Quality Assurance and Quality Control in Biobanking

Fay Betsou

Abstract An increasing number of biospecimens are being collected in the context of multicenter and international clinical studies and diagnostics. This has revealed the need to optimize management of these biospecimens such that research biorepositories can guarantee that samples distributed to industry or academic researchers are comparable and without institute-dependent intrinsic bias. Acceptance of biological samples and associated data between countries will be facilitated if biobanks can propose validation protocols for their samples and ensure the accuracy of the results obtained from the samples. Certification or accreditation to international standards of the International Standards Organization (ISO) by an independent auditing body provides proof of effective organization, operational consistency and management of the production of "annotated specimens". Subcontracting to testing laboratories, which are themselves accredited to international standards such as ISO 17025 (General Requirements for the Competence of Testing and Calibration Laboratories) or ISO 15189 (Medical Laboratories—Particular Requirements for Quality and Competence), is proof of reliable sample characterization and production of "qualified specimens". Despite the fundamental importance of these standards, compliance remains essentially voluntary to each individual biobank. Development of a system of international technical standards for research biobanks is a critical step, currently being addressed in ISO Technical Committee 276 "Biotechnology".

Keywords Accreditation • Best practices • Certification • ISBER • ISO 9001 • ISO 17025 • ISO Guide 34 • Quality assurance • Quality control • SPREC

F. Betsou (✉)
IBBL (Integrated Biobank of Luxembourg),
6 rue Ernest Barblé, 1210 Luxembourg, Luxembourg
e-mail: fay.betsou@ibbl.lu

P. Hainaut et al. (eds.), *Biobanking of Human Biospecimens*,
DOI 10.1007/978-3-319-55120-3_2

1 Background

Biospecimen collection is fundamental to both diagnostics and clinical studies, and is often performed in an international multicenter context [1]. Results of analyses of biological samples can be influenced by conditions that samples have been exposed to during sampling, processing, and storage prior to usage, known as preanalytical variations [2]. Biobanks need to ensure that samples are interchangeable, without institute-dependent intrinsic bias, offering industry/academia researchers an assurance of the accuracy, reproducibility and comparability of research results. This guarantee may come from sample validation accredited by an external body. A biobank certification/accreditation system requires documentation of the collection of biological samples of known quality, including traceability of sample collection, preparation, aliquoting, storage and retrieval procedures. Assessment of the technical competence and granting of accreditation will give confidence to biobank sample end users, close the current "asymmetric information gap", and facilitate the increasing international/inter-institutional use of research materials from biobanks.

This chapter provides a comprehensive overview of the concepts relevant to quality assurance (QA) and quality control (QC) in the context of biorepositories, presents guidelines and best practices, and certification/accreditation systems currently in use in biobanks, and describes unmet needs and a future strategy.

2 Definitions of Terms

Quality management system (QMS): Organizations control the quality of their activities by implementing a QMS which defines the organization's quality policy and objectives and ensures that these are achieved through Quality Assurance (QA) and Quality Control (QC), the former focusing on the processes through which the product is obtained and the latter on the product. The quality of any product or process can thus be demonstrated by comparison with a quality standard and organizations that can show that they meet the requirements of the standard can gain certification or accreditation.

Quality assurance (QA): This is defined as the part of quality management that focuses on providing confidence that quality requirements will be fulfilled. QA requires systematic monitoring and evaluation of all aspects of a biobank's processes, covering both how the biobank operates as well as the quality of the samples and data held.

Quality control (QC): This is defined by the operational techniques and activities used to verify that a product or service adheres to a defined set of quality criteria.

Best Practice: A management idea asserting that there is a technique, method, process, or activity that is more effective at delivering a particular outcome than any other technique, method, process, or activity. Guidelines or Recommendations are synonyms of Best Practices.

Evidence-based practices: interventions for which there is consistent scientific evidence, either recognized by one or more published articles in scientific journals or provided by on-site experimental work.

Certification: The procedure by which a third party gives written assurance (a certificate) that a product, process or service conforms to specific requirements.

Accreditation: The procedure by which an independent authoritative body gives formal recognition that a body or person is competent to carry out specific tasks. Accreditation requires method validation.

Standards or norms: A format applicable because it is recognized by an official organization or is implemented by a majority of users. It is mandatory for biobanks seeking certification or accreditation to conform to applicable standards.

ISO Certification norm: A norm geared around management which includes feasible Standard Operating Procedures (SOPs) (e.g. ISO/IEC 9001:2015).

ISO Accreditation norm: A norm geared around competence which includes SOPs that are evidence-based and scientifically validated (e.g. ISO 17025:2005).

Preanalytical phase: processes that include, in chronological order, the biological material request, preparation and identification of the origin of the biological materials (donor or environmental site), collection of the primary sample(s), temporary storage, transportation to and within the biobank processing laboratory, processing, isolation of analytes, aliquotting, retrieval, and that end when the biological material is delivered for analysis.

Qualification: process of examination of a biospecimen or a collection of biospecimens, and verification, based on objective analytical evidence, of their suitability for research use, either in a specific disease area or on a specific downstream analytical platform.

Quality stratification: process of examination of a biospecimen or a collection of biospecimens, and their classification, based on objective analytical evidence, into distinct categories, each category corresponding to a specific in vivo biological characteristic (e.g., level of inflammation, % tumour, protein content) or to a specific ex vivo preanalytical condition (e.g., pre-centrifugation conditions).

3 Approaches to Implementing Quality Assurance

A number of guidelines and best practices for collecting biological specimens have been developed, addressing such issues as ethical guidelines for population biobanks or hospital-based biobanks, technical guidelines, IT guidelines, and cost-recovery guidelines. Likewise, certain national and international norms exist, which although not always specific to biobanks, may be applied.

A biobank can be compliant to recognized guidelines, and can also be certified and/or accredited. Compliance to national and/or international guidelines is declared by the biobank itself, but an external audit is not conducted. A self-assessment tool is available from the International Society for Biological and Environmental Repositories (ISBER, http://www.isber.org/?page=SAT), however this remains confidential. Biobanks may be certified by an external body according to a national or international certification norm, providing a guarantee of consistency. For accreditation, a biobank may either be accredited by an external body according to a national or international norm, or can collaborate with an accredited laboratory for testing/characterizing the samples. A description of available best practices and ISO norms used for certification and accreditation in support of biobanking QA follows.

3.1 Best Practices and Recommendations

In 1999, the Organisation for Economic Co-operation and Development (OECD) recommended 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 [3]. While some moves have been made in this direction, accreditation systems established by a body dedicated to the development and dissemination of such standards are lacking. An overview of the guidelines published to date—by the OECD itself, the European Council, the US National Cancer Institute (NCI), and the ISBER—is presented below.

Recommendations were published in 2006 by the Council of Europe which provided Recommendation Rec(2006)4 of the Committee of Ministers to member states for research on biological material of human origin [4]. In 2007, the OECD itself published Best Practice Guidelines for Biological Resource Centers (Paris, France) addressing the certification of repositories containing samples of human and microbial origin to conform to national and/or international standards, with an influence from microbiological material collections [5]. Moreover, the NCI Best Practices for Biospecimen Resources (Bethesda, MD, USA, 2016) were developed for NCI-supported biorepositories which store biological samples of human origin [6]. They focus mainly on management, quality and protection of data associated with the biological material, as well as addressing intellectual property issues.

The most complete best practices for repositories can be found in the ISBER Best Practices for Repositories: Collection, Storage, Retrieval and Distribution of Biological Materials for Research (3rd edition), first published in 2005 with revised editions in 2008 and 2012 [7]. They reflect the collective experience of the ISBER members and provide repository professionals with a comprehensive tool to guide them in a wide range of activities, covering infrastructure, equipment, security, and training. They are applicable to biobanks which manage material of either human or non-human origin, with a focus on the establishment and day-to-day management of a biobank. They take into account regulatory compliance as well as the ethical,

legal and social issues relevant to repositories. Both managerial and technical aspects are covered providing a practical guide to the overall establishment, management and operations of a repository with advice on a wide range of aspects including repository development, facilities and equipment, quality management, cost management, security (pertaining to specimens, handlers and data) and training, material tracking, packing and shipping, sample collection, processing and destruction, and legal issues. These Best Practices are reviewed periodically and revised to reflect advances in research and technology.

3.2 Certification

Biobanks can obtain certification according to the international ISO 9001:2015 (Quality Management Systems Requirements), a flexible and generic management standard that can be applied to any business. It is focused on the implementation of QMS, client satisfaction and continuous improvement, and is highly customer service oriented, with documentation of all complaints, and implementation of corrective and preventive measures. It is applicable to an organization's structure for managing its processes (activities) that transform resource inputs into a product (biological sample or derivative) or service (biostorage) to meet the organization's objectives, such as satisfying the customer's quality requirements or complying with regulations [8]. ISO 9001 certifies that a business has official written procedures and training documentation in the area of customer service, product processing, analysis, packaging, and shipping, as well as for accounting. As long as a repository is consistent in its documented actions, it can remain ISO 9001-certified.

In addition, some countries have developed national standards. In France, the NF S96–900 (Management System of a Biological Resource Center and Quality of Biological Resources of Human or Microbial Origin) were developed on the basis of the ISO 9001 [9]. In addition to the above-mentioned system requirements, it also includes specific technical requirements for biorepositories. In the UK, the National Cancer Research Institute (NCRI) has developed a Biobank standard [10]. In the USA, the College of American Pathologists has also developed a checklist towards biobank accreditation [11].

3.3 Accreditation

While ISO 9001 is a suitable standard for the certification of the QMS of a biobank's activities, ensuring its core processes are consistent, it does not provide assurance of the quality of the technical aspects, the accuracy of any measurements it performs or the professional competence of its staff. This includes qualification of equipment, validation of methods, measurement traceability, use of control and

reference materials, participation in proficiency testing schemes and handling of samples and data—and hence that samples and derived data are fit-for-purpose. To this end, biobanks should also operate in accordance with other international reference documents focused on aspects of competence. The two main references for accreditation are the international ISO 17025:2005 and the ISO 17034:2016.

The ISO 17025:2005 (General Requirements for the Competence of Testing and Calibration Laboratories) is used by biobanks to implement a quality system aimed at improving consistent production of valid results. ISO 17025 incorporates all ISO 9001 requirements relevant to the scope of testing services and further specifies the technical requirements for technical competence of a laboratory. It is applicable to all organizations performing tests, including laboratories where testing is part of product certification. ISO 17025 certifies that quality-oriented tests are performed correctly, establishing that the product (biological sample or derivative) is a quality product. All aspects of QC activities are examined by this standard. The qualification, education, and training of personnel are examined against job responsibilities. Every quality critical specification, including the qualifications of suppliers and collaborators, is checked. To be ISO17025 accredited, a biobank must not only be consistent, but also proficient in testing the quality of their products (biological samples or derivatives) [12].

In addition, the ISO 17034:2016 (General Requirements for the Competence of Reference Material Producers) concerns manufacturers of references materials or certified reference materials. All methods used by the manufacturer to certify their materials must be validated and proven accurate. It requires that any uncertainties, which include all of sources of error involved in characterizing the materials, be reported on the Certificate of Analysis. ISO 17034 provides the highest level of QA, stating that the manufacturer's materials are produced correctly and competently. Currently, the ATCC is the only biobank accredited with ISO 17034 for bacterial, fungal, and cell line cultures. The role of biobanks as reference material producers is discussed in the following chapter.

Existing guidelines for biobanks have been compiled into a single document according to the structure of ISO accreditation standards [13, 14] and incorporating color coding to allow the reader to distinguish between the original texts. This document contains previously published Best Practices that biobanks should follow if they wish to demonstrate that they operate a quality system and are able to provide biological samples that conform to specified requirements.

4 Biospecimen Quality Control

4.1 Sample Characterization

Homogeneity of collection procedures, shipping and storage conditions is critical to the quality of multicenter research studies. QC procedures are designed to ensure data and sample quality. Data QC includes control of demographic, pathology,

clinical, processing data accuracy, while biospecimen QC includes assays on sample authenticity, integrity and identity [15]. Biospecimen QC is required to ensure accurate sample characterization and categorisation and avoid introducing bias in downstream research due to intrinsic heterogeneity in samples. Accurate characterization of the samples supplied by a biobank concerns both the authentication and the integrity of the biomaterial.

Effective QC can be performed by biobanks in a number of ways. QC can be performed on every specimen received; this is strongly recommended and cost-effective in some cases, e.g. hemocytometry on all incoming blood samples. QC can be performed on every sample going into storage, e.g. quantification and purity of all DNA samples. QC can be performed on outgoing samples, before their distribution to researchers, e.g. RNA integrity measure, provided it is not destructive to the samples.

QC assays may be performed by the biobank, the end user or a sub-contracting laboratory. They should be done by the biobank according to GLP (Good Laboratory Practice), or where a biobank does not have the facility, by a subcontracted laboratory compliant to ISO 15189:2012 (Medical Laboratories—Particular Requirements for Quality and Competence), to ISO 17025:2005 or to CLIA (Clinical Laboratory Improvement Amendments). Retrospective QC may be applied to either a randomly selected percentage of the collected specimens or to samples considered to have undergone the most "inconsistent" processing. The first approach allows comparisons between different collection sites and the second allows targeted assessment of the "highest risk" samples.

4.2 Sample Authenticity and Integrity

Sample authenticity refers to providing a guarantee that a sample is indeed what it is refers to as, such as when a biobank provides a serum sample from a patient with primary melanoma, there must be proof of the primary melanoma (authenticity) and that the sample was not compromised by any pre-analytical bias (integrity). In this case, QC requires a histopathologic validation on fixed and/or frozen sections to validate the tissue sample. The evaluation must be performed by a trained pathologist to confirm the tissue type (tumor or normal) and the basic histopathological diagnosis and classification (International Classification of Diseases), based on standard hematoxylin-eosin staining. The test includes assessment of cellular composition, which is of critical importance in any downstream molecular analysis. Highly heterogeneous cellular composition makes molecular analysis irrelevant and the minimum percentage of tumor is often set at 70%. Standard histologic control also includes assessment of morphologic degradation. Histopathologic analysis allows identification and marking of the block areas which are the most suitable for tissue microarray cores. The exact nature of the integrity QC tests performed depends on the intended end use.

QC tests allowing assessment of processing, shipping and storage conditions may include microparticle counts in serum or plasma to assess centrifugation conditions and efficiency, platelet activation components to assess platelet activation during sample processing, serum sCD40L measurement to assess the time samples were exposed to ambient temperature [16], plasma protein S activity to assess cryostorage duration and conditions [17], matrix metalloproteinases in serum or plasma to assess storage conditions [18], hemoglobin measurement in serum or plasma to assess hemolysis which may have taken place during collection or prolonged pre-centrifugation delays of blood samples, and levels of cytokines such as G-CSF, CXCL10, MIF, serpin E1, CXCL12 in plasma samples, which decrease with increasing freeze-thaw cycles [16].

QC tests which allow more accurate sample characterization and ensure more efficient downstream analyses include (but are not limited to) C-reactive protein measurement in serum to assess inflammation degree and corresponding normalization of downstream proteomic analyses; creatinine and cystatin-C measurement in urine to normalize protein content in view of downstream proteomic analyses. Serum IgM detection in acutely infected patients allows assessment of the possible use of the serum samples in immunologic assays targeting specific IgM. Assessment of tissue integrity by immunohistochemistry may include vimentin, cytokeratin, surface kinases, hypoxia-related molecules and hormone receptors. Serum fingerprinting can be performed to assess the identity of different serum samples [19].

DNA QC assays include DNA quantification and purity analysis by spectrophotometry/fluorometry and gel electrophoresis. PCR assays can assess the DNA cross-linking degree and fitness-for-purpose in downstream whole genome amplification or comparative genomic hybridization arrays [20]. Possible inhibitors can be detected by the SPUD real-time PCR assay [21].

RNA QC assays include total RNA quantification by spectrophotometry/fluorometry and RNA integrity assessment by RNA Integrity Number (RIN) measure. Reverse transcriptase (RT)-PCR, by amplification of specific cDNA targets (eg. GAPDH) using combinations of primers designed to amplify fragments with progressively increasing sizes (100, 200, 300, and 400 basepairs) can be used to assess the maximum amplifiable size of RNA. miRNAs, which are increasingly used in cancer research can be measured with real-time RT-PCR for ubiquitously expressed miRNAs, such as the miR16.

Samples used as a reference in diagnostic commercialized kits must be tested for HIV, HBC and HCV. This can be performed by a central QC laboratory. The critical steps in each assay should be documented and controlled.

QC assays used to characterize biospecimens are different for viable and non-viable specimens. Viability and functionality (e.g. pluripotency, response to antigens, motility) are assessed through microscopy, flow cytometry or immunoenzymatic assays. For non-viable specimens, molecular integrity (e.g. protein phosphorylation status, epitope conformation, rRNA degradation, DNA cross linking degree) is generally assessed through immunoenzymatic, electrophoretic and molecular biology assays [20].

5 Tools for Assisting QA/QC Implementation

5.1 Self-Assessment Tool

In 2009, the ISBER developed a self-assessment tool (SAT) to assist individuals managing repositories in determining how closely their organization conforms to the ISBER Best Practices for Repositories [22]. The assessment is confidential and allows biorepositories and biobanks to strengthen their practices by identifying areas in need of improvement. The survey consists of 158 questions that are divided into sections corresponding to sections of the ISBER Best Practices. Participants receive personalized feedback that includes a risk-balanced assessment score measuring the level of risk to the specimens for a given practice, the frequency of implementation of each practice, and the ease with which deviations from the recommended practice can be detected. The score can be used to evaluate how closely their current practices conform to the recommendations. In addition, participants are notified of the most critical areas in which their responses deviate from the recommended best practices.

5.2 Method Validation

Method validation is an important aspect in all sample or derivative characterization assays, and is an essential requirement of the ISO 17025. Method validation provides confidence that detected analytical differences are due to true clinical differences and not to different organism strains, different human genetic backgrounds, or different methodologies.

Several recent studies have recognized the influence of preanalytical variables (e.g. warm/cold ischemia times, or delays in processing) on the integrity of biomolecules or gene expression [23, 24]. The potential impact of these influences is illustrated in the case of gene profiling of peripheral blood cells to identify biomarkers for improving diagnosis and clinical management, where variables that may alter gene expression would result in artefactual changes unrelated to the disease of interest. Identifying and controlling potential bias in molecular analyses which can result from biospecimen processing remains a fundamental challenge to biobank QA and biospecimen science.

Biobanking processing method validation requires knowledge of both the preanalytical variables that need to be controlled as well as factors that do not impact the quality of the biospecimen for a given type of research. Controlling preanalytical variables is a particularly challenging and complex issue, since the influence of a sample's quality on the molecular data obtained from its analysis depends on both the nature of the biomolecule analyzed (DNA, RNA, protein, metabolite), the type of analytical method (multiplex vs singleplex; qualitative vs quantitative), and the specificity, sensitivity, and robustness of the method with respect to specific preanalytical variations.

To address these issues, three main approaches are used in biospecimen science-driven biobanking. The first is to validate the biospecimen processing methods. Processing method validation includes validation of the reproducibility, the robustness and the fitness-for-purpose of the method [25]. The second is to optimize the quality of biospecimens and thus directly minimize and/or control the preanalytical bias. However, in most clinical settings the ability to control certain preanalytical variables influencing biomolecule integrity, such as surgery or warm ischemia time, is limited. To counter this, a third approach ensures appropriate tests are applied retrospectively to accurately assess the global biomolecular integrity of each biospecimen. This process is critical for high-throughput, quantitative downstream assays implemented in clinical molecular diagnostics.

Once the key points in a biospecimen processing method have been identified, specific tests or markers to assess the biospecimen quality are needed. These may be called "surrogate quality biomarkers" or "quality indicators". Currently, there are few appropriate QC tools that are predictive of downstream method feasibility (e.g. DNA cross-linking and CGH array applications) and reliability (e.g. feasibility of CGH array analysis does not guarantee its accuracy), or are diagnostic of upstream biospecimen processing steps (e.g. tissue fixation time). QC, in the form of diagnostic tests for upstream biospecimen processing steps is termed "biospecimen molecular diagnostics" or "preanalytical characterization". Ultimately, preanalytical characterization should allow researchers to assess the reliability of specific downstream analyses, done with the samples. A Technical Report, presenting the assays that can be used for qualification or quality stratification of clinical biospecimens has been published by the ISBER Biospecimen Science Working Group [26].

5.3 SPREC, a System for Documenting Pre-Analytic Conditions

The concept of "quality" with respect to biospecimens cannot be uniquely defined since processing conditions optimizing a specimen for use vary according to the downstream analyses. If samples are intended to be used for immunological, molecular biology, or proteomic analyses, critical *in vitro* preanalytical steps should be accurately recorded for biological fluids or solid tissues collected. For biological fluids, this information includes type of primary collection tube, pre-centrifugation time delay and temperature, centrifugation conditions, post-centrifugation time delay and temperature, and long-term storage duration and temperature. For solid tissues, it includes warm and cold ischemia times, type and duration of fixation, and long-term storage duration and conditions. If samples will be used in metabolomics applications, *in vivo* preanalytical data including the time of the day when the samples were collected, and food and medication intake should also be collected.

Sample management to ensure its quality and suitability for specific purposes requires meticulous documentation of the conditions of collection, processing and storage. Consistency of sample quality can be ensured by (1) rigorous documentation of preanalytical steps (prospective collections), and by (2) QC assays, diagnostic for a sample's preanalytics and for fitness-for-purpose (historical collections).

The ISBER has developed a system for identifying and documenting pre-analytical factors that can impact the integrity of biospecimens and their simple derivatives during collection, processing and storage. The SPREC (Standard PRE-analytical Code) is a specimen or pre-analytical "barcode" recording details about pre-analytical sample processing in a standardized format [27]. It is a 7-element code, where each element corresponds to a critical pre-analytical variable. It can be applied to both primary samples and derivatives. For fluid samples, the SPREC contains information on the sample type, type of primary container, initial and subsequent centrifugation conditions, conditions (delay and temperature) between collection and processing and between centrifugation and storage, and long-term storage conditions. For solid samples, SPREC reports on the nature of the sample and method of sampling, warm/cold ischemia times, fixation type and time, and long-term storage conditions. Tables 1 and 2 present the SPREC version 02 [28].

This simple code assists researchers and biobankers to identify the most important pre-analytical variables associated with a sample. It is easy to understand and does not require special knowledge, simply "good recording practices" and can be used via a free online tool. Implementation leads to an increased awareness among the medical, scientific and technical staff implicated in the process, of the importance of accurate and standardized sample collection and processing, thus reducing deviations from established processes and improving sample quality. For biobanks with formal QMS, SPREC annotation of samples and regular evaluation against project-specific or general quality targets permits quantitative measurement of quality objectives. This allows the biobank to implement corrections or improve its processes.

The selection of a sample for a specific research project takes into consideration biological, clinical and pre-analytical components. The scientific community needs to agree on data elements that should be documented in scientific publications, as proposed in the Biospecimen Reporting for Improved Study Quality (BRISQ) recommendations [29]. Samples qualified with SPREC and BRISQ [30] data items, have a high value for end users, since biological samples and their annotations (clinical as well as pre-analytical data) should not be dissociated. Combined use of samples from multiple biobanks can be achieved more efficiently, due to an unambiguous, very simple and easily shareable sample description. It can significantly reduce potential misunderstandings about the suitability of samples for end users' purposes and thus avoid inappropriate experiments.

Table 1 Preanalytical variables, version SPREC 2.0, applied to fluid samples

Type of sample	
Ascites fluid	ASC
Amniotic fluid	**AMN**
Bronchoalveolar lavage	**BAL**
Blood (whole)	**BLD**
Bone marrow aspirate	**BMA**
Breast milk	**BMK**
Buccal cells	**BUC**
Unficolled buffy coat, viable	**BUF**
Unficolled buffy coat, non-viable	BFF
Ficoll mononuclear cells, viable	**CEL**
Fresh cells from non-blood specimen type	**CEN**
Cells from non blood specimen type (e.g. ascites, amniotic), viable	**CLN**
Cord blood	**CRD**
Cerebrospinal fluid	**CSF**
Dried whole blood (e.g. Guthrie cards)	**DWB**
Nasal washing	**NAS**
Ficoll mononuclear cells, non viable	**PEL**
Cells from non blood specimen type (e.g. ascites, amniotic), non-viable	**PEN**
Pleural fluid	**PFL**
Plasma, single spun	**PL1**
Plasma, double spun	**PL2**
Red blood cells	RBC
Saliva	**SAL**
Semen	**SEM**
Serum	**SER**

Sputum	**SPT**
Stool	**STL**
Synovial fluid	SYN
Tears	**TER**
24 h urine	U24
Urine, random (“spot”)	**URN**
Urine, first morning	URM
Urine, timed	URT
Other	ZZZ
Type of primary container	
Acid citrate dextrose	**ACD**
Additives	ADD
Serum tube without clot activator	CAT
Citrate phosphate dextrose	**CPD**
Cell Preparation Tube®	CPT
EDTA and gel	EDG
Lithium heparin	**HEP**
Hirudin	HIR
Lithium heparin and gel	**LHG**
Oragene collection container *or equivalent*	**ORG**
PAXgene® blood RNA+	**PAX**
Potassium EDTA	**PED**
Polyethylene tube sterile	PET
S8820 protease inhibitor tablets *or equivalent*	**PI1**
Protease inhibitors	PIX
Polypropylene tube sterile	PPS

(continued)

Table 1 (continued)

PAXgene® blood DNA		PXD
PAXgene® bone marrow RNA		PXR
Sodium citrate		**SCI**
Sodium EDTA		**SED**
Sodium heparin		SHP
Sodium fluoride/potassium oxalate		**SPO**
Serum separator tube with clot activator		**SST**
Tempus® tube		**TEM**
Trace elements tube		TRC
Unknown		XXX
Other		ZZZ
Pre-centrifugation (delay between collection and processing)		
RT[a]	<2 h	A
2–10 °C	<2 h	B
RT	2–4 h	C
2–10 °C	2–4 h	D
RT	4–8 h	E
2–10 °C	4–8 h	F
RT	8–12 h	G
2–10 °C	8–12 h	H
RT	12–24 h	I
2–10 °C	12–24 h	J
RT	24–48 h	K
2–10 °C	24–48 h	L
RT	>48 h	M
2–10 °C	>48 h	N

35–38 °C	<2 h	O
Unknown		X
Other		Z
Centrifugation		
RT 10–15 min	<3000 g no braking	A
RT 10–15 min	<3000 g with braking	B
2–10 °C 10–15 min	<3000 g no braking	C
2–10 °C 10–15 min	<3000 g with braking	D
RT 10–15 min	3000–6000 g with braking	E
2–10 °C 10–15 min	3000–6000 g with braking	F
RT 10–15 min	6000–10,000 g with braking	G
2–10 °C 10–15 min	6000–10,000 g with braking	H
RT 10–15 min	>10,000 g with braking	I
2–10 °C 10–15 min	>10,000 g with braking	J
RT 30 min	<1000 g no braking	M
No centrifugation		N
Unknown		X
Other		Z
Second centrifugation		
RT 10–15 min	<3000 g no braking	A
RT 10–15 min	<3000 g with braking	B
2–10 °C 10–15 min	<3000 g no braking	C
2–10 °C 10–15 min	<3000 g with braking	D
RT 10–15 min	3000–6000 g with braking	E
2–10 °C 10–15 min	3000–6000 g with braking	F
RT 10–15 min	6000–10,000 g with braking	G

(continued)

Table 1 (continued)

2–10 °C 10–15 min	6000–10,000 g with braking	H
RT 10–15 min	>10,000 g with braking	I
2–10 °C 10–15 min	>10,000 g with braking	J
No centrifugation		N
Unknown		X
Other		Z
Post-centrifugation delay		
<1 h 2–10 °C		A
<1 h RT		B
1–2 h 2–10 °C		C
1–2 h RT		D
2–8 h 2–10 °C		E
2–8 h RT		F
8–24 h 2–10 °C		G
8–24 h RT		H
>24 h 2–10 °C		I
>24 h RT		J
Not applicable		N
Unknown		X
Other		Z
Long-term storage		
PP tube 0.5–2-mL[b]	(−85) to (−60) °C	A
PP tube 0.5–2-mL	(−35) to (−18) °C	B
PP tube 0.5–2-mL	<−135 ° C	V
Cryotube 1–2-mL	LN[c]	C
Cryotube 1–2-mL	(−85) to (−60) °C	D

Cryotube 1–2-mL	Programmable freezing to <−135 °C	E
Plastic cryo straw	LN[c]	F
Straw	(−85) to (−60) °C	G
Straw	(−35) to (−18) °C	H
Straw	Programmable freezing to <−135 °C	I
PP tube ≥5 mL	(−85) to (−60) °C	J
PP tube ≥5 mL	(−35) to (−18) °C	K
Microplate	(−85) to (−60) °C	L
Microplate	(−35) to (−18) °C	M
Cryotube 1–2-mL	LN[c] after temporary (−85) to (−60) °C	N
Plastic cryo straw	LN[c] after temporary (−85) to (−60) °C	O
Paraffin block	RT[a] or 2–10 °C	P
Bag	LN[c]	Q
Dry technology medium	RT	R
PP tube 40–500-L	(−85) to (−60) °C	S
PP tube 40–500-L	(−35) to (−18) °C	T
PP tube 40–500-L	<−135 ° C	W
Original primary container	(−35) to (−18) °C or (−85) to (−60) °C	Y
Unknown		X
Other		Z

Codes in bold come from the Laboratory Data Management System (LDMS)
Volumes refer to container size
[a]RT, room temperature: 18–28 °C
[b]PP, polypropylene
[c]LN, liquid nitrogen, referring to either vapor- or liquid-phase (this information being documented in the biobank's SOPs)

Table 2 Preanalytical variables, version SPREC 2.0, applied to solid samples

Type of sample	
Fresh cells from non blood specimen type (e.g. biopsy)	**CEN**
Cells from non blood specimen type (e.g. dissociated tissue), viable	**CLN**
Cells from fine needle aspirate	FNA
Hair	**HAR**
Cells from laser capture microdissected tissue	LCM
Cells from non blood specimen type (e.g. dissociated tissue), non viable	**PEN**
Placenta	**PLC**
Solid tissue	**TIS**
Disrupted tissue, non-viable	TCM
Other	ZZZ
Type of collection	
Autopsy <6 h post-mortem	A06
Autopsy 6–12 h post-mortem	A12
Autopsy 12–24 h post-mortem	A24
Autopsy 24–48 h post-mortem	A48
Autopsy 48–72 h post-mortem	A72
Biopsy in culture media	BCM
Biopsy	**BPS**
Biopsy in normal saline or phosphate buffered saline	BSL
Biopsy in tissue low temperature transport media	BTM
Fine needle aspirate	FNA
Punction	PUN
Surgical excision in culture media	SCM
Surgical excision	SRG
Surgical excision in normal saline or phosphate buffered saline	SSL

Surgical excision in tissue low temperature transport media	STM
Surgical excision in vacuum container	VAC
Swab	**SWB**
Other	ZZZ
Warm ischemia time	
< 2 min	A
2–10 min	B
10–20 min	C
20–30 min	D
30–60 min	E
>60 min	F
Unknown	X
Not applicable (e.g. biopsy)	N
Other	Z
Cold ischemia time	
< 2 min	A
2–10 min	B
10–20 min	C
20–30 min	D
30–60 min	E
>60 min	F
Unknown	X
Not applicable (e.g. autopsy)	N
Other	Z
Fixation/stabilization type	
Non-aldehyde with acetic acid	ACA

(continued)

Table 2 (continued)

Aldehyde-based		ALD
Allprotect ® tissue reagent		ALL
Alcohol-based		ETH
Non-buffered formalin		FOR
Heat stabilization		HST
Snap freezing		**SNP**
Non-aldehyde based without acetic acid		NAA
Neutral buffered formalin		NBF
Optimum cutting temperature medium		**OCT**
PAXgene® tissue		PXT
RNA Later®		**RNL**
Unknown		XXX
Other		ZZZ
Fixation time		
<15 min		A
15 min to 1 h		B
1–4 h		C
4–8 h		D
8–24 h		E
24–48 h		F
48–72 h		G
Not applicable		N
Unknown		X
Other		Z
Long-term storage		
PP tube 0.5–2-mL[b]	(−85) to (−60) °C	A
PP tube 0.5–2-mL	(−35) to (−18) °C	B

PP tube 0.5–2-mL	<−135 ° C	V
Cryotube 1–2-mL	Liquid nitrogen[c]	C
Cryotube 1–2-mL	(−85) to (−60) °C	D
Cryotube 1–2-mL	Programmable freezing to <−135 °C	E
Plastic cryostraw	Liquid nitrogen	F
Straw	(−85) to (−60) °C	G
Straw	(−35) to (−18) °C	H
Straw	Programmable freezing to <−135 °C	I
PP tube ≥5 mL	(−85) to (−60) °C	J
PP tube ≥5 mL	(−35) to (−18) °C	K
Microplate	(−85) to (−60) °C	L
Microplate	(−35) to (−18) °C	M
Cryotube 1–2-mL	LN[c] after temporary (−85) to (−60) °C	N
Straw	LN[c] after temporary (−85) to (−60) °C	O
Paraffin block	RT[a] or 2–10 °C	P
Bag	LN[c]	Q
Dry technology medium	RT	R
PP tube 40–500 L	(−85) to (−60) °C	S
PP tube 40–500 L	(−35) to (−18) °C	T
PP tube 40–500-L	<−135 ° C	W
Original primary container	(−35) to (−18) °C or (−85) to (−60) °C	Y
Unknown		X
Other		Z

Codes in bold come from the Laboratory Data Management System (LDMS)
Volumes refer to container size
[a]RT, room temperature: 18–28 °C
[b]PP, polypropylene
[c]Liquid nitrogen refers to either vapor or liquid phase (this information being documented in the biobank's SOPs)

6 Addressing QA/QC Gaps

While both international and national certification norms exist, none of the international norms are specific to biobanks, while none of the national biobanking norms cover all biobank technical specificities, revealing some clear gaps in the current system. Likewise, there is a need to standardize the assays used to assess molecular integrity of biospecimens procured in a clinical setting.

This gap can be defined as an absence of technical specifications including requirements and methodologies for validating biospecimen processing. Current standards include requirements for validation of testing methods (where the output is an analytical measurement) but not for validation of processing methods (where the output is a sample), with integration of the different steps during bioprocessing (tube and rack formats, LIMS integration, traceability of the whole bioprocessing chain, time stamps etc). The gap is broadening as novel specimen collection and processing methods are commercialized (e.g. room temperature technologies, whole genome amplification) without adequate validation.

In 2013, an ISO Technical Committee, ISO/TC 276 dedicated to biotechnology-related issues, which are either not addressed or poorly addressed was established. For biobanking, this principally concerns validation of biospecimen processing methods. Biobanks typically process materials using previously published protocols or those communicated by colleagues. However, in both cases formal validation in terms of a demonstration of the reproducibility, robustness, stability and fitness-for-purpose of the biospecimen processing method for downstream applications is lacking.

If the issue is not addressed, biobanks will continue to produce biospecimens applying non-validated methods, and thus producing specimens which may not be fit-for-purpose or of comparable quality. Consequences are heavy in terms of loss of time and money by the industrial and academic biotechnology application scientists, wasted specimen donations, and also unreliability of clinically relevant biomarker identification—which is obviously critical to diagnostics. As long as this remains the *status quo*, quality of the output will be compromised, hampering international collaborations between biotechnology application scientists.

6.1 Technical Specification Documents

One way to address this gap is to introduce ISO technical standards, in the form of ISO Technical Reports (TR) and ISO Technical Specifications (TS).

Three groups of technical standards are needed. The first group is for informative Technical Reports on processing and qualification (e.g., “Processing and qualification of tumor tissue specimens”, “Processing and qualification of fecal specimens”). These should include information on processing methods (further elaborated in a second group of Technical Specifications), definition of material properties,

performance metrics, and validation protocols with well-defined analytical endpoints (further elaborated in a third group of Technical Specifications) and specific acceptance criteria.

The second group is for Technical Specifications on specific bioprocessing methods (e.g., "Protein extraction from FFPE tissue", "Human tissue culture"). These should include evidence-based recommendations and methodology for the validation of bioprocessing in terms of performance (or "fitness-for-purpose"), reproducibility (or "consistency"), robustness to pre-analytical variations, biosafety, and stability.

The third group is for Technical Specifications on specific biospecimen QC methods (e.g., "Methods to determine the relative accuracy of cell counting methods", "Methods to determine the concentration of total nucleic acids"). Such a system of ISO technical standards would offer modularity and flexibility, and could be used either in combination with ISO9001 (or equivalent) certification or in combination with ISO 17025 (or equivalent) and ISO 17034 accreditation (Fig. 1).

6.2 External Quality Assurance/Proficiency Testing

External quality assurance (EQA) refers to an objective method that allows for comparison of a laboratory's testing to an external source—either a peer group of laboratories or a reference laboratory. In the context of biobanks, it can assess (1) performance of specimen processing or (2) accuracy of specimen testing.

Performance (1) can be assessed indirectly by evaluating performance in processing, producing, and storing of biospecimens relative to metrics collected by a central laboratory. The central laboratory produces an average (e.g., DNA yield or ratio) obtained from all participating biobanks, and assesses the performance of each participant relative to others. This evaluation is notably performed with respect to challenging materials, such as DNA or RNA extracted from FFPE tissues.

A second EQA option (2) which is taking on an increasingly prominent role is proficiency testing (PT), such as the ISBER-endorsed IBBL PT program [31]. This program allows a biobank to evaluate the accuracy of their sample testing methods and compare their results with other laboratories. PT can be used to identify interlaboratory differences, testing problems that may be related to individual staff performance or calibration of instrumentation used in biospecimen QC and provide guidance for remedial actions. It can also be used to determine the performance characteristics of new biospecimen QC methods and comparability with current methods. PT programs provide an additional layer of confidence to biospecimen end users, offering a means of accreditation, while also promoting collaboration between academic biobanks and the diagnostic and pharmaceutical industries. These programs are expected to improve biobank QMS and promote the quality and the economic health of the biobank industry by diminishing the "asymmetric information gap" between biospecimen providers and biospecimen end users.

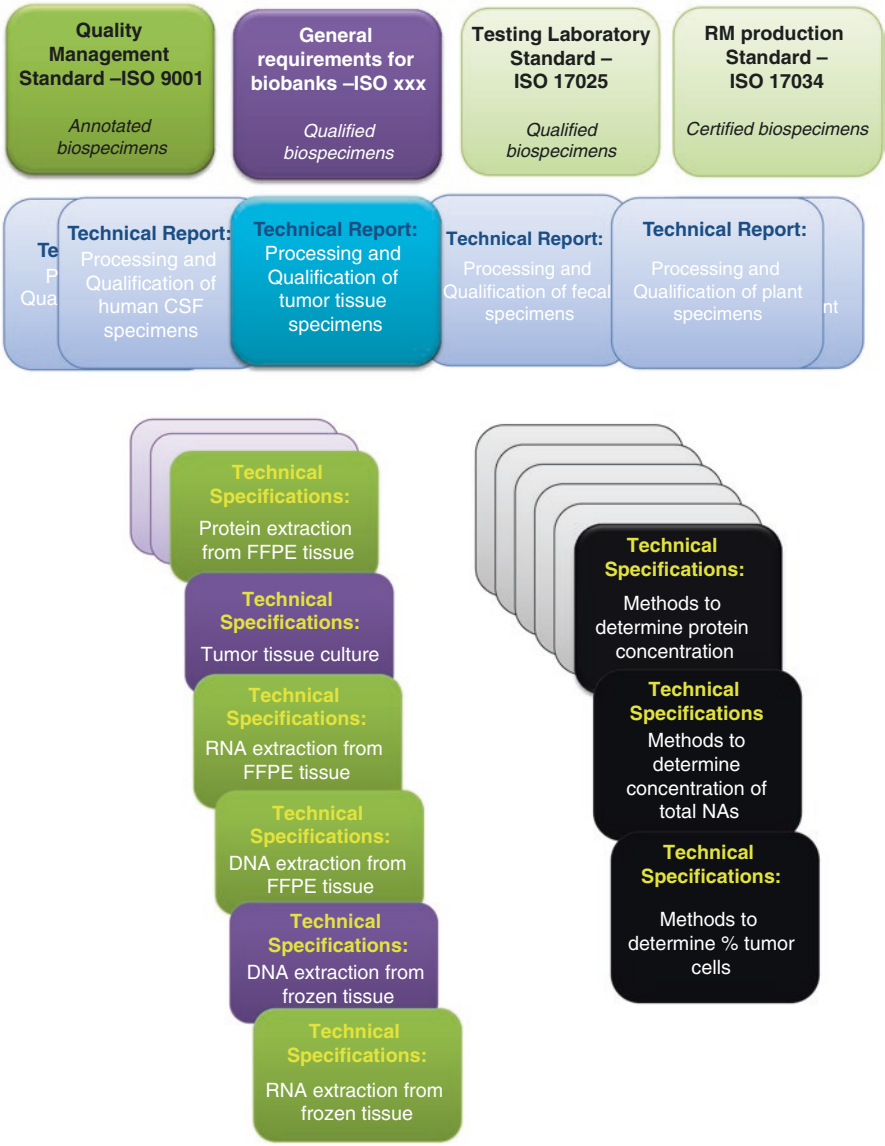

Fig. 1 Application of existing international standards (in green) to biobanks, in combination with—not yet existing—specific technical standards (in colours other than green)

The potential of the ISBER-endorsed PT Program lies in the development and implementation of schemes providing objective characterization of biospecimens that are independent of the specific processing method that has been used for their preparation and storage. Advancing the collaboration between academic biobanks and the diagnostic and pharmaceutical industries is an important step for the biobank

community. Accreditation of laboratories for performing these QC assays is a desirable future outcome of PT programs and could represent a major service of technical assistance to biobanks and/or sample end users [32].

6.3 Biobanks as Reference Material Producers

Some biobanks may fall under 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 17034' [33]. ISO 17034, 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 [34]. This General Assembly had resolved that accreditation of technically competent bodies producing reference materials with assigned values must be conducted according to harmonized criteria based on ISO Guide 34 and ISO/IEC 17025. When biobanks carry out some specific testing, such as safety testing for blood-borne viruses, they are not attempting to fully characterize the samples. As such, they are not producing well-characterized materials in the same sense as a reference material producer. Some biobanks do not carry out any testing on the samples collected at all, because of the limited nature of the material. Use of ISO 17025 and ISO 17034 is not appropriate for these biobanks. See the following chapter for a review of biobanks as RM producers.

7 Towards a Global Biobank QA System

Biological samples and associated data from biobanks will be accepted by academia and industry as fit-for-purpose if biobanks are required to be certified and/or accredited to international standards. [35].

Figure 1 shows the optimal combination of existing and necessary new normative tools of quality assurance for biobanks. The current international normative framework (ISO) includes QMS and testing laboratory standards, which can be applied to biobanks. Furthermore, the European Committee CEN/TC140 "In vitro diagnostic medical devices" has recently developed eight Technical Specification standard documents addressing specific processing methods ("specifications for pre-examination processes"). However, the current system lacks technical standards including the general requirements for biobanks, but also technical standards applicable to specific biobank fields (as outlined in 1.6.1). Such specific technical standards are yet to be developed by ISO.

For the moment, professional biobanks can be certified to existing general QMS standards, and produce consistently "annotated specimens". Some biobanks can either be accredited to existing laboratory standards or collaborate with accredited

laboratories, and produce “qualified specimens”. Finally, some biobanks can be accredited as reference material producers meeting international standards, which also exist, and produce “certified specimens” (as further discussed in the next chapter).

References

1. Riegman PHJ, Morente MM, Betsou F et al (2008) Biobanking for better healthcare. Mol Oncol 2:213–222
2. Spruessel A, Steimann G, Jung M et al (2004) Tissue ischemia time affects gene and protein expression patterns within minutes following surgical tumor excision. BioTechniques 36:1030–1037
3. Organisation for economic co-operation and development (OECD) (2001) OECD biological resources centers. Underpining the future of life sciences and biotechnology. Paris, France. https://www.oecd.org/sti/biotech/2487422.pdf. Accessed 04 July 2016
4. Council of Europe Recommendation Rec (2006) 4 of the Committee of Ministers to member states on research on biological materials of human origin. http://www.coe.int/t/dg3/healthbioethic/texts_and_documents/Rec_2006_4.pdf. Accessed 04 July 2016
5. Organisation for economic co-operation and development (OECD) (2007) OECD best practice guidelines for biological resource centres. http://www.oecd.org/science/biotech/38777417.pdf. Accessed 04 July 2016
6. Office of Biorepositories and Biospecimen Research National Cancer Institute National Institutes of Health (2011) NCI Best Pratices for Biospecimen Research. http://biospecimens.cancer.gov/bestpractices/2011-NCIBestPractices.pdf. Accessed 04 July 2016
7. No authors listed (2012) 2012 ISBER best practices for repositories collection, storage, retrieval, and distribution of biological materials for research international society for biological and environmental repositories. Biopreserv Biobank 10:79–161
8. International Organization for Standardization (2008) ISO 9001:2008-Quality Management Systems-Requirements
9. Director General of the AFNOR (2011) French Standard NF S 96–900 Quality of Collections of BiologicalResources.http://www.p3gobservatory.org/download/projet+norme+Biobanque+Eng.pdf. Accessed 04 July 2016
10. National Cancer Research institute (2014) Biobank Quality Standard—Collecting, storing and providing human biological material and data for research Version 1. http://ccb.ncri.org.uk/wp-content/uploads/2014/03/Biobank-quality-standard-Version-1.pdf. Accessed 04 July 2016
11. College of American Pathologists (CAP) (2013) Standards for biorepository accreditation. www.cap.org/apps/docs/laboratory_accreditation/build/pdf/bap_standards.pdf. Accessed 04 July 2016
12. International Organization for Standardization (2005) ISO/IEC 17025:2005—General requirements for the competence of testing and calibration laboratories
13. http://www.bbmri-eric.it/binary/eric/cont/Compilation_Biobanque_de_Picardie_avril_2008.pdf
14. Betsou F, Luzergues A, Carter A et al (2007) Towards norms for accreditation of biobanks for human health and medical research: compilation of existing guidelines into an ISO certification/accreditation norm-compatible format. Qual Assur J 11:221–294
15. Betsou F, Barnes R, Burke T et al (2009) Human biospecimen research: experimental protocol and quality control tools. Cancer Epidemiol Biomark Prev 18:1017–1025
16. Lengellé J, Panopoulos E, Betsou F (2008) Soluble CD40-ligand as a biomarker for storage-related preanalytic variations of human serum. Cytokine 44:275–282

17. Betsou F, Roussel B, Guillaume N et al (2009) Long-term stability of coagulation variables: protein S as a biomarker for preanalytical storage-related variations in human plasma. Thromb Haemost 101:1172–1175
18. Betsou F, Gunter E, Clements J et al (2013) Identification of evidence-based biospecimen quality control tools. J Mol Diagn 15:3–16
19. Beaumont K, Betsou F (2010) An immunological fingerprinting method for differentiation of serum samples in research-oriented biobanks. Clin Vaccine Immunol 17:735–740
20. van Beers EH, Joosse SA, Ligtenberg MJ et al (2006) A multiplex PCR predictor for aCGH success of FFPE samples. Br J Cancer 94:333–337
21. Nolan T, Hands RE, Ogunkolade W et al (2006) SPUD: a quantitative PCR assay for the detection of inhibitors in nucleic acid preparations. Anal Biochem 351:308–310
22. International Society for Biological and Environmental Repositories webpage (ISBER). http://www.isber.org/?page=SAT. Accessed 04 July 2016
23. Ransohoff DF, Gourlay ML (2010) Sources of bias in specimens for research about molecular markers for cancer. J Clin Oncol 28:698–704
24. Moore HM, Compton CC, Lim MD et al (2009) Biospecimen research network symposium: advancing cancer research through biospecimen science. Cancer Res 69:6770–6772
25. Betsou F (2015) Biospecimen processing method validation. Biopreserv Biobank 13:69
26. Betsou F, ISBER Biospecimen Science Working Group (2016) Assays for qualification and quality stratification of clinical biospecimens used in research: a technical report from the ISBER biospecimen science working group. Biopreserv Biobank 14(5):398–409. doi:10.1089/bio.2016.0018
27. International Society for Biological and Environmental Repositories (ISBER) Standard Preanalytical Code (SPREC) V2.0. www.isber.org/?page=SPREC. Accessed 04 July 2016
28. Lehmann S, Guadagni F, Moore H et al (2012) Standard preanalytical coding for biospecimens: review and implementation of the sample PREanalytical code (SPREC). Biopreserv Biobank 10:366–374
29. Moore HM, Kelly AB, Jewell SD et al (2011) Biospecimen reporting for improved study quality (BRISQ). Cancer Cytopathol 119:92–101
30. Betsou F, Lehmann S, Ashton G et al (2010) Standard preanalytical coding for biospecimens: defining the sample PREanalytical code. Cancer Epidemiol Biomark Prev 19:1004–1011
31. International Society for Biological and Environmental Repositories (ISBER) Proficiency Testing General Information. www.isber.org/default.asp?page=PTGI. Accessed 04 July 2016
32. Gaignaux A, Ashton G, Coppola D et al (2016) A biospecimen proficiency testing program for biobank accreditation: four years of experience. Biopreserv Biobank 14(5):429–439. doi:10.1089/bio.2015.0108
33. International Organization for Standardization (2016) ISO 17034:2009 General requirements for the competence of reference material producers
34. International Laboratory Accreditation Cooperation. Adopted resolutions of the eighth ILAC general assembly, Cape Town, South Africa, 10&12 October 2004. http://ilac.org/publications-and-resources/ga-resolutions/. Accessed 04 July 2016
35. Carter A, Betsou F (2011) Quality assurance in cancer biobanking. Biopreserv Biobank 9:157–163

http://www.springer.com/978-3-319-55118-0

Biobanking of Human Biospecimens
Principles and Practice
Hainaut, P.; Vaught, J.; Zatloukal, K.; Pasterk, M. (Eds.)
2017, XII, 239 p. 20 illus., 16 illus. in color., Hardcover
ISBN: 978-3-319-55118-0