. The steady decline of temperature can be achieved by the use of commercially available freezing devices that control the rate of freezing.

Storage – The temperature at which frozen preparations are stored affects the length of time after which cells can be recovered in the viable state. The lower the storage temperature the longer the viable storage period.

Handling – In addition to temperature of storage, handling during removal from storage will affect the viability of cells and may result in degradation of cellular components. Every time an ampoule/vial is

exposed to a warmer environment even briefly it experiences a change in temperature.

Reconstitution (Thawing) – Although slow cooling is generally best to insure cell viability, the opposite is required when thawing from the frozen state. Agitation of the vial/ampoule in a 37°C water bath is preferable, but may be detrimental to certain cell types if the process is too lengthy.

Determination of recovered cells

There are several methods to estimate the number of viable cells in a non-motile population accurately, usually by a dye exclusion method (e.g. trypan blue).

The reference material producer shall establish whether the sample has received adequate preparation for its indented use. Procedures for sample preparation should include, where appropriate:

(a) Qualitative analysis for verification of sample type.
(b) Machining, grinding, blending, sieving and riffling (i.e. dividing into representative samples).
(c) Drying (including lyophilization) and sterilization.
(d) Packaging (e.g. bottling, etc.) representative samples from the batch.
(e) Stability testing over a range of conditions which may affect the property values and/or matrix composition of the reference materials being produced (e.g. different levels of humidity, temperature, light, magnetic fields, etc.).

5.8.2

The biobank shall have a system for identifying samples. The identification shall be retained throughout the life of the sample in the biobank. The system shall be designed and operated so as to ensure that samples cannot be confused physically or when referred to in records or other documents. The system shall, if appropriate, accommodate a sub-division of groups of samples and the transfer of samples within and from the biobank.

A unique collection number is allocated to the biological material, which is never reassigned if the biological material is later discarded.

Biorepository Informatics: Data

Management and Inventory Control and Tracking

Assign a unique identifier (such as a number or barcode) to each biospecimen at the time of collection.

Identify specific clinical and epidemiological data by the same number and/or barcode. Use the number or code to track a biospecimen from collection through processing, storage, and distribution.

5.8.3

Upon receipt of the samples, abnormalities or departures from normal or specified conditions, as described in the acquisition, maintenance and provision of biological materials and validation/authentication method, shall be recorded. When there is doubt as to the suitability of a biospecimen for acquisition, maintenance and provision of biological materials and validation/authentication, or when a biospecimen does not conform to the description provided, or the acquisition, maintenance and provision of biological materials and validation/authentication required is not specified in sufficient detail, the biobank shall consult the customer for further instructions before proceeding and shall record the discussion.

Biobanks should only accept deposits of biological material that meet its acquisition criteria and fall into the groups of its specialist expertise.

5.8.4

The biobank shall have procedures and appropriate facilities for avoiding deterioration, loss or damage to the samples during handling, preparation and storage. Handling instructions provided with the sample shall be followed. When samples have to be stored or conditioned under specified environmental conditions, these conditions shall be maintained, monitored and recorded. Where a sample or a portion of a sample is to be held secure, the biobank shall have arrangements for storage and security that protect the condition and integrity of the secured samples or portions concerned.

NOTE 1 Where validation/authentication items are to be returned into biobank after validation/

authentication, special care is required to ensure that they are not damaged during the handling, testing or storing/waiting processes.

NOTE 2 A sampling procedure and information on storage and transport of samples, including information on sampling factors influencing the validation/authentication result, should be provided to those responsible for taking and transporting the samples.

NOTE 3 Reasons for keeping a sample secure can be for reasons of record, safety or value, or to enable complementary validation/authentication to be performed later.

A maintenance plan (i.e. a scheme for periodic control of the preserved material) should be in place for each item stored. Several aspects determine the frequency of the maintenance checks (e.g. the type of biological material, the preservation method, turnover of the material, etc.). The maintenance check should be appropriate to the biological material and be laid down in the domain specific criteria.

The biological material should be stored under environmental parameters that assure the stability of its properties (see domain specific obligations).

Details of the inventory control, lead times and re-stocking practices should be documented.

A duplicate collection should be maintained, preferably on another site as a disaster protection measure and to avoid accidental loss.

The condition of all stored/stocked items and materials shall be assessed at appropriate intervals throughout their storage life, in order to detect possible deterioration.

The reference material producer should ensure that the integrity of the reference materials is maintained until the seal has been broken, or up to the point when presented for analysis. The producer cannot be held responsible for material once its seal has been broken. This may require, in some cases, that the reference material be packaged in unit quantities sufficient for a single use.

Where appropriate, the property values to be assessed should be measured periodically, ideally over the range of conditions under which the materials is to be stored prior to distribution to the user. The effects of light, moisture, heat and time shall be quantified in order to provide advice on storage location and lifespan (and hence a suitable shelf life/expiry date).

Where appropriate, an assessment of the stability of the assigned property values of the reference material

Performed at periodic intervals after characterization to confirm that all values are maintained from production under its expiry date. Wherever appropriate, the reference material producer shall provide an expiry date for the usable life of the reference materials produced, based on initial and on-going stability studies in compliance which ISO Guide 35. It should be made clear on the certificate of analysis on what criterion the expiry date is based (e.g. the date of shipment or the date of opening the packaging).

5.9 Assuring the Quality of Validation/Authentication Results

5.9.1

The biobank shall have quality control procedures for monitoring the validity of validation/authentication undertaken. The resulting data shall be recorded in such a way that trends are detectable and, where practicable, statistical techniques shall be applied to the reviewing of the results. This monitoring shall be planned and reviewed and may include, but not be limited to, the following:

(a) Regular use of certified reference materials and/or internal quality control using secondary reference materials.
(b) Participation in inter-biobank comparison or proficiency-testing programmes.
(c) Replicate validation/authentication using the same or different methods.
(d) Validation/authentication of retained items.
(e) Correlation of results for different characteristics of an item.

NOTE The selected methods should be appropriate for the type and volume of the work undertaken.

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5.9.2

Quality control data shall be analysed and, where they are found to be outside pre-defined criteria, planned action shall be taken to correct the problem and to prevent incorrect results from being reported.

5.10 Reporting the Data

5.10.1 General

The data associated with each sample and validation/authentication carried out by the biobank shall be reported accurately, clearly, unambiguously and objectively, and in accordance with any specific instructions in the acquisition, maintenance and provision of biological materials and validation/authentication methods.

The data shall be reported, usually in a sample report, and shall include all the information requested by the customer and necessary for the interpretation of the sample-associated data and all information required by the method used. This information is normally that required by 5.10.2, and 5.10.3.

In the case of internal customers, or in the case of a written agreement with the customer, the data may be reported in a simplified way. Any information listed in 5.10.2 to 5.10.3 that is not reported to the customer shall be readily available in the biobank.

NOTE 1 Validation/authentication is sometimes called validation/authentication certificates and validation/authentication reports, respectively.

NOTE 2 Validation/authentication reports or validation/authentication certificates may be issued as hard copy or by electronic data transfer provided that the requirements of this International Standard are met.

Data and Informatics

The biobank should manage and store data and produce electronic catalogues based on authenticated and validated information.

The authentication of data may differ from centre to centre, but a BRC should:

- provide traceability of data through a history of modifications (dates and signatures of inputs, validations, modifications and deletions);
- give signature for data entry, validation, modification or deletion.

The BRC should use a standard terminology and formats for data management and exchange and standard protocols for data transmission to networks (domain, regional or global networks):

1. Select data format, data representation and data transportation taking into consideration existing standards for data processing, e.g. DarwinCore/DiGIR (Distributed Generic Information Retrieval) and ABCD (Access to Biological Collection Data) schema/BioCASE (Biological Collection Access Service for Europe) for strain data, CCINFO (Culture Collection INFO) for the organizational information of BRCs.
2. Check vocabulary against standard reference lists or thesauri.
3. Keep consistency among BRCs for searching and retrieving of information from catalogues and databases:

Each biological material record should contain a minimum data set, a recommended data set and/or a full data set in accordance with domain-specific criteria.

Spell checking for every field should be a basic requirement.

International English should be chosen as preferred language of data (in addition to local language if different).

A standardized approach should be adopted to certain scientific symbols (to avoid any errors due to incorrect reading of a character set, standard ASCII alternatives to symbols should be used, e.g. Greek letters cannot be used, they should be fully spelled (write alpha, gamma, beta…); the ° symbol for temperature is to be omitted entirely (e.g. 37C replaces 37°C); no subscripts or superscripts are allowed (e.g. cm^3 replaces cm^3 and CO2 replaces CO^2).

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Biological Resource Centres should adopt procedures to detect errors in data to improve their quality and consistency. This is an essential part of information management and should be both applied to the input of new data as well as to pre-existing information in current databases:

(a) For existing data, a series of checks should be carried out to ascertain their validity and completeness. As more BRCs become associated, more searches should be made for common classes of error to allow more efficient error correction.
(b) For new data, wherever possible, inputting should be checked against authorized lists of not only scientific names but also thesaurus/ontology to prevent errors such as mistyping.

Biological Resource centres should present evidence that they have applied a recognized protocol appropriate for each data element.

Data Processing

The informatics system employed by BRCs should provide appropriate facilities for information management, linkage and exchange of the BRC.

Access to Data and Publication

The BRC should make available data describing the biological material and its origin and provide electronic catalogues to users through their own facilities (e.g. website) or through focused, national, regional or global networks. Data should also be retained for traceability in compliance with relevant national laws and regulations.

Collecting and Managing Clinical Data

Strive to collect and store all relevant clinical or epidemiological data associated with a biospecimen, including, as study requirements dictate, longitudinal data. Follow applicable informed consent requirements and institute appropriate security/data-access control measures to address privacy issues.

Use an informatics system that tracks all aspects of biospecimen collection, processing, and distribution to prevent biospecimen identification discrepancies and to support annotation.

NOTE The NCI Center for Bioinformatics (NCICB) has developed additional bioinformatics guidelines and tools that address the issues of functionality of informatics systems, integration with existing systems, and interoperability among individual systems at biorepositories. The NCICB has developed the **Ca**ncer **B**iomedical **I**nformatics **G**rid, or *caBIG*™. caBIG (see https://cabig.nci.nih.gov/) (NCI 2005) is a voluntary network or grid connecting individuals and institutions to enable the sharing of data and tools. caBIG silver-level compatibility is recommended for NCI-supported biorepositories (see https://cabig.nci.nih.gov/guidelines_documentation).

Security

Electronic records should be backed up daily on a network or remote server, and weekly on a CD, or diskette or other appropriate media. Consideration should be given to establishing an arrangement with an offsite data security company that retrieves and stores all critical data at a remote location.

Archival System

A biobank may develop a system for archiving records that are older than one year and fewer than ten years. This system should be accessible for audits and inspection.

Specimen Location

Each freezer, refrigerator or room temperature storage cabinet should have a unique identifier. A convention should be established for numbering shelves, racks, boxes, as well as each location within the container.

Other Specimen Descriptors

The inventory system should track sample identifiers such as sample ID, bar code ID (if different), date of collection and sample type. Information should be included on the availability and volume of aliquots, the history of sample movement, sample thaws (as appropriate), and shipment to and from external sites.

Additional Information for Human Specimens

In addition to the information regarding specimen location, information relating to the following may be maintained (if relevant and/or available):

- Donor information: age of donor at the time of donation; gender, occupation; race/ethnicity.
- Diagnosis: site, histology, stage at diagnosis, date of diagnosis.
- Diagnostic procedures: procedure, date of procedure.
- Type of treatment (e.g. chemotherapy, radiation, hormonal, immunotherapy) prior to specimen donation.
- Surgical procedure information: surgery, primary site, metastatic site, stage of disease at time of surgery, diagnosis code (ICDO), diagnosis text.
- Medical history: drug name, dose/frequency, date started.
- Family history: relationship, diagnosis, age at diagnosis.
- Smoking history: smoke type, smoke years, date quit.
- Vitals: Height (cm), weight (kg), alcohol history, recreational drug history, special diet, date of last menstrual period, date last follow-up, disease status at follow-up, cause of death.
- Clinical laboratory values (e.g. calcium, hemoglobin, etc.).
- Availability of other biological specimens (e.g. normal vs. diseased tissue, other tissues, blood, buffy coat, and plasma, paraffin embedded tissue, H&E slide, formalin fixed tissue, DNA, RNA, urine, faeces, saliva, ascites fluid, and synovial fluid) from the same donor.

A repository may also incorporate digitally scanned documents into their database. For example, surgical pathology report, H&E slide of representative portion of the tissue, clinical lab reports, and the signed patient consent form.

Validation

A system should be in place to maintain the accuracy of the inventory. The system can employ either periodic counts of inventory storage units or a cycle counting methodology. Formal validation of computer systems and software is required for some biobanks, including organizations subject to FDA regulations and by clients if it is a commercial operation. In addition, the inventory system should be subject to regular QA audits.

Inventory Verification

A random check of the specimen inventory system (database) should be conducted on a small percentage of samples on an annual basis. This verification will confirm that the appropriate specimens are in the correct freezer locations as indicated by the computerized inventory system.

Use a data management system that includes a computerized inventory tracking system with appropriate security/access-control safeguards.

Certificates and Information for Users

The reference material producer shall issue a statement or certificate, as appropriate, communicating information about the reference material; this shall include information on the property values, their meaning, their uncertainties at a defined confidence level

and, where appropriate, the expiry date of the material. The statement or certificate shall also contain information for the user on the proper application of the reference material and on potential problems in its use. The contents of the certificates shall comply with the requirements of ISO Guide 31.

5.10.2 Validation/authentication reports and validation/authentication certificates

Each test report or calibration certificate shall include at least the following information, unless the biobank has valid reasons for not doing so:

(a) A title (e.g. 'Validation/Authentication Report' or 'Validation/Authentication Certificate').
(b) The name and address of the biobank, and the location where the validation/authentication were carried out, if different from the address of the biobank.
(c) Unique identification of the validation/authentication report or validation/authentication certificate (such as the serial number), and on each page an identification in order to ensure that the page is recognized as a part of the validation/authentication report or validation/authentication certificate, and a clear identification of the end of the report certificate.
(d) The name and address of the customer.
(e) Identification of the method used.
(f) A description of, the condition of, and unambiguous identification of the item(s) validated/authenticated.
(g) The date of receipt of the validation/authentication item(s) where this is critical to the validity and application of the results, and the date(s) of performance of the validation/authentication.
(h) Reference to the sampling plan and procedures used by the biobank or other bodies where these are relevant to the validity or application of the results.
(j) The validation/authentication results with, where appropriate, the units of measurement.
(h) The name(s), function(s) and signature(s) or equivalent identification of person(s) authorizing the validation/authentication report or validation/authentication certificate.
(i) Where relevant, a statement to the effect that the results relate only to the items validated/authenticated.

NOTE 1 Hard copies of validation/authentication reports and validation/authentication certificates should also include the page number and total number of pages.

NOTE 2 It is recommended that biobanks include a statement specifying that the validation/authentication report or validation/authentication certificate shall not be reproduced except in full, without written approval of the biobank.

5.10.3 Sample Reports

The biobank should preferably choose standard data schema and protocols to make the databases distributed and interoperable. Confidential data should be clearly identified in relation with user authentication capability, encryption techniques and other related information security tools.

5.10.3.1

In addition to the requirements listed in 5.10.2, sample reports shall, where necessary for the interpretation of the sample-associated data, include the following:

(a) Deviations from, additions to, or exclusions from the agreed methods, and information on specific conditions, such as environmental conditions.
(b) Where relevant, a statement of compliance/non-compliance with requirements and/or specifications.
(c) Where applicable, a statement on the estimated uncertainty of measurement;

information on uncertainty is needed in sample reports when it is relevant to the validity or application of the sample-associated data, when a customer's instruction so requires, or when the uncertainty affects compliance to a specification limit.

(d) Where appropriate and needed, opinions and interpretations (see 5.10.5).

(e) Additional information which may be required by specific methods, customers or groups of customers.

5.10.3.2

In addition to the requirements listed in 5.10.2 and 5.10.3.1, sample reports containing the results of sampling shall include the following, where necessary for the interpretation of sample-associated data:

(a) The date of sampling.

(b) Unambiguous identification of the aliquots sampled. The location of sampling, including any diagrams, sketches or photographs.

(c) A reference to the sampling plan and procedures used.

(d) Details of any environmental conditions during sampling that may affect the interpretation of the sample-associated data.

(e) Any standard or other specification for the sampling method or procedure, and deviations, additions to or exclusions from the specification concerned.

5.10.4 Calibration Certificates

Not applicable.

5.10.5 Opinions and Interpretations

When opinions and interpretations are included, the biobank shall document the basis upon which the opinions and interpretations have been made. Opinions and interpretations shall be clearly marked as such in a sample report.

NOTE 1 Opinions and interpretations should not be confused with inspections and product certifications as intended in ISO/IEC 17020 and ISO/IEC Guide 65.

NOTE 2 Opinions and interpretations included in a validation/authentication report may comprise, but not be limited to, the following:

- an opinion on the statement of compliance/non-compliance of the results with requirements;
- fulfilment of contractual requirements;
- recommendations on how to use the results;
- guidance to be used for improvements.

NOTE 3 In many cases it might be appropriate to communicate the opinions and interpretations by direct dialogue with the customer. Such dialogue should be written down.

5.10.6 Validation/Authentication Results Obtained From Subcontractors

When the validation/authentication report contains results of validation/authentication performed by subcontractors, these results shall be clearly identified. The subcontractor shall report the results in writing or electronically.

When a validation/authentication has been subcontracted, the laboratory performing the work shall issue the validation/authentication certificate to the contracting biobank.

5.10.7 Electronic Transmission of Data

In the case of transmission of data by telephone, telex, facsimile or other electronic or electromagnetic means, the requirements of this International Standard shall be met (see also 5.4.7).

Depositors are responsible for assuring the quality of data associated with the biological material.

The BRC may require evidence to assure the validity of the data.

The databases should contain either information relating to samples held by a BRC (which at least, should be retained as long as a sample remains available), or other relevant data items or composite data needed by the BRC (e.g. users' records). On the loss

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of a sample the database record should be either printed and stored on file or copied to a digital archive before the entry is removed from the working database, placed in reserve or annotated to indicate that it is no longer available.

The BRC should respect a defined update frequency for data publication (online or not), in accordance with the flow of available biological resources.

Biological Resource Centres should ensure the quality and consistency of data sets and provide data to users while ensuring information security, bio-security, protection of IPRs (Intellectual Property Rights), client information and human dignity. National data protection regulations shall be adhered to. Exchange of information should be in line with the OECD Guidelines on the Protection of Privacy and Transborder Flows of Personal data.

Biological Resource Centres should restrict access to the electronic catalogues where appropriate.

Users should be authenticated. Specific identities and passwords should be provided by BRCs to users to access different categories of information and services. The validity of identifiers and passwords should be checked.

5.10.8 Format of Reports and Certificates

The format shall be designed to accommodate each type of sample and to minimize the possibility of misunderstanding or misuse.

NOTE 1 Attention should be given to the layout of the validation/authentication report or sample report, especially with regard to the presentation of the data and ease of assimilation by the reader.

NOTE 2 The headings should be standardized as far as possible.

5.10.9 Amendments to Validation/ Authentication Reports and Sample Reports

Material amendments to a validation/authentication report or sample report after issue shall be made only in the form of a further document, or data transfer, which includes the statement: 'Supplement to Validation/Authentication Report [or sample report], serial number . . . [or as otherwise identified]', or an equivalent form of wording.

Such amendments shall meet all the requirements of this International Standard.

When it is necessary to issue a complete new validation/authentication report or sample report, this shall be uniquely identified and shall contain a reference to the original that it replaces.

6. Supply

The BRC should only supply to users who have the appropriate facilities and meet the specific requirements for receipt as required by relevant national and international regulations and policies.

The materials should be distributed according to the policy of each depository. This policy should take into account the nature of the biological materials and meet all relevant national and international regulations and policies.

An order should only be accepted when the required accompanying documentation is completed, signed and returned.

If a biological material cannot be delivered within the specified delivery time, the BRC should contact the user with an estimated supply date. The BRC should recommend where possible other national or foreign BRCs to supply biological materials not held.

The BRC should provide at least the following information to the user:

- Biological material identifier, accession number and batch number.
- An estimate of shelf life, storage conditions, storage instructions and if appropriate, conditions of growth.
- Instructions for opening ampoules or vials (when appropriate and in all cases where materials are being provided to new users).
- A safety data sheet including the containment level required for handling the biological

material, disposal measures and measures to take in case of spillage.
- A Material Transfer Agreement: an essential requirement to protect IPR and mandatory where they are required by national law. They are used to relay the depositor's and/or country of origin requirements on use of the biological material.
- Fax-back sheet to acknowledge receipt of materials may be desirable.

Establish rules for biospecimens disposal before storing the biospecimens in the biobank and monitor compliance with the rules. Consider the anticipated storage interval when selecting storage conditions.

Retrieve biospecimens from storage according to SOPs that safeguard biospecimen quality.

When it is necessary to control biospecimens' temperature during shipping, consider the shipping time, distance, climate, season, and method of transportation and modify distribution schedules accordingly, if possible.

Ensure proper temperature during shipment, taking into account the type of biospecimen and its intended use.

Tracking devices may be useful to ensure proper temperature throughout the shipment duration.

Prior to shipment, execute appropriate Material Transfer Agreements (MTAs) addressing donor privacy, as appropriate, intellectual property (IP), data sharing, and other similar requirements.

Consult International Society for Biological and Environmental Repositories (ISBER) best practices (ISBER 2005) for guidance on international transport regulations (governed by the International Air Transport Association) and information on classifying biospecimens for shipment. Train personnel in the shipment of biospecimens and update their training every two years. Maintain training records for all employees involved in shipping.

Establish indemnification agreements with users of biospecimens.

NOTE 1 Locating Specimens in Storage

Specimens to be retrieved must be located in the appropriate specimen inventory system. A specimen requisition is generated according to procedures applicable to the institution's tracking and inventory system. The requisition is checked for accuracy before transmission to the biobank, according to established SOPs.

NOTE 2 Specimen Retrieval

At the biobank, locate and pull specimens as documented on specimen requisition.

As required according to specimen type, maintain proper temperature of specimens during the retrieval process. For frozen specimens keep vials on dry ice or in liquid nitrogen during the process.

Confirm that all requisitioned specimens are accounted for in the freezer or other storage container. If specimens are missing, follow established protocols to locate the specimens. A deviation report should be produced to indicate that specimens listed in the inventory system could not be located.

Place specimens in appropriate boxes or other containers and label according to standards established for the required shipping and storage conditions.

All steps should be recorded in the record management system.

NOTE 3 Documentation of Retrieval

Checklists and other forms are desirable to document the specimen retrieval process including steps taken above to confirm completeness of the process and steps occurring after retrieval to document shipment and quality checks.

If specimens are to be shipped to an outside location, the recipient should be contacted at least 24 hours prior to shipment.

Quality control checks should be performed to confirm that all specimens listed on the requisition were retrieved. Confirmation at least a second time by a separate person is recommended.

Records should be kept on any special considerations such as the number of times specimens have been thawed and refrozen if applicable.

Records should be kept on problems noted with any individual containers, such as: no visible specimen, volume significantly less than documented in inventory system, container is cracked, label missing or unreadable.

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NOTE 4 Shipping Log

Each repository should maintain a shipment log to record the receipt and dissemination of shipments sent from the repository. The log may be computerized or it may be kept in a logbook. If computerized, ideally it would be included in the functionality of the inventory management system described above. Each shipment entry should be given a unique shipment number. The log should track the following elements:

- shipment/invoice number;
- recipient/source;
- date received or shipped;
- courier name and id for tracking package;
- sample description;
- number of samples received or sent;
- study name if available;
- study number if available;
- key investigator name(s);
- signature of individual receiving the specimen.

Adhere to biosafety, packaging, and shipping regulations. Use a tracking system for biospecimen shipments. The biorepository should notify a recipient before shipping to confirm that the recipient can accept the package and properly store the biospecimen.

NOTE 1 General

Packaging and shipping should conform to all regulations. Air shipments should conform to International Air Transport Association (IATA) standards. All personnel involved in the dangerous goods (including infectious materials) shipping process must be trained properly for both air and ground shipments. Dry ice (solid carbon dioxide) and liquid nitrogen employed for frozen shipments are hazardous materials, and appropriate labelling must be included. The rules for dry nitrogen shippers are less stringent. Shipments of material that are subject to cold chain management should be shipped with sufficient refrigerant to maintain temperature throughout the shipping cycle.

NOTE 2 Regulatory Requirements

The shipper must first determine how to classify the specimens that are to be transported. Shipments of aetiological agents must be transported by the most expedient means possible. This is generally interpreted to mean overnight air shipments.

Specimens routinely shipped from repositories may be considered dangerous goods such as infectious substances, diagnostic specimens, biological products, genetically modified organisms and microorganisms or toxic substances. The preservatives that have been applied to the specimens may be considered toxic, flammable liquids, non-flammable gases, or corrosives, all of which are dangerous goods. In order to properly classify the specimens to be included in a shipment, one should consult the International Transport Regulations (International Civil Aviation Organization (ICAO) and IATA).

Training of personnel is required to transport dangerous goods.

NOTE 3 Temperature Requirements

Specimens may be exposed to temperature fluctuations during transit. The following are typical temperature conditions required for transport of specimens and the insulation/refrigerant required to maintain that temperature:

- ambient (20°C to 30°C): insulated packaging to protect from extreme heat/cold ambient conditions;
- refrigerated (2°C to 8°C): gel packs designed for refrigerated temperatures, conditioned at −15°C or phase change material rated for refrigerated transport;
- frozen (−20°C): gel packs designed for frozen temperatures, conditioned at or below −20°C;
- frozen (−70°C): dry ice pellets or sheets;
- frozen (at or below −150°C): liquid nitrogen dry shipper.

NOTE 4 Humidity Requirements

Specimens sensitive to humid conditions may need to be shipped in sealed bags with desiccant to prevent exposure to moisture during transit.

NOTE 5 Light Sensitivity Requirements

Light-sensitive material should be sent in packaging that does not allow penetration of light such as amber vials or amber coated bags.

NOTE 6 Arrival Time Requirements

Time sensitive specimens such as fresh whole blood must be consigned to couriers with a proven reputation of successful on-time delivery. Time required for processing should be considered as well. For cold or frozen shipments, sufficient refrigerant

should be included to allow for a 24-hour delay in transport.

For example, an overnight (24 hours) shipment should have sufficient refrigerant for 48 hours.

Temperature-sensitive material should be consigned with a courier capable of replenishing refrigerant in the event of a delay.

NOTE 7 Sample Quantities

The quantity of specimens to be transported will affect the type of packaging and amount of refrigerant required to maintain appropriate temperatures for *all* specimens in the shipment.

NOTE 8 Review of Packaging Test Report

The shipper is responsible for choosing appropriate packaging for the material being shipped. This includes a review of all test reports from the testing of the packaging to meet the regulation requirements.

Packaging that has undergone stringency testing must be used in the same configuration under which it was tested (i.e. primary cryovials of equivalent rating, blood collection devises of equivalent rating).

NOTE 9 Validation of Packaging

Packaging should be checked prior to use on specimens. These tests should include measuring all parameters that could influence specimen integrity (i.e. temperature, humidity, light sensitivity, structural quality, and spill containment).

Shipments of specimens with high value or those with critical temperature requirements should include a temperature-recording device that can verify the temperature of the material being shipped throughout the transport cycle.

NOTE 10 Test Shipments

In some situations, especially relating to extremely valuable samples, repositories may choose to send a test shipment that approximates the characteristics of the actual shipment. This may inform the shipper as to the adequacy of packing coolants and also to identify any potential obstacles for the successful shipment.

NOTE 11 International Shipments

Special permits or other requirements may be unique to certain countries and regions.

Best Practice: Identify all requirements for shipping to a designated country prior to the initiation of the shipment.

General

The shipper and recipient should track all packages while in transit.

Notification of Shipment

The recipient should be notified prior to the package being released by the shipper to confirm that they are able to receive the package and have the proper facilities available for storage.

The shipper should provide a 24-hour emergency contact for all packages transporting dangerous goods.

Shipping Manifest

The Shipper should send a shipping manifest (preferably electronic) to the recipient. A hard copy must also be included in this shipment itself to accommodate regulatory requirements.

Confirmation of Receipt

Confirmation of receipt and the condition upon arrival should be obtained for every shipment coming to or leaving a biobank.

Tracking – General

In order to make certain that specimens can be tracked effectively from the site at which they are collected through their arrival and subsequent shipment from the biobank, certain systems must be in place. Such systems include the use of labels that identify the samples as they are transported and stored, shipping logs which document specimen arrival and departure from the repository and an inventory system that allows specimen location within the repository to be known to all appropriate staff.

Standardization of tracking methodologies for banked specimens will increase the efficiency of sample transport. It should facilitate interactions between organizations dedicated to sample procurement and institutions needing specimens for research purposes. Furthermore,

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the standardization of specimen tracking should expedite the exchange of scientific data among collaborating institutions.

Use of standardized labelling techniques such as bar codes and sample identification information comprises the first step toward the standardization of sample identification and tracking across the industry.

NOTE 1 Bar Coding

A base standard for labels is that they should be imprinted using a linear (one-dimensional) bar code that includes human readable indication of contents. It is not necessary that a standard system of symbols be implemented. Current bar code scanners are capable of reading a wide variety of symbols and the capacity of many scanners to read additional types of symbols can be expanded in many cases by the procurement of software upgrades. Under some circumstances two-dimensional (2D) bar codes may be desired; 2D bar codes have the added features that scanning error rates may be lower, more information can be contained on the label, they may be faster, and minimize physical stress for the technician from repetitive motion. Cost considerations will need to be made when procuring systems for reading and creating bar codes as scanners that read 2D bar codes are likely to cost more than those that read linear bar codes.

NOTE 2 Labels for Human Specimens

The unique identifier for the specimen may reflect the date of collection/banking and/or sample type. (Under certain circumstances this information may need to be excluded in order to blind a laboratory that is performing tests on the sample.) This identifier should be a 'license plate' number linked to a computerized inventory management system. If included, the date of collection/banking and sample type should be presented in human readable form on the label. (Including a date and sample type in a unique identifier that is bar coded requires the use of a very dense 2D bar code.) If space permits and appropriate circumstances exist, additional information such as the name or identifying number of the research/healthcare institution from which the specimen was procured and the method of procurement may be included on the label. Whenever information is included on a label that may allow for retracement of a specimen to its donor, specific Institutional Review Board (IRB) issues must be considered by the repository.

The reference material producer should also provide an advisory service to offer guidance (including a complaints procedure) and technical services to users. Where the goods are subject to resale through a distributor, the reference material producer should arrangements with the distributor to keep records of purchasers of the reference materials.

The BRC should pack and send its biological material according to current postal, IATA and ADR regulations. It should also meet additional requirements imposed by other regulations such as quarantine, biosafety and/or biosecurity regulations.

Invoices should normally be despatched at the same time as the material unless otherwise instructed or where *pro forma* invoices have been paid in advance.

The BRC should keep records of all requests for biological materials, including those requests refused for any reason, showing the biological material, method and date of shipment, and name and address of the person to whom sent. Where recorded delivery, courier or similar shipping mechanisms are used records of shipment receipt should be maintained. The records should be maintained to meet national law, regulations and policies.

Despite rigorous quality control and standard procedures being followed, it may be possible that the biological material provided may not have the property stipulated in the order or that is reasonably expected of it on receipt. If the user is not deemed at fault it is normal policy to provide the user with a replacement free of charge where this is possible. If refunds are considered appropriate they should be given.

All work carried out for a client should be treated as strictly confidential to that client unless national requirements apply. This should apply to all requests for biological materials, safe and patent deposits, information supplied relating to these and to the fact that the product or service was requested in accordance with national law, regulations and policies. Information may be included in statistics produced to show BRC activities in a way that the customer is not identified.

The names of past or present clients should only be revealed with the clear permission of the client.

7.1 Ethics – Privacy

To protect the health information of patients, adhere to privacy laws with respect to informatics systems.

Institute the level of security appropriate to the type of biobank and to protect study participant privacy for the biospecimens stored in the biobank.

In applications for support, include documentation of policies, mechanisms for auditing the effectiveness and enforcement of policies, required training, and security measures pertaining to employee access to data or biospecimens.

Institute the level of security appropriate to the type of biobank.

Risks and Benefits

The risks for the persons concerned and, where appropriate, for their family, related to research activities, in particular the risks to private life, should be minimized, taking into account the nature of the research activity. Furthermore, those risks should not be disproportionate to the potential benefit of the research activities.

Possible risks for the individuals in the same group as the person concerned should also be taken into consideration in this context.

Non-discrimination

Appropriate measures should be taken, in the full range of research activities, to avoid discrimination against, or stigmatization of, a person, family or group.

Justification of Identifiability

Biological materials and associated data should be anonymized as far as appropriate to the research activities concerned.

Any use of biological materials and associated data in an identified, coded, or linked anonymized form should be justified by the researcher.

Wider Protection

None of the provisions of this recommendation should be interpreted as limiting or otherwise affecting the possibility for a member state to grant a wider measure of protection than is stipulated in this recommendation.

Confidentiality and Right to Information

The principles of chapter VIII (confidentiality and right to information) of the Additional Protocol concerning biomedical research (CETS No. 195, 2005, Additional Protocol to the Convention on Human Rights and Biomedicine, concerning Biomedical Research, Strasbourg, 25.I.2005) should be applied to any research project using biological materials and associated personal data.

NOTE 1 Code of Federal Regulations

In the United States (US), most federally funded research on human subjects is regulated by the Code of Federal Regulations (CFR). The CFR is the codification of the general and permanent rules published in the Federal Register by the executive departments and agencies of the Federal Government. The US human subjects' regulations do not specifically address use of specimens except by allowing exemption from the regulations for unidentified existing specimens and allowing expedited review of existing data, documents, records, pathological specimens or diagnostic specimens. By practice, all other uses of specimens are subject to the regulations, though often considered minimal risk research that is eligible for waiver of the requirement for informed consent. Title 45 (Public Welfare) Part 46 (Protection of Human Subjects) of the CFR (45 CFR 46) or the 'common rule' applies to most federally funded research on human subjects and 17 US agencies that support research. Research on human specimens is different from other types of human research in that there is generally no interaction with the patient and

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the risks are primarily from loss of privacy or confidentiality. Research that will lead to a filing with the US Food and Drug Administration (FDA) is subject to regulation by the FDA under 21 CFR 50 and 21 CFR 56. The common rule and the FDA regulations state the requirement of institutions conducting federally funded research to utilize an Institutional Review Board (IRB) to review and approve any research involving the use of human subjects. In addition, the regulations state that no investigator may involve a human being as a subject in research unless the investigator has obtained the legally effective informed consent of the subject or the subject's legally authorized representative. While there are substantial similarities between the common rule and the FDA regulations, the one essential difference is that the FDA does not allow waiver of consent.

NOTE 2 Health Insurance Portability and Accountability Act (HIPAA) of 1996

In August of 2002 the Department of Health and Human Services published the Health Insurance Portability and Accountability Act of 1996 with a compliance date of 14 April 2003. The HIPAA 'Privacy Rule' provides very specific requirements for the protection of patient data which apply to research uses as well as to a variety of other uses such as billing, insurance claim processing, etc. The Privacy Rule establishes a category of health information, referred to as protected health information (PHI), which may be used or disclosed to others only in certain circumstances or under certain conditions. Protected health information is a subset of what is termed individually identifiable health information. Repositories may permit researchers to review PHI in medical records or elsewhere to prepare a research protocol, or for similar purposes preparatory to research. To permit the researcher to conduct a review preparatory to research, the Repository must receive from the researcher representations that:

- the use or disclosure is sought solely to review PHI as necessary to prepare the research protocol or other similar preparatory purposes;
- no PHI will be removed from the covered entity during the review;
- the PHI that the researcher seeks to use or access is necessary for the research purposes.

NOTE 3 Release of De-Identified Data Sets

The Privacy Rule permits the release of data that have been de-identified without authorization and without further restrictions because de-identified data is not PHI. PHI may be de-identified in one of two ways:

- The 'safe harbour' method is to remove all 18 identifiers enumerated at section 164.514(b)(2) of the regulations:

(a) names of the individual or of relatives, employers, or household members of the individual;
(b) all geographic subdivisions smaller than a state, except for the initial three digits of the ZIP code if the geographic unit formed by combining all ZIP codes with the same three initial digits contains more than 20,000 people;
(c) all elements of dates except year, and all ages over 89 or elements indicative of such age;
(d) telephone numbers;
(e) fax numbers;
(f) e-mail addresses;
(g) social security numbers;
(h) medical record numbers;
(i) health plan beneficiary numbers;
(j) Account numbers.
(k) Certificate or license numbers.
(l) Vehicle identifiers and license plate numbers.
(m) Device identifiers and serial numbers.
(n) URLs.
(o) IP addresses.
(p) Biometric identifiers
(q) Full-face photographs and any comparable images.
(r) Any other unique, identifying characteristic or code, except as permitted for re- identification in the Privacy Rule.

- The second way is to have a qualified statistician determine that the risk is very small that the information could be used, alone or in combination with other reasonably available information, by the anticipated recipient to identify the subject of the information. The qualified statistician must document the methods and results of the analysis that justify such a determination.

The Privacy Rule permits a repository to assign to, and retain with, the de-identified health information, a code or other means of record re-identification if that code is not derived from or related to the information about the individual and is not otherwise capable of being translated to identify the individual.

NOTE 4 Release of Limited Data Sets

Where only certain identifiers are needed, the Privacy Rule allows for a repository to provide a researcher with a limited data set. Limited data sets may be used or disclosed only for public health, research, or health care operations purposes. Before disclosing a limited data set to a researcher, the repository must enter into a data use agreement with the researcher, identifying the researcher as the recipient of the limited data set, establishing how the data may be used and disclosed by the recipient, and providing assurances that the data will be protected, among other requirements. The following 16 direct identifiers must be removed for PHI to qualify as a limited data set:

(a) Names.
(b) Postal address information, other than town or city, state, and ZIP code.
(c) Telephone numbers.
(d) Fax numbers.
(e) Email addresses.
(f) Social security numbers.
(g) Medical record numbers.
(h) Health plan beneficiary numbers.
(i) Account numbers.
(j) Certificate or license numbers.
(k) Vehicle identifiers and license plate numbers.
(l) Device identifiers and serial numbers.
(m) URLs.
(n) IP addresses.
(o) Biometric identifiers.
(p) Full- face photographs and any comparable images.

Best Practice: The collection, storage and use of human specimens and associated data must be done in a way that respects the individual and maintains privacy and confidentiality.

Best Practice: Users of the specimens and data must sign an agreement specifying how the specimens and data will be used and to whom they may be transferred. For unidentified specimens and data, users must sign an explicit agreement not to seek information about the subject's identity.

7.2 Ethics – Informed Consent

Use a process of informed consent for each biospecimen collection event. Biobanks should adapt the template to their needs. The consent form should address the use of biospecimens or data by private entities, the possible future development of commercial products through research, and the release of individual research results to participants.

Allow research participants to specify the types of research for which their biospecimens may be used, including use in additional future projects.

Document clear policies for biospecimen and data access.

Develop policies to handle biospecimens and data for which consent has been withdrawn.

Monitor the need for obtaining informed consent when the biorepository houses identifiable biospecimens and data from children, that were obtained with parental or guardian permission, when a child reaches the legal age to consent for a research study.

Consider regulations concerning research on existing biospecimen collections. These regulations do not exempt in vitro studies from the requirement for documented, institutional review board (IRB)-approved consent from the sources, even in cases where biospecimens have been de-identified.

Establish and document transparent policies governing the retention of records and biospecimens. For clinical biospecimens, laws may also govern how long records must be retained. For research specimens, the ideal is permanent storage if resources and storage space are sufficient. However it should be noted that biospecimens degrade over time and/or may no longer be useful due to changes in science and technology.

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Right to Change the Scope of, or to Withdraw, Consent or Authorization

When a person has provided consent to storage of identifiable biological materials for research purposes, the person should retain the right to withdraw or alter the scope of that consent. The withdrawal or alteration of consent should not lead to any form of discrimination against the person concerned, in particular regarding the right to medical care.

When identifiable biological materials are stored for research purposes only, the person who has withdrawn consent should have the right to have, in the manner foreseen by national law, the materials either destroyed or rendered unlinked anonymized.

Where authorization has been given on behalf of a person not able to consent, the representative, authority, person or body provided for by law should have the rights referred to in paragraph 1 above.

Where a person on whose behalf authorization has been given attains the capacity to give consent, that person should have the rights referred to above.

Identifiable biological materials

If the proposed use of identifiable biological materials in a research project is not within the scope of prior consent, if any, given by the person concerned, reasonable efforts should be made to contact the person in order to obtain consent to the proposed use.

If contacting the person concerned is not possible with reasonable efforts, these biological materials should only be used in the research project subject to independent evaluation of the fulfilment of the following conditions:

(a) The research addresses an important scientific interest.
(b) The aims of the research could not reasonably be achieved using biological materials for which consent can be obtained.
(c) There is no evidence that the person concerned has expressly opposed such research use.

The person concerned may freely refuse consent for the use in a research project of his or her identifiable biological materials, or withdraw consent, at any time. Refusal to give consent or the withdrawal of consent should not lead to any form of discrimination against the person concerned, in particular regarding the right to medical care.

Unlinked Anonymized Biological Materials

Unlinked anonymized biological materials may be used in research provided that such use does not violate any restrictions placed by the person concerned prior to the anonymization of the materials.

Anonymization should be verified by an appropriate review procedure.

Informed Consent

Informed consent should be obtained from each prospective subject or the subject's legally authorized representative. Consent should be sought only under circumstances that provide the prospective subject or the representative sufficient opportunity to consider whether or not to participate and that minimize the possibility of coercion or undue influence. The information that is given to the subject or the representative should be in language understandable to the subject or the representative.

Best Practice: Subject consent should be obtained unless waived by an authorized institutional review board constituted in accordance with applicable law or regulation. Consent can be for a specific research use or for future unspecified uses. If the use is unspecified, an IRB review of the research must be conducted to assure that the use is consistent with the original consent.

Best Practice: Subjects should always retain the right to withdraw consent and to have specimens and data removed from the repository once that consent is withdrawn. The logistics for such withdrawal of consent must

be clearly defined and conveyed to all subjects at the time of consent. Even if an opt-out procedure is used, patient notification must include instructions for later withdrawal of consent.

7.3 Ethics – Access to Samples and Data

Obtaining Biological Materials for Research

Biological materials should be obtained for research in accordance with the provisions of this chapter. Information and consent or authorization to obtain such materials should be as specific as possible with regard to any foreseen research uses and the choices available in that respect.

Interventions on a Person

An intervention should only be carried out to obtain biological materials for storage for research purposes if it complies with the additional protocol concerning biomedical research (CETS No. 195, 2005).

Residual Biological Materials

Biological materials removed for purposes other than storage for research should only be made available for research activities with appropriate consent or authorization, or in accordance with the provisions of article *Ethics – Informed Consent*.

Whenever possible, information should be given and consent or authorization requested before biological materials are removed.

Biological Materials Removed After Death

Biological materials should not be removed from the body of a deceased person for research activities without appropriate consent or authorization.

Biological materials should not be removed or supplied for research activities if the deceased person is known to have objected to it.

General Rule

Research on biological materials should only be undertaken if it is within the scope of the consent given by the person concerned. The person concerned may place restrictions on the use of his or her biological materials.

Prohibition of Financial Gain

Biological materials should not, as such, give rise to financial gain.

Principles Applicable to all Collections of Biological Materials

Clear conditions governing access to, and use of, the samples should be established.

Oversight of Population Biobanks

Regular audits should be conducted of the implementation of procedures on access to, and use of, samples.

Access to Population Biobanks

Member states should take appropriate measures to facilitate access by researchers to biological materials and associated data stored in population biobanks.

Such access should be subject to the conditions laid down in this recommendation; it may also be subject to other appropriate conditions.

7.3 Ethics – Access

Access to Biospecimens and Data

Establish clear guidelines for sample distribution (and clinical data sharing) consistent with ethical principles, prevailing laws, and, if applicable, consent form language. The guidelines should be flexible so that biobanks may respond to changing scientific needs.

Ensure that investigators have timely, equitable, and appropriate access to human biospecimens and associated clinical data without undue administrative burden. Access should be

guided by policies and procedures such as the following:

- Scientific validity of the research proposal.
- Investigator's agreement covering confidentiality, use, disposition, and security of biospecimens and associated data.
- Investigator's written agreement in a Material Transfer Agreement
- Investigator and institutional research qualifications.
- Ethical oversight where required by regulations or local institutional requirements.
- Adequate funding for the biorepository. In addition to the above, the following points should also be considered while assessing access privileges:

(a) Specimens and associated clinical data should be appropriately matched with the specific scientific investigations for which they are intended.
(b) The local decision-making body should take local principles into account. Ethical considerations should come first among principles that guide the decision-making process.
(c) Biorepositories should establish an appeals process for addressing disputes over allocation decisions.

Apply guidelines to all new collections and, whenever possible, to existing collections.

If applicable and where monetary charges are necessary, charge only to recover costs as appropriate to retrieve and disseminate specimens.

If a biobank must close due to lack of funding or otherwise cannot maintain or use the biospecimens, the availability of biospecimens should be announced for transfer to the research community (e.g. via a website).

Transfer should be consistent with the informed consent and allowable use of biospecimens.

Within the biobank, use a system of data access with defined levels of access privileges. Restrict access to research subjects' identities and medical, genetic, social, and personal histories to necessary biobank staff members who need such access as part of their duty or to persons permitted access by law.

Monitor personnel compliance with access restrictions.

Store human biospecimens only for research purposes according to approved protocols, not to serve individual research participants' needs or wishes.

7.4 Ethics – Custodianship

In the application for proposal for biobank funding, propose plans for formal and continuing responsibility for custodianship (not ownership) of collected biospecimens and associated data as part of the biobank protocol.

In the application for proposal for biobank funding, also address plans for the handling and disposition of biospecimens and associated data at one or more of the following points:

(a) End of the active support of the grant,
(b) Accomplishment of the specific research objectives of the study,
(c) Depletion of biospecimens, and/or
(d) Achievement of critical data endpoints.

Require disclosure of financial or professional conflicts of interests of biobank personnel, consistent with institutional procedures and policies.

Use clear and specific informed consent language to ensure that those who contribute biospecimens and/or data for research purposes are fully informed that the research done with these biospecimens may help develop products, tests, or discoveries that may have commercial value.

Independent review

Research should only be undertaken if the research project has been subject to an independent examination of its scientific merit, including assessment of the importance

of the aim of the research, and verification of its ethical acceptability. National law may additionally require approval by a competent body.

Member states should apply the provisions concerning ethics committees contained in chapter III of the Additional Protocol concerning biomedical research (CETS No. 195, 2005, Additional Protocol to the Convention on Human Rights and Biomedicine, concerning Biomedical Research, Strasbourg, 25.I.2005) to the review of research.

Review procedures may be adapted to the nature of the research and the extent to which the persons concerned could be identified from their biological materials or associated data.

General

Key discussions of ethics in human subjects' research are found in the Declaration of Helsinki adopted by the World Medical Association in 1964 and revised several times subsequently, most recently in 2004 and the Belmont Report published by the US Department of Health and Human Services in April 1979. There are several fundamental key concepts:

- Freely given informed patient consent is necessary before research on humans may be conducted.
- Research should be well designed, conducted by persons with appropriate expertise and lead to meaningful conclusions.
- Every measure should be taken to reduce the risk and ensure that the risk does not exceed the benefit of the expected finding.
- Studies in animals should provide reason to believe that the study of humans is needed and is the only way to get the necessary information.

Institutional Review Board

An Institutional Review Board (IRB) is any board, committee, or other group formally designated by an institution to review biomedical research involving humans as subjects, to approve the initiation of and conduct periodic review of such research.

Best Practice: A repository's processes and procedures for storage of human specimens for research should be available for review by an IRB to assure that they are appropriate to protect human subjects.

Best Practice: Specimens should only be made available for studies that are expected to expand medical knowledge and contribute to the well being of the world's people. The rigour of the review should be related to the value of the specimens and data that are available. As a general rule the greater the data annotating a specimen the more rigorous the review should be and the more important the expected result of the research should be.

7.5 Ethics – Intellectual Property

For the transfer of materials in academic-industrial collaborations, use a Letter Agreement.

Recognize that biobank staff members as custodians of biospecimens are not *a priori* considered inventors under patent law for inventions made using materials distributed by the biorepository. In general, the staff should be informed that one whose sole contribution to an invention consists of the routine collection, handling, storage, and disbursement of biospecimens might not rise to the level of 'inventor' of an invention. Inventorship is determined by patent law and must be considered on a case-by-case basis by trained legal personnel.

Recognize that biobanks have no inherent rights to future IP, including reach-through rights in inventions made by investigators using samples obtained from the biobank.

Ensure through Material Transfer Agreements (MTAs) that research data developed using biospecimens are made available to the research community.

Re-examination of the recommendation

This recommendation should be re-examined not more than five years after its adoption, notably in the light of the experience acquired in the implementation of its guidelines.

Inset 1

Table	Name	Comments
1	Vocabulary changes	• Changes made in the compilation document. • The organization responsible for the publication of each term is shown in parentheses. • A colour code was used to keep track of the organization responsible for each publication (http://www.biobanque-picardie.com/compilation.pdf).
2	ISO 17025 summary	'Requirements for the competence of testing and calibration laboratories' contents
3	ISO Guide 34 summary	'General requirements for the competence of reference material producers'
4	Compilation against ISO 17025	See above

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