

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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Abstract

In recent years, biobanks have evolved into professional infrastructures which acquire, validate, process, store, manage and distribute biological material of human origin to public or private end-users/researchers. This article 1) 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, 2) 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 3) provides a compilation of all existing guidelines against an International Organization for Standardization (ISO) format.

Keywords

Biobank, norm, human samples, medical research, standards

Introduction

Research biobanks¹ (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 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 scientific importance and contribution, 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 biologic 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 which 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 Co-operation 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

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.

National Cancer Institute (NCI) [4] and the OECD itself [5]. However, none of the above organizations has the production and promulgation of such standards as its primary purpose.

So, in spite of the availability of several guidelines, no relevant international norm exists that can be applied to biobanks. Nowadays, multi-center (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 article 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/accreditation² of biobanks for health and medical research.

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.

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.

Inset 1

Table	Name	Comments
1	Vocabulary changes	<ul style="list-style-type: none">• Changes made in the compilation document.• The organization responsible for the publication of each term is shown in parentheses.• A color code was used to keep track of the organization responsible for each publication (http://www.marblearchgroup.org/guidelines.compilation.htm)
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 below

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. Implementation guidelines that were characterized as notes are the following (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 from

<http://www.marblearchgroup.org/guidelines.compilation.htm> or <http://www.biobanque-picardie.com/guidelines.compilation.htm>.

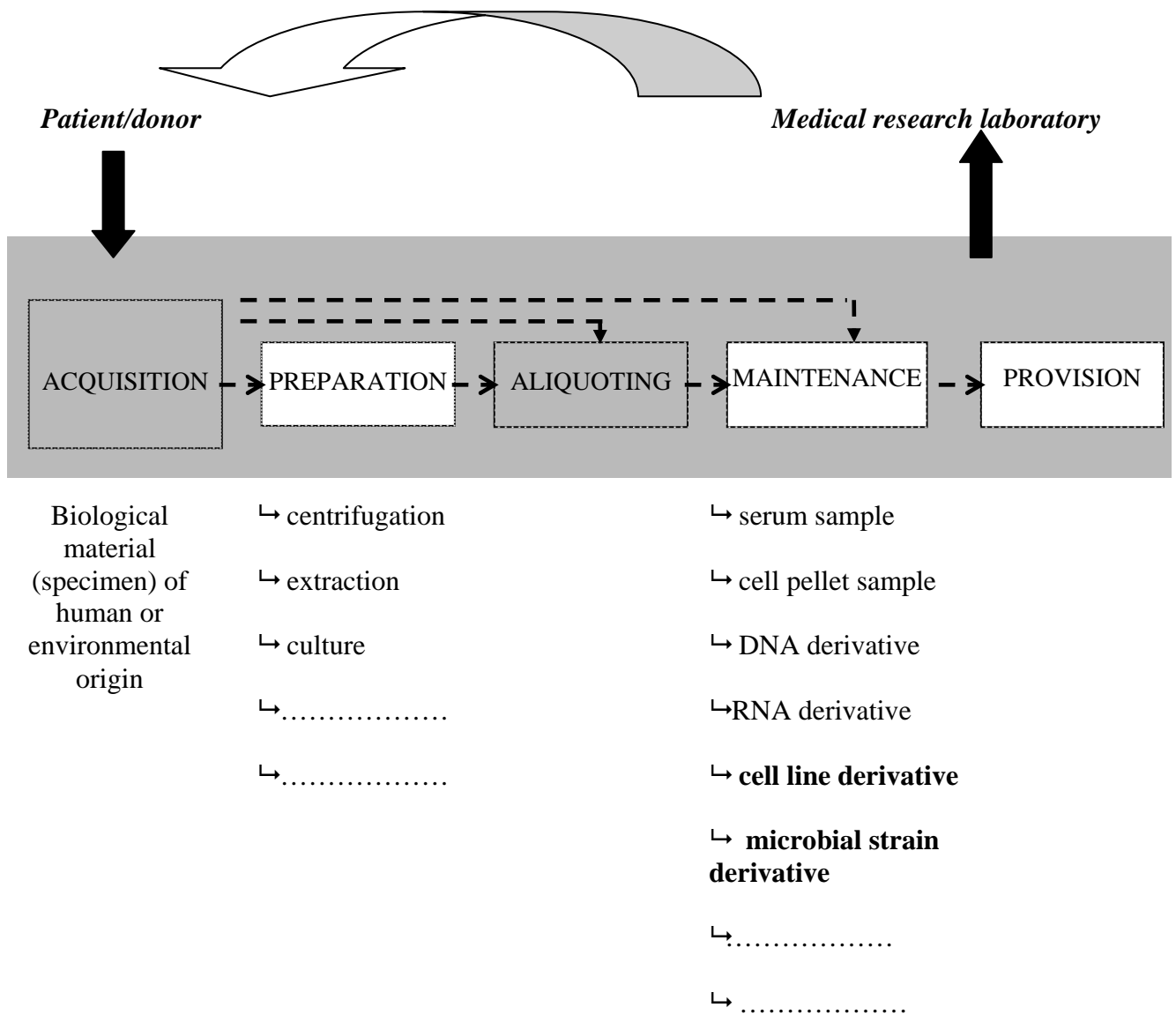
Despite the availability of several guidelines, no relevant international norm covering all of the activities of a biobank exists. One international and flexible norm that could apply to biobanks is ISO 9001:2000, but this remains a generic norm for the implementation of quality management systems, client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

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'

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)

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 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/guidelines.compilation.htm> or <http://www.marblearchgroup.org/guidelines.compilation.htm> where a color code is used allowing to make distinction 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 carefully define its processes and scope of activities. 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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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

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	<i>General</i>
4.3.2	<i>Document Approval and Issue</i>
4.3.3	<i>Document Changes</i>
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	<i>General</i>
4.11.2	<i>Cause Analysis</i>
4.11.3	<i>Selection and Implementation of Corrective Actions</i>
4.11.4	<i>Monitoring of Corrective Actions</i>
4.11.5	<i>Additional Audits</i>
4.12	Preventive Action
4.13	Control of Records
4.13.1	<i>General</i>
4.13.2	<i>Technical Records</i>
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	<i>General</i>
5.4.2	<i>Selection of Methods</i>
5.4.3	<i>Laboratory-developed Methods</i>
5.4.4	<i>Non-standard Methods</i>
5.4.5	<i>Validation of Methods</i>
5.4.6	<i>Estimation of Uncertainty of Measurement</i>
5.4.7	<i>Control of Data</i>
5.5	Equipment
5.6	Measurement Traceability
5.6.1	<i>General</i>
5.6.2	<i>Specific Requirements</i>
5.6.3	<i>Reference Standards and Reference Materials</i>
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	<i>General</i>
5.10.2	<i>Test Reports and Calibration Certificates</i>
5.10.3	<i>Test Reports</i>
5.10.4	<i>Calibration Certificates</i>

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

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 I					
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					

ISO 17025	OECD	REC 2006(4)	ISBER	NCI	Guide 34
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 4.3.3.1, 4.3.3.2, 4.3.3.3	36-37-38		C1.500		
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 4.5.1, 4.5.2, 4.5.3, 4.5.4					5.2.1.
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					

ISO 17025	OECD	REC 2006(4)	ISBER	NCI	Guide 34
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, 4.14.3					
4.14.4	93-94				
4.15 Management Reviews					
5 Technical Requirements					5.1.1. 5.3.3
5.1 General					
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					

ISO 17025	OECD	REC 2006(4)	ISBER	NCI	Guide 34
5.3.1	22-23-24-25-26-27		D1.000 D2.000 D2.100 D2.200 D3.000 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	1D1 1C7 1D9 1D8 1D3	
5.3.2	33			1C4 1D5	
5.3.3	28-29-30		G6.100 G6.200 G6.300 G6.400 G6.500 G6.600 G7.000	1D11 1D7 1D2 1D10	
5.3.4.	32		D4.300		
5.3.5			E4.000	1C6	
5.4.					
5.4.1	55 63				5.10.1
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					

ISO 17025	OECD	REC 2006(4)	ISBER	NCI	Guide 34
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 5.5.1			E2.000 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					
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ISO 17025	OECD	REC 2006(4)	ISBER	NCI	Guide 34
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