Universidade do Minho
Escola de Engenharia

Anabela de Castro Carneiro Martins

Desenvolvimento de uma proposta de referencial para a gestão da qualidade em Centros de Recursos Biológicos

novembro de 2022

Desenvolvimento de uma proposta de referencial para a gestão da qualidade em Centros de Recursos Biológicos
Anabela de Castro Carneiro Martins
UMinho | 2022

Universidade do Minho
Escola de Engenharia

Anabela de Castro Carneiro Martins

Desenvolvimento de uma proposta de referencial para a gestão da qualidade em Centros de Recursos Biológicos

Tese de Doutoramento
Doutoramento em Engenharia Química e Biológica

Trabalho efetuado sob a orientação do
Professor Doutor Nelson Lima
e do
Professor Doutor Paulo Sampaio

novembro de 2022

ACKNOWLEDGEMENTS

I would like to express my deep and sincere gratitude to my research supervisors, Professor Doutor Nelson Lima and Professor Doutor Paulo Sampaio, for providing me invaluable guidance and inspiration throughout this research and for giving opportunity to closely collaborate with many culture collections and standardisation bodies, what enriched my research. It was a great privilege and honour to work and study under their guidance.

I´m extremely grateful to my family, specially to my parents, for all the support they always provided me.

This research had partial financial support from Portuguese national funds through the FCT (Foundation for Science and Technology) within the framework of the CEB project UIDB/
04469/2020 and BioTecNorte operation (NORTE-01-0145-FEDER-000004) funded by the European Regional Development Fund under the scope of NORTE2020 – Programa Operacional Regional do Norte. It also had the partial support of the European Union's Horizon 2020 research and innovation programme under grant agreement No 871129 - IS_MIRRI21 Project.

STATEMENT OF INTEGRITY

I hereby declare having conducted this academic work with integrity. I confirm that I have not used plagiarism or any form of undue use of information or falsification of results along the process leading to its elaboration.

I further declare that I have fully acknowledged the Code of Ethical Conduct of the University of Minho.

University of Minho, _____

Full name: _____

Signature: _____

Development of a quality management system standard for the Biological Resource Centers

SUMMARY

Microbial biobanks are repositories dedicated to the long-term preservation of microorganisms. Microorganisms are a critical component of the scientific and biotechnology infrastructure being used worldwide by industry many different fields.

Global access to high-quality microorganisms is key to biotechnology. While some efforts have been made to establish a global network, no concrete outcome has been seen so far. One of the reasons is the absence of an international standard for microbial biobanking that may be used to create certification scheme: the most efficient way to build confidence between biobanks and their interested parties.

The main objective of the present research was to establish a standard for microbial biobanking certification, as part of the International Infrastructure.

The research started with a bibliographic review focusing three main points: the International Quality Infrastructure (understanding its features, rules and recognition schemes), the existing standards that might apply to microbial biobanks (their objectives and scope) and process validation in the pharmaceutical industry (searching inspiration to develop a clause for process validation).

Before starting to develop the standard, we felt the need to have a standard-setting-strategy to give direction and consistency to the development of the standard. This strategy has been conceived based on the standard setting strategies from ISO and ISEAL.

The present research resulted in (1) the development of a management system standard for biobanking including provisions for process validation, that may be used for an accredited certification and (2) a standard-setting-strategy that might contribute to discuss the standard setting methods undertaken by standardisation bodies. Parts of the developed standard were adopted by the technical committee 276 form the International Organisation for Standardisation in two different biobanking international standards: ISO20387:2018 and ISO/WD24088-1.

The quality management model currently adopted by the microbial biobanks (based in a quality by testing approach) was also analysed and an alternative model, based on quality by design is proposed.

Keywords: biobank, culture-collections, standardisation, standards, standard-setting.

Desenvolvimento de uma proposta de referencial para a Gestão da Qualidade em Centros de Recursos Biológicos

RESUMO

Os biobancos de microrganismos são repositórios que se dedicam à preservação a longo prazo de microrganismos. Os microrganismos estes são um componente crítico das infraestruturas científica e biotecnológica, dado o amplo uso no âmbito industrial e científico. A facilidade de acesso aos microrganismos, a nível global, é, pois, uma condição chave para o desenvolvimento da biotecnologia. Vários esforços têm vindo a ser realizados no sentido de criar uma rede global de biobancos no domínio microbiológico sem que, no entanto, se tenham conseguidos resultados concretos até à data. Uma das razões é a ausência de padrões comuns de desempenho e qualidade, condição indispensável para construção de confiança mútua. O estabelecimento de esquema de certificação, reconhecido internacionalmente, seria a forma mais eficiente de construir confiança.

O objetivo principal deste trabalho foi desenvolver uma norma específica para biobancos no domínio microbiológico, que possa ser usada como base para um esquema de certificação. Esta norma proporcionaria os critérios mínimos de desempenho para obtenção de uma certificação acreditada, isto é, uma certificação integrada na Infraestrutura Internacional da Qualidade.

O trabalho começou com uma pesquisa bibliográfica versando três áreas principais: a Infraestrutura Internacional da Qualidade (enquadramento, regras e esquemas de reconhecimento), as normas de que os biobancos de microrganismos dispõem atualmente (objetivo e âmbito de aplicação, situação face à infraestrura da qualidade), e o método para validação de processos na indústria farmacêutica (procurando inspiração para elaborar a cláusula na norma dedicada à validação de processos).

Antes de iniciar a escrita da norma, houve necessidade de definir uma estratégia para o seu desenvolvimento, no sentido de priorizar tarefas e traçar um caminho claro a seguir que garanta o atingimento dos objetivos. Esta estratégia foi desenhada com base nos procedimentos para desenvolvimento de normas de dois organismos de normalização, a Organização Internacional de Normalização e a ISEAL Alliance.

Deste trabalho resultou o desenvolvimento de (1) uma norma destinada a uma certificação acreditada de biobancos do domínio microbiológico e (2) uma estratégia para desenvolvimento de normas. A norma desenvolvida poderá se adotada por um organismo de normalização para implementar um programa de certificação de biobancos. Partes da norma desenvolvida foram integradas, pelo comité técnico 276 da Organização Internacional de Normalização, em duas normas internacionais, a ISO20387:2018 e a ISO/WD24088-1. A estratégia estabelecida para o desenvolvimento da norma, poderá contribuir para discutir os atuais procedimentos adotados pelos organismos de normalização.

Para a escolha do método de gestão no qual a norma se iria basear (um dos passos da estratégia para desenvolvimento da norma), foi analisado o método de gestão da qualidade que vigora na generalidade dos biobancos – *quality-by-testing* - e proposta uma abordagem alternativa - *quality-by-design*.

Palavras chave: biobancos, coleções-de-culturas, desenvolvimento de normas, infraestrutura da qualidade, certificação.

INDEX

LIST OF ABBREVIATIONS AND ACRONYMS

AB – Accreditation Body

AFRAC - African Accreditation Cooperation

APLAC - Asia Pacific Laboratory Accreditation Cooperation

ARAC - Arab Accreditation Cooperation

BPG - Best Practice Guidelines

BRC - Biological Research Centres

Bb – Biobank(s)

CAB – Conformity assessment body

CASCO - Committee on Conformity Assessment

CC - Culture Collections

CPP - Critical process parameters

CQA - Critical quality attributes

CS - Control space

DOE - Design of Experiments

DS - Design space design space

EA - European Cooperation for Accreditation

FMEA - Failure Mode and Effects Analysis

GMP - Good manufacturing practices

FDA - Food and Drug Administration

GBRCN - Global Biological Resource Centres Network

HLS - High-Level-Structure

IAAC - Inter-American Accreditation Cooperation

IAF - International Accreditation Forum

ILAC - International Laboratory Accreditation Cooperation

iQI - International Quality Infrastructure

ISL – International standards for laboratories

ISO - International Organisation for Standardisation

JTCG - Joint Technical Coordination Group

mCQA – Microbial Critical quality attributes

MMS - Management system standards

MRA - Mutual recognition arrangement

NAB - National Accreditation Body

OECD – Organisation for Economic Co-operation and Development

PDCA – Plan, Do, Check, Act

PFM - Potential failure modes

PV - Process validation

QbD - Quality by design

QbT - Quality-by-testing

RCB - Regional Cooperation Bodies

RA - Risk assessment

RPN - Risk priority number

SADCA - Southern African Development Community in Accreditation

SSS - Standard-Setting Strategy

VIM - International Vocabulary of Metrology

WFCC - World Federation for Culture Collections

WTO - World Trade Organisation

WADA – World Antidoping Agency

TBT - Technical Barriers to Trade

TC – Technical Committee

LIST OF FIGURES

LIST OF TABLES

OBJECTIVES AND CONTRIBUTIONS

Main objective

The main objective of the present research was to develop a standard providing the criteria to establish a certification scheme for microbial biobanks. This certification scheme should be included in the International Quality Infrastructure.

Other objectives and contributions

The existence of a certification scheme specific for microbial biobanks would provide a strong support for the foundation of an international network on this domain. The developed standard may be the cornerstone to the establishment of such scheme.

A standard-setting strategy for the construction of the standard was developed. With this standard-setting strategy it was also intended to contribute to the discussion of the methods currently used for the international standardisation.

Under the umbrella of the Microbial Resource Research Infrastructure (MIRRI, https://ismirri21.mirri.org/, accessed 03.01.2021) a very important project - ESFRI European Project - has been developed under the work-package 3 which looks to establish a common understanding of Quality Management and appropriate standards and best practice models. This research intends to contribute to this discussion too.

During the development of the work presented here, the International Organisation for Standardisation started to develop several standards for biobanks such as the ISO20387:2018 and the ISO/WD 24088 The research presented here has contributed with text for the standards previously mentioned as follows:

- ISO20387:2018: by providing the clause “Externally provided processes, products and services”;
- ISO/WD 24088-1: by providing different parts of the following sub-clauses:
    - National/federal, regional, and local regulations
    - Biosafety
    - Biosecurity
    - Reception/Deposit
    - Review of deposit request

Four articles were published in connexion with this research:

Martins, A., Lima, N., Sampaio, P. (2017), A Standard Proposal for Biological Resource Centers, International Journal of Quality & Reliability Management, Vol. 34, No. 2, 2017, pp147 – 162, Emerald Publishing Limited.

Martins, Anabela; Sampaio, Paulo; Lima, Nelson (2017), The ISO DIS 20387 standard disclosed, WFCC Newsletter, December 2017.

Allocca, Clare & Bledsoe, Marianna & Albert, Monique & Anisimov, Sergey & Bravo, Elena & Castelhano, Marta & Cohen, Yehudit & De Wilde, Mieke & Furuta, Koh & Kozlakidis, Zisis & Martin, Dunja & Martins, Anabela & McCall, Shannon & Morrin, Helen & Pugh, Rebecca & Schacter, Brent & Simeon-Dubach, Daniel & Snapes, Emma (2020), Biobanking in the COVID-19 Era and Beyond: Part 1. How Early Experiences Can Translate into Actionable Wisdom, Biopreservation and Biobanking, 18. 10.1089/bio.2020.0082.

Allocca, Clare & Snapes, Emma & Albert, Monique & Bledsoe, Marianna & Castelhano, Marta & De Wilde, Mieke & Furuta, Koh & Kozlakidis, Zisis & Martin, Dunja & Martins, Anabela & McCall, Shannon & Schacter, Brent (2020), Biobanking in the COVID-19 Era and Beyond: Part 2. A Set of Tool Implementation Case Studies, Biopreservation and Biobanking. 18. 10.1089/bio.2020.0083.

MOTIVATION

Our motivation was the opportunity to strengthen both the microbial biobanking performance and the microbial biobanking community. By developing a certification standard, microbial biobanks will have the opportunity to improve their standards of operation and to be included in the International Quality Infrastructure.

STRUCTURE OF THE THESIS

This thesis is composed by two parts:

- **Part one**: Bibliographic review.
- **Part two**: Results

Part one is composed by two chapters:

- Chapter 1 - Brief introduction about the role the microbial biobanks' play in biotechnology; The importance of standards for diffusion of knowledge, innovation, and access to global markets; Introduction to the International Quality Infrastructure, its rules and organisation, including the certification and accreditation schemes; Snapshot of the current standardisation status in microbial biobanks and a short analysis of the most relevant standards.
- Chapter 2 - Overview of the pharmaceutical quality system, trying to reap insights for the clause related to process validation.

Part two has three different chapters:

- Chapter 3 – Presentation of the developed standard.
- Chapter 4 – Description of the development of the standard. It starts by explaining the adopted principles for the standard-setting activities and describes how the standard-setting strategy was defined.

  The development of the standard is then described, following the order of the different stages on the standard-setting strategy:
    - Definition of the terms of reference for the standard (justification study, objectives, risk management and principles for biobanking);
    - The management approach for the standard that fits better the microbial biobanks objectives;
    - How the drafting was made: the sources, the rules and the control of the drafting;
    - The validation of the standard;
    - How the public consultation would be done;
    - Definition of different levels for compliance for the certification scheme.
- Chapter 5 - This chapter describes how the process validation (a new clause in management system standards) could be implemented in microbial biobanks and presents examples of such implementation.

The following chapters are dedicated to the conclusions, limitations and further research.

PART 1 – MICROBIAL BIOBANKS AND QUALITY MANAGEMENT: STATE OF THE ART

CHAPTER 1. Culture collections, the quality infrastructure and role of standards

CHAPTER 2. The pharmaceutical quality system

CHAPTER 1. CULTURE COLLECTIONS, THE QUALITY INFRASTRUTURE AND ROLE OF STANDARDS

1.1 INTRODUCTION

The invention of the microscope in the sixth century and the report by Antoine van Leeuwenhoek about his first observations of microscopic single-celled organisms on October 1676 opened a window to a new and fascinating universe that has boosted the development of life sciences: the world of microbes. If making microbes visible was a huge achievement, to preserve them with their unique characteristics for the long term, was an even greater challenge which Culture Collections (CC) first embraced 120 years ago (Santos and Lima, 2001).

Culture Collections, Biological Research Centres (BRC) on microbial domain, and Microbial Biobanks (mBb) are all designations for the systematised *ex-situ* repositories dedicated to the collection and preservation of microorganisms. The concept of BRC was underlined by the Organisation for Economic Co-operation and Development (OECD) (2001) referring to the repositories and providers of high-quality biological material complying with international quality standards.

More recently, under the work of International Organisation for Standardisation (ISO) Technical Committee 276 – Biotechnology, the term Biobank (Bb) was adopted as the umbrella designation for all the BRCs holding human, microorganism, animal and plant resources. In this work, the designations CC, BRC and mBb are used indistinctly.

CC are a critical component of the scientific infrastructure as they allow us to learn more about microorganism forms, functions, origins and distribution, and advance scientific discovery and innovation, whilst studying the impacts of humans on biodiversity, advancing biomedical research, developing improved crops, biocontrol agents, and pharmaceuticals, enriching education, connecting communities to nature and science, and preserving Earth's biological heritage (Lima, 2007; NASEM, 2020).

Microorganisms are key to our ecosystem balance (UN, 2015) and greatly impact our economy by providing services delivered in multiple fields (food, medicines, industry among others). Microbial diversity is being rapidly destroyed (Boundy-Mills, 2012) so CC are key in contributing to the achievement of the of the United Nations' Sustainable Goals[1].

[1] More information may be found at https://sdgs.un.org/goals (accessed 05 02 2021).

The Convention on Biological Diversity estimates that US$150-$440 billion per year is required to discontinue the loss of biodiversity at a global level by the middle of this century (UN, 2015). Threatens are the natural disasters caused by ecosystems disrupted by human impact and climate change, deforestation and forest degradation which results in loss of habitat for all species, a decrease in water quality, an increase in soil erosion, land degradation and higher emissions of carbon dioxide into the atmosphere. If no actions are taken, in short, the health of the planet and of our communities will be seriously impacted (UN, 2015).

To maintain the microbial diversity, microorganisms must be preserved in the same state in they were isolated so that the preserved cultures are representative of species in nature. For the biotechnological point of view, the strains preserved in microbial Biobanks must maintain the characteristics that made them of interest to preserve in the first case (e.g. enzyme production, mycotoxins, antibiotics).

The existing 801 service CC in 78 countries and regions (www.wfcc.info/ccinfo/, accessed 22 02 2021) play a vital role by expertly preserving microorganisms and make them promptly available to users. As biotechnology suppliers, CC have a major responsibility: to preserve and supply authentic microorganisms (microorganisms that fulfil the characteristics claimed in their catalogues) in order to assure reliable and reproducible use and results.

CC were formerly considered as individual research initiatives hosted by universities and research institutes. However, the rise in the scientific and biotechnological importance of the biological material (BM) along with an increased awareness by governments of the necessity of protecting the microbial materials origin and the implementation of mechanisms to assure biosecurity, has resulted in a global understanding of the need to create stable and well managed operations inside CC, assuring that only authentic microbial strains of known origin are preserved and supplied.

We have been witnessing a significant improvement in the ability to store, access, and use collections by means of new methods of automation, preservation, information extraction, data integration, and related technologies. Producing specimen data in digital formats has been a vital step toward enhancing the discoverability and use of biological collections. Biodiversity and omics have been providing us with a huge amount of biological material and “big data” both crucial to the R&D in life sciences and biotechnology and making the role of CC even more important (OECD, 2001; NASEM, 2020).

The OECD recommended the creation of a CC network, the Global Biological Resource Centres Network (GBRCN) (OECD, 2001), each Biological Resource Centre member working under a certification or accreditation scheme based on scientifically acceptable international criteria. The recognition scheme

would be supported by national governments (OECD, 2001), and would have an audit programme implemented to evaluate the BRC's compliance with the requirements (the audit criteria) (OECD, 2004). These recommendations brought to light the fact that a standard providing the audit criteria needed for this specific field is absent (Forti et al, 2016).

So, a standard providing mandatory provisions for biobanking, liable to be included in the International Quality Infrastructure would need to be developed prior to the establishment of the GBRCN.

1.2 THE QUALITY INFRASTRUTURE AND ROLE OF STANDARDS

Being part of the international Quality Infrastructure (iQI) is one of the most positive and practical steps that a microbial biobank can take on the path forward global recognition of competence and quality. It implies compliance with international standards and is used as a way of harmonising practices, achieve consistent results and improve confidence and communication. Being part of the iQI paves the way for cooperation and interoperability.

The Quality Infrastructure is a system created worldwide to conquer the confidence of companies/organisations, consumers and governments in each other's work. It covers essential aspects such as policies, high-level objectives, procedures, overseeing-institutions, independence and impartiality, and the value-adding use of international standards.

Standards are a key mechanism for the diffusion of technological knowledge (Ernst et al., 2014) with macroeconomic impacts (Blind et al., 2011) by promoting productivity growth and economic advancement (Allen & Sriram, 2000; Tassey, 2000). They may spur innovation by establishing a baseline of accumulated efficient technological experience from which new technologies emerge and by increasing global competitiveness, which in turn boosts innovation.

Additional recognised purposes and advantages of standards are:

a) to enable or facilitate the access to markets in other countries, by reducing the number of tests required in national and international trading - because validity and global comparability of test results is ensured;
b) to transfer and render useful data and other information across geographically dispersed systems, organisations, applications, or components (Gasser & Palfrey, 2013) making products compatible and able to interact with other products;
c) to safeguard consumer safety and simplify product development speeding up the time it takes for a product to get to market;

d) to ensure the quality and safety of products and services (CEN-CENLEC, 2013);

e) to help companies complying with relevant international legislation (CEN-CENLEC, 2013).

Standardisation is sometimes accused of decreasing flexibility and potentially blocking innovation however, it seems that the potential disadvantages are outweighed by the benefits (Allen & Sriram, 2000; Raven & Blind, 2017).

There are two commonly used definitions of "standard".

The ISO/IEC Guide 2 (ISO/IEC 2004a) defines a standard as a "document established by consensus and approved by a recognised body, which provides, for common and repeated use, rules, guidelines or characteristics for activities or their results, aimed at the achievement of the optimum degree of order in a given context". Standards are established by consensus; however, this does not imply unanimity. Consensus is a general agreement, characterised by seeking to take into account the views of all parties concerned and to reconcile any conflicting argument. It implies an absence of sustained opposition to substantial issues by any important part of the concerned interests (ISO/IEC, 2004).

The Agreement on Technical Barriers to Trade (TBT) from the World Trade Organisation (WTO), in his turn, defines "standard" by highlighting some aspects that are important for the Agreement, such as the fact that they are voluntary, and restricts its definition to products (WTO, 2012). Hence, from the Quality Infrastructure perspective, the ISO definition is probably more useful. Nevertheless, the fact that standards in themselves are considered voluntary, as defined in the WTO TBT Agreement, should always be kept in mind.

Several kinds of standards exist. They may be categorised according to the function they need to perform. According to ISO, standards may be categorised as follows: "Specification", which sets out detailed requirements often used for safety purposes; "Methods" another kind of standard also highly prescriptive that sets out a way of measuring, testing or specifying what is reliably repeatable in different circumstances and places; "Codes of practice", standards that recommend sound good practice and have a certain degree of flexibility in the application; "Vocabulary", that provides a set of terms and definitions aiming to harmonise language in different fields; "Guides", which give less prescriptive advice and reflect the current thinking and practise amongst experts in particular disciplines.

When developing a standard there are, at least, three issues that must be defined:

a) the field of standardisation, which is the domain or group of related subjects to standardise (e.g., engineering, transport, agriculture, quantities and units, biobanking);

b) the subject of standardisation or topic to be standardised (e.g., type of material, component, equipment, system, activity);

c) the specific aim(s) (e.g., protection of the environment, safety, compatibility, variety control) (ISO/IEC, 2004).

When the standardisation activity is open to relevant bodies from all countries, it is considered international standardisation.

1.3 THE QUALITY INFRASTRUCTURE: HOW AND WHY

1.3.1 ACCREDITATION BODIES AND CONFORMITY ASSESSMENT BODIES

In modern society, for reasons of safety, health, environmental protection, market fairness, or fraud prevention, it is often required to assess and state objectively conformity of services and products, including microorganisms, with specified requirements. Such assessments and the resulting conformity statements are assigned to the Conformity Assessment Bodies (CABs). These organisations are responsible for testing products and services for conformity with established requirements and for issuing certificates and reports accordingly.

To ensure that all interested parties have confidence in both the CABs assessment and the assessment outputs (the results issued in CABs certificates and reports), an international accreditation infrastructure was established aiming to ensure CABs' competence, impartiality and capability of acting consistently.

For that purpose, the work performed by each CAB is assessed by an Accreditation Body (AB) which grants accreditation to the CAB. On his turn, confidence in ABs work around the world is achieved through a mutual recognition arrangement (MRA), also known as the International Laboratory Accreditation Cooperation (ILAC) Arrangement. According to this agreement all the ABs follow the same rules of operation and are peer-evaluated for them. ILAC MRA signatories[2] agree to accept the results of each other's accredited CABs so that the results of each CAB accredited by an ILAC MRA signatory are internationally recognised.

ILAC MRA underpins a global network of laboratories, inspection bodies, proficiency testing providers and reference material producers, that have been accredited to provide accurate and reliable results which are used extensively by regulators for the public benefit in the provision of many services that promote, for example, an unpolluted environment, safe food, clean water, energy, health and social care services.

[2] The complete list of signatories and their scope of accreditation is available at https://ilac.org/ilac-mra-and-signatories/ (accessed 21.01.2021).

ILAC MRA also enhances international trade through the removal of technical barriers to trade, in the form of retesting and re-inspection, every time a product enters a new market.

Accreditation is the top level in the Quality Infrastructure. It is ruled by two key international entities: the ILAC and the International Accreditation Forum (IAF). ILAC and IAF work together to coordinate efforts in managing the accreditation and conformity assessment worldwide.

While IAF responsibilities fall in the programmes of the conformity assessment of management systems, products, services, personnel and other similar programmes, ILAC is the international authority on accreditation of laboratories, inspection bodies and other entities serving those through accreditation such as proficiency testing providers and reference material producers.

A diagram representing the international accreditation infrastructure is presented in Fig. 1.

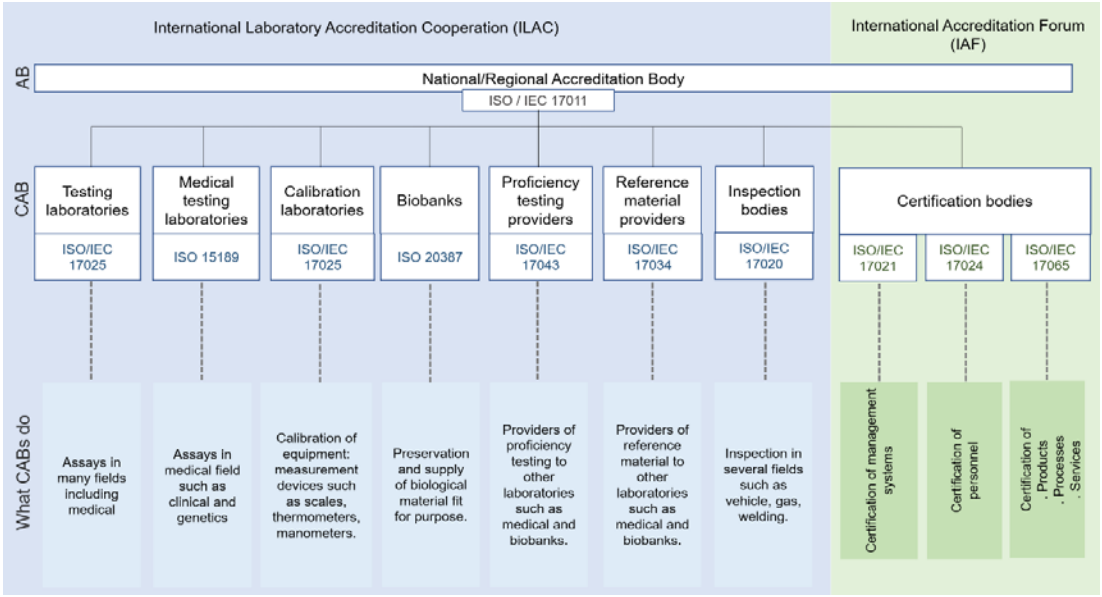


Figure 1. Diagram describing the international accreditation infrastructure, the standards the parties need to conform with and the activities performed by CABs.

1.3.2 THE ILAC ARRANGEMENT

ILAC counts as its members' accreditation bodies (AB) representing over 124 economies[3]. It manages the MRA, commonly known as the "ILAC Arrangement", between its members. The agreement bases on the ABs peer-evaluation for compliance with established requirements (e.g., ISO17011 standard) and the mutual acceptance of the results issued by different ABs MRA signatories. In 2020, almost 82 000

[3] More information may be found at https://ilac.org/about-ilac/facts-and-figures/ (accessed 21.01.2021).

laboratories, over 550 proficiency testing providers and almost 200 reference material producers were accredited by the ILAC MRA 102 signatories[2].

For an AB to be accepted into the ILAC Arrangement it must have been successfully evaluated by peers from another AB for compliance with specific criteria: the ISO/IEC17011 standard and additional mandatory documents (not included in the ILAC Arrangement Structure [please see 1.3.3] defined by the IAF and ILAC.

The results of the ILAC MRA signatories routine peer-evaluations are reviewed by a special committee which decides on whether or not the body meets the requirements.

The accreditation programmes included in the Arrangement are under ILAC's responsibility. The procedures to be used by ILAC to consider and approve new international accreditation programmes for which ILAC Arrangement might expand, such as biobanking, are documented and communicated in the ILAC website (ILAC, 2019).

1.3.3 THE ILAC ARRANGEMENT STRUCTURE

The Arrangement structure establishes the technical areas for which international agreements exist and the criteria for compliance under those agreements. ILAC controls the *Level 1* criteria, the *Level 2* activities and the *Level 3* standards of the Arrangement.

The infrastructure of the Arrangement is represented in Fig. 2.

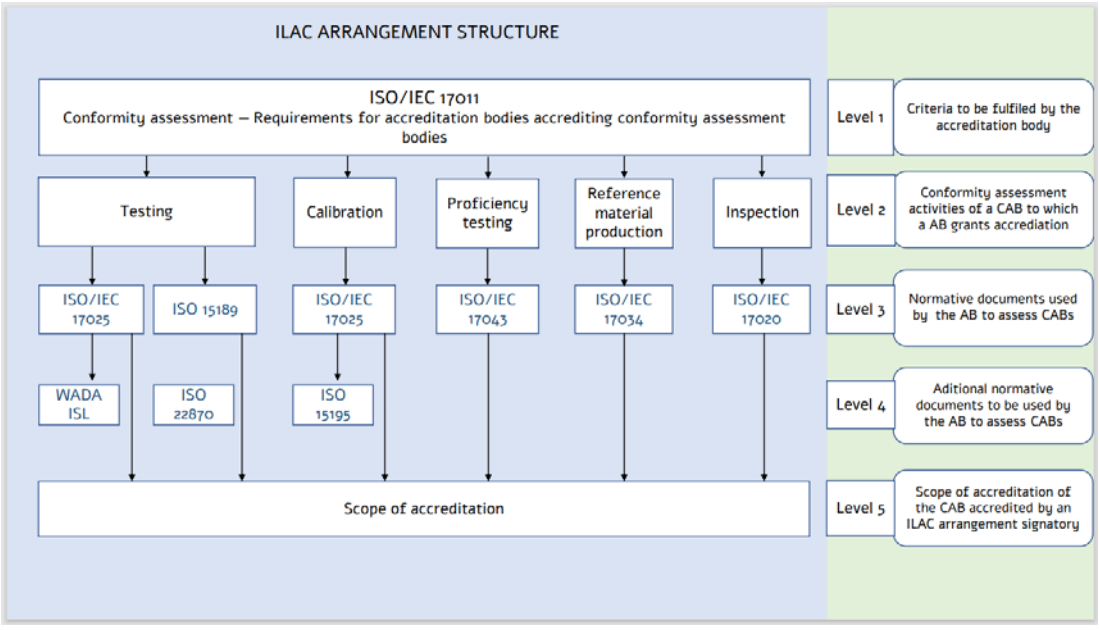


Figure 2. Structure of the ILAC Arrangement (adapted from "Structure of the ILAC Mutual Recognition Arrangement and Procedure for Expansion of the Scope of the ILAC Arrangement" (ILAC, 2019).

Level 1 contains the criteria with which the AB must comply: the ISO/IEC17011 standard.
Level 2 refers to the conformity assessment activities of a CAB to which the AB grants accreditation according to the generic, normative documents listed in *Level 3*. These activities are: Testing, Calibration, Inspection, Proficiency Testing Provision, and Reference Material Production.
Level 3 contains the generic normative documents - recognised by the ILAC as meeting the accreditation requirements – used by the AB to assess CAB's competence for each activity in *Level 2*. These are the standards for CABs currently covered by the ILAC MRA (Fig. 2) that are indicated in the ILAC Arrangement Text (ILAC, 2019):

- For testing: ISO/IEC17025 and ISO15189;
- For calibration: ISO/IEC17025;
- For inspection: ISO/IEC17020;
- For proficiency testing providers: ISO/IEC17043;
- For reference material production: ISO17034.

MRA signatories may be recognised for one or more activities in *Level 2* and *Level 3* normative document.
In *Level 4* we have sector-specific normative documents which specify internationally recognised applications of the generic, normative document listed in *Level 3*. These application documents are used by the AB, in combination with the generic, normative documents listed in *Level 3*, to assess the CAB's competence in the relevant sector. To be used in combination with ISO/IEC17025, there is (1) the WADA ISL for anti-doping testing laboratories also accredited by the WADA and (2) the ISO15195 to be used by medical reference measurements laboratories.
For point-of-care testing there is the ISO22870 to be used in combination with ISO15189.
Level 5 contains the scope of accreditation of the CAB accredited by an ILAC arrangement signatory. *Level 5* is maintained by each ILAC Arrangement signatory as well as *Level 4* to which, each ILAC Arrangement signatory, may add additional requirements to those established by the ILAC arrangement.

1.3.4 REGIONAL COOPERATION BODIES

ILAC builds on the activities of its Regional Cooperation Bodies (RCB) members. The ILAC MRA builds on existing regional MRAs established worldwide by RCBs which coordinate peer evaluations between AB that are signatories to the regional MRA. RCB recognised by ILAC also adhere to ILAC's procedures and requirements and undergo routine peer evaluations by the members of another RCB or ILAC.

RCBs may develop their own accreditation programmes for activities and standards (respectively, *Levels 2* and *3*) out of the ILAC Arrangement opening a window of opportunity for microbial biobanks to build mutual recognition agreements at a regional level.

The currently recognised RCBs of ILAC are the African Accreditation Cooperation (AFRAC), the Arab Accreditation Cooperation (ARAC), the Asia Pacific Laboratory Accreditation Cooperation (APLAC), the European Cooperation for Accreditation (EA), and the Inter-American Accreditation Cooperation (IAAC). The Southern African Development Community in Accreditation (SADCA) is currently in process of developing its MRAs and their associated evaluation procedures to further seeking recognition with ILAC.

1.3.5 THE ILAC MRA Mark

CABs of ILAC MRA signatories that have signed an agreement with ILAC for the use of the ILAC MRA Mark may use the Accredited CAB Combined ILAC MRA Mark (ILAC MRA Mark in combination with the accreditation symbol which the accredited CAB is entitled to use) (ILAC, 2015). This allows these CABs to provide an instantly recognisable link to the ILAC MRA on their reports and certificates containing the results of activities carried out under the scope of their accreditation as well as, for example, in online applications such as websites and newsletters.

1.4 ACCREDITATION

1.4.1 GENERAL

Accreditation is a conformity assessment technique specifically related to the assessment of the conformity of a CAB by a third-party entity, the AB.

There is no competition between ABs to avoid the creation of a "*market for accreditation*, leading to the commercialisation of accreditation, which would jeopardise the added value and role of accreditation as a public authority activity and last level of control of the conformity assessment chain"[4]. ABs are though regulated at a technical level to ensure their competence is not compromised by cost optimisation resulting from market competition.

[4] More information can be found at Regulation (EC) 765/2008 of the European Parliament and of the Council, of 9 July 2008, Article 7, p.31. Available at https://eur-lex.europa.eu/legal-content/EN/TXT/PDF/?uri=CELEX:32008R0765&from=PT (accessed 21.01.2021).

According to the Regulation (EC) 765/2008 of the European Parliament and of the Council, of 9 July 2008, CABs are required to request accreditation by the national AB (NAB) of the Member State in which they are established[5]. However, a CAB may request accreditation with a NAB in another Member State in the following situations:

- there is no NAB in its own Member State;
- the NAB does not offer the requested accreditation service;
- the NAB has not received a positive outcome in the peer-evaluation in relation to the conformity assessment activity for which accreditation is requested.

In such cases, the national accreditation body of the Member State in which the requesting conformity assessment body is established may participate as an observer.

The impartiality rule[6] underlying the accreditation process requires that the AB is impartial in deciding on accreditation, meaning that the AB shall not have any conflict of interest with the CAB applying for accreditation, and that the AB shall not be subject to any other pressure of any nature, such as political, commercial, or financial. Impartiality also means that the decision of accreditation shall be made by persons different from those having conducted the assessment.

CABs wishing to be accredited are required to comply with appropriate international standards and additional applicable documents for the consistent application of those standards (ILAC, 2019). Accreditation involves the use of auditing techniques by assessment teams which include expertise in both the organisational aspects - such as those related to the management system - and the specific technical activities of the CAB. At the end of the assessment the evidence data of conformity, gathered by the assessment team, is summarised in a report in sufficient detail. The assessment report may also include the description of any major or minor non-conformities (for which corrections and corrective actions must be defined planned and undertaken by the CAB) and comments/concerns.

An accredited CAB will be provided with an accreditation certificate and an annexe to the certificate where the accredited activities whether they are assays, calibrations, exams, certifications or inspections are to be listed.

The framework for the accreditation of biobanks is represented in the diagram in Fig. 3.

[5] More information can be found at Regulation (EC) 765/2008 of the European Parliament and of the Council, of 9 July 2008, p.36 and 27.

[6] More information can be found at Regulation (EC) 765/2008 of the European Parliament and of the Council, of 9 July 2008, p.31 and 37.

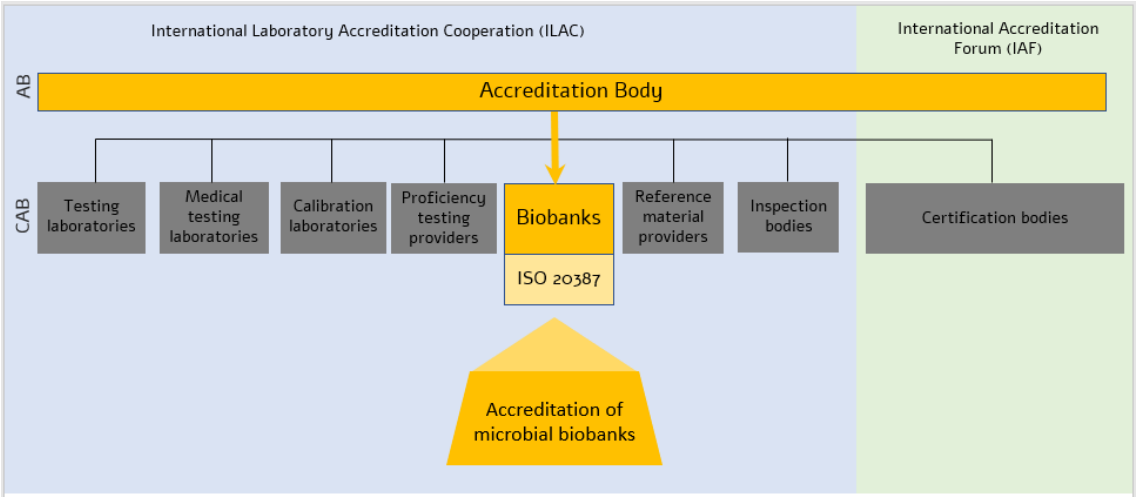


Figure 3. Diagram representing the entities involved in the accreditation of microbial biobanks under the framework of the international Quality Infrastructure.

1.4.2 STANDARDS FOR ACCREDITATION

The development of international standards, including those intended for accreditation purposes, is assigned to ISO. The decision of adopting a certain standard for conformity assessment purposes lays on ILAC/IAF.

International standards, intended for both certification and accreditation, are developed in response to a request from industry or other interested parties such as consumer groups. In general, a sector or group communicates the need for a standard to its national standardisation body which in turn contacts ISO. If the proposal meets a market need within a specific area the development of the standard is assigned to a group of experts from all over the world inside a technical committee. These experts negotiate all aspects of the standard, including its scope, terms and definitions and content. During the process, interested parties are invited to comments on the standard. Their comments are further analysed and taken into account.

The standards intended for accreditation are assigned to the ISO Committee on Conformity Assessment (CASCO). CASCO is responsible for the development of international standards intended for "the practice of testing, inspection and certification and to the assessment of management systems, testing laboratories, inspection bodies, certification bodies, accreditation bodies and their operations and acceptance".

However, in very particular cases, accreditation standards may also be developed by technical committees other than CASCO. In such cases, the standard is developed by the assigned technical committee in coordination with CASCO. Some examples include the ISO20387 (ISO, 2018b) and

ISO15189 standards which were developed respectively by the technical committees (TC) 276-*Biotechnology*[7] and 212-*Clinical laboratory testing and in vitro diagnostic test systems*.

The standards intended for conformity assessment have:

- a common structure (general headings/main clause sequence), that should be kept unchanged while adapting the sub-headings (ISO, 2020a);
- six common elements (''impartiality'', ''confidentiality'', “competence”, ''complaints”, “appeals'' and ''management system'') which include obligatory wording (ISO, 2020b).

1.5 CERTIFICATION

1.5.1 GENERAL

In the context of the International Quality Infrastructure, certification is the action carried out by a conformity assessment body (certification body), which declares that an organisation, person, product, process or service meets the requirements defined in a certain document, usually a standard. To obtain evidence of compliance with this document, the conformity assessment body performs an audit against the audit criteria (the provisions on the document). In a biobank, the certification audit encompasses more processes than those directly related to assays and tests (as it happens in accreditation), considering the total business including strategy, planning, risks, biosafety and biosecurity.

ISO19011 standard (ISO, 2018c) provides guidance on planning and conducting audits (first-, second- or third-part audits) to management systems. The standard includes information about the principles of auditing, how to manage an audit programme and how to evaluate the competence of auditors, among others.

The framework for the certification of biobanks under the ISO9001 (the ISO standard most sought by microbial biobanks) is represented in the diagram in Fig. 4.

[7] More details can be found at http://www.iso.org/iso/home/standards_development/list_of_iso_technical_committees/iso_technical_committee.htm?commid=4514241 (accessed 02.01.2021).

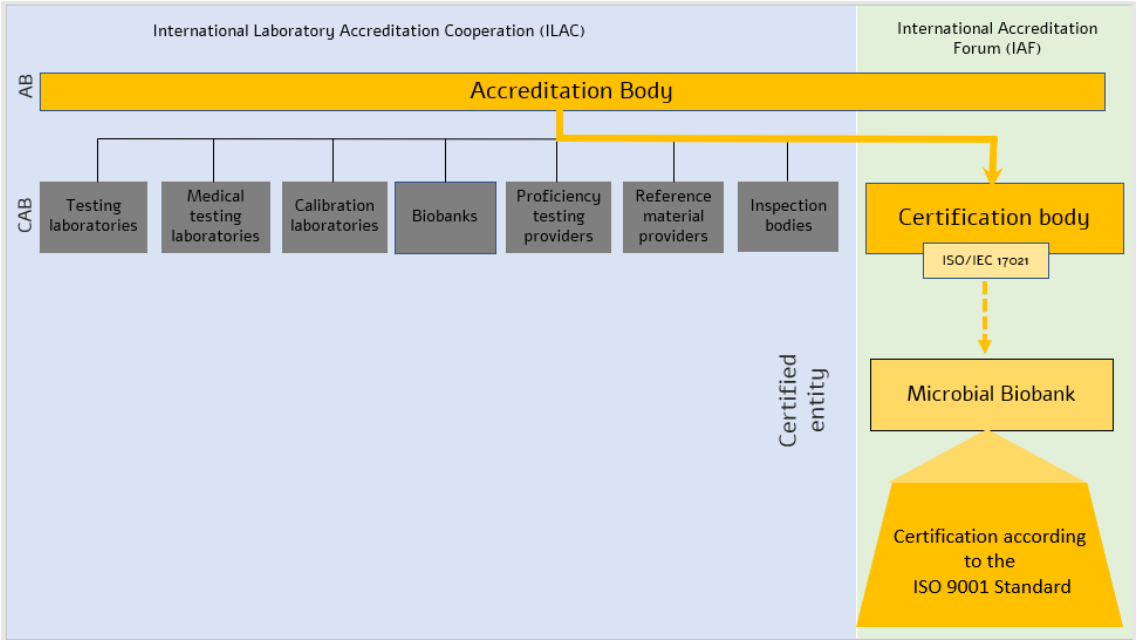


Figure 4. Diagram representing the entities involved in the certification of microbial biobanks according to the ISO 9001 standard, under the framework of the international Quality Infrastructure.

1.5.2 STANDARDS FOR CERTIFICATION

There are three main groups of standards liable to certification:

(a) management system standards (MMS);

(b) standards providing certification of people;

(c) standards providing certification of products, services and processes.

MMS are the most sought for certification. They cover many different technical areas[8] namely Quality, Industry, Safety and Security, General Management, Health and Medical, Environmental and Energy, Information Technology and Services.

A management system may be defined as a set of inter-related elements of an organisation to establish policies and objectives and processes to meet those objectives (ISO, 2015a). In a microbial biobank, a management system supports the management of the interrelated parts of the biobank – equipment, personnel, premises, procedures, methods, policies, for instance – to enable it to achieve its objectives. These objectives may relate to several different topics such as the quality of the biological material

[8] More information can be found at https://www.iso.org/management-system-standards-list.html (accessed 21.01.2021).

preserved and supplied, biosafety, biosecurity, the competence of the personnel, operational efficiency and the microbial biobank overall performance.

MMS may be used with three main purposes: (1) for the establishment and development of a management system, (2) for assessment, by clients or other interested parties, and (3) as a criterion for certification. Some benefits of implementing a management system include improvement of the performance, more efficient use of resources, improved risk management and increased customer satisfaction (Domingues et al., 2016).

There are two different types of MMS: A and B. While type A conveys requirements (mandatory provisions) for the management system, type B provides recommendations. Type B MSS are often standards providing recommendations for the implementation of type A MSS.

Organisations may implement more than one MSS (with different aims): quality and environment for instance or safety and security. The possibility of easy integration of several management system standards is a long-awaited wish that has recently become reality.

The integration idea started in the early 1990s when the Technical Management Board required both the TC 176 and the TC 207 to work together to ensure alignment of their standards. However, TC 207 chose to go for the PDCA approach while TC 176 had chosen the process approach. Those developments caused a lot of delays in making progress on alignment.

The two committees recognised however that they needed to work to (1) creating a common structure (main clause sequence) for their standards and (2) to make their texts as "identical" as possible. This resulted in the production of the "Joint Vision" for identical requirements MSS, and the High-Level-Structure (HLS). The alignment work was expanded by the Joint Technical Coordination Group_(JTCG) from ISO resulting in huge progress (personal communication from Joana dos Guimarães Sá). Nowadays HLS is mandatory for new MSS and for all the MSS in revision (ISO, 2006a)

1.6 STANDARDS FOR MICROBIAL BIOBANKS

Culture Collections were formerly considered as individual research initiatives hosted by universities and research institutes. However, the rise in the scientific and biotechnological importance of the biological material along with increased awareness by governments of the necessity of protecting the microbial materials in its three vectors - quality, origin and misuse - has resulted in a global understanding of the need to create stable and well managed operations inside CC, assuring that only authentic microbial strains of known origin are preserved and supplied.

Timeline

For at least three decades, many CC have been managing their operation under the recommendations of the Best Practice Guidelines (BPG) issued by the World Federation for Culture Collections (WFCC, 2010). The WFCC BPG convey recommendations to assist the affiliate CC in offering services outside their institution (service collections) and also to in-house or research collections.

In 2001, the OECD introduced a new concept for CC – the Biological Resource Centres - referring to the repositories and providers of *high-quality* biological material complying with international standards on quality matters. Also recommended the creation of a BRC network - the Global Biological Resource Centres Network (GBRCN) – each member working under a national certification or accreditation scheme - supported by national governments - based on scientifically acceptable international criteria (OECD, 2001) and having conformity assessment programmes in place (OECD, 2004).

Six years later a set of BPG for BRC - developed and endorsed by the OECD's Committee on Scientific and Technological Policy - were published (OECD, 2007) targeting plant, animal, microorganism and human biobanking.

In 2007, AFNOR (the French standardisation body) published a standard specifically developed to certify BRCs from human and microorganism domain, the "NF S 96-900 – Qualité des Centre de Ressource Biologiques" (AFNOR, 2008). The standard was based on the provisions of the OECD BPG and the ISO9001 standard. In total, 31 French CC are certified under the NF S 96-900 (personal communication from Dominique Clermont, 2017). This certification is not an accredited one.

Brasil also developed a standard for microbial biobank accreditation. The Brazilian standard NIT-DICLA-061 (INMETRO, 2020) based on the recommendations of OECD BPG.

ISO Guide 34, although not implemented in this technical area, is also considered for microbial biobanks producing reference biological material (Smith and Ryan, 2012).

By the end of 2014, through its TC 276 – Biotechnology, ISO started to develop an international standard for biobanks in four domains - microorganisms, human, animal and plants. With this standard, the term Biobank was adopted as the umbrella designation for all the BRCs holding human, microorganism, animal and/or plant resources.

The new ISO standard was published in 2018 and based in various standards including the OECD BPG (Furuta & Schacter, 2015).

In 2020 was published the ISO21710 *Biotechnology — Specification on Data Management and Publication in Microbial Resource Centers,* conveying requirements for data management and publication in microbial biobanks in order to enable consistent formatting, and a quality control workflow to improve the overall quality of data. It also provides recommendations for microbial biobanks to improve data sharing and integration of microbial material and associated data.
A new standard for bacteria and archaea is currently under development in ISO TC 276.

In Fig. 5 is presented a timeline with the main standards for microbial biobanks.

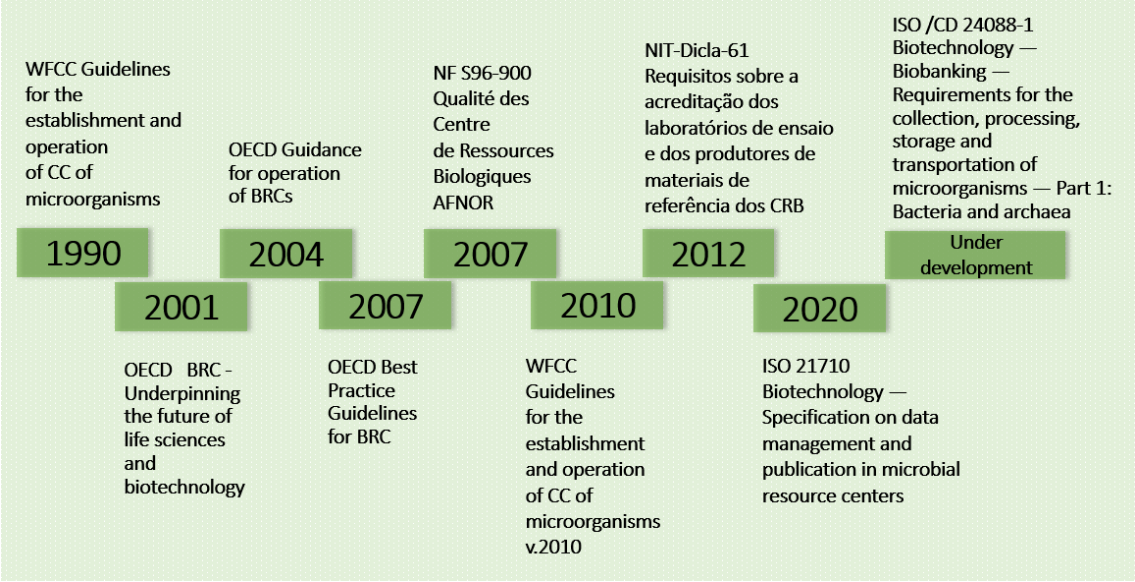


Figure 5. Timeline presenting the main standards developed for microbial biobanks.

1.7 QUALITY ASSURANCE AND PROCESS VALIDATION IN MICROBIAL BIOBANKS

OECD considers that standardisation initiatives should include validation of methods and procedures (OECD, 2007) as a means to achieve quality assurance[9] and consistency[10] (OECD, 2001). This is in line with current quality practice in the majority of the life science industries, as validation is generally a regulatory requirement (PharmOut, 2016).

[9] Quality assurance is the part of the quality management focused on providing confidence that quality requirements will be fulfilled (ISO, 2015a).
[10] For this work, process consistency is defined as the degree to which a process leads to identical results over time.

Current approaches for validation include the determination of the process capability, a statistical measure that expresses the inherent process variability for a given characteristic[11] (Gijo, 2006). The capability of a process to consistently deliver quality while tolerating variability in inputs enables demonstration of the process consistency (Yu, 2008) and effectiveness[12] (Maropoulos & Ceglarek, 2010; Patel et al., 2015).

Accepted statistical guidelines indicate that processes with C_{pk}>1.33 are deemed capable (they are performing well within statistical control) (Alsmeyer et al., 2015) while processes with CpK<1.0 are incapable (Alsmeyer et al., 2015) and actions to reduce variability of the process are recommended.

Process validation leads to economic benefits as it is related to cost reduction by increased efficiency[13] (Patel et al., 2015). The efficient use of resources is necessary for sustainability: microbial biobanks use expensive materials, sophisticated equipment and facilities and have highly qualified personnel. The cost of preservation and authentication failures, biological material loss, complaints and reworks may be a significant part of the total preservation costs.

Despite recommending the use of methods such as blind tests, comparing the results of the same method performed at different times or comparing results obtained with different methods, the OECD BPG do not provide guidance on how to implement process validation.

1.8 ISO STANDARDS IN MICROBIAL BIOBANKS

From the 790 WFCC member Culture Collections, 22 are certified according to ISO9001 and 5 are accredited by ISO/IEC17025 (ISO/IEC, 2017) (Lima, 2020).

1.8.1 THE ISO9001 STANDARD

ISO9001 is the most sought among the ISO standards[14]. It bases on the seven quality management principles and the clause structure is built around the Plan-Do-Check-Act (PDCA) sequence. However, the

[11] Process capability may be determined by the Process Capability Index which considers the tolerance specified for a particular characteristic divided by the process variability (expressed as a standard deviation).

[12] Defined as the extent to which planned activities are realized and planned results are achieved (ISO, 2015a)

[13] Efficiency is defined as the relationship between the result achieved and the resources used (ISO, 2015a).

[14] The ISO9001 certification is one of the indicators used to explore a broad vision of innovation - Global Innovation Index, available at: www.globalinnovationindex.org/home (accessed 21.01.2021).

process approach is still the standard's underlying concept - now with improved application by the explicit requirements for risk-based thinking.

It is a generic standard that has been applied to BRCs for several years with many advantages, such as: (a) helping in establish the biobanking-processes, (b) helping qualify the resources, (c) supporting process control, analysis of the results and implementation of measures for process improvement and d) enhancing proactivity by promoting risk-based thinking.

ISO9001 standard provides requirements to manage the flow of information generated through the microbial biobanking activity and to control external providers of products, services and processes. ISO9001 provisions might also support the microbial biobank in establishing a business strategy. As a MSS it bases in the HLS structure facilitating the integration or transfer to any other MSS.

Our interpretation of the ISO 9001 standard model for quality management, showing the overarched activities, is represented in Fig. 6.

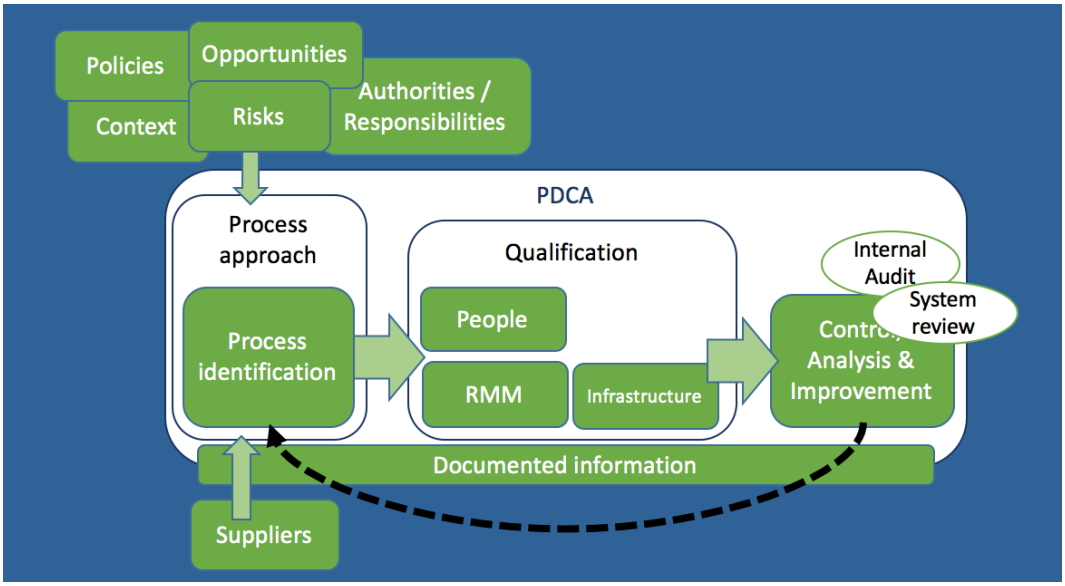


Figure 6. Diagram representing the activities covered by the ISO 9001:2015 standard and their relationship (management model).

1.8.2 THE ISO/IEC17025 STANDARD

The ISO/IEC17025 standard is not a management system standard although, it requires the implementation of a management system. For this reason, ISO/IEC17025 follows a similar management model to that of ISO9001, which is presented in Fig. 7. Major differences are the inclusion of provisions for the *verification and validation of methods*, *sampling requirements*, *calculation of the uncertainty of the testing results*, and provisions to ensure *impartiality and confidentiality*.

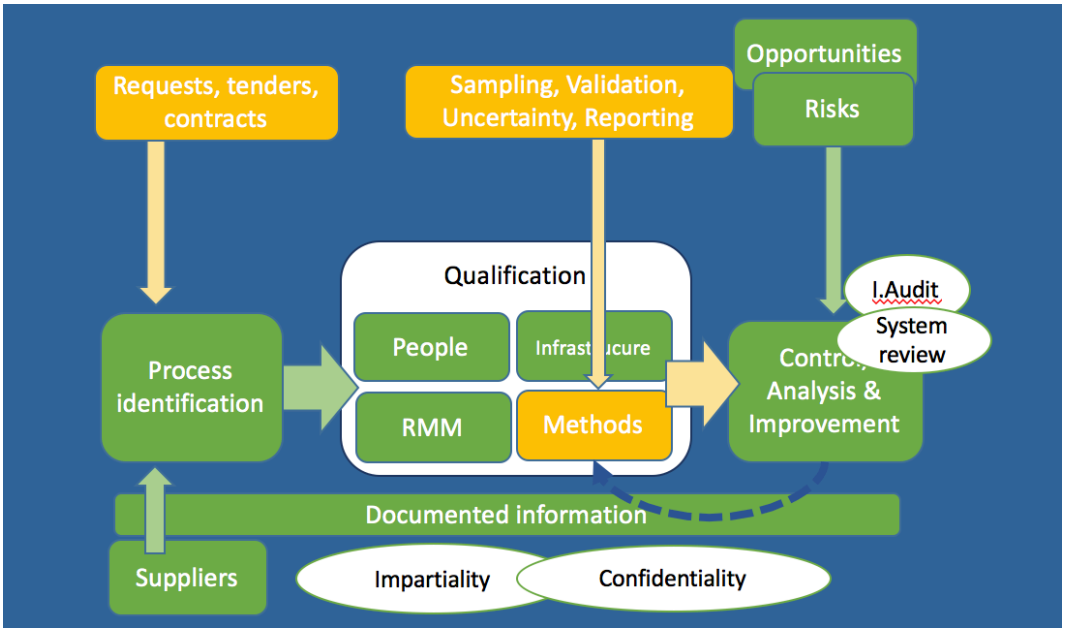


Figure 7. Diagram representing the activities covered by the ISO/IEC17025 standard and their relationship (management model).

1.8.3 THE ISO20387 STANDARD

The decision of using a certain standard for conformity assessment purposes, such as accreditation of microbial biobanks, is assigned to ILAC/IAF. Through resolution GA 22.19[15], ILAC's General Assembly has decided that "*the standard applicable to biobanks for the purposes of accreditation will be ISO 20387 Biobanking – General requirements for biobanking, to be used as a standalone standard*".

[15] Available at https://ilac.org/publications-and-resources/ga-resolutions/ (accessed 21.01.2021).

CHAPTER 2. THE PHARMACEUTICAL QUALITY SYSTEM

2.1 GENERAL

The manufacture in the pharmaceutical industry is supported by a quality system based on ISO quality concepts and good manufacturing practices (GMP) (FDA, 2011; EMA, 2016; European Commission, 2015), with major emphasis on process validation (PV). The pharmaceutical process validation is a quality assurance method that uses scientific tools to control the process performance (Alsmeyer et al., 2015). The implementation of this quality system allows to establish an effective control the processes, to reduce variability, and to consistently comply with the requirements thereby providing assurance of continued process capability (ICH, 2008).

2.2 PROCESS VALIDATION AND GOOD MANUFACTURING PRACTICES

2.2.1 HISTORICAL PERSPECTIVE

Validation approaches were proposed to pharmaceutical industry in the mid 1970's by two officials from Food and Drug Administration (FDA) of the USA, Ted Byers and Bud Loftus. Former validation approaches were focused on the processes directly involved in manufacturing. However, it soon became apparent that validation would need to be extended to the associated processes such as environment control, media fill and equipment sanitation (Parthasarathy & Krishna, 2012). The key outcome to achieve from PV would be the assurance that equipment and all the processes involved in manufacturing and testing would be fit for purpose (PharmOut Pty, 2016).

Former PV approaches placed great emphasis on testing for conformity (Chatterjee & Wong, 2012). PV was seen as a one-time event performed just prior to commercial launch. The underlying philosophy was the traditional quality-by-testing (QbT) (Kan et al., 2014) where the quality of the product is ensured by testing activities carried out throughout the manufacturing process and before the product "release".

Considering that "testing alone cannot be relied on to ensure product quality" and that quality must be "built into the product", the current PV model is based on a three stages approach, as presented in Fig. 8 (Pluta, 2011). It links (1) product and process design and development, (2) process performance qualification, and (3) maintenance of the process and product in a state of control (FDA, 2011).

Figure 8. Three stage approach to process validation in the pharmaceutical industry.

2.2.2 STAGE 1 - PROCESS DEVELOPMENT

Process design and development, also known as "process understanding", is the first stage of the PV. It includes activities relating to product and process research and development generally performed using pilot batch studies and scale up activities (Patel et al., 2015). The goals are to develop product and process by building process knowledge and to establish a strategy for process control.

The process control strategy facilitates timely implementation of appropriate corrective and preventive actions and includes:

(1) monitoring and measuring parameters and attributes related to drug substance, raw materials, facility and equipment, operating conditions, finished product specifications and

(2) the methods and frequency of measuring and monitoring.

Process knowledge includes:

(1) the identification of the critical quality attributes[16] (CQA) and potential critical process parameters (CPP)[17] and the extent to which their variation can impact on the quality of the final product,

(2) knowledge of product performance over a wide range of raw material attributes, manufacturing process options and process parameters.

The existence of many process parameters and input and output variables, makes it difficult to identify the CPP and very difficult - if not impossible - to experimentally study each of them. For this reason,

[16] CQA is "a physical, chemical, biological, or microbiological property or characteristic that should be within an appropriate limit, range, or distribution to ensure the desired product quality" (ICH, 2009). CQA are typically those aspects affecting the pharmaceutical purity, dosage strength, drug release among others.

[17] Critical process parameters, are process inputs that have a direct and significant influence on CQA when they are varied within regular operating range (Yu, 2008).

investigators need to select key input and output variables and key process parameters to be investigated. Several approaches such as quality by design (QbD) [2.2.2.1], design of experiments (DOE) [2.2.2.4], risk assessment [2.2.2.3], process analytical technology [2.2.2.6] knowledge management [2.2.2.2] might be used with this purpose.

2.2.2.1 QUALITY BY DESIGN

Quality by design, first outlined by Joseph Moses Juran (1992), is a holistic, systematic, scientific, risk-based, proactive tool for quality assurance which enables to plan, set and reach quality goals. This approach bases on understanding and controlling product characteristics and manufacturing variables. The principles underpinning the QbD approach have been increasingly used to advance the product and process quality in many industries (Skrdla et al., 2009; Sangshetti et al., 2014). In pharmaceutical industry, it is being used with several purposes such as formula optimization (Girotra et al., 2016), scale up activities (Agrawal & Pandey, 2015) and monitoring operations (Largoni et al., 2015). It has also been considered as a strategy for analytical method development in robustness domain (Boussès el al., 2015; Debrus et al., 2011; Mallik et al., 2015; Rozet el al., 2013).

The implementation of QbD begins by establishing the project objectives (generally the targeted product quality profile) and continues by seeking product and processes understanding through the acquisition of data/information in a knowledge-driven manner. The understanding of all operation/process is explored and maximised within three main stages: (1) identification of the raw materials' attributes and the CPP that might influence the product CQA, (2) determination of the functional relationships linking raw materials' attributes and process parameters to the product CQA, (3) the design and development of the manufacturing process (Verma et al., 2009).

Having its manufacturing process designed, the organisation is provided, on a regular basis, with information resulting from process measuring and monitoring activities. As a result, both product and manufacturing process can be updated in an ongoing basis to support new knowledge, contributing to a consistent quality (Zidan et al., 2007).

The consistency achieved through QbD comes from the design and control of the manufacturing process: product quality is assured by controlling product formulation (composition) and manufacturing variables. Final product testing is not part of the manufacturing consistency or process control; it is merely used to

confirm the product's quality (Yu, 2008)). The proactive essence of QbD comes from identifying the process steps whose failure could result in failure to meet quality targets, during the design phase.
In sum, QbD includes the following activities (Yu, 2008; Badawy et al., 2012):

1. Definition of the target product quality profile[18];
2. Design of both product and manufacturing process in order to consistently meet product critical quality attributes;
3. Identification of the raw material attributes, process parameters, CQA, and sources of variability;
4. Identification of the potential critical process parameters (building understanding of the impact of process parameters and raw materials on CQA);
5. Control of those critical sources of process variability (that might have an impact on product quality);
6. Establishment of a control[19] strategy.
7. Continuous control of processes using suitable control strategies and process improvement to produce consistent quality over time.

QbD makes use of several tools such as knowledge management, risk assessment (RA), experimentation and design space (DS). RA is performed to identify the main variables influencing the product quality attributes. Design of Experiments (DOE) studies are done to (1) determine the most significant factors affecting product quality and process parameters and (2) to obtain the exact relationship between the product CQAs and the various factors (Kan et al., 2014). Afterwards, the design space is established. It is the multidimensional combination of input variables that have been demonstrated to provide quality assurance; in other words, the design space includes the critical factors and their acceptable ranges. The ideal design space will be one in which the process parameters have no impact on the process stability and product quality. In reality, normal operation will be done inside a small space inside the DS, the control space (CS) to achieve more flexibility.

[18] A target product profile can include attributes such as identity, dosage form, purity and stability.

[19] For this work, "control" means verification that the acceptance criteria are met, which may be accomplished by measuring, monitoring and interpreting the results.

2.2.2.2 KNOWLEDGE MANAGEMENT

The so called "knowledge management" is a systematic approach aiming to acquire, analyse, store, and disseminate information related to final products, manufacturing processes, and raw materials (ICH, 2008). In the validation context, this information comprises knowledge about the way manufacturing processes and raw materials affect the CQA of the final product (Badawy et al., 2012).

Sources of knowledge include, but are not limited to, documented knowledge (previously established), pharmaceutical development studies, technology transfer activities, PV studies over the product lifecycle, manufacturing experience, innovation experiments and activities for process control.

2.2.2.3 RISK ASSESSMENT

It is commonly understood that risk is defined as the combination of the likelihood of occurrence of harm and the severity of that harm. So, RA is a proactive approach to identify and evaluate potential risks to quality aiming to increase quality of methods or processes. It is also determinant for identifying the effect of input variables (factors) on methods or processes (Sangshetti et al., 2014).

The early identification of factors most affecting process performance and product final quality, is useful to (1) establish a suitable development program prioritising tasks (Pluta, 2011), (2) understand the sources of variation and control of variation commensurate with risk tasks (Pluta, 2011), (3) identify and prioritise areas for continual improvement (ICH, 2008), (4) establish the control system (for process performance and product quality) improvement (ICH, 2008).

Several risk assessment tools can be applied to identify the CPP and CQA aiming to reduce the number of parameters potentially affecting the CQAs (Ahmed, 2007; Kan et al., 2014; Boussès el al., 2015).

Understanding the risks and the sources of variation provides (1) confidence to go into ongoing routine commercial production and (2) the basis to establish the key performance indicators (KPIs) necessary to create an ongoing monitoring program that will track and trend data for continuous improvement (Long et al., 2011).

Some methodologies can be used, such as:

- The Ishikawa cause-and-effect diagram, which was developed in 1950 by the late Professor Kaori Ishikawa. This method enables to determine and break down the main causes of a given problem (Kan et al., 2014; Dale et al., 2007) and is of universal use in every conceivable application (Juran & Godfrey, 1999). The diagram is created by placing the "effect" at the head of the arrow. A set of major categories of causes is identified and the potential causes are added to complete

the diagram; This will illustrate in a clear manner the possible relationships between the identified effect and the causes influencing it. The most common categories of causes consist of personnel, work, method, materials, and equipment (Kume, 1989).

- Failure Mode and Effects Analysis (FMEA), which was developed around 1962 in the aerospace and defence industries (Kan et al., 2014; Dale et al., 2007) to identify and ranking potential failure modes, assessing existing and planned provisions to detect, contain or eliminate the occurrence of failure (Hoyle, 2011; Carlson, 2015; Hradesky, 1988). There are two categories of FMEA: process and design. Process FMEA deals with the reasons for potential failure during manufacture as a result of non-compliance with the original design. As a risk assessment technique, it involves five stages:
  1. Description of the stage of the process;
  2. Potential failure modes (PFM) identification;
  3. Examination of the effect of each PFM;
  4. Identification of current controls for the detection of the PFM;
  5. Determination of the Risk Priority Number (RPN), comprising an assessment of occurrence, detection and severity, which should always be confirmed against past experiences with similar processes.

2.2.2.4 DESIGN OF EXPERIMENTS

A process is a transformation of inputs (factors or process variables such as people, materials, methods, environment, machines and procedures) in outputs (such as performance or quality characteristics of a product). Factors can be either qualitative (the equipment A, B or C) or quantitative (a temperature of 10°, 15° or 20°, for example) (Moen et al., 1991). In pharmaceutical processes, examples of inputs (or factors) are the raw material particle size or purity (raw material attributes) and process temperature, speed or time (process parameter). Outputs are the final product CQA, such as tablet friability and hardness (Yu, 2008). Process/product performance can be assessed by measuring the performance characteristics of the outputs (Antony, 2014).

Widely performed in manufacturing industry, design of experiments (also known as formal experimental design) refers to the process of planning, designing and analysing an experiment enabling that valid and objective conclusions are efficiently drawn (Antony, 2014).

When performing a formal experimental design, changes will intentionally be made to the process inputs in order to observe the corresponding changes in the process output (ICH, 2009). This allows to evaluate multiple factors and their interactions while fully controlling the number of experiments (Hwan & Noack, 2011). The gained information can be used to undertake changes to the design parameters in order to find the optimum set of operating conditions and making the design performance insensitive to all sources of variation (Leon et al., 1993).

DOE has been applied to the bio-resources investigation (Hallenbeck et al., 2015) to gather knowledge about process behaviour and better estimating the amount of variability and its impact on process.
In Pharmaceutical industry DOE has been used to develop and optimise formulations and the manufacturing process (Hwan & Noack, 2011).

2.2.2.5 DESIGN SPACE AND CONTROL SPACE

A thorough understanding of the process is achieved by (1) identifying the raw material critical attributes (Yu, 2008) and critical process parameters (CPP) that affect product and (2) understanding how those parameters affect the product CQA (Badawy et al., 2012). As a result, the manufacturer is able to identify the design space as well as the control space (Yu, 2008). The establishment of the design space (DS) is a key component of the QbD. It is defined as the "*multidimensional combination and interaction of input variables"* such as raw material attributes "*and process parameters that have been demonstrated to provide quality assurance"* (ICH, 2009). DS corresponds to a subspace - whose dimensions are the factors used during development (Debrus et al., 2011) - where assurance of quality has been proved (Rozet el al., 2013). In other words, the design space includes the critical factors (identified through the process characterisation studies) and their acceptable ranges (Rathore & Winkle, 2009). The size of this space is established by the set of combinations of the key factors ranges (Rathore & Winkle, 2009; Debrus et al., 2011).
The ideal design space will be one in which the process parameters have no impact on the process stability and product quality.
DS is usually defined at small scale batches using DOE and prior knowledge and is dependent upon the equipment design principle and batch size (Yu, 2008).
The control space (CS) is the set of normal operating ranges during production. In the pharmaceutical industry it is defined as the upper and/or lower limits for the critical raw material attributes and process parameters between which the parameter and material are routinely controlled (during production) in

order to assure process reproducibility (Yu, 2008). The control space is a narrower portion of the design space (then it should be within the design space) representing the recommended limits that will be allowed during production (Chatterjee & Wong, 2012). When the control space is much smaller than the design space, the process is considered robust, i.e, it has the ability to tolerate the expected variability of materials, equipment, environmental conditions and human factors (Glodek, 2006). Otherwise, stringent process control may be needed to assure that the process can be constantly operated within the design space (Yu, 2008).

2.2.2.6 PROCESS ANALYTICAL TECHNOLOGY

Process analytical technology (PAT) is a system that collects measurements of the critical factors during the manufacturing process that will be used to design, analyse and control the manufacturing process. The goal of PAT is to enhance understanding and control of the process and its results are closely connected to the establishment of the design space due to its contribution to the process characterisation. Besides its contribution to demonstrate/confirm that the process operates within the approved control space, it provides continuous feed-back contributing to improve process robustness (Rathore & Winkle, 2009).

2.2.3 STAGE 2 - PROCESS QUALIFICATION

Process qualification, also known as "process validation" (Patel et al., 2015) or "process performance validation" (Pluta, 2011) aims to demonstrate that the process is reproducible[20] and will consistently deliver quality products during commercial manufacturing (Pluta, 2011). The work performed on the previous stage (product and process design and development) is confirmed at this second stage by evaluating the capability of reproducible commercial manufacture. This stage involves a high level of testing and sampling (Pluta, 2011).

Two elements compose the process qualification: (1) design of the facility and qualification of the utilities and equipment and (2) process performance qualification (FDA, 2011).

Premises, construction materials, utilities, equipment (including measuring and monitoring resources) should be evaluated for its fitness for purpose. They must be verified to ensure:

[20] A reproducible process is a process that can be repeated in time (ISO, 2013).

- that are built and/or installed properly and properly maintained and controlled (by calibration, for example);
- they operate and are qualified to operate within the intended operating ranges (the ranges required by the processes), under production-level loads and for production-level durations.

When planning the qualification of premises, equipment and utilities, the organisation should consider the (1) use of risk management tool in order to prioritise activities and documentation needs, (2) type of studies or tests to perform, (3) criteria to assess outcomes, (4) schedule qualification activities, (5) responsibilities, (6) procedure for approval and documentation of the process qualification (Pluta, 2011). Usual outputs from process qualification are specific recommendations for the design of the facility, plans and methods to control the infra-structure, utilities and equipment.

2.2.4 STAGE 3 - CONTINUOUS IMPROVEMENT

This stage may be described as “maintaining the validated state”. It requires frequent review of all the process related information to assure that there have been no changes, deviations, failures or modification to the production parameters (Patel et al., 2015). Any deviation must be identified, corrected if possible, and corrective actions or improvements prioritised.

PART 2 - THE PROJECT STANDARD AND DESCRIPTION OF ITS DEVELOPMENT (standard setting activities)

CHAPTER 3. THE PROJECT-STANDARD

Management system for microbial Biobanks – requirements for consistency and effectiveness

INDEX

1 Objectives and Scope

1.1 Objective

The objective of the present standard is to provide requirements for the microbial biobanks consistency & effectiveness management system (C&EMS) to ensure (1) the authenticity of the preserved and supplied microorganisms, (2) an effective and consistent microorganism preservation (through process validation, competence of human resources and qualification of the infrastructure and equipment), (3) that fundamental procedures on biosafety and biosecurity are in place, (4) compliance with international statutory and regulatory requirements, in order to meet the interested parties' requirements.
This standard also provides the necessary reference for certification of microbial biobanks by competent bodies."

1.2 Scope

The present standard applies to biobanks acting in the microorganism domain which need to ensure (1) effectiveness and consistency in preserving and supply authentic microorganisms, (2) effective biosafety and biosecurity procedures in place and (3) compliance with applicable statutory and regulatory requirements, in order to meet the interested parties' requirements through the effective application of the standard's provisions.
This standard applies to all biobanks that receive, preserve, store and supply material of microbial origin.

2 Normative references

There are no mandatory documents for the application of the present standard, although the following standards may support its implementation. For undated references, the latest edition of the referenced document (including any amendments) applies.

- OECD BP Guidelines for Biological Resources Centres (OECD BPG)
- WFCC Guidelines

3 Terms and definitions

For this document, the following terms and definitions apply.

- Authentication: process by which biological materials are characterised up to a defined level using appropriate technology to establish a conclusive basis for accepting the material as genuine. Such level of characterisation includes testing to achieve identification (taxonomic), purity, and viability testing. Authentication is defined in the domain specific best practice guidelines for BRCs [OECD BPF, 2007]. In microbial biobanking context, genuine and authentic may be used as synonyms.
- Biosafety - Biosafety entails the use of containment principles, technologies and practices that are implemented to prevent unintentional exposure to pathogens and toxins, or their accidental release. [source: OECD BPF, 2007]
- Biosecurity is intended to deter or detect the loss or theft of dangerous biological materials for illicit or malicious purposes. [OECD BPF, 2007]
- Capacity building refers to the process of enhancing individual skills or strengthening the competence of an organization or set of organizations to undertake specific tasks [source: UN, 1997].
- Process consistency: degree to which a process leads to identical results over time.
- Process effectiveness: extent to which planned activities are realized and planned results achieved [source: ISO 9000:2015, 3.7.11]

4 Context of the organization

4.1 Understanding the mBiobank and its context

The mBiobank shall determine external and internal issues that are relevant to its purpose and strategic direction and that affect its ability to achieve the intended result(s) of its C&EMS.
The mBiobank shall monitor and review information about these external and internal issues.

NOTE 1 Issues can include positive and negative factors or conditions for consideration.

NOTE 2 Understanding the mBiobank' s external context can be facilitated by considering issues arising from legal, regulatory regulations or voluntary international conventions, technological, social and economic environments.

NOTE 3 Legal, regulatory or voluntary international conventions issues can include:

- Applicable health and safety requirements.
- Microorganism classification based on risk.
- Applicable quarantine regulations.
- Intellectual property rights.
- Safety information to provide to the biological material recipient.
- Regulations governing shipping of microorganism.
- Control of distribution of microorganism.
- National data protection regulations

NOTE 4 Understanding the mBiobank' s internal context can be facilitated by considering issues related to values, culture, knowledge, state of the art vs competence.

4.2 Understanding the needs and expectations of interested parties

Due to their effect or potential effect on the mBiobank' s ability to consistently and effectively preserve and supply authentic microorganisms meeting the interested parties and applicable statutory and regulatory requirements, the mBiobank shall determine:

- the interested parties that are relevant to the C&EMS, and
- the requirements of these interested parties that are relevant to the C&EMS.

The organization shall monitor and review information about these interested parties and their relevant requirements.

4.3 Determining the scope of the C&E management system

The mBiobank shall determine the boundaries and applicability of the C&EMS to establish its scope. When determining the scope, the mBiobank shall consider:

- the external and internal issues referred to in 4.1;
- the requirements of relevant interested parties referred to in 4.2.;

- the microbiological domain it operates;
- the nature of the microorganism preserved;
- the safe operational level or safety limit for the handled microorganism;
- the technical capacity for the intended-to-preserve microorganism.

The mBiobank shall apply all the requirements of this standard if they are applicable within the determined scope of its C&EMS.

The scope of the mBiobank's C&MS shall be available to interested parties and be maintained as documented information. The scope shall state the nature of the biological material held and provide justification for any requirement of this standard that the Biobank determines is not applicable to the scope of its C&MS.
Conformity to this Standard may only be claimed if the requirements determined as not being applicable do not affect the mBiobank' s ability to ensure and demonstrate the effectiveness and consistency in microorganism preservation.
The mBiobank shall ensure that the preservation methods are improved in such a way that a safe and long preservation is ensured.

4.4 C&E management system

The mBiobank shall establish, implement, maintain and continually improve a C&MS, including the processes needed for microorganism reception, preservation, authentication and supply and their interactions, and biosafety and biosecurity procedures, in accordance with the provisions of this Standard.
The mBiobank shall determine the processes needed for the C&EMS and their application throughout the organisation, and shall:

a. determine the inputs required and the outputs expected from these processes;
b. determine the sequence and interaction of these processes;
c. assign the responsibilities and authorities for these processes;
d. determine and apply the criteria and methods (including monitoring, measurements and related performance indicators) needed to ensure the affective and consistent operation and control of these processes;
e. evaluate these processes and implement any changes needed to ensure that these processes consistently achieve their intended results;

f. scientifically justify any change in defined criteria arising from non-conformity identification;
g. determine the resources needed for these processes, ensure their availability and qualification;
h. determine the requirements for the equipment and infrastructure qualification;
i. address the risks and opportunities as determined in accordance with the requirements of 6.1;
j. improve the processes and the C&EMS.

To the extent necessary, the mBiobank shall:

a. maintain documented information to support the operation of its processes;
b. retain documented information to have confidence that the processes are being carried out as planned.

5 Leadership

5.1 Leadership and commitment

5.1.1 General

Top management shall demonstrate leadership and commitment with respect to the C&EMS by:

a) taking accountability for the management of the C&EMS;

b) ensuring that the policies and quality objectives are established for the C&EMS and are compatible with the context, the mBiobank' s principles and its strategic direction;

c) ensuring the mBiobank , or the organization of which the mBiobank is a part, shall be an entity that can be held legally responsible for its activities;

d) promoting the use of the process approach and risk-based thinking;

e) ensuring that the resources needed for the C&EMS management system are available;

f) ensuring that the C&EMS achieves its intended results;

g) engaging, directing and supporting the personnel to contribute to the C&EMS management and improvement;

h) communicating the importance of conforming to the C&EMS requirements;

i) ensuring that the Biobank shall not operate beyond the established safe operational level or safety limit (see 4.3 scope);

j) establishing a contingency plan to ensure that preserved microorganisms are maintained during emergency situations or other conditions when laboratory services are limited or unavailable (see also 6.1);

k) supporting other relevant management roles to demonstrate their leadership as it applies to their areas of responsibility.

5.1.2 Customer and key interested parties focus

Top management shall demonstrate leadership and commitment with respect to customer and key interested parties focus by ensuring that:

a) customer and key interested parties and applicable statutory and regulatory requirements are determined, understood and met;
b) the risks and opportunities that can affect conformity of the preserved microorganisms and the ability of the mBiobank to consistently and effectively preserve the microorganisms are determined and addressed;
c) the focus on complying the customer and key interested parties' requirements is maintained.

NOTE: Key interested parties include entities with major interest in the effective preservation of microorganisms (funders and persons affected by the microbial diversity preservation).

5.1.3 Competence focus

Top management shall demonstrate leadership and commitment with respect to the personnel competence, ensuring that:

a) competence requirements are determined, understood and consistently met;
b) the risks and opportunities for the C&EMS efficiency that can affect competence of person(s) doing work under its control that affects efficiency of the C&EMS are determined and addressed;

5.2 Policies

5.2.1 Establishing the C&E policy

Top management shall establish, implement and maintain a C&E policy that:

- is appropriate to the purpose and the context of the mBiobank and supports its strategic

direction;

- provides a framework for setting C&E objectives;
- provides a framework for the process validation (level of compliance 3);
- includes a commitment to avoid any involvement in activities that could lessen the reliability of the interested parties;
- includes a commitment to comply with the laboratory best practice;
- includes a commitment to ensure that person(s) participating in business processes know and apply the policies and procedures in their work;
- includes a commitment to satisfy applicable requirements;
- includes a commitment to continual improvement of the C&EMS.

5.2.2 Policy for microorganism deposit

Top management shall establish, implement and maintain a microorganism deposit policy that:

- is appropriate to the specific domain of the Biobank;
- includes the criteria on which the acceptance of new microorganism intended to integrate the collection is based;
- includes a commitment of treating all information related to the clients strictly confidential, unless national requirements apply,
- includes a commitment to only accept deposits of biological material that meets the here present access criteria and falls into the groups of its specialist expertise,
- includes a commitment to only accept deposits which are proven to be obtained legitimately,
- includes a disclaimer of responsibility of all information about the microorganism provided by the depositor;
- fulfils the statutory and regulatory requirements.

5.2.3 Microorganism supply policy

Top management shall establish, implement and maintain a microorganism supply policy that:

- includes the criteria upon which the microorganism supply is based;
- meets the specific requirements for supply as required by national and international statutory and regulatory requirements and relevant sectorial policies.

The mBiobank microorganism supply policy shall include, at least a commitment to:

- only supply to users who have the appropriate facilities;
- treat all information related to the clients strictly confidential, unless national requirements apply;
- only supply microorganisms to laboratories trained in microbiology and having access to properly equipped laboratories.

5.2.4 Communicating the policies

The mBiobank policies shall be

- available as documented information,
- communicated and applied within the organization,
- available to relevant interested parties, as appropriate,
- reviewed for continuing suitability.

The policies should not contradict the microbial Biobank' s Principles.

5.3 Organizational roles, responsibilities and authorities

Top management shall ensure that the responsibilities and authorities for relevant roles are assigned, communicated, understood and made available as documented information within the organization. Responsibilities and authority assigned shall include but not be limited to:

- grant permission to visitors;
- grant access to security areas;
- grant access to microorganism stored within the security areas;
- microorganism testing;
- method amendments;
- process validation master plan definition and implementation;
- establishing the competence requirements for person(s) doing work under its control;
- ensure compliance with the requirements of this standard;
- reporting and advising on the performance of the C&EMS and on opportunities for improvement (see 10.1) in particular to top management;
- ensure that the integrity of the C&EMS is maintained when changes to the system are planned and implemented;
- ensure overall operation and administration of the mBiobank including budget planning and financial management;

- relate with regulatory agencies, the community, users, suppliers and providers of formal agreements;
- implement a safe laboratory environment in compliance with applicable statutory and regulatory requirements;
- implement the security measures in compliance with applicable statutory and regulatory requirements;
- establish, implement and revise the contingency plan to ensure that preserved microorganisms are maintained during emergency situations or other conditions when laboratory services are limited or unavailable (see also 6.1);
- ensure compliance with this standard and biosecurity and biosafety provisions.

NOTE: Relevant roles are those that directly affect the microbial biobank's ability to achieve the C&EMS objectives.

6 Planning

6.1 Actions to address risks and opportunities

When planning for the C&EMS, the mBiobank shall consider the issues referred to in 4.1 and the requirements referred to in 4.2 and determine the risks and opportunities that need to be addressed to:

- prevent or reduce undesired effects;
- enhance desirable effects;
- achieve improvement;
- ensure the C&EMS can achieve its intended result(s);
- ensure the existence of the necessary capacity building.

The risk assessment shall include, but not be limited to:

- infrastructure, equipment and processes;
- information system,
- microorganism potential to cause harm to the health of humans, crops, livestock or infrastructure;
- the nature of the microorganisms in the mBiobank inventory in order to assign it to the appropriate biosecurity risk levels;

- the security of the mBiobank' s information;
- the mBiobank sustainability;
- improper influence on staff that may negatively affect safety and security;
- externally provided processes (prior to determine the type and extent of control to apply);
- integrity of the system when alterations are planned and implemented;
- the potential misuse of the microorganisms in the mBiobank repository.

The potential misuse risk assessment shall be based, at least, on the following key factors (considering the significance of each factor):

- availability: the number of facilities that stock the biological material and their geographical distribution;
- amplification: the ease with which the biological material can be replicated, for example whether it can be grown in culture and its growth rate;
- skills and knowledge: the ubiquity or rarity of the skills and knowledge necessary to amplify and/or genetically modify the biological material;
- dispersal: the ease and effectiveness with which the biological material can be dispersed, such as by air, water, food or by other means into the environment; this might include (but not be limited to) a biological material's aerosolisation and inhalation characteristics;
- environmental viability: the hardiness of the biological material across a range of temperatures, humidity levels, light exposures;
- countermeasures: the existence of and ease of access to prophylaxis, post-exposure treatments and detection and decontamination measures;
- economic consequence: the extent to which the biological material may be used to bring about harmful economic consequences for humans, crops, livestock or infrastructures the mBiobank shall assess virulence based on the following key factors:
    - Infective dose: the smallest quantity of the biological material necessary to cause infection.
    - Pathogenicity: the disease-causing ability of the biological material.
    - Lethality: the ability of the biological material to cause death to the host.
    - Transmissibility: the base with which the biological material can spread either by vector to host, or host to host.

When doubts exist, the microorganism shall be assigned to the higher of two possible levels.

The risk assessment shall be reviewed at planned intervals, at least once per year. The results shall be retained as documented information.

The mBiobank shall plan:

a) actions to address identified risks, including but not limited to:
   - health protection,
   - biosafety and biosecurity assurance;
   - process variability mitigation;
   - ensure integrity of the key holdings;
   - control of external provided processes;
   - protection of the customer's property.

b) actions to address identified opportunities;

c) how to
   - integrate and implement the actions into its C&EMS processes (see 4.4)
   - evaluate the effectiveness of these actions.

Actions taken to address risks and opportunities shall be commensurate to the risk they represent to the achievement of the mBb's objectives. The results and actions taken from risk determination shall be retain as documented information.

NOTE 1 Options to address risks can include avoiding risk, taking risk in order to pursue an opportunity, eliminating the risk source, changing the likelihood or consequences, sharing the risk, or retaining risk by informed decision.

NOTE 2 Opportunities can lead to the adoption of new practices, launching new services, opening new markets, addressing new customers, building partnerships, using new technology and other desirable and viable possibilities to address the mBiobank's or its customers' needs.

6.2 C&E objectives and planning to achieve them

The organization shall establish the C&E objectives at relevant functions, levels and processes needed for the C&EMS.

The C&EMS objectives shall:

- be consistent with the C&E policy

- be measurable;
- take into account applicable requirements;
- be relevant to conformity of the biological material and preservation performance, to the competence of the Biobank and to the enhancement of customer and relevant interested parties' satisfaction;
- be monitored;
- be communicated;
- be updated as appropriate.

The organization shall maintain documented information on the C&E objectives and its results.

When planning how to achieve its C&E objectives, the mBiobank shall determine:

- what will be done;
- what resources will be required;
- who will be responsible;
- when it will be completed;
- how the results will be evaluated.

6.3 Planning of changes

When the mBiobank determines the need for changes to the C&EMS, the changes shall be carried out in a planned manner (see 4.4).

The mBiobank shall consider:

- the purpose of the changes and their potential consequences (see 6.1);
- the integrity of the Q&CMS management system;
- the availability of resources;
- the allocation or reallocation of responsibilities and authorities.

7 Support

7.1 Resources

7.1.1 General

The mBiobank shall determine and provide the resources needed for the establishment, implementation, maintenance and continual improvement of the C&EMS.

The mBiobank shall consider:

- the capabilities of, and constraints on, existing internal resources;
- what needs to be obtained from external providers.

7.1.2 Personnel

The mBiobank shall determine and provide the personnel necessary for the implementation of its C&EMS and for the operation and control of its processes.

7.1.3 Infrastructure

The mBiobank shall determine, provide and maintain the infrastructure necessary for the operation of its processes and to achieve conformity with biosafety, biosecurity and microorganism's preservation requirements (see NOTE 1).

The mBiobank shall have its infrastructure (including all areas under its responsibility):

- in conformity with the containment level appropriate for the risk group of the preserved microorganisms;
- qualified according to the validation requirements and reflecting any seasonal variation;
- described and documented.

The mBiobank shall determine the appropriate areas to accommodate its activities (with an effective separation between nearby areas where incompatible activities are carried out (see NOTE 2) including, but not limited to:

- receipt and storage of the initial microorganisms;
- preparation, regeneration, handling and processing microorganisms;
- microorganism storage area and back-up or safety duplicate collection (see NOTE 3).
- supply, delivery/sales kept separated from incoming accessions;

- decontamination and cleaning of equipment and processing of wastes.

The mBiobank building and other associated areas shall:

- respect the containment level appropriate for the risk group of the microorganisms worked with;
- be classified and identified according to risk level associated to the nature of the hold biological material (“high”, “restricted” and “general” security areas, as appropriate;
- be structurally sound;
- be unobstructed, clean and free from laboratory materials.

The procedures for the management of the mBiobank’ s equipment shall:

- include the necessary information for use, control of performance and maintenance (see 7.1.5);
- be available to the authorised users;
- be maintained as documented information.

NOTE 1: mBiobank’s infrastructure include:

- building and utilities (such as steam, water, air);
- equipment, including hardware, software, safety and security devices and source of energy (electrical power supply);
- transportation resources;
- information and communication technology.

NOTE 2: There are several ways to achieve the above as an alternative to having separate areas. For example: a) to construct the laboratory 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.

NOTE 3: Duplicate collection should be preferably in a remote building or alternative site.

7.1.4 Environment for the operation of processes

The mBiobank shall determine, provide and maintain the environment necessary for the operation of its processes.

NOTE: A suitable environment can be a combination of human and physical factors, such as:

a) social (e.g. non-discriminatory, calm, non-confrontational);

b) psychological (e.g. stress-reducing, burnout prevention, emotionally protective);

c) physical (e.g. temperature, heat, humidity, light, airflow, hygiene, noise).

7.1.5 Monitoring and measuring resources

7.1.5.1 General

The mBiobank shall determine and provide the resources needed to ensure valid and reliable results when monitoring or measuring is used to process control and microorganism testing.

The mBiobank shall ensure that the provided resources are:

a) suitable for the specific type of monitoring and measurement activities being undertaken;

b) qualified for operation including at least:

- confirmation of the correct installation;
- calibration, if appropriate;
- testes to confirm the upper and lower operating limits and/or worst case conditions;

c) re-qualified at planned intervals, to confirm the state of control;

d) are maintained to ensure their continuing fitness for their purpose.

The mBiobank shall retain appropriate information as evidence of fitness for purpose of the monitoring and measurement resources.

7.1.5.2 Measurement traceability

When measurement traceability is a requirement, or is considered by the mBiobank to be an essential part of providing confidence in the validity of measurement results, measuring equipment shall be:

a) calibrated and/or verified at planned intervals, and prior to use, against measurement standards traceable to international or national measurement standards; when no such standards exist, the basis used for calibration or verification shall be retained as documented information;

b) identified in order to determine their status and, when relevant, its usual location;

c) safeguarded from adjustments, damage or deterioration that would invalidate the calibration status and subsequent measurement results.

The mBiobank shall determine if the validity of previous measurement results has been adversely affected when measuring equipment is found to be unfit for its intended purpose and shall take appropriate action as necessary.

7.1.6 Organizational knowledge

The mBiobank shall determine the knowledge necessary for the operation of its processes and to achieve a consistent effectiveness in processes results. This knowledge shall be maintained and be made available to the extent necessary.

When addressing changing needs, the mBiobank shall consider its current knowledge and determine how to acquire or access any necessary additional knowledge and required updates.

The mBiobank shall continually update knowledge relevant to the taxonomy, handling, processing, storing and transport of microorganisms.

A procedure shall be established and implemented for the:

- identification of key literature;
- its communication inside de mBiobank, as appropriate;
- periodicity for analysis.

NOTE 1 mBiobank knowledge is knowledge specific to the organisation; it is gained by experience and studies. It is information that is used and shared to achieve the mBiobank' s objectives.

NOTE 2 Biobank knowledge can be based on:

a) internal sources (e.g. intellectual property; knowledge gained from experience and performed studies; lessons learned from failures and successful projects; capturing and sharing undocumented knowledge and experience; the results of improvements in processes, products and services; experiments performed at low scale operations).
b) external sources (e.g. standards; academia; conferences; gathering knowledge from customers or external providers).

7.2 Competence

The mBiobank shall

- determine the necessary competence of person(s) doing work under its control that affects the performance and effectiveness of the C&EMS.
- ensure that these persons are competent on the basis of appropriate education, training, or experience;
- where applicable, take actions to acquire the necessary competence, and evaluate the

effectiveness of the actions taken;

- retain appropriate documented information as evidence of competence, including authorisation to use specialist equipment, perform special tasks.

NOTE 1: Applicable actions may include, for example: the provision of training to, the mentoring of, or the reassignment of currently employed persons; or the hiring or contracting of competent persons.

7.3 Awareness

The mBiobank shall ensure that persons doing work under its control are aware of:

- the system policies;
- relevant objectives;
- the importance to comply with the procedures related the appropriate level of containment for the microorganisms being handled to avoid sample contamination, risk of infection and environmental dispersion;
- the importance to comply with biosecurity procedures;
- their contribution to the effectiveness of the C&EMS, including the benefits of improved performance;
- the risks arising from breaches on biosafety and biosecurity procedures;
- the implications of not conforming with the C&EMS requirements.

7.4 Communication

The mBiobank shall determine the internal and external communications relevant to the C&EMS, including:

a) on what it will communicate;
b) when to communicate;
c) with whom to communicate;
d) how to communicate (see NOTE 1);
e) who communicates.

Communication with customers shall include:

- obtaining customer feedback relating to products and services, including customer complaints
- handling or controlling customer property

- make available data describing the biological material (Minimum Data Set (MDS) shall be available – see NOTE 2) and its origin;
- ensure information security, protection of intellectual property rights and client information, while providing data to users;
- comply with the Protection of Privacy and Transborder Flows of Personal Data;
- the requirements for deposit and/or supply.

The organization shall retain documented information on the requirements for the BM supply or deposit, including any amendments to the established requirements.

The Biobank shall establish the criteria to apply on deciding which information related to the microorganisms held will enter the public domain.

NOTE 1: Customers should be provided with electronic catalogues.

NOTE 2: Additional data may be included in the Recommended Data Set (RDS) and Full Data Set (FDS). The MDS comprises essential information to identify a unique item in the mBiobank. The RDS includes useful information for an improved description of the material. The FDS provides all remaining information that is available at the BRC for any given biological materials. The MDS should always be recorded and made available whereas the RDS is recommended, and the FDS is additional optional information. The MDS and RDS information is provided by OECD Best Practice Guidelines (2007).

7.5 Documented information

7.5.1 General

The mBiobank' s C&EMS shall include:

- documented information required by this standard;
- documented information determined by the mBiobank as being necessary for the effectiveness of the C&EMS;
- documented information necessary for legal purposes;
- a description of the mBiobank' s C&EMS, the identification of the biobanking domain and, the processes of the C&EMS and its interactions.

The mBiobank' s documented information shall be communicated to relevant person(s) doing work under its control. The Biobank shall ensure that this information is understood and that is easily available to relevant persons.

The mBiobank shall establish and implement a procedure to ensure the quality and consistency of data sets.

7.5.2 Creating and updating

When creating and updating documented information the mBiobank shall ensure:

- Appropriate format and media (see NOTE 1);
- The availability of media to immediate record of observations, data and calculations (see NOTE 2);
- Review and approval for reliability and accuracy;
- Identification of reference documents against which new data shall be introduced to ensure its correctness;
- Procedures to detect errors in data (see NOTE 3);
- Procedures to ensure the quality and consistency of data sets and each data element.

NOTE 1: Examples of different format are language - English should be the preferred language of data, in addition to local language, if different - software version and graphics; examples of different media are paper, electronic.

NOTE 2: Sometimes referred as "temporary records";

NOTE 3: An example of such procedures is spell checking to ascertain validity and completeness of data.

7.5.3 Control of documented information

Documented information required by the C&EMS and by this standard shall be controlled to ensure:

a) it is available and suitable for use, where and when it is needed;
b) it is adequately protected (e.g. from loss of confidentiality, improper use, or loss of integrity).

For the control of documented information, the organization shall address the following activities, as applicable:

- distribution, access, retrieval and use;
- storage and preservation, including preservation of legibility;
- control of changes;
- retention and disposition.

Documented information of external origin determined by the organization to be necessary for the planning and operation of the C&EMS shall be identified as appropriate and be controlled.

Documented information retained as evidence of conformity shall be protected from unintended alterations.

NOTE: Access to documented information can imply a decision regarding the permission to view the documented information only, or the permission and authority to view and change the documented information.

7.5.4 Information system

The mBiobank shall maintain and continually update:

a) a data base for internal use of the held microorganisms and related information;
b) an electronic catalogue providing information to users about the microorganisms held.

The data base and information system shall:

- enable restricted access and information classified with different access levels;
- protection for confidential data;
- request user authentication and check identifiers and password validity;
- have mechanisms in place to avoid the loss of data and ensure its integrity.

8 Operation

8.1 Operational planning, development and maintenance

The mBiobank shall plan, design, qualify, implement, and control the process(es) (see 4.4) need(ed) to meet the requirements for the microorganisms' preservation (processing and storage) and supply, and to implement the actions determined in clause 6, by:

a) determining the requirements for the microorganism preservation and supply,
b) establishing criteria for:

1) the processes;
2) the acceptance of the microorganism preservation (processing and storage) and supply;

c) determining the resources needed to achieve conformity to the microorganism preservation and supply;
d) implementing control of the processes in accordance with the criteria;
e) determining, maintaining and retaining documented information with the extent necessary:
    1) to have confidence that the processes have been carried out as planned;
    2) to demonstrate the conformity of preservation (processing and storage) and supply to their requirements.

The output of planning shall be suitable for the organization's operations.

The o mBiobank shall control planned changes and review the consequences of unintended changes, taking action to mitigate any adverse effects, as necessary. Changes to the approved procedures including acceptance criteria or operating parameters, shall be documented and scientifically justified.

The mBiobank shall ensure that outsourced processes are controlled (see 8.4).

8.2 Control of externally provided processes, products and services

8.2.1 General

The Biobank shall determine and document the requirements for the externally provided processes, products and services, communicate these requirements to the external provider and ensure that the externally provided processes, products and services conform to requirements.

The Biobank shall determine the controls to be applied to externally provided processes, products and services when:

- products and services from external providers are intended for the microorganism preservation, testing and/or transport;
- services from external providers are intended for validation purposes;
- microorganism is supplied directly to the customer by external providers on behalf of the mBiobank;
- microorganism intended to preserve is received from the customer by an external provider under the responsibility of the mBiobank;
- a process, or part of a process, is provided by an external provider as a result of a decision by the mBiobank.

The mBiobank shall determine and apply criteria for the selection, monitoring, evaluation and re-evaluation of performance of external providers based on their ability to provide processes or products and services in accordance with requirements. The mBiobank shall retain documented information of these activities and any necessary actions arising from the evaluations.

When the Biobank decides to externally provide the preservation (processing and storage) and /or testing activities, or part of these, the Biobank shall ensure that this (these) process(es) are validated according to this standard' s provisions.
The Biobank shall determine which external provided processes, or part of these, shall be communicated to the customers. When storage of the preserved microorganisms is externally provided customers shall be informed.

8.2.2 Type and extent of control

The Biobank shall ensure that externally provided processes, products and services do not adversely affect the mBiobank's ability to consistently preserve and supply authenticated microorganisms. The mBiobank shall determine the risks of externally provided processes, products and services to the effectiveness and consistency of the preservation process and microorganism authentication and, when necessary, take measures to avoid negative effects.
The mBiobank shall:

a) ensure that externally provided processes remain within the control of its C&EMS;
b) define both the controls that it intends to apply to an external provider and those it intends to apply to the resulting output;
c) take into consideration:
    - the potential impact of the externally provided processes, products and services on the mBiobanks' s ability to consistently meet customer and applicable statutory and regulatory requirements;
    - the effectiveness of the controls applied by the external provider;
d) determine the verification, qualification or other activities, necessary to ensure that the externally provided processes, products and services meet the requirements.

When the Biobank decides to externally provide microorganism processing intended for preservation the process shall be validated according to the provisions of this International Standard, and the related

activities, equipment and infrastructure are qualified for performance. Documented information shall be retained for evidence.

When the mBiobank decides to externally provide microorganism processing and storing, first part audits shall be carried out to externally provided processes, at planned intervals commensurate to risk. Documented information shall be retained.

8.2.3 Information for external providers

The mBiobank shall communicate to external providers its requirements for:

a) the processes, products and services to be provided;
b) the approval of:
   - products and services;
   - methods, processes and equipment;
   - the release of products and services;
c) competence, including any required qualification of persons;
d) the external providers' interactions with the organization;
e) control and monitoring of the external providers' performance to be applied by the organization;
f) verification or validation activities that the organization, or its customer, intends to perform at the external providers' premises.

8.3 Biosafety

The Biobank shall ensure that all biological materials are assigned to appropriate risk groups; this includes a positive assignment to risk group 1 unless otherwise considered hazardous.

Risk group information shall be maintained as documented information and made available to recipients of the microorganisms.

The Biobank shall establish and document procedures to ensure safety during operation. Those shall be appropriate to the type of biological materials handled and according to definition as minimum handling procedures for pathogenic microorganisms as established by appropriate authorities at national level.

NOTE: Various microorganism classification systems exist. The key references can be the definitions for classification made by the World Health Organisation (WHO).

8.4 Biosecurity

8.4.1 Internal access to hazardous BM

The Biobank shall ensure that microorganisms assigned to a high biosecurity risk are stored and handled within the high security area, by authorized person(s). A chain custody for the microorganisms that present a moderate or high biosecurity risk movement from outside the high security or restricted area (see 7.3) shall be established, documented and implemented.

The Biobank shall determine the requirements for security screening of person(s) doing work under its control, in line with national privacy law, before granting access to a higher security level.

The Biobank shall control the access of visitors and persons doing work under the Biobank' s control, to the security areas (see 6.1) ensuring that only authorized person(s) have access to microorganisms that are pathogenic or toxic to human, animals and plants; security devices should be used. All persons in the mBiobank shall carry, except in circumstances where doing so would present a health and safety risk, an identification item indicating the maximum level of security access (see NOTE 1).

The Biobank shall capture the identification item upon termination of employment / work / visit under its control and retain the related information.

NOTE 1: Exceptions are situations where the person cannot use the identification such as when wearing a biohazard suit.

8.5 Media and reagent preparation

Accurate preparation, storage and preservation of culture media is one of the fundamental steps in the growth and maintenance of biological materials.

The Biobank shall establish, document, implement and qualify procedures to prepare culture media for the growth and/or maintenance of the living biological materials held. The results from qualification shall be retained. The procedures used for the preparation of culture media shall be maintained as documented information and shall include, at least:

- media formula;
- criteria for reagents acceptance;
- sterilization;
- storage conditions;

- method to estimate the expiry date;
- identification method (e.g by labeling).

8.6 Cleaning / sterilisation

The Biobank shall establish, document and implement cleaning and decontaminating procedures on the material and areas liable to influence biological material quality such as its purity, viability. Cleaning and sterilization procedures shall be qualified for performance.

A contamination monitoring program shall be established and implemented. It shall include but not be limited to:

- equipment;
- benches surfaces;
- material;
- all microorganism containment areas;
- a contamination monitoring program.

8.7 Production and service provision

8.7.1 Inventory

The mBiobank shall maintain documented the identification of all microorganisms preserved.

8.7.2 Control of production and service provision

The mBiobank shall implement microorganism preservation and supply under controlled conditions. Controlled conditions shall include, as applicable:

a) the availability of documented information that defines:
   - the required activities to perform biological material preservation, testing and supply;
   - the results to be achieved;
b) the availability and use of suitable monitoring and measuring resources;
c) the implementation of monitoring and measurement activities at appropriate stages of the processes to confirm that acceptance criteria have been met;
d) the use of suitable infrastructure and environment for the operation of processes considering the

biosecurity and biosafety risk level; suitable infrastructure shall include measures to prevent direct access of persons to areas where its presence can influence the conformity of the biological material.

e) the appointment of competent personnel;
f) the implementation of actions to prevent error and decrease variability in process results;
g) the implementation of release, delivery and post-delivery activities;
h) the conduction of all activities with biological material in areas corresponding to the appropriate biosecurity risk level resulting from the application of the biosecurity risk assessment (see 6.1).
i) the implementation of measures to restrict the access to areas liable of influence the quality of in-process-microorganisms.

8.7.3 Accession to Deposit

The Biobank shall establish, document and maintain procedures for the reception, acceptance or denial of requests for microorganism deposit.

The Biobank shall communicate to the customer the conditions for the microorganism deposit. Transparency regarding intellectual property rights shall be provided (see NOTE).

Before accepting requests for biological material deposit, the Biobank shall:

- ensure the authenticity (legitimacy) of the applicant; all biological material requests, including those refused, shall be documented and retained.
- perform a biosecurity risk assessment as established (see 6.3), unless biological material is being transferred from other mBiobank along with the respective risk assessment methodology and results and there are not new circumstances or information that can affect the results of the original assessment;
- confirm the risk level of the biological material asked for deposit;
- confirm the risk level of the biological material asked for deposit is within safety containment level of the mBiobank (see 6.2);
- ensure the following information about the biological material is provided:
  a) name and other identifier or a culture description;
  b) name and address of the applicant [depositor];
  c) source, substrate or host from which the biological material was isolated or derived from (where identified) and date of isolation;
  d) geographical origin of the biological 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;

g) cell preservation or storage conditions, where known;

h) risk information.

The mBiobank shall require documented evidence to assure the validity of the provided information. This information shall be maintained.

Alternative mBiobanks shall be recommended when request is outside the Biobank's expertise.

NOTE: To protect assigned intellectual property rights deposit conditions can be laid down in a material transfer agreement, for example.

8.7.4 Material reception

The mBiobank shall establish, document and implement procedures for the biological material reception, including but not limited to:

a) identification;

b) quarantine requirements;

c) appropriate contention conditions for opening the package received, in order to assure its safe handling and disposal;

d) the tests to perform in order to confirm:

- purity;
- identity;
- viability;
- stability of key features;
- growth requirements.

The results from the confirmation procedures shall be documented and maintained; they shall be used as base line when in-storage maintenance checks are performed and for authentication after preservation (see 8.2).

NOTE: Recommended quality control procedures during reception can be found in several documents such as the OECD BPG.

8.7.5 Material preservation

In order to ensure a minimum number of transfers of generations from the original biological material, for each biological material, the Biobank shall maintain a master cell bank and a stock for distribution for each type of biological material preserved. Master stock shall be produced from the original biological material and shall be used to generate the distribution stock. The distribution stock shall be used to supply purposes.

The mBiobank shall give a unique identifier to the biological material preserved which shall never be re-used, even when the biological material is eliminated from the mBiobank.

The mBiobank shall establish, document and maintain procedures for the biological material preservation including, but not limited to:

- the type of container for the microorganism (tubes, vials, ampoules);
- storage conditions;
- method for the assignment of a unique identifier;
- method for the assignment of the expiry date;
- labelling requirements which shall include, at least, the unique identifier, preparation date and expire date;
- the storage site of each item;
- the method to identify master cell banks and stock for distribution;
- the established re-stocking practices;
- the method for the preserved microorganism control (quality-checks);
- levels of access;
- the records to maintain.

The biological material shall be preserved by at least two methods, under environmental parameters that ensure the stability of its properties. The methods for preservation shall be selected according to recommendations from the depositor (if appropriate) and previous experience of the mBiobank. These shall ensure:

- high viability/recovery of the preserved culture;
- absence of contaminant in the preserved culture (this does not include any recognised co-culture e.g. symbiotic micro-organisms, which are not regarded as contaminants if the constituents are correctly specified and checked by microbiological and molecular analysis, as applicable).
- authenticity of the preserved culture and genome integrity (molecular, phenotypic analysis), where applicable.

Where two distinct methods are not applicable, cryopreserved stocks shall be maintained in separate locations. A duplicate collection of relevant biological material shall be maintained, preferably on another site as a 'disaster' protection measure and to avoid accidental loss.
The size of the masters and distribution stocks shall be established according to the anticipated distribution rate.
Key parameters of the preservation procedure shall be monitored and retained.
The mBiobank shall maintained data relating to lost microorganisms; these shall be identified as no longer available as living material.

NOTE 1: The commonly used approach for sustainable preservation of microbial cultures is long-term preservation employing liquid nitrogen, deep freezing, freeze-drying or L-drying methods. These methods allow high quality long-term storage, recovery and use of the micro-organism.

NOTE 2: Recommended methods for storage and preservation of microorganisms can be found in several documents such as the OECD BPG (2007).

8.7.6 Microorganism supply

The mBiobank shall identify, establish and document the requirements for the biological material supply, including, but not be limited to:

- approval of customers (e.g. confirm requester's identity, confirm whether it is an authorised requester, confirm that possesses the required skills and infrastructure);
- approval of requests, including requests of hazardous microorganisms;
- the information to be provided along with the material;
- transport requirements (see NOTE 1, 2, 3) including measures to ensure the safe and secure packaging and transportation;
- legal requirements;
- the documented information to be retain.

All the requests for biological materials shall be documented. The information retained from the supplies shall include:

- the biological material identification;
- method and date of shipment;
- name and address of the person to whom sent.

The mBiobank shall retain at least the following information related to the supplies:

- the supplied microorganism identification;
- method and date of shipment;
- name and address of the person to whom sent.

The mBiobank shall implement control activities to ensure that the microorganisms to supply comply with the requirements. The information resulting from the control activities shall be retained. It shall include, but not be limited, to:

a) evidence of conformity with the acceptance criteria;
b) traceability to the person(s) authorising the release

The mBiobank shall provide the following information to the customer:

- the unique identifier of the supplied microorganism and batch number;
- an estimate of shelf-life;
- storage conditions;
- storage instructions and (if appropriate), conditions of growth;
- the risk group of the microorganism;
- the containment level required for handling the microorganism;
- the results of the risk assessment;
- requirements for the safe handling and disposal of the microorganism;
- disposal measures;
- measures to take in case of spillage;
- instructions for opening culture container;
- transportation conditions of the microorganism.

The mBiobank shall provide the user with a Material Transfer Agreement, or an equivalent document, requesting acknowledge receipt of the received materials and documents.

The Biobank shall only supply microorganisms pathogenic or toxic to humans, animals and plants to authorised institutions and/or person(s). The information provided by the potential user shall be confirmed and maintained as documented information. The method used for confirmation and its results shall be retained as documented information.

- Documented information proving that the potential user has the appropriate containment means and the authorisation to import and handle such biological material shall be obtained and retained.

NOTE 1: Transport requirements include packaging and delivery conditions of microorganism according to current postal, IATA, ADR or other applicable regulations.

NOTE 2: Biobank should follow the WHO Guidelines on International Regulations for the Packaging and Transport of Infectious Substances.

NOTE 3: The International Air Transport Association and Dangerous Goods Regulations are legally binding for shippers and carriers of dangerous goods (including infectious substances) to be transported by air. For transportation via road, rail and waterways, regional and/or national regulations exist. mBiobanks should follow the IATA, DGR and other respective regulations, to ensure that all applicable requirements for packaging and shipping dangerous goods on ground and air are met.

NOTE 4: Customers who wish to obtain cultures of plant pathogens underlying quarantine regulations shall first obtain a permit to import, handle and store from the appropriate authority. Under the terms of such a license the mBiobank is required to see and record a copy of a permit before such strains can be supplied.

8.7.7 Maintenance checks (viability tests)

The mBiobank shall determine the viability testes to perform for each item preserved. The testes shall be performed at planned intervals and shall include, at least:

- viability (counting the number of cells or equivalent method);
- check growth on appropriate medium;
- check contamination from mycoplasma, bacteria, fungi and virus;
- authentication of the cell line by appropriate tests (PCR, immuno-phenotypic tests, microsatelite tests).

NOTE: The frequency needed for the maintenance checks depends on several aspects such as the type of biological material, the preservation method, the turnover of the material.

8.7.8 Microorganism testing

The mBiobank shall establish and document the methods used for the microorganism testing, including but not limited to viability, identity, purity.

Testing methods shall be qualified for performance and the qualification results shall be retained.

NOTE: As applicable the following parameters can be used for the microorganism characterization in view of its identification:

- history of the strain or cellular line, such as origin, source, when and where it was first characterised, taxonomic description;
- physical description, such as microscopic and colony morphology, Gram reaction, mobility, spore formation (weather present or not);
- physiologic parameters such as optimal temperature, optimal pH, aerobic, anaerobic, and other requirements related to gas atmosphere;
- biochemical and molecular markers and / or other properties determined by relevant essays;
- nutritive necessities: nitrogen, carbon and other sources of energy, growth factors, vitamins, minerals;
- absence of undesirable agents: cell lines shall not contain undesirable virus or mycoplasma; bacteria shall not contain undesirable phages.

8.7.9 Identification and traceability

The mBiobank shall use suitable means to obtain, identify and retain outputs when it is necessary to ensure the conformity.

The mBiobank shall identify the status of outputs with respect to monitoring and measurement requirements throughout the microorganism preservation lifecycle.

The mBiobank shall ensure and control the unique identification of the outputs when traceability is a requirement and shall retain the documented information necessary to enable traceability.

The mBiobank control microorganisms belonging to the customer while it is under the mBiobank' s control. The mBiobank shall identify, verify, protect and safeguard the customer's microorganism.

When microorganism belonging to the customer is lost or otherwise found to be unsuitable for use, the mBiobank shall report this to the customer.

8.7.9.1 Post-delivery activities

The mBiobank shall meet requirements for post-delivery activities associated with the supplied microorganism. In determining the extent of post-delivery activities that are required, the mBiobank shall consider:

a) statutory and regulatory requirements;
b) the potential undesired consequences associated with the microorganism handling;
c) the nature of the biological material;
d) customer feedback.

NOTE: Post-delivery activities can include actions under warranty provisions or contractual obligations.

8.8 Process validation

Before performing routine preservation, the mBiobank shall establish, document, and implement a procedure for the validation of the processes included in the microorganism preservation lifecycle, in order to ensure effectiveness and consistency in preservation and supply. It shall include, but not be limited to:

- the scope of validation and extent of performance qualification (see NOTE 1) and its rational;
- the use of scientific approaches to achieve enhanced knowledge about process factors and its influence on microorganism quality attributes (see NOTE 2);
- the sampling plan for process development and design and the rationale behind it;
- statistical methods for data analysis;
- the approach for qualification procedures;
- the rational for the comprehensiveness of the qualification procedures (see NOTE 3);
- strategy to maintain the process in a state of control providing assurance of continued suitability and capability;
- strategy to continually improve process knowledge and understanding;
- the methods for recording and evaluating results, including, where appropriate, statistical tools to support any conclusions with regard to the variability and capability of processes.

The validation activities shall be planed (see NOTE 4).

Evidence of preservation process effectiveness and consistency shall be retained.

NOTE 1: The scope of validation and qualification should be based on the results of a risk assessment.

NOTE 2: Scientific approaches can include, among others: knowledge management, risk assessment tools, quality by design, design of experiments.

NOTE 3: E.g., equipment, infrastructure, bio-analytical methods and other processes

NOTE 4: Validation plan should refer, but not be limited, to the chosen validation approach, the scope of validation including qualification, the documented procedures, schedule and responsibilities.

8.9 Control of changes

The mBiobank shall review and control changes to implement throughout the microorganism preservation lifecycle to the extent necessary to ensure continuing conformity with requirements. The mBiobank shall retain documented information describing the results of the review of changes, the person (s) authorising the change and any necessary actions from the review.

8.10 Control of nonconforming process outputs, products and services

The mBiobank shall ensure that outputs that do not conform to their requirements are identified and controlled to prevent their unintended use or delivery.

The mBiobank shall take appropriate action based on the nature of the nonconformity and its effect on the conformity of the held microorganisms. This shall also apply to nonconforming microorganism detected after supply.

The organization shall deal with nonconforming outputs in one or more of the following ways:

a) correction;
b) segregation, containment, return or suspension of provision of microorganisms;
c) informing the customer.

Conformity to the requirements shall be verified when nonconforming outputs are corrected.

The organization shall retain documented information that:

a) describes the nonconformity;
b) describes the actions taken;
c) describes any concessions obtained;

d) identifies the authority deciding the action in respect of the nonconformity.

9 Performance Evaluation

9.1 Monitoring, measurement, analysis and evaluation

9.1.1 General

The mBiobank shall determine:

a) what needs to be monitored and measured;
b) the methods for monitoring, measurement, analysis and evaluation needed to ensure valid results;
c) when the monitoring and measuring shall be performed;
d) when the results from monitoring and measurement shall be analysed and evaluated.

The mBiobank shall evaluate the performance of the C&EMS and retain appropriate documented information as evidence of the results.

9.1.2 Customer satisfaction

The mBiobank shall monitor customers' perceptions of the degree to which their needs and expectations related to the microorganism received or under preservation have been fulfilled. The mBiobank shall determine the methods for obtaining, monitoring, analysing and take actions upon this information.

NOTE: Examples of monitoring customer perceptions can include customer surveys, customer feedback on delivered products and services, meetings with customers, market-share analysis, compliments, warranty claims and dealer reports.

9.1.3 Analysis and evaluation

The mBiobank shall analyse and evaluate data and information arising from monitoring and measurement.

The results of analysis shall be used to evaluate:

a) conformity of the biological material supplied;
b) consistency of the preservation methods;

c) the degree of customer satisfaction with the preservation service and the microorganism supply;
d) the performance and effectiveness of the C&EMS;
e) if planning has been implemented effectively;
f) the effectiveness of actions taken to address risks and opportunities;
g) the performance of external providers;
h) the need for improvements to the quality management system.

9.2 Internal Audit

The mBiobank shall conduct internal audits at planned intervals, at least one per year, to provide information on whether the C&EMS:

a) conforms to:
   - the mBiobank' s own requirements for its C&EMS;
   - the requirements of this Standard;
b) is effectively implemented and maintained.

The mBiobank shall:

a) plan, establish, implement and maintain an audit programme(s) including the frequency, methods, responsibilities, planning requirements and reporting, which shall take into consideration the importance of the processes concerned, changes affecting the organization, and the results of previous audits. It shall include a microorganism deposit trail through to storage and supply trail from receipt of order to supply. These should be chosen at random.
b) define the audit criteria and scope for each audit;
c) select auditors and conduct audits to ensure objectivity and the impartiality of the audit process;
d) ensure that the results of the audits are reported to relevant management;
e) take appropriate correction and corrective actions without undue delay;
f) retain documented information as evidence of the implementation of the audit programme and the audit results.

NOTE: See ISO 19011 for guidance.

9.3 Management Review

9.3.1 General

Top management shall review the organization's C&EMS at planned intervals, to ensure its continuing suitability, adequacy, effectiveness and alignment with the strategic direction of the organization.

9.3.2 Management review inputs

The management review shall be planned and carried out taking into consideration:

a) the status of actions from previous management reviews;

b) changes in external and internal issues that are relevant to the quality management system;

c) information on the performance of the C&EMS, including trends in:

- customer satisfaction and feedback from relevant interested parties;
- the extent to which quality objectives have been met;
- preservation effectiveness and consistency;
- nonconformities and corrective actions;
- monitoring and measurement results;
- audit results;
- the performance of external providers;

d) the adequacy of resources;

e) the effectiveness of actions taken to address risks and opportunities (see 6.1);

f) opportunities for improvement.

9.3.3 Management review outputs

The outputs of the management review shall include decisions and actions related to:

- opportunities for improvement;
- any need for changes to the C&EMS;
- resource needs.

The mBiobank shall retain documented information as evidence of the results of management reviews.

10 Improvement

10.1 General

The mBiobank shall determine and select opportunities for improvement and implement any necessary actions to:

- improve effectiveness and consistency of the preservation process,
- microorganism authentication,
- effectiveness of biosafety and biosecurity measures.

10.2 Nonconformity and corrective action

When a nonconformity occurs, including any arising from complaints or security breaches, the mBiobank shall:

a) react to the nonconformity and, as applicable:
   - take action to control and correct it;
   - deal with the consequences;

b) evaluate the need for action to eliminate the cause(s) of the nonconformity, in order that it does not recur or occur elsewhere, by:
   - reviewing and analysing the nonconformity;
   - determining the causes of the nonconformity;
   - determining if similar nonconformities exist, or could potentially occur;

c) implement any action needed;

d) review the effectiveness of any corrective action taken;

e) update risks and opportunities determined during planning, if necessary;

f) make changes to the C&EMS, if necessary.

Corrective actions shall be appropriate to the effects of the nonconformities encountered.

The organization shall retain documented information as evidence of:

a) the nature of the nonconformities and any subsequent actions taken;

b) the results of any corrective action.

NOTE 1: The Biobank can establish an incident response plan to be followed by the mBiobank staff for documenting, reporting and investigating security breaches.

10.3 Continual improvement

The mBiobank shall continually improve the suitability, adequacy and effectiveness of the C&EMS.

CHAPTER 4. THE STANDARD DEVELOPMENT

4.1 GENERAL

In most of the standard-setting organisations[21], when there is a proposal for a new standard in a specific technical field, a team of experts is nominated to accomplish the project. The standard development is executed by following the standard-setting-strategy adopted by the organisation. That strategy must be in line with the adopted principles for standard setting. When the standard is completed it is then published. This procedure is represented in Fig.9.

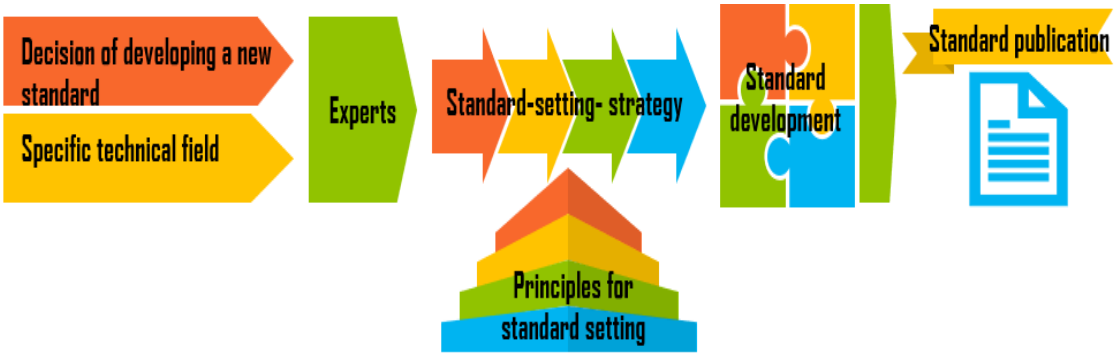


Figure 9. Diagram representing the activities for standard development.

4.2 PRINCIPLES FOR THE STANDARD SETTING

We believe that the establishment of principles for the standard development, will reinforce the authority of the standard and will help to ensure that it will be accepted by a wide range of microbial Biobanks.

4.2.1 HOW WERE THE PRINCIPLES DEFINED?

Our principles for the standard-setting development were defined based on the ISO and ISEAL principles. The procedure we followed is presented in Fig. 10.

[21] Standard-setting organisations are the organisations that are responsible for managing the development or revision of standards (ISEAL, 2014).

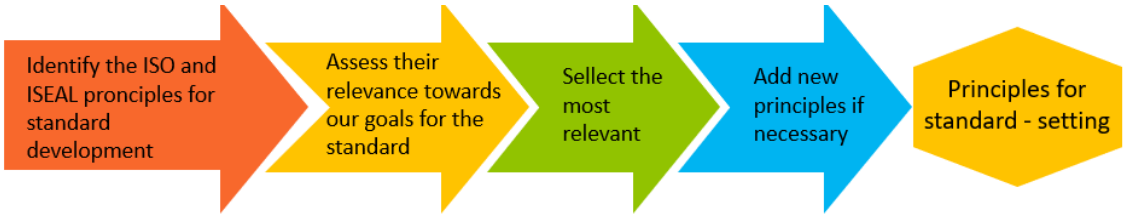


Figure 10. Procedure to establish the principles supporting the standard-setting.

4.2.2 THE ISO AND ISEAL PRINCIPLES

The principles adopted by ISO reflect its adherence to the World Trade Organisation Technical Barriers to Trade (WTO TBT) Agreement. According to WTO (2012), these principles clarify and strengthen the concept of "international standard" and ensure the effective application of the Code of Good Practice for the preparation, adoption and application of standards[22]. The TBT Agreement aims to ensure that technical regulations, standards, and conformity assessment procedures are non-discriminatory and do not create unnecessary obstacles to trade.

The principles adopted by ISEAL – the Credibility Principles - were defined based on a year-long global consultation including contributions from more than 400 stakeholders on five continents (ISEAL, 2014). The ISO and ISEAL principles are presented in Table 1.

Table 1. Principles for standard-setting form ISO (WTO TBT) and ISEAL.

ISO	Transparency, Relevance and effectiveness, Impartiality and consensus, Coherence, Development dimension, Openness
ISEAL	Transparency, Relevance, Impartiality, Engagement, Improvement, Accessibility, Truthfulness, Efficiency, Sustainability, Rigour

4.2.3 RELEVANCE ASSESSMENT, SELECTION AND NEW PRINCIPLES

The relevance of the principles adopted by ISO and ISEAL towards our objectives (presented in the sub-chapter 4.3 and summarised in three goals) was assessed. The results are presented in Table 2.

[22] The Code of Good Practice for the Preparation, Adoption and Application of Standards (also known as the WTO TBT Code of Good Practice) is the Annex 3 of the TBT Agreement (available at https://www.wto.org/english/tratop_e/tbt_e/tbt_e.htm, accessed 22.02.2021).

Table 2. ISO and ISEAL principles' relevance towards our goals for the standard; New principles are included.

		GOALS		
		Accurate, relevant and easily understandable provisions (1, 2, 6, 7, 9)	Can be easily integrated with other ISO standards of the same type (4)	Is capable of conquer the interested parties' interest and confidence (3, 5, 8)
ISO and ISEAL principles	Transparency			+++
	Openness			++
	Impartiality and consensus			++
	Relevance and effectiveness	++		++
	Coherence			++
	Development dimension			
	Sustainability			
	Improvement	+		++
	Relevance	++		++
	Rigour	++		
	Engagement	++		
	Impartiality			++
	Accessibility		+	+++
	Truthfulness	+		++
	Efficiency	++	++	++
New	Credibility			+++
	Consistency	+++		+
	Alignment		+++	+

4.2.4 OUR PRINCIPLES FOR THE STANDARD-SETTING

The principles we adopted for the standard development (that underpin the standard-setting-strategy and though the standard development) were based on the principles adopted by ISO and WTO (2012, 2000) and ISEAL (2014) and are presented in Fig. 11.

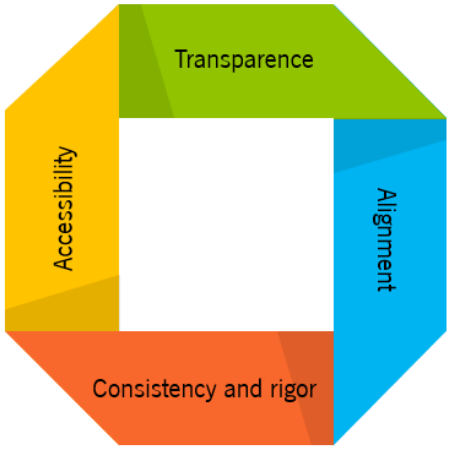


Figure 11. Principles adopted for the standard development.

The rational for each principle and the way they were implemented is presented in Table 3.

Table 3. Principles supporting the standard-setting-strategy, its rational and how they are implemented during the standard development.

PRINCIPLE	RATIONAL	OPERATIONALISATION (How it was achieved during the development)
Transparency and Credibility (WTO, ISEAL)	Transparency builds confidence and credibility, as the public is more trusting of institutions that are open. In order to prevent unnecessary trade barriers, international standards need to be relevant and to effectively respond to market needs, as well as scientific and technological developments. They should not have adverse effects on fair competition and should not block innovation and technological development. Whenever possible, the strategy should ensure that the standard is performance-based rather than based on design or descriptive characteristics. Relevant information about the development of the standard should be freely available, as well as information about how the development system is governed, how the interested parties can engage and the results from the evaluation of the comments received. All essential information regarding the work programmes should be effectively disseminated to at least the interested parties. It should be ensured adequate time and opportunities for written comments. Transparency is a way of demonstrating impartiality. It ensures that the standard users are treated fairly and objectively. Can be ensured through interested parties' engagement; the risk of conflict of interest is much lower by being under the scrutiny of stakeholders.	Ensuring the participation of all relevant interested parties in order to ensure that the development process will not give privilege to, or favour the interests of, a particular supplier/s or country/ies; consensus procedures should be established that seek to take into account the views of all parties concerned and to reconcile any conflicting arguments. Ensuring traceability during drafting to guarantee capability of a transparent and consistent dialog with the interested parties during public consultation. Following reference documents, at international level, providing credible practices. Ensuring the relevance of the standard. Making the standard setting procedures available to the interested parties. Ensuring that the standard is fit for purpose: a) it addresses the most significant microbial-biobanking issues, b) it includes only requirements that contribute to the achievement of its objectives, c) it reflects relevant international standards (ISEAL).
Alignment	If the standard is aligned with the ISO standards of the same type, it will be easily integrated, resulting in diminishing the period of time needed for implementation and decrease the need for consultation. This will motivate CC for the standard's uptake.	Adopting a structure that enables the integration with other international standards; adopting as much as possible ISO terms and definitions.
Consistency and rigour (ISEAL)	The standard must provide replicable results across different organizations - it is capable of achieving the same results when applied in different contexts. The strategy should be defined at the performance level so that the results are measurable.	Consistency within the standard and with other international (ISO) standards is achieved by being in accordance with ISO Directives for standard development.

PRINCIPLE	RATIONAL	OPERATIONALISATION (How it was achieved during the development)
		Consistency within the entire body of the standard may be assured by clearly identifying the link between each requirement on the standard, the relevant objective and the relevant principle for the microorganism biobanking.
Accessibility (WTO)	The strategy should include ways for reduce barriers to the standard implementation, by minimizing costs and avoid burdensome requirements. The strategy should be such that the standard is likely to be implemented by a wide range of CC regardless its dimension and objectives.	Establishing different levels of assessment.

4.3 THE STANDARD-SETTING-STRATEGY

4.3.1 PROCEDURE

We decided to develop our own strategy for the standard development based on existing strategies. To do so, we first defined the characteristics the standard should have (the goals for the standard) and then we defined the standard-setting strategy (SSS) needed to achieve those goals, in other words, the stages we should follow to develop a standard complying with the pre-established goals. The procedure undertaken to establish the SSS is presented in Fig. 12.

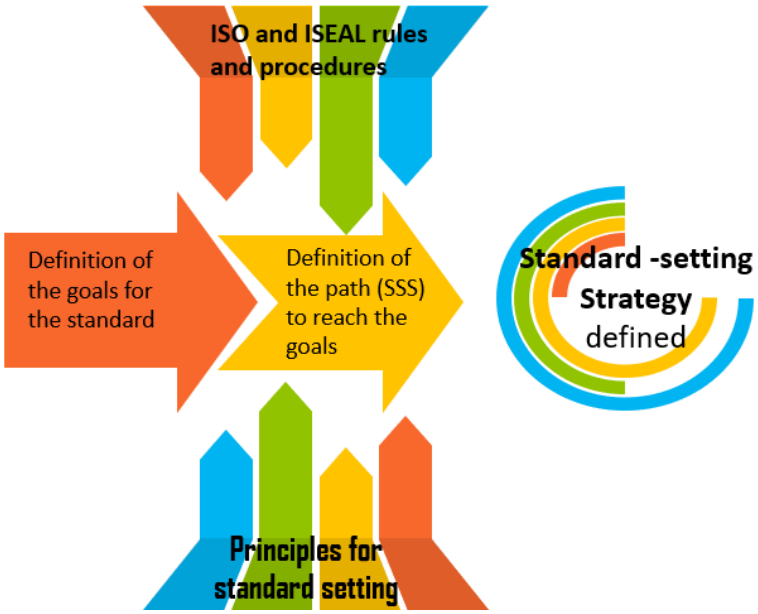


Figure 12. Procedure undertaken to establish the standard-setting strategy (SSS).

4.3.2 THE GOALS FOR THE STANDARD

To be valuable, the standard would need to accomplish the goals presented in Fig. 13.

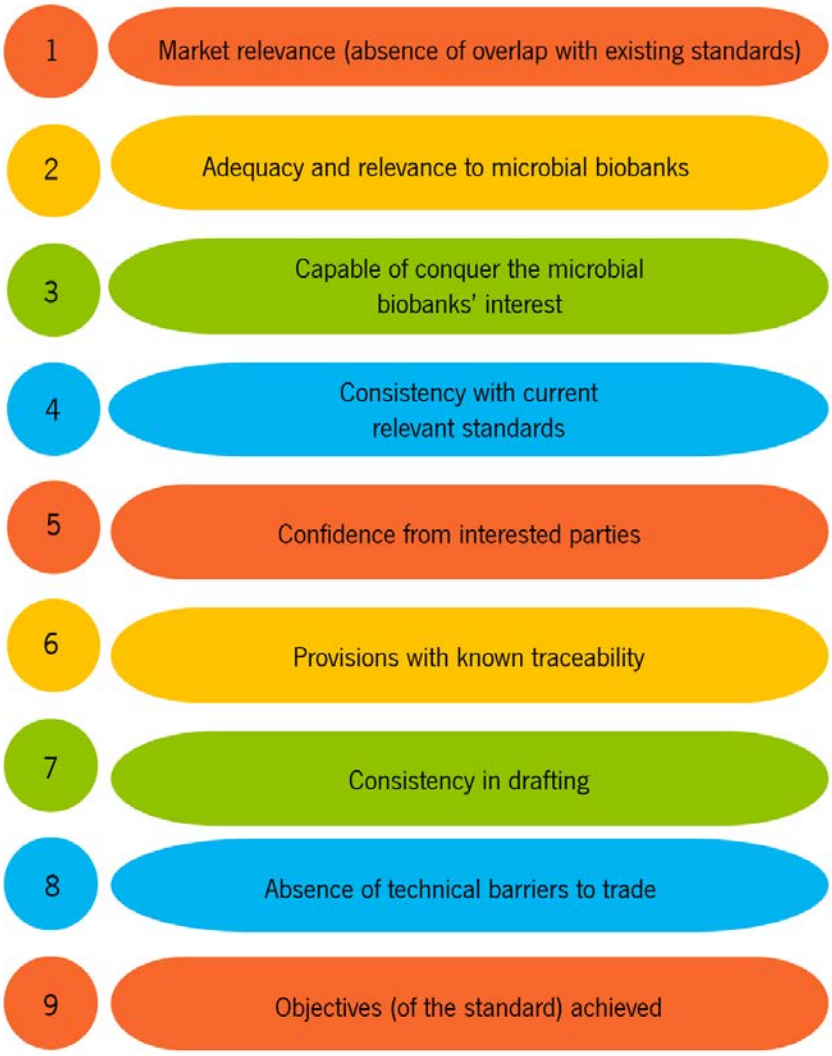


Figure 13. Goals for the standard.

4.3.3 THE STANDARD-SETTING STRATEGY

The SSS was developed based on the ISO[23] and ISEAL[24] rules and procedures and having in mind the principles for standard setting (presented in the sub-chapter 4.2) and the goals for the standard.

The ISO rules for standard development are gathered in two main documents:

- ISO/IEC Directives Part 1 and Consolidated ISO Supplement, which conveys the official procedures to be followed when developing and maintaining an International Standard and procedures specific to ISO (ISO/IEC 2020c).
- ISO/IEC Directives Part 2, which conveys the principles to structure and draft documents

[23] More information available at https://www.iso.org/home.html, accessed 22.02.2021.
[24] More information available at https://www.standardsimpacts.org, accessed at 22.02.2021.

intended to become International Standards, Technical Specifications or Publicly Available Specifications (ISO/IEC 2021).

The ISEAL procedures and rules are mainly presented in the ISEAL Code of Good Practice "Setting Social and Environmental Standards (ISEAL, 2014).

Both ISO and ISEAL strategies were merged and new steps were added. The standard-setting strategy is presented in Fig. 14.

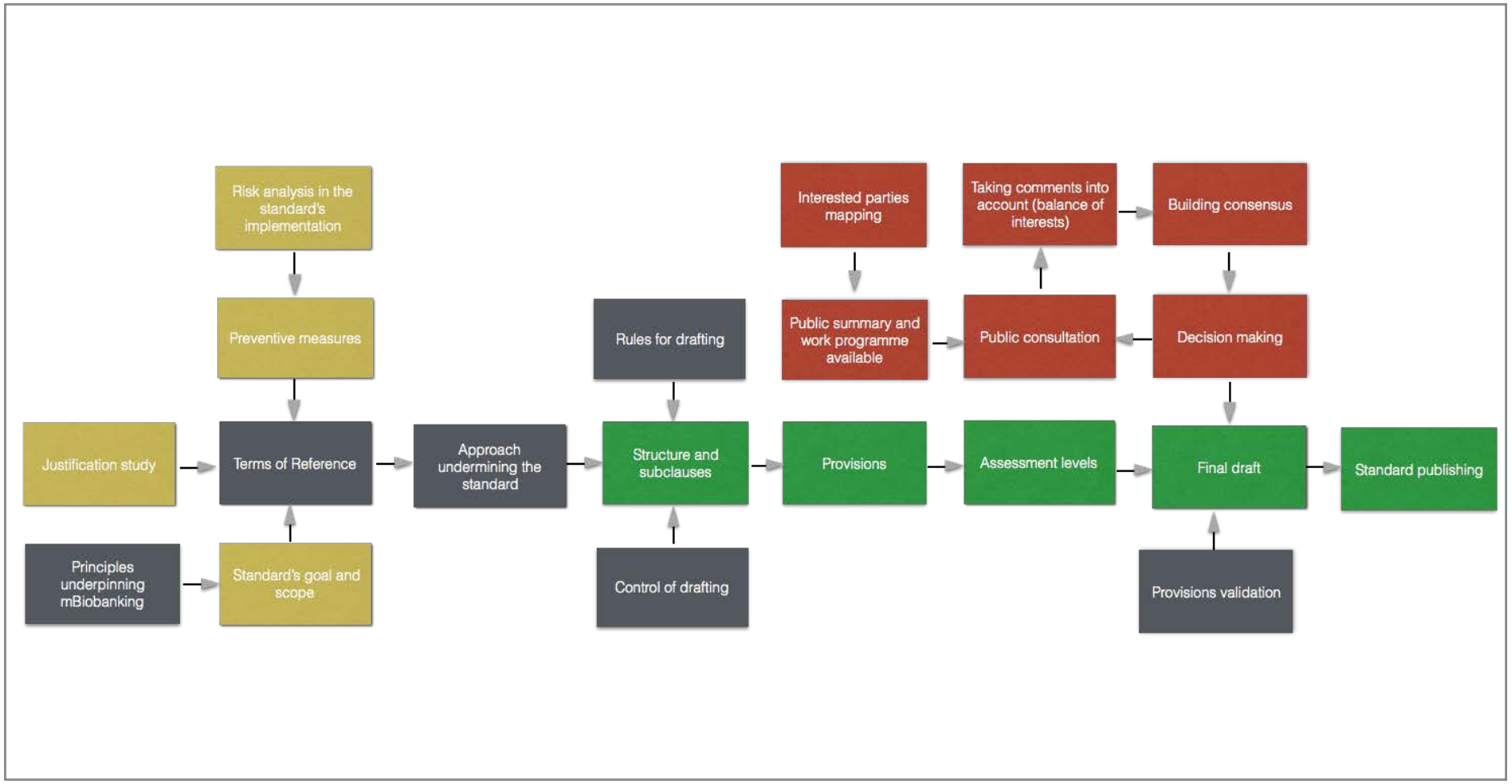


Figure 14. Standard-setting strategy used for the development of the standard.

ISEAL rules for defining the terms of reference and the validation of the standard's content are key to ensure that the provisions in the standard are linked to the user needs and that there is consistency between the "*standard's objectives"* and the "*standard's content"*. The steps replicated from ISEAL were:

(1) the risk analysis in implementation and definition of mitigation measures;

(2) considering the biobanking principles/values as pillars for the standard development;

(3) verifying/validating the provisions against the standard's objectives and the biobanking principles.

The steps replicated from ISO were:

(1) the definition of the structure according to the annex SL;

(2) the definition of the rules for drafting.

The first one is key to improve compatibility, alignment and integration between management system standards. The second is significant to achieve consistency within the standard and with other ISO standards and to enhance reproducibility of conformity assessment activities.

Both ISO and ISEAL use a similar strategy for public consultation. ISEAL emphasises the interested parties' mapping as a way if receiving input from a wide range of interests.

Table 4 presents the origin of each stage on the standard-setting-strategy.

ISO and ISEAL procedures are similar, compatible, and complement each other. Most part of the standard-setting stages are shared by both. Both strategies were combined an adapted to achieve a concise procedure for developing standards.

The strategy focused strictly the development activities. Activities needed to manage people involved are not included as well as those related to the definition of the conformity assessment.

Table 4. Standard-setting strategy stages and its origin.

Stage	How it was done	ISO procedure	ISEAL procedure
Justification study	By assessing market relevance. By comparing existing standards for absence of duplication and significant overlap. Procedure in Fig. 15.	Very detailed for the justification study and criteria; source ISO Directive part 1 (ISO/IEC, 2014)	Short procedure including: communication of the main issues to the interested parties, the way the expressed need will be met and, information of other applicable standards; source ISEAL (2014), clause 5.1.
Scope	According to ISO provisions	ISO/IEC (2018b) clause 14 and Annex A.	ISEAL (2014), clause 1 and clause 5.2.
Biobanking principles	Based on the main issues raised for microbial biobanking	Not included	ISEAL credibility principles (ISEAL, 2014), pp.8-9.
Risk analysis in implementation	Inspired in FMEA method	Not included	Risk assessment advised, but no procedure is given (ISEAL, 2014), clause 5.1.
QM approach underpinning the standard	Our own design. Analysis of the mBb's goals; based in the pharmaceutical quality system.	Not included	Not included
Rules for drafting	According to the rules from ISO Directive part 2; Foreword and introduction not included.	ISO/IEC (2018b)	Rules for a consistent interpretation (ISEAL, 2014), clause 1 and clause 6.1.
Structure and sub-clauses	HLS	Source ISO/IEC (2020), Annex SL	Not provided
Control of drafting	Our own design. Procedure in Fig. 32.	Not provided	Not provided
Public consultation	Assembled form ISO and ISEAL.		Procedure is given (ISEAL, 2014), clauses 5.3, 5.4, 5.6
Provisions' validation	Inspired in an ISEAL's procedure.	Not provided	ISEAL, Assuring Compliance with Social and Environment Standards Code of Good Practice (ISEAL, date unknown)

4.4 TERMS OF REFERENCE

The first stage in the project-standard development was the definition of the terms of reference (ToR), which include:

(1) the justification study;

(2) the definition of the standards' objectives and scope;

(3) the foreseeable risks in the standard's implementation;

(4) the mitigation measures to include in the standard and in the SSS.

The principles for microbial biobanking were also defined and served as input for the ToR.

4.4.1 THE JUSTIFICATION STUDY

4.4.1.1 Objective and procedure

The purpose of the justification study was to assess the market relevance for the standard we intended to develop, avoiding standard duplication or overlap.

To do so, we were required to confirm that there is a need for a new specific standard for the mBb certification.

The general procedure for the justification study is presented in Fig. 15.

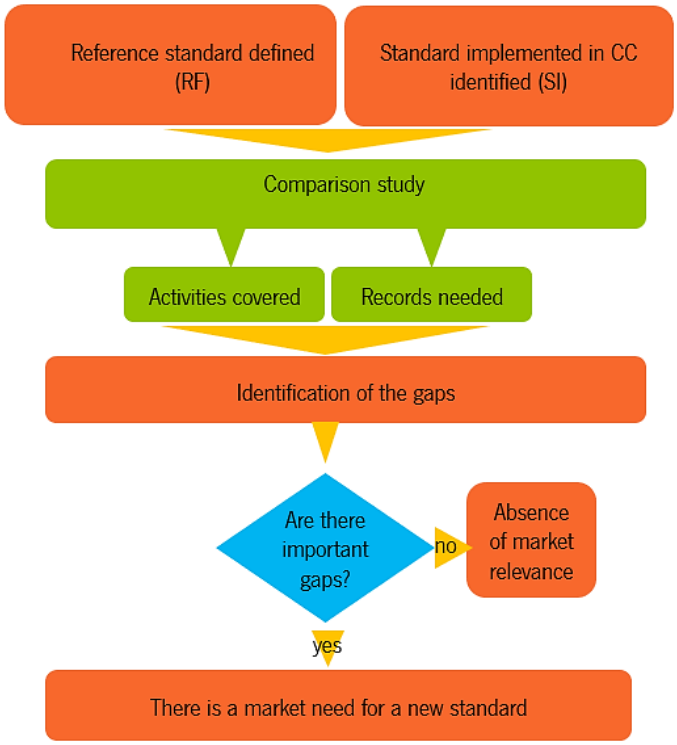


Figure 15. Procedure for the justification study.

4.4.1.2 Which reference to use?

4.4.1.2.1 Results

There was no doubt about the greatest coverage provided by the OECD BPG. Even so, the most implemented standards for microbial biobanks (OECD BPG, WFCC guidelines, NF S 96-900 and ISO9001 standards), were compared to collect objective evidence of the subjects/issues covered.

The results are summarised in Table 5.

The issues/subjects in the OECD BPG were categorised and are presented in the first column (each subject in one different line) of the table. The second column presents the subjects found in the WFCC BPG that match those from OECD BPG (in the same row). Similarly, the third and fourth columns present respectively the subjects found in the NF S 96-900 and ISO9001 that match those found in the OECD BPG.

The biobanking-specific categories of provisions are highlighted in dark blue.

The provisions of general character are highlighted in light blue.

Table 5. Issues covered by each document and its importance for the microbial biobanks (dark blue: specific provisions; light blue: general provisions).

	OECD BPG	WFCC BPG	NF S 96-900	ISO9001
Issues covered	Long-term sustainability	Organisation, Funding		
	Management responsibilities		Management responsibility	Leadership and commitment
	Staff qualification and training (specific provisions)	Staff, Training	Responsibility and authority, staff competence and training	Roles, responsibilities and authorities, competence, awareness
	Premises (specific provisions)		Facilities, spaces and workflow management (specific provisions)	Infrastructure
	Equipment (maintenance and control)			Measuring and monitoring resources
	Control of documents	Documentation	Documentation requirements	Documented information
	Informatics (data processing, management and access)	Catalogues	IT system, data management	
	Preparation of media and reagents			
	Access to deposits (handling BM, quality checks)		Procurement (acquisition), Traceability, reception biological material, preparation biological material	
	Preservation (control of stock, storage, user validation, validation of methods and procedures)	Preservation	Conservation, validation of methods	
	Supply (information provided, package, traceability, complaints, confidentially)	Culture supply	Transport, provision BM, confidentiality	
	Audits (risk management, 1st, 2nd, 3rd part audits)		Internal audits	Internal audit
	Quality checks	Culture authentication	Quality control	
	Biosecurity requirements	Security		
	Biosafety	Safety		

	OECD BPG	WFCC BPG	NF S 96-900	ISO9001
		Holdings		
		Other services		
		Research		
		National and international collaboration		
		Compliance with legislation		
			General requirements for the management system	
			Stakeholders needs and expectations	Understanding the needs and expectations of interested parties
			Quality policy	Quality policy
			Planning the quality management system	
			Communication	Communication
			Management review	Management review
			Measuring and monitoring (stakeholder satisfaction, process, biological material)	Performance evaluation
			Control of non-conforming biological material	
			Data analysis	
			Corrective and preventive actions	Actions to address risks and opportunities, control of non-confirming outputs, improvement
			Laboratory equipment and consumables	

	OECD BPG	WFCC BPG	NF S 96-900	ISO9001
				Context
				Customer focus
				Planning of changes
				Organisational knowledge
				Operation
No. of specific issues (categories)	15	14	8	0
No. of general issues (categories)	0	0	13	All
No. of words on the provisions of the document (approximate)	12885	2954	8057	8021

4.4.1.2.2 Discussion

All the provisions on OECD BPG are biobanking-specific, and it includes a greater amount of information than any other: *12885* words against *8057* from the NF S 96-900 and *2954* from the WFCC BPG (Fig.16).

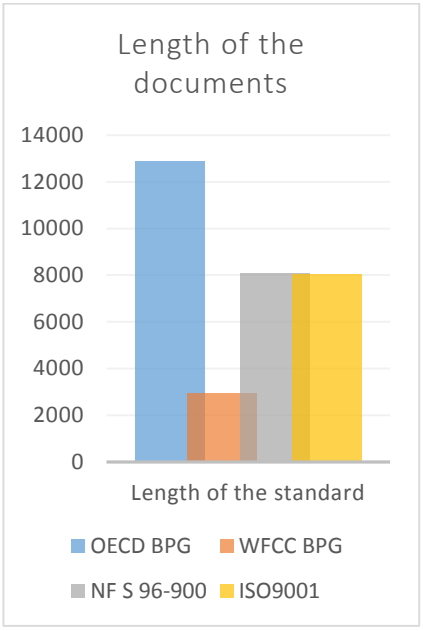


Figure 16. Number of words (length of the document) in the 4 standards (OECD BPG, WFCC BPG, NF S 96-900 and ISO9001).

Figure 17. Specific issues (number of categories) tackled in each of the 4 standards (OECD BPG, WFCC BPG, NF S 96-900 and ISO9001).

As can be observed in Fig.17, the WFCC BPG addresses biobanking specific issues (almost the same categories as OECD BPG), although, as can be observed in Fig.16, it is a short document. Furthermore, we also note that the WFCC BPG itself refers OECD BPG as the next level of guidance.
The NF S 96-900 addresses around a half of the issues addressed by the OECD BPG, the specific issues addressed are all tackled in the OECD BPG and conveys around 2/3 of the information.
For these reasons, we decided to have the OECD BPG as the reference that provides the (specific) requirements needed for the CC in the justification study – "Disclosing the gaps".

4.4.1.3 Disclosing the gaps

To test the hypothesis that a new standard for the mBiobanking certification is needed, we assessed the standards currently used for the CC certification (ISO9001 and NF S 96-900), against the OECD BPG, to find the gaps (if any) and evaluate their significance. According to the gaps found and their importance, we would conclude about the need for a new standard.
The first step to assess the fitness of the current standards to be used as criteria for an accredited certification scheme specific for mBiobanking, was to select a document including all the issues/provisions/requirements that are important for the culture collections. This document was decided to be the OECD BPG (OECD 2007) as presented in the previous sub-chapter.
To unveil possible gaps in the standards currently used for the CC certification (second step), the provisions on NF S 96-900 (AFNOR 2008) and ISO9001:2015 were compared with those conveyed by the OECD BPG. The comparison comprised the activities covered and the mandatory records.
Four comparison studies were made:

- The clauses in OECD BPG applied to all BRC that have no correspondence on NF S 96-900 and ISO 9001;
- The clauses in OECD BPG applied to the microbial domain that have no correspondence on NF S 96-900 and ISO 9001;
- Mandatory records in OECD BPG and NFS 96-900;
- Mandatory records in OECD BPG on Microbial Domain and NF S 96-900.

4.4.1.3.1 Results

As may be observed in Tables 6, 7 and 8, and Fig. 18 and 19, approximately 59% of the OECD BPG

topics applied to all BRC and 34% of the OECD BPG topics applied to the microbial domain are missing in the NF S 96-900 standard and 84% are missing in the ISO9001 standard.

ISO 9001 fails in establishing requirements for (1) key-operational processes such as shipping, handling and authentication of the biological material, (2) validation of methods and procedures, (3) preparation and production of culture media, (4) microbial BRC competence for the MB supply and preservation, (5) specific needs for the management of documented information, (6) biosecurity mechanisms and (7) CCs' long-term sustainability.

The NF S 96-900, does not cover critical issues such as biosecurity mechanisms, long term sustainability, quarantine requirements, BM supply, and validation of methods and procedures. It also does not include provisions for the documented information on "Minimum", "Recommended" and "Full data set" for biological material, results of audit reviews and record reviews, part of the information to retain from shipment, batch date or number and the accession number (on the biological material label), user queries and complaints, results of quality checks on preserved material, identification of the batch number and expiry date in media and reagents labelling, evidence given by depositors to assure the validity of data. Tables 9 and 10 summarise the records recommended by the OECD BPG that are not addressed in the NF S 96-900 standard.

Some examples of the documented information recommended by the OECD BPG that is not included in the French standard are: the safe operational level or safety limit for the resources held, the authorisation to use specialist equipment, the nature of the biological material held, cleaning and decontamination procedures, procedures for all preparations used in the growth and/or maintenance of the living biological materials held, procedures for storage, methods used for the risk assessment.

As expected, the ISO 9001 standard fails in addressing the key operational processes and specific BRCs' management issues. Some of these are (1) the handling and shipping of BM, (2) the preparation and use of reagents, culture media and other supplies, (3) the establishment of biosecurity mechanisms and (4) the strategy to ensure the long-term sustainability of the BRC.

Table 6. Clauses of OECD BPG applied to all BRC that have no correspondence on NF S 96-900 and ISO 9001:2015.

	NF S 96-900		ISO 9001
4	Organisational requirements		
4.1	Long term sustainability	4.1	Long term sustainability
5	Premises		
		5.1	Biological resource centre operations

	NF S 96-900		ISO 9001
5.2	Construction and operation	5.2	Construction and operation
		5.3	Access
7.1	Compliance with internal documentation	7.1	Compliance with internal documentation
		8	Data and informatics
		8.1	Data management
		8.2	Data processing
		9	Preparation of media and reagents
		10	Accession of deposit to the BRC
		10.1	Receipt and handling of biological materials
10.2	Accession	10.2	Accession
		10.3	Quality checks on the biological material
		11	Preservation and maintenance
11.1	Methodology (of preservation)	11.1	Methodology (of preservation)
11.2	Stock control of the preserved biological materials	11.2	Stock control of the preserved biological materials
11.3	Storage of preserved biological materials	11.3	Storage of preserved biological materials
11.4	Validation of methods and procedures	11.4	Validation of methods and procedures
12	Supply of material	12	Supply of material
		12.1	Order placement
12.2	Availability of the biological material ordered	12.2	Availability of the biological material ordered
12.3	Information provided with the biological material supplied	12.3	Information provided with the biological material supplied
		12.4	Packaging
12.5	Invoicing for supply charges	12.5	Invoicing for supply charges
12.6	Traceability of biological materials supplied	12.6	Traceability of biological materials supplied
12.7	Handling complaints and anomalies		
12.8	Refunds	12.8	Refunds
		12.9	Confidentiality
13.1	Purpose		
13.2	Responsibility		
Total	19		27
%	59%		84%

Table 7. Clauses of OECD GPG applied to the Microbial Domain that have no correspondence on NF S 96-900 and ISO 9001:2015.

	NF S 96-900		ISO 9001
10.1	Long-term preservation	10.1	Long-term preservation
11.2	User validation	11.2	User validation
11.5	Traceability of hazardous biological materials	11.5	Traceability of hazardous biological materials
12	Micro-organism BRCs compliance with national and international law	12	Micro-organism BRCs compliance with national and international law
12.1	Classification of micro-organisms according to the risk groups	12.1	Classification of micro-organisms according to the risk groups
12.2	Quarantine regulations	12.2	Quarantine regulations
12.3	Intellectual Property Rights	12.3	Intellectual Property Rights
12.4	Safety information provided to the recipient of micro-organisms	12.4	Safety information provided to the recipient of micro-organisms
12.5	Control of distribution of hazardous micro-organisms	12.5	Control of distribution of hazardous micro-organisms
Total	9		9
%	34%		34%

Table 8. Summary of the gaps (in %) found in NF S96-900 and ISO 9001:2015 when compared with OECD BPG.

	% of missing clauses* (from the OECD BPG applied to all BRC missing)	% of missing clauses* (from the OECD BPG applied to microbial domain
NF S96-900	59%	34%
ISO 9001	84%	34%

*Round values.

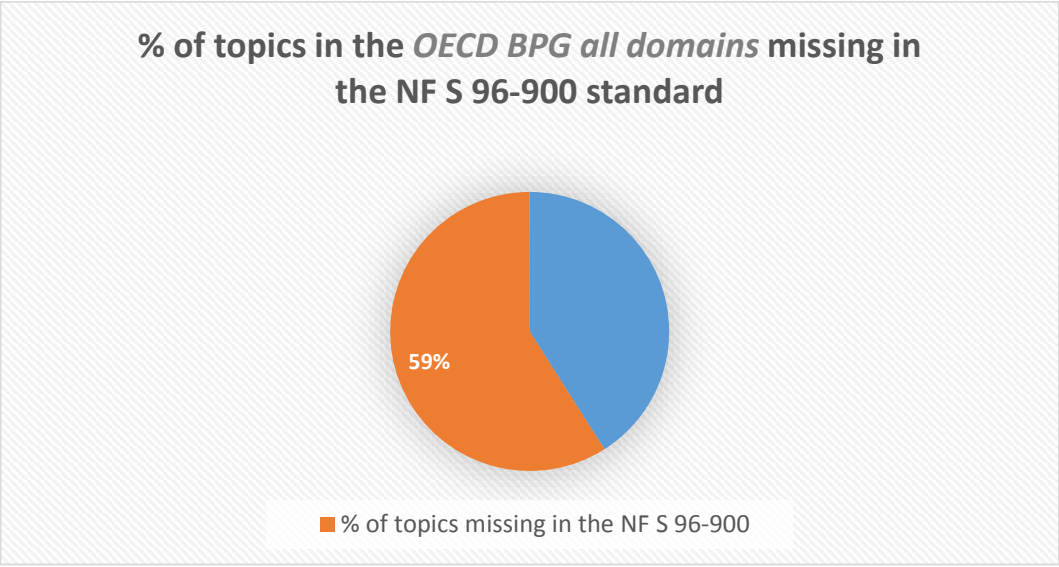


Figure 18. Percentage of topics in the *OECD BPG for all domains* that are missing in the NF S 96-900.

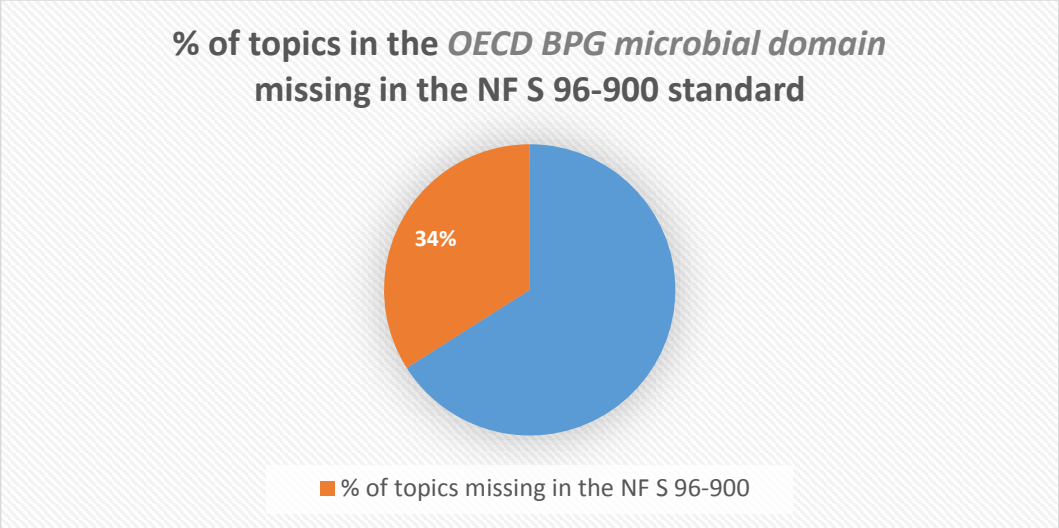


Figure 19. Percentage of topics in the *OECD BPG for microbial domain* that are missing in the NF S 96-900.

Table 9. Mandatory records in OECD Best Practice Guidelines and NFS 96 900.

Clause	Holding recommendation	OECD BPG for all BRC	NFS 96 900	Holding recommendation	Clause
4.3		Training records for specialist equipment use	Training courses ought to be record (including internal training)		7.1.2
5.5	"Held on file"	Copies of purchase orders	Records of the results of suppliers' evaluation		8.1
5.5	Five years	Records of suppliers			
6	Held in the BRC EMCLog books	Records from service management (equipment management procedures) and key documents	Records of maintenance and cleaning of premises		7.2.2
			Inventory of laboratory material		7.3.1 b)
			Records from laboratory material and equipment maintenance		7.3.1 c)
			Records from equipment maintenance		7.3.1 d)
7.1		SM permission and justification for departures from documented procedures			
7.1		Deviation report (AC) – when a procedure is not followed			
			Traceability of data changes and updates		9.9.4
8.1		Evidence to assure the validity of data (given by depositors)			
8.1		Minimum data set/Recommended Data set/ Full data set, for biological			

Clause	Holding recommendation	OECD BPG for all BRC	NFS 96 900	Holding recommendation	Clause
		material (in accordance with domain specific criteria).			
8.2		Records of a loss strain must be either printed and stored on file or copied to a digital archive			
8.3		Data (made available to users) describing the biological material and its origin	Record the received biological material		9.4
10.3	"Should be retained"	Quality testes on the received biological material			
11.		Key parameters of "preservation and maintenance" process	Records ought to be maintained for (1) monitoring and recording freezers temperatures, (2) control of nitrogen levels, (3) thresholds exceed alert, (4) a storage equipment failure	7.3.2	
11.1		Batch date or number and the accession number (on the biological material label).			
11.1		Where possible the expiry date must be record for user knowledge			
11.3		Details of inventory control, lead times and re-stocking practices should be documented.			
11.4		The results of preservation methods and procedures validation must be recorded			
12.6		Records of all requests for biological materials, including those refused			

Clause	Holding recommendation	OECD BPG for all BRC	NFS 96 900	Holding recommendation	Clause
12.6		Records of biological material sent	Records of biological material sent		9.8
12.6		Records of shipment receipt			
12.7		All user queries			
12.7		All user complaints			
12.7		Records of responses/solutions should be stored			
13.3		Enquiry			
13.3		Database			
13.3		Results of audit reviews and record reviews			
13.3		Results of third-party audit reviews and record reviews			
13.3		Results of the annual review			
			Results of quality control of biological material in all processes		9.2
			Demands of stakeholders of scientific projects	Must be kept	4.2 f)
			Quality Manual		4.2.2 a)
			Control of documents		4.2.3
			Control of records		4.2.4
			Management review		5.7.1
			Internal audits reports		6.1.3
			Records of NC and CA		6.2

Table 10. Mandatory records in OECD BPG on Microbial Domain and NF S 96 900.

Clause	Holding time	OECD BPG on Microbiological Domain	NF S 96 900	Holding time	Clause
8.		Media [and reagents] should be labelled with batch number and expire date			
10.2		Results of quality checks on preserved material			
		Individual records of all requests for hazardous biological materials, including those refused			
11.5		Individual records of hazardous biological material sent			
12.3		Terms and conditions for further distribution of deposited micro-organisms			

4.4.1.3.2 Discussion

The justification study was done to evaluate whether or not exists a market need for a new standard.
The standard with grater coverage was, as expected, the French standard. However, it misses approximately 59% of the provisions conveyed by the OECD BPG to all BRC and 34% of those on OECD BPG to microbial domain.
The revealed voids in the French standard are relevant not only for their number as for their impact on traceability and conformity of the all operation. Examples of crucial provisions missing for operation and to ensure traceability are: requirements for shipping, handling and authentication of the biological material, competence, documented information, biosecurity mechanisms and long-term sustainability, information to retain from shipment, batch date or number on the biological material labelling, results of quality checks, and evidence given by depositors to assure the validity of data.
The extent and weight of the revealed gaps clearly led to the decision of developing a new standard for the microbial biobanking as these gaps point out, with no doubt, the market relevance of the project.

4.4.1.3.3 Limitations

During the comparison studies two main difficulties arose:

1) the provisions displayed in one clause in one of the standards were, sometimes, spread across different clauses in the other standard so extensive matching-exercises were needed;
2) the detail put into the provisions varies from standard to standard. In result, some judgment to evaluate the relevance of "missing issues" in order to decide whether or not correspondence exists, was made. While this might have introduced some subjectivity to the evaluation, ultimately it ended up occurring in a few isolated cases having a very low contribution to the overall results.

4.4.2 DEFINITION OF THE OBJECTIVES AND SCOPE

Clear objectives, aligned with the biobanking principles, facilitate the definition of the outcomes that the standard seeks to achieve and are crucial in standard development since they are the pillars upon which the standard will be built.
The objectives are presented in clause 1.1 of the standard.

4.4.3 THE RISK ANALISYS AND MITIGATION MEASURES

Potential risks that would arise from the standard's implementation were identified as well as how to mitigate for these. The research aimed to unveil (1) the factors that may have a negative impact on the ability of the standard to achieve its intended results, (2) the unintended negative consequences that could arise from the standard's implementation and (3) preventive actions that could be taken during the standard development to address the potential risks.

The needs and expectations of the relevant interested parties (with which the standard's goals should be aligned), were identified using an Ishikawa diagram (Fig. 20). The risk of not attending those needs and expectations, their cause/s, potential failure/s and preventive actions are presented in Table 11.

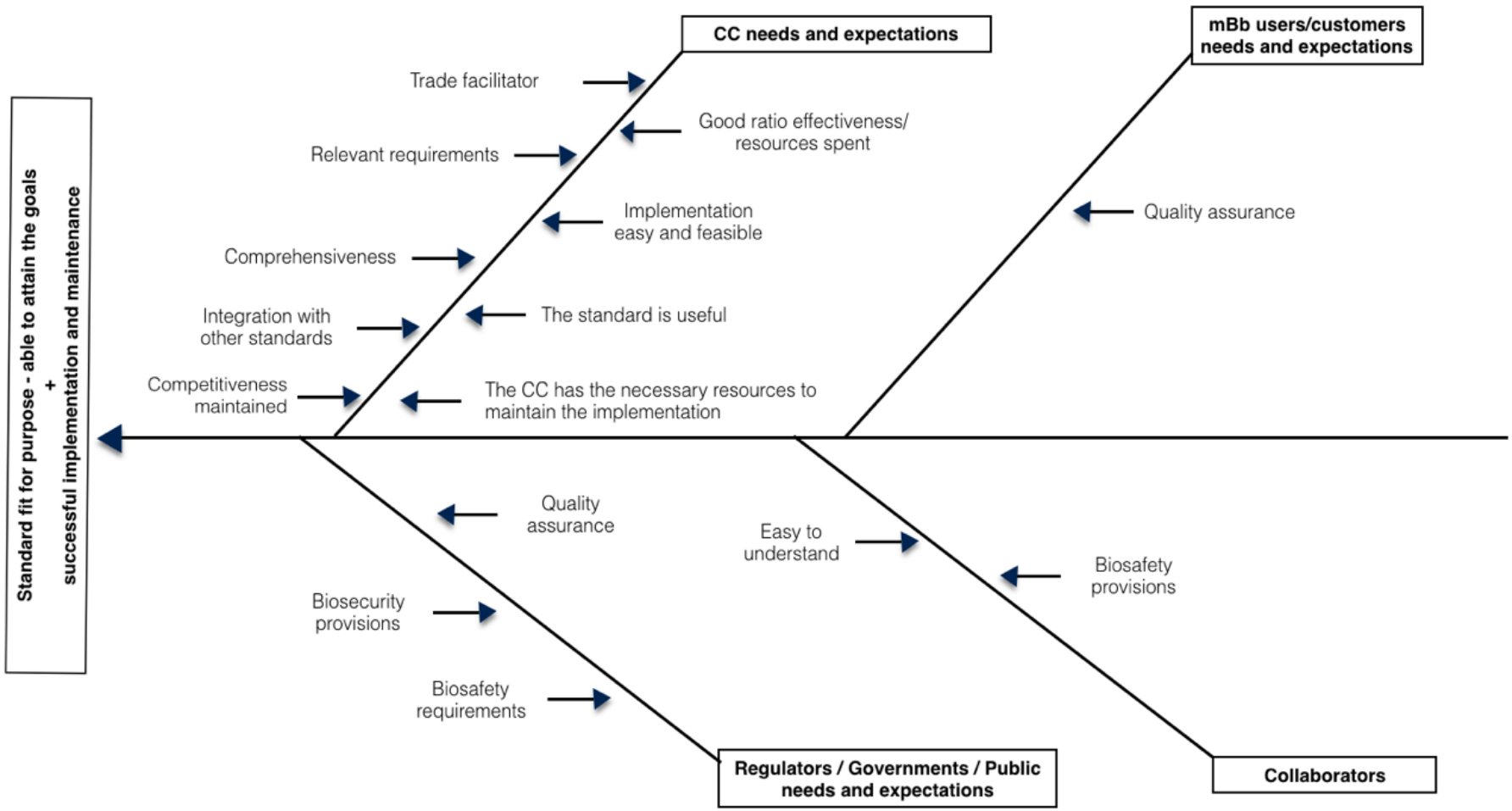


Figure 20. Ishikawa diagram for the standards' risks in implementation (risk of not attending the goals and possible negative consequences after implementation).

Table 11. Risks, root causes and mitigation measures for the project-standard implementation.

Risk	Cause	Mitigation measure to implement
Absence of quality assurance	Reactive approach is being used	The standard should convey proactive approaches
Absence of biosafety and biosecurity requirements	Reference document not considering these issues	Include biosafety and biosecurity provisions (OECD BPG consider these issues)
Provisions difficult to understand	- Using unknown terms and definitions - Lack of consistency in drafting - Unclear requirements - Difficulty in transpose the requirement to practice - Requirements can be interpreted in different ways	- Follow ISO rules for drafting - Use ISO terms and definitions when possible - Define new terms - Write the requirements in terms of management process or performance criteria - Criteria must be objective, clear and liable to be verified - Avoid language that can cause ambiguity
Barriers to trade	Unnecessary obstacles to trade, discriminatory provisions	The standard should be developed having the TBT Agreement into consideration
Requirements not relevant	They do not add value to the mBb because: - are not necessary to attain the standard goal - they fall out the mBb's scope	- Establish clear and relevant objectives - Ensure that only requirements that contribute to attain the objectives are included - identify the link between the requirements (necessary to validate the provision)
Existing voids	- Follow OECD BPG - Ensure that there are provisions for all the standard's objectives	Validate the provision
Difficulty in integration	- The standard is not aligned with other standards - The standard uses different terminology and concepts	- Use the annex SL (alignment with ISO MSS) - Use as much as possible ISO terms and definitions (Using ISO terminology and concepts helps to keep alignment and consistency between standards)
Difficult implementation/not-feasible	- The standard has unknown model and approaches - CC have different dimensions/objectives/resources	- Use known models (such as MSS) - Create different levels of assessment (include CC with different objectives and resource availability)
Lack of competitiveness after implementation	- Lack of resources	Create different levels of assessment

4.4.4 PRINCIPLES FOR BIOBANKING

The microbial-biobanking principles provide the foundation for the standard's objectives and content. To our best knowledge, the microbial-biobanking principles are not formally established.

For this reason - based in the fundamental beliefs, values and rules that govern the biobanking activity - a set of nine biobanking principles (and its rational) is proposed (Fig.21).

These principles may also serve as an anchor for guidance on decisions that CC may need to make in unexpected situations.

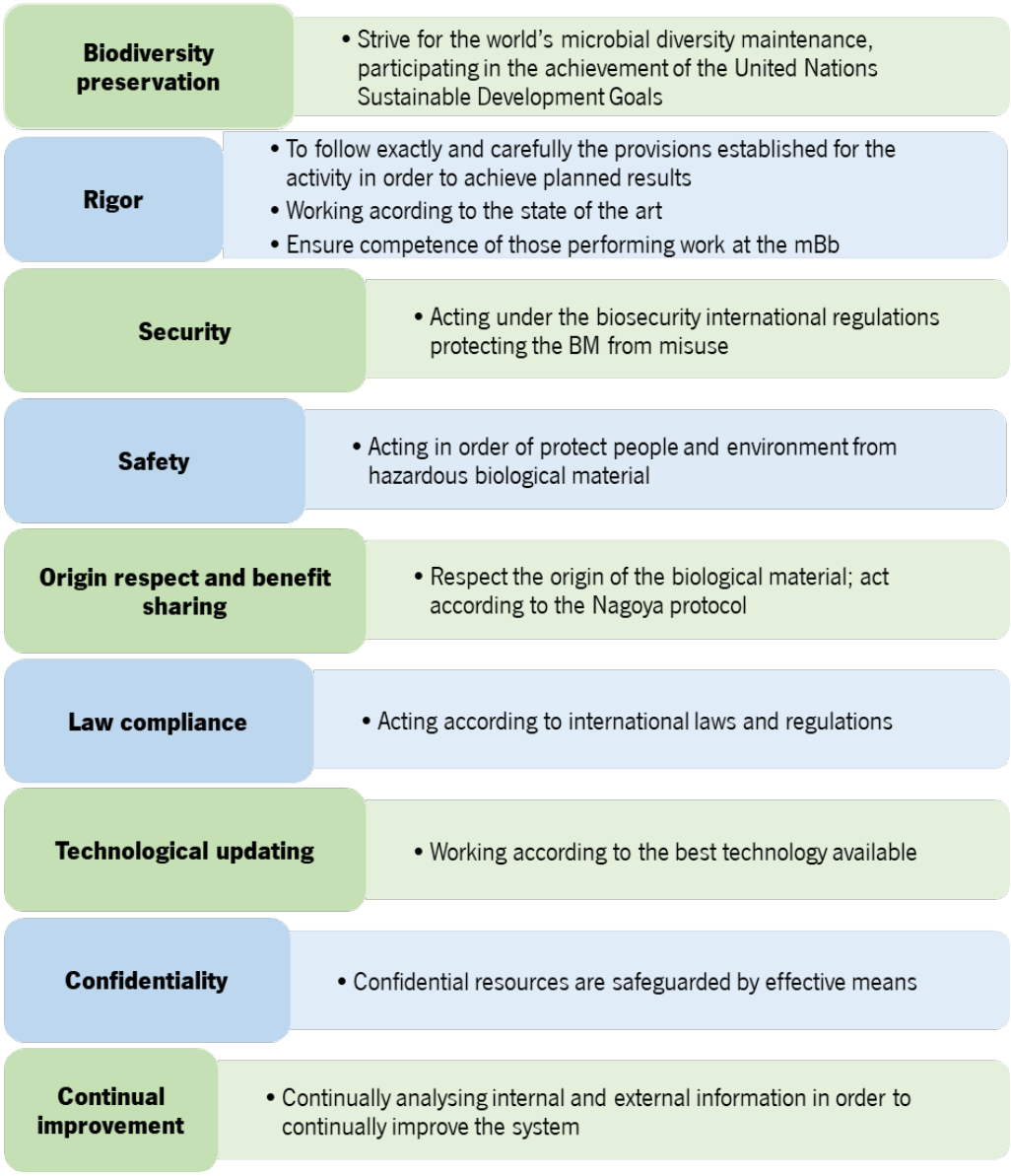


Figure 21. Principles for the microbial biobanking.

4.5 THE MANAGEMENT APPROACH UNDERPINNIG THE STANDARD

4.5.1 PROCEDURE TO IDENTIFY THE MANAGEMENT MODEL CURRENTLY IMPLEMENTED IN CC

We believe that to really improve the organisation's performance, MMS should base on recognised and extensively tested management models.

To our best knowledge, the management model in CC has never been clearly investigated/studied. To uncover that model, assess its suitability, and define the model for the standard, the procedure in Fig. 22 was followed.

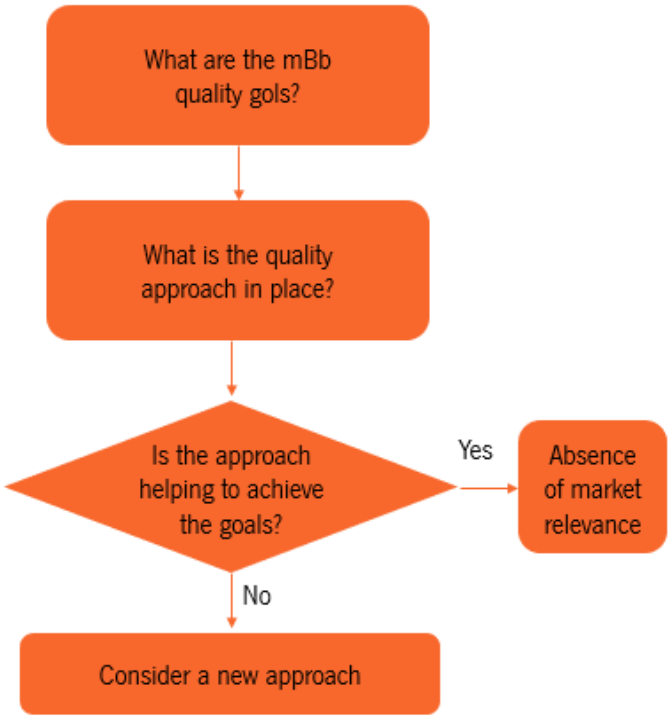


Figure 22. Procedure followed to decide the management model on the standard.

The analysis was based on a "lifecycle thinking" as it provides a coherent system where biobanking activities can be analysed, understood and optimised.

4.5.2 THE MICROORGANISM PRESERVATION LIFECYCLE

The products we use every day have a lifecycle. The lifecycle is the course of events in the products' life from development, use, and discontinuation of use (European Commission, 2015). They are produced from raw materials, then are transported to the shops, market, bought and used by consumers and, eventually, eliminated (UNEP/SETAC, 2005). Equal to products, microorganisms used in biotechnology

processes have a lifecycle as well: they are collected from nature, cultured, manipulated, transported, supplied, used and discarded (MCT, 2002).

To avoid misunderstanding between the lifecycle in the biotechnology context and the biological-lifecycle (that happens to microorganisms in nature), we will designate the former as the microorganism *"technological lifecycle*". As represented in Fig. 23, it includes several stages between the microorganism collects from nature to its use and discard.

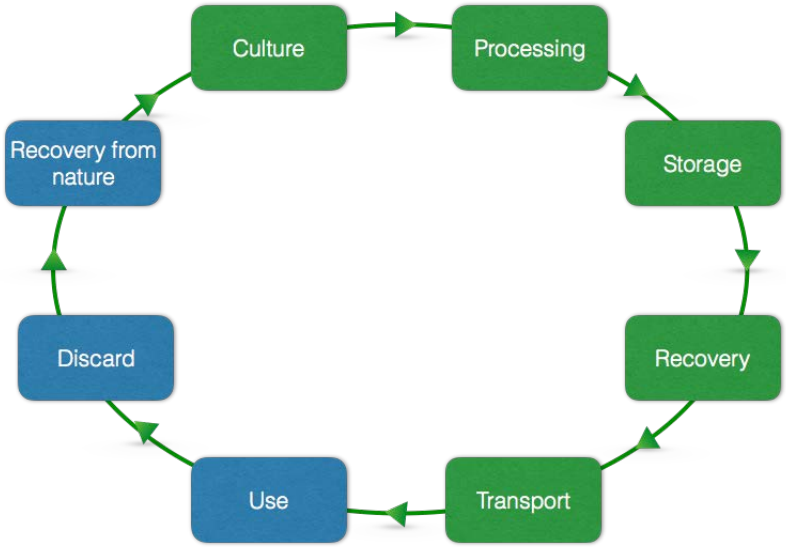


Figure 23. General description of the microorganism *technological lifecycle*.

Eight different stages can be distinguished throughout the microorganism technological lifecycle. During the first and second stages, the microorganism is taken from nature and set to grow. It is cultured by inoculation in a culture medium that will provide the necessary nutrients to support its growth. When appropriate cultures are obtained, it passes to the processing stage. During processing preservation techniques are applied to the microorganism preparing it to live (without changings) for the long-term storage. Examples of preservation techniques are deep-freeze at -80 °C, liquid nitrogen cryopreservation and freeze-drying. During this period, the microorganism is stored under specific conditions of temperature, relative humidity and/or other, according to the undertaken preservation technique. When the microorganism is intended for supply, it is submitted to a recovery technique whose purpose is to bring it "back to life". After recovery, the microorganism is shipped under specific transport conditions to the final user. After its use (in industry, research and teaching, for instance) the microorganism is discarded (eliminated).

Within the microorganism *technological lifecycle*, five stages can be distinguished as accountable to the microbial biobank: the microorganism culture, processing, storage, recovery and transport to the final user. We will designate these five stages as the microorganism *preservation lifecycle* (Fig. 24).

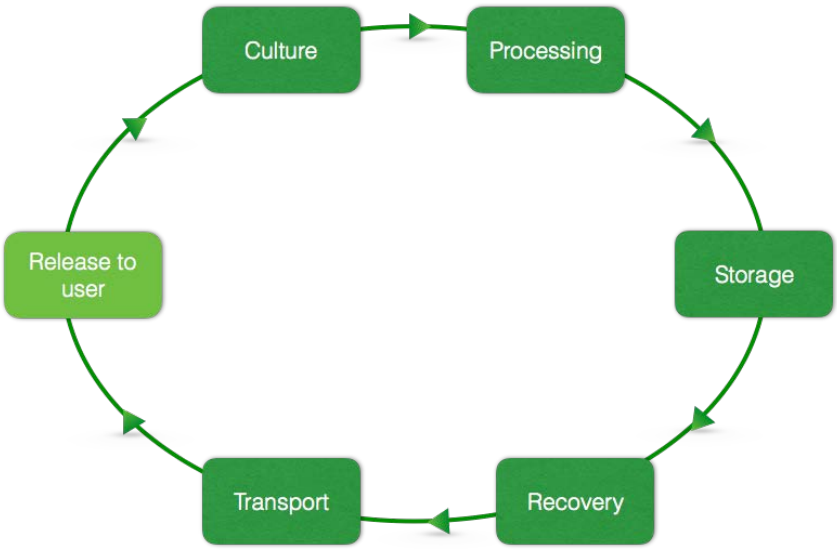


Figure 24. Microorganism preservation lifecycle.

4.5.3 BIOBANKING OBJECTIVES

The diagram in Fig. 25 presents the activities[25] for the "microorganism supply". Adopting a process approach[26], this set of interrelated activities (yellow boxes) might be managed as a process, with inputs, outputs and criteria for the output approval. The process input is the customer request. The process output is the microorganism delivery/supply and the criteria (for the output approval) is the microorganism authenticity (compliance with the supplier's requirements). If no other attribute is expected from the microorganism the authenticity criteria are identity, purity and viability.

Failure in this process may be corrected by a new (conform) supply.

[25] People collaborating within a process to carry out their daily activities. Some activities are prescribed and depend on the organisation, while others are not and react to external stimuli to determine their nature and execution (adapted from ISO, 2015a).

[26] Way of managing an organisation as a system of processes. By controlling the interrelationships among these processes, the overall performance of the organisation can be enhanced (adapted from ISO, 2015b).

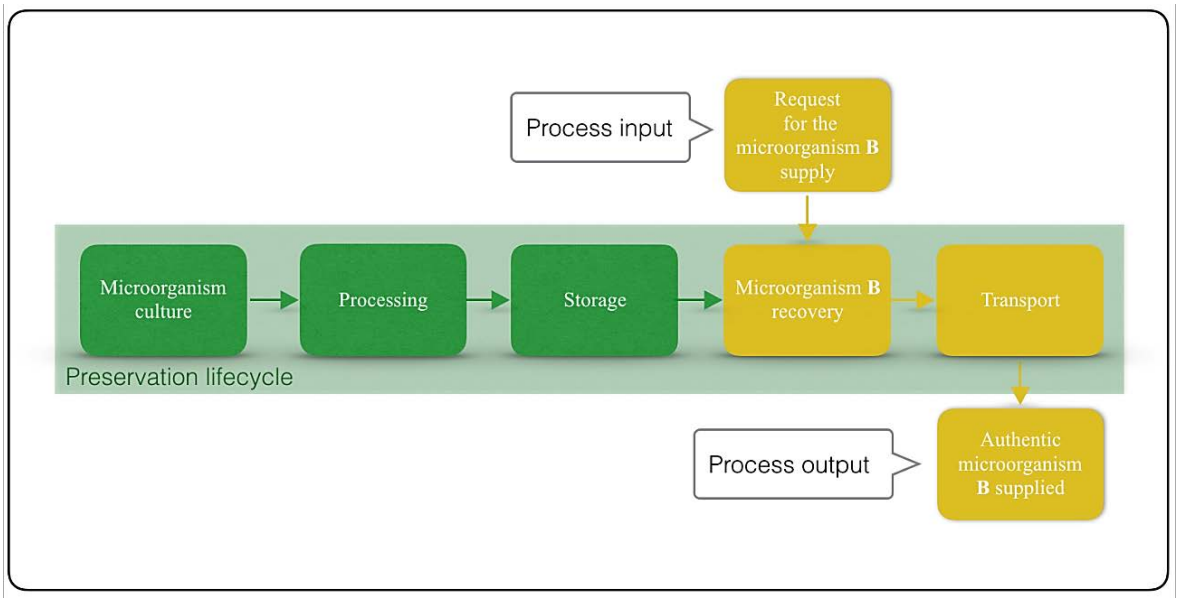


Figure 25. Sequence of activities for the microorganism supply (yellow boxes); identification of the process input and output.

The diagram in Fig. 26 represents the process "microorganism deposit". The process input is the customer's request for deposit, and the output is the maintenance of the microorganism authenticity during the established period for deposit; the customer may be supplied several times with the microorganism during this period; eventually, the microorganism might be returned to the customer, once finished the established period for deposit. The microbial biobank must ensure that during the deposit period the authenticity of the microorganism is preserved. Failure in this process may be impossible to correct if the microorganism is unique and/or has unique characteristics.

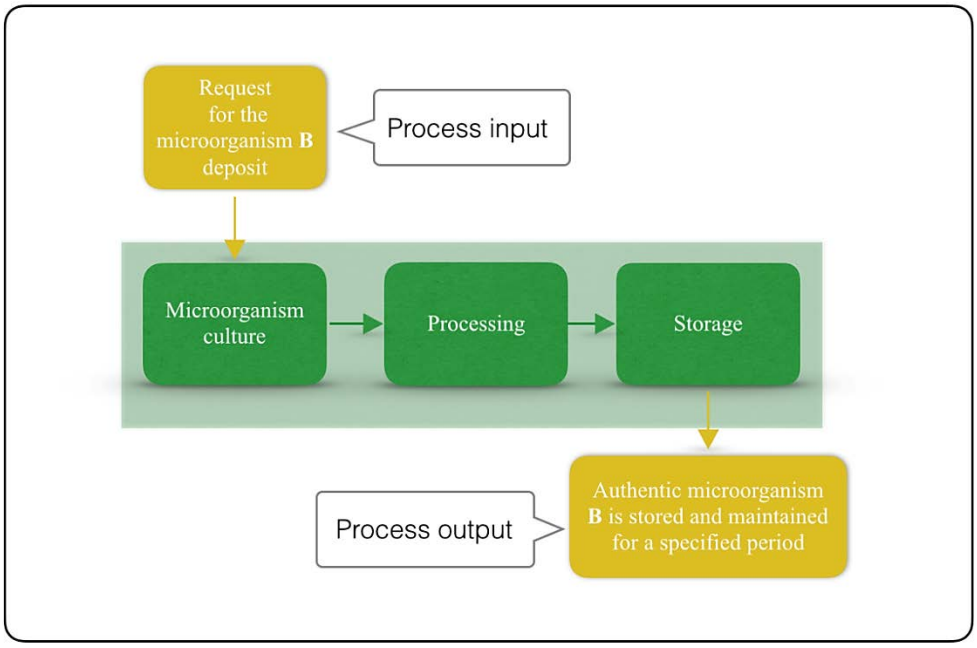


Figure 26. Sequence of activities involved in the request for deposit of microorganisms; identification of the process input and output.

Customers' requirements for both services (supply and deposit) and the expected results from the corresponding processes are:

- authentic microorganisms preserved, for deposit process
- authentic microorganisms supplied, for supply process

Lack of consistency[27] in both cases may lead to irretrievable consequences affecting not only the microbial biobank but all the interested parties. One failure may lead to wrong investigation results, inconsistencies in industrial processes, loss of achieved knowledge, loss of unique strains, complaints, re-works, damage in the microbial biobanks' market-image, waste of resources, and amends resulting from accountability issues.

In sum, the biobanking level of performance depends much on the consistent achievement of the following objectives:

a) Ensure that the microorganisms to preserve are authentic;

b) Ensure the supplied microorganisms are authentic;

c) Ensure the authenticity over time of the deposited microorganisms.

[27] For this work, process consistency is defined as the degree to which a process leads to identical results over time.

To consistently achieve *a)* and *b),* proper testing making use of proper resources (competent personnel and controlled equipment) must be in place.

To consistently achieve *c)*, high process capability throughout the preservation lifecycle must be ensured. Processes should operate in such a way that predictable outcomes (results conforming with the requirements) are ensured.

The management model[28] in place must then focus on "effectiveness" and "consistency" giving the microbial biobank and the interested parties confidence about the system's ability to (1) preserve at all times the authenticity of the microorganisms, and (2) supply authentic microorganisms.

The microbial biobank management targets and their relationship with the microorganism preservation-lifecycle, are represented in Fig. 27.

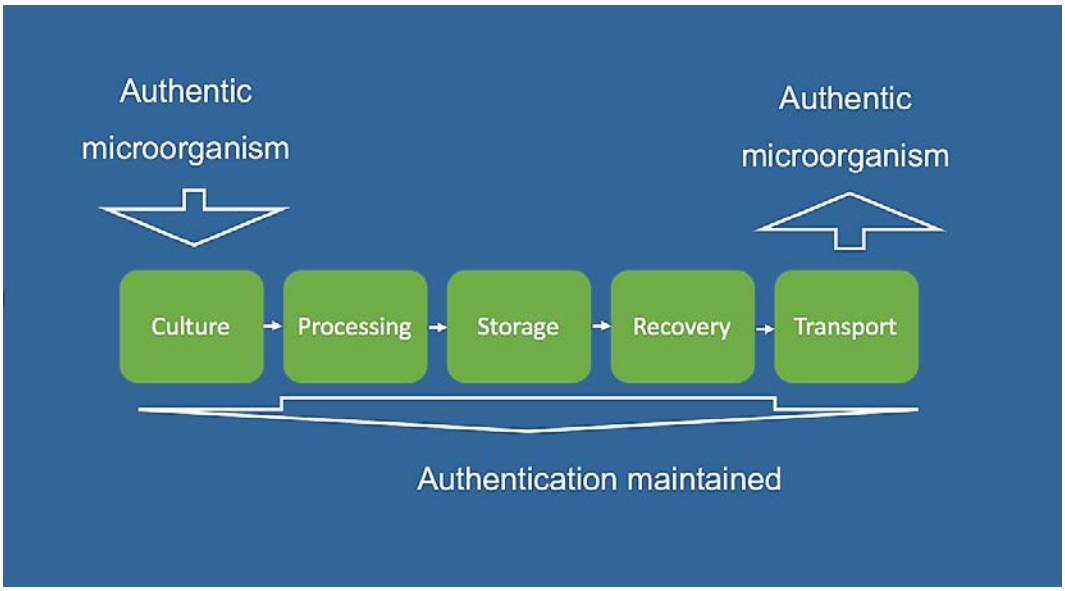


Figure 27. Objectives/targets for the (quality) management model in microbial biobanks.

4.5.4 CURRENT MANAGEMENT APPROACH IN mBb

The diagram in Fig. 28 presents the current management model for microbial biobanks to manage the quality of their activities throughout the microorganism lifecycle.

[28] For this work, management model is the set of methods (included in a management system) established to attain defined management goals.

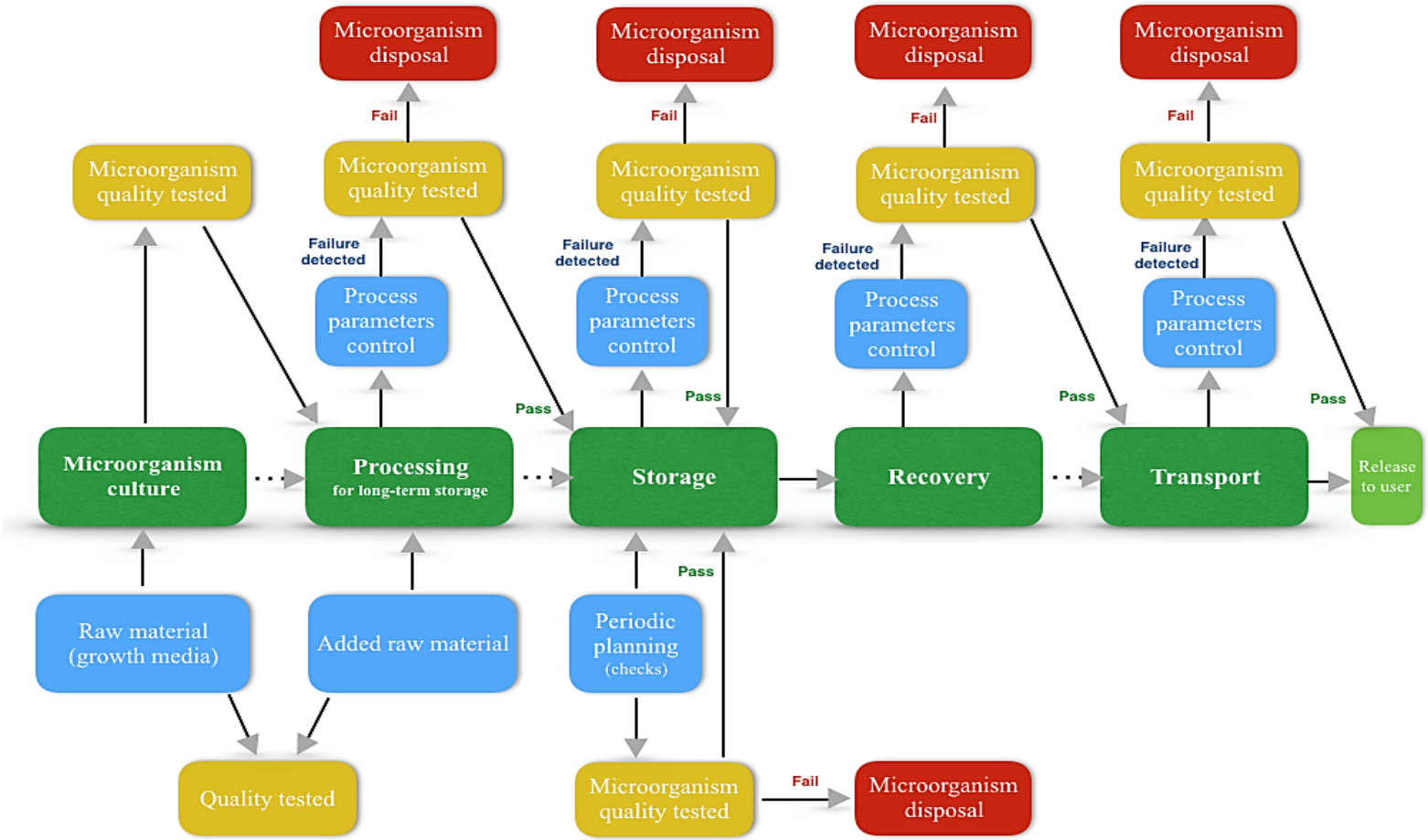


Figure 28. Diagram representing the current model for quality management in microbial biobanks, based in the microorganism preservation lifecycle.

At stage one, a microorganism is accepted for deposit. It is cultured and tested for authenticity[29]. In case of failure during the testing for authentication, a wrongly authenticated microorganism is at risk of being preserved (different identity, not pure, not viable or loss of a particular characteristic). The motive of failure in authentication might be related to several different causes such as the testing method, the equipment and the operator.

All raw materials entering the process are tested before use (inside or outside the biobank); raw material shall only be accepted if compliance with the requirements has been proven.

The second stage on the microorganism preservation lifecycle - processing - is undertaken to enable the microorganism long-term preservation[30] . The activities undertaken during the processing stage are well established so as to attain conformity: activities are fixed and the process factors (inputs) are stringently set (no deviation is permitted for both). Several control points (measuring and monitoring activities) are implemented to early detect possible non-conformities. This enables the microbial biobank to timely re-establish conformity in case of any deviation, to avoid damage in microorganism integrity. If any failure is detected microorganisms could have been affected so, testing is made to identify possible loss of microorganism authenticity.

During stage 3 - storage - the microorganisms under preservation are tested for authenticity at planned intervals. This monitoring (and measuring) procedure enables the microbial biobank to detect any consequence of undetected failures.

Stage 4 - microorganism recovery - begins with a requested for supply. As in stage 2, the recovery activities (procedures) are very well established, the process variables stringently set and control points are implemented to detect any failure.

Before supply, microorganisms are tested for its authenticity and subsequently transported to the user. During transport, the procedures are fixed, the process parameters are stringently set, and if necessary measured and monitored.

Red boxes represent microorganism loss – non-conforming product. In general, failure is detected by control activities represented by the blue boxes: each process variable is monitored and measured and the results interpreted according to the criteria for acceptance. If some process variable is out of specification, correction and corrective actions are triggered. Processes may be readjusted as a consequence.

---

[29] For this work, authenticity is defined as the compliance with the claimed characteristics.

[30] To preserve: to maintain the biological material in such specific conditions that its authenticity is ensured. It includes any necessary processing activity and storage.

Red box non-conformities born mostly at the green level. They may arise from failure during culture, processing, storage, recovery and transport to the user. These failures are not predictable as they result from input variability (operator, equipment, materials and premises). By the time a failure is detected, any process parameter might already be out of specification, so microorganisms might be already damaged.

According to the current management model in microbial biobanks, represented in Fig. 28:

1. Consistency in preservation for the long term [objective c)] is not ensured as microorganism might be lost at almost all stages.
2. Consistency in preserving and supplying authentic microorganisms [objectives a) and b)] might be achieved as long as valid results are ensured from testing; might be achieved by verification and validation of methods/examinations, as required for example by ISO20387 and ISO/IEC17025.

Variability results in lack of consistency so, as microbial biobank goal is to achieve consistency, rather than focus on "variability detection" microbial biobanking management model should focus on "variability control".

Variability detection is in its essence related to a quality model known as quality by testing (QbT) while variability control is related to a model called quality by design (QbD).

4.5.5 QUALITY BY TESTING

The mBiobanks' current paradigm to reach quality is a classic, empiric, reactive approach known as quality -by-testing according to which product quality (final product and in-process-product) is assured by the combination of fixed (and thus inflexible) manufacturing steps and extensive testing carried out through the manufacturing process.

The process through which the product is built or transformed is well established, and the activities, parameters and product quality characteristics are stringently settled and tightly controlled as they are used to ensure process consistency.

The quality of used raw materials/reagents is monitored by testing to verify if specifications (quality criteria) are met. The final-product is tested for conformity with specifications before release, an operation

known as verification[31] (Maropoulos & Ceglarek, 2010)). Final-product specifications are, most of the times, set out by observing data from a small number of batches believed to be acceptable and then establishing the acceptance criteria for future batches (Yu, 2008).

QbT is a reactive approach to quality management: when a final product testing fails to comply with specification, (1) the corresponding batch is discarded, (2) the root cause of the failure is identified and corrected and, (3) steps on the process might be modified in order to obtain testing results within the predefined limits.

Some of the characteristics found in QbT approach are (Yu, 2008):

- Root cause for failure is usually not well understood, which can lead to re-occurrence;
- Production can be halted until root causes of failure are understood and addressed or acceptance criteria revised;
- Limited characterization of variability;
- Lack of process understanding;
- Changes in the process will usually require more testing and additional controls.

Rather than striving for failure identification and correction, microbial biobanks should strive to prevent failure opting for a proactive approach. Proactive approaches to quality are, in general, related to early stages of the product lifecycle, while reactive approaches are more related to the last stages of the product lifecycle (Kolaric, 1995).

4.5.6 QUALITY-BY-TESTING VS QUALITY-BY-DESIGN

Under both approaches QbT and QbD the role that the product specification (criteria for quality) plays is completely different. While under QbT each batch must be tested to assure its quality and manufacturing consistency, under QbD batches may not be tested as process understanding and control provides sufficient evidence that the product will meet specification (if tested). This allows the final products' real-time release. Specifications for the final product are solely used for the confirmation of product quality, not to assure manufacturing consistency and process control (Yu, 2008).

[31] Verification is a quality control procedure which is used to evaluate whether or not a product, service, or system complies with requirements imposed at the start of a development phase.

To facilitate the understanding of differences between QbT and QbD, a diagram contrasting both approaches is presented in Fig. 29.

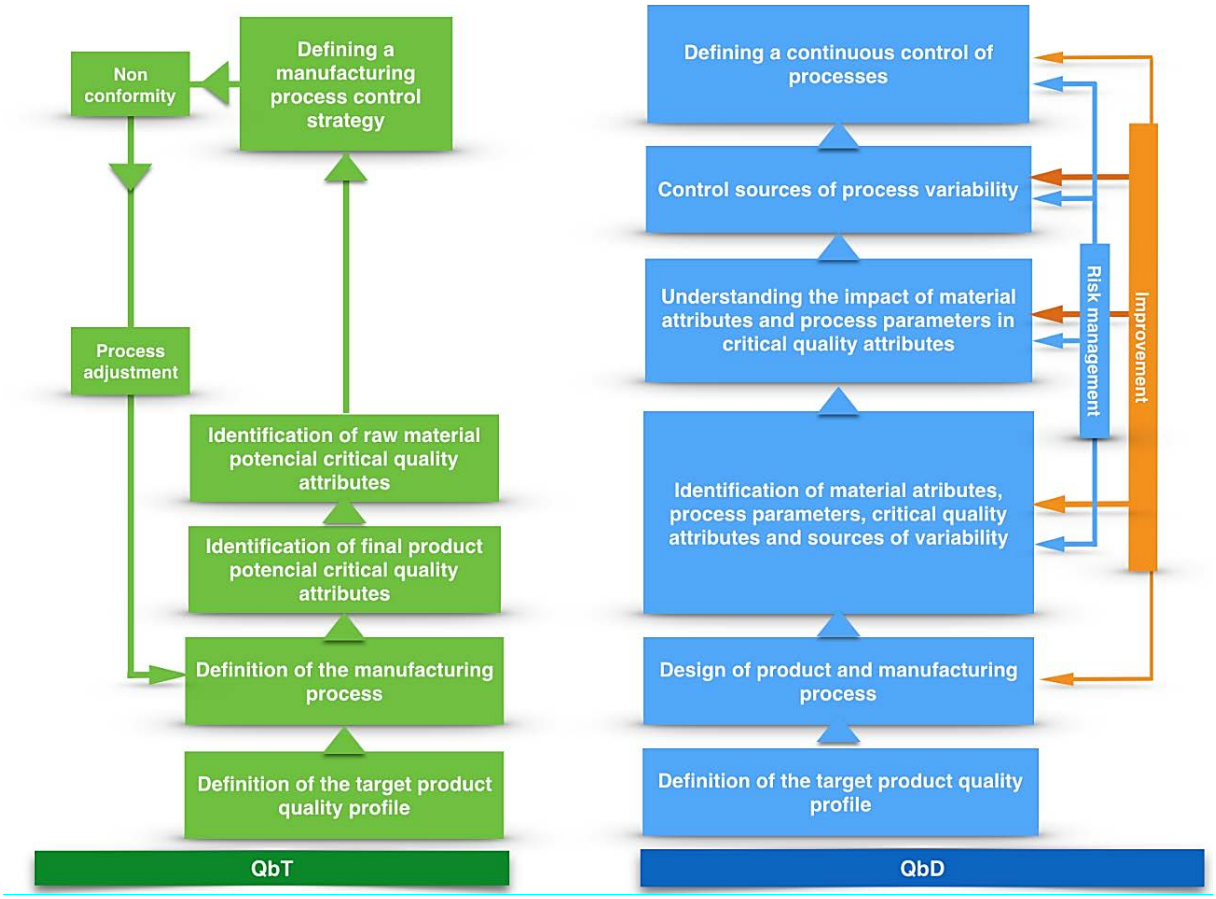


Figure 29. Comparison of the Quality by testing and quality by design approaches.

4.5.7 QUALITY MODEL FOR THE STANDARD

The project standard bases in a proactive approach as represented in Fig. 30. As a first step, the biobanking processes are designed building process knowledge and establishing a strategy for process control, secondly equipment, infrastructure, personnel and methods are qualified. Then the control state is maintained by continually receiving information from the processes and delivering new information and actions to improve the process design.

Fig. 31 presents the clauses included in each stage.

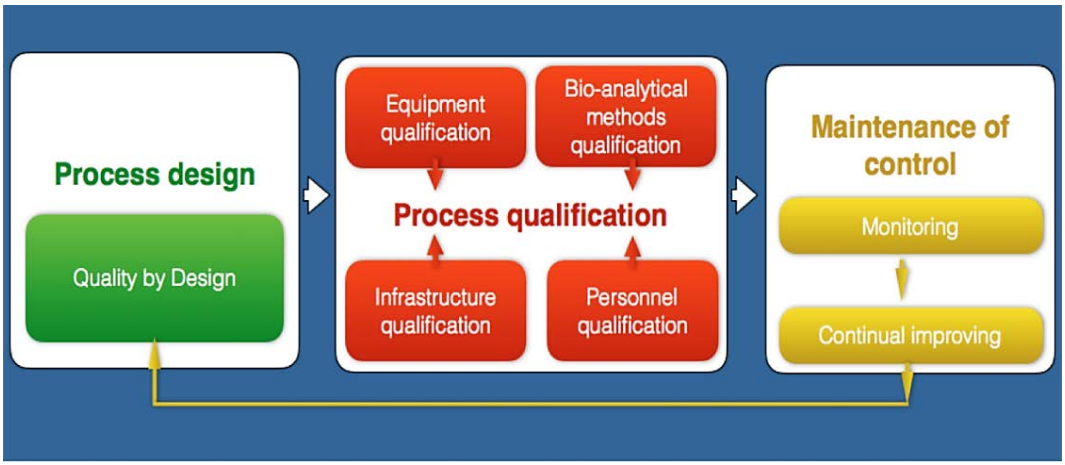


Figure 30. General model for the (proactive) approach in the standard.

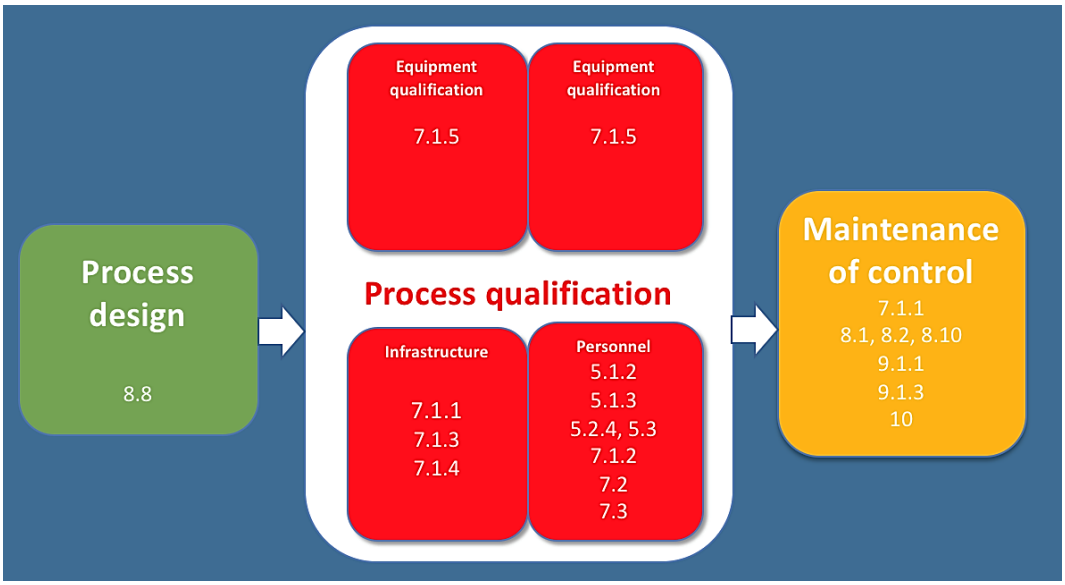


Figure 31. Clauses directly related to the (proactive) approach in the standard.

4.5.8 DISCUSSION

To our best knowledge, both ISO and ISEAL, do not have included in their standard-setting strategy the choice of a management approach for the standard. According to our knowledge, standard-developers base on other standards to develop their own standard, not having a clear idea about what kind of approach is being followed or what alternatives exist. Although in some cases this step may not be required (e.g., development of "Specifications") we believe that, for management system standards, it is key for the standard to achieve its purpose –standards must take on the mission of using science to promote improvement in organisations.

The choice of a proactive approach to management is crucial as the biotechnology environment is changing fast, probably faster than ever before. To keep up with it, being prepared to face new challenges, mBiobanks have to change too: have to become more efficient than they are now.

As demonstrated, effectiveness and consistency in preserving and supplying BM are the basic main goals for CC. To efficiently achieve consistency in microorganism long-term preservation, a proactive approach to microorganism management is mandatory. The current strategy in CC to avoid the loss of microorganisms is having a duplicate of the collection stored in a different place. Despite it diminishes the likelihood of losing BM, it is not an efficient solution. Moreover, failure still may happen in both main collection and its duplicate.

4.6 DRAFTING: SOURCES, RULES, TRACEABILITY

4.6.1 SOURCES

The standard content was developed by assembling and rewriting the provisions from the several sources presented below:

- OECD BPG (OECD, 2007)
- NIT DICLA 61 (INMETRO, 2012),
- NP EN 1619 (IPQ 1999)
- ISO 9001 (ISO, 2015b)
- ISO/IEC 17025 (ISO/IEC, 2005)
- ISO 15189 (ISO, 2012)
- Annex SL (ISO/IEC, 2014)

The first three documents were used for they are specific for biobanking. The ISO standards were selected for there applicability to biobanking. The Annex SL because is mandatory for management system standards.

The text from the annex SL was used without changings. The text form the other sources was rewritten. New text was added as required.

During the standard's development, several reference sources were revised and new versions were published. This was the case of the ISO Guide 83 that was replaced by the Annex SL and the ISO 9001:2008 that was successively replaced by the ISO/WD 9001 (2012), the ISO DIS 9001:2014, and

ISO FDIS 9001 (2015). In all cases, the working draft was fully revised to reflect the new version of the documents.

4.6.2 CONSISTENCY IN TERMINOLOGY

To ensure consistent terminology several documents providing terms and definitions were considered:

- ISO 9000 Standard (ISO, 2015a
- ISO/IEC Guide 2 (ISO/IEC, 2004a)
- ISO Guide 73 (ISO, 2009)
- OECD Glossary of Key Terms in Evaluation and Results Based Management [OECD, 2010)
- ISO/IEC 17000 (2004b)
- International Vocabulary of Metrology (VIM) - Basic and general concepts and associated terms – JCGM 200:2012 (BIPM, 2012)
- IEC Electropedia, available at http://www.electropedia.org, accessed 22.02.2021
- ISO online browsing platform, available at https://www.iso.org/obp/ui/, accessed 22.02.2021

In case of conflicting terminology, preference was given to the ISO terms and definitions.

4.6.3 RULES FOR DRAFTING

Across its full geographic scope, the users of the standard have to be able to interpret and apply the provisions of the standard. For this reason and to ensure uniformity of structure and style, drafting followed the rules established by the ISO/IEC Directives (ISO/IEC, 2014) except for the rules applied to “notes”.

Provisions are expressions in the standard taking several forms such as statements, requirements, recommendations, possibilities, permissions. The provisions are distinguished by the form of wording they employ:

- Recommendations are expressed by the use of the auxiliary “should”;
- The requirements by the use of the auxiliary “shall”;
- The instructions (requirements in procedures or test methods) are in the imperative mode;
- Permissions are distinguished by “may” and “need not”;
- Possibility and capability are distinguished by the use of “can”.

The requirements in the standard were established in order to be clear, objective and verifiable. They were expressed in terms of process management and performance criteria, giving space for innovation

and flexibility. By expressing the requirements in terms of process management and performance criteria we are ensuring that all the requirements convey criteria and that there is a method to evaluate the fulfilment of the criteria.

When necessary, explanations were added in order to facilitate transposition of pure performance requirements into practical solutions. Explanations and examples for the requirements' implementation were added as notes.

Other reference documents considered for drafting were:

- CEN/CENELEC Guide 17 (CEN/CENELEC, 2010)
- ISO Guide 82 (ISO, 2014)
- ISO/IEC Guide 59 (ISO/IEC, 1994)
- WTO Agreement on Technical Barriers to Trade[32] (WTO, 2012)

4.6.4 PROVISIONS TRACEABILITY AND CONTROL OF DRAFTING

Knowing the provenance of each provision on the final standard (original source) may be important to for the discussions during public consultation.

Maintaining the provisions traceability is not an easy task and difficulty increases with the number of sources. So, a procedure to maintain source-traceability in the final standard was established (Fig. 32). The overall procedure to control drafting is presented in Annex 1.

[32] Technical Barriers to Trade are measures (conveyed by technical regulations, standards, testing and certification procedures that may apply to both domestically produced and imported goods) adopted by governments establishing product requirements for fulfilment of public policy objectives such as human health and safety, environmental protection, consumer information, or quality. The TBT Agreement aims to ensure that these measures do not create unnecessary obstacles to trade.

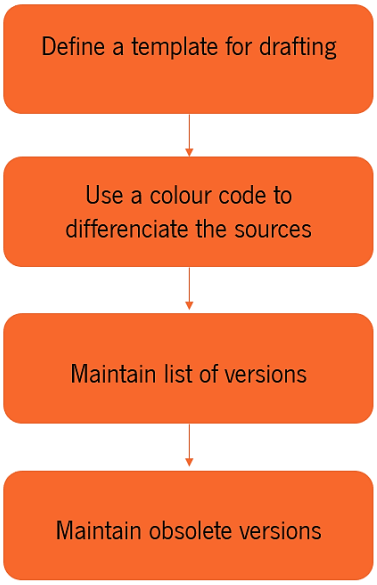


Figure 32. Procedure for drafting.

The template used for drafting is presented in Fig. 33. It enables to identify the version and date of the draft as well as the different "working areas".

Figure 33. Template for drafting the project-standard.

Each provision was copied from the source and pasted to the area B, according to the colour-code presented in Fig. 34 - for example, the text from OECD BPG text was recorded in blue and the text form ISO 9001 was recorded in green. Next, the raw text in the area B was assembled and re-written in area A, maintaining the colour of the source from which it was originated.

	Appendix 2 Annex SL
	OECD BP Guidlines
	ISO 9001
	NIT DICLA
	ISO 17025
	EN 1619
	ISO 15189
	New provions
	EudraLex_vol 4, annex 15

Figure 34. Colour code for drafting the standard's provisions.

An example of the standard at the moment of completion is presented in Fig. 35.

6 Planning

6.1 Actions to address risks and opportunities

6.1.1

When planning for the Q&C management system, the Biobank shall consider the issues referred to in 4.1 and the requirements referred to in 4.2 and determine the risks and opportunities that need to be addressed to

- give assurance the Q&C management system can achieve its intended result(s);
- to enhance desirable effects;
- to identify sources of variation on processes;
- prevent or reduce undesired effects;
- achieve improvement;
- ensure the existence of the necessary capacity building.

6.1.2

The risk determination shall include, but not be limited to:

- the lifecycle of the biological material;
- infrastructure, equipment and processes;
- the impact of variables in the transportation process (see Note 1);
- the nature of the biological material in the Biobank inventory to assign biological materials to biosecurity risk levels;
- the BRC's information, such as archives and electronic communication means;
- information security and customer's property rights;
- the capacity building of the Biobank and its long-term sustainability.

The risk determination shall be:

- conducted upon potential internal or external improper influence on staff of commercial, financial or other that may negatively affect the quality of work, the safety and security of the BRC;
- conducted to assign activities that can diminish confidence on Biobank competence, impartiality, evaluation capacity or operational integrity;
- done to external (outsourced?) processes, prior to determine the type and extent of control to apply;
- conducted to ensure the system integrity when alterations are planned and implemented;
- reviewed at planned intervals, at least on an annual basis;
- repeated in case of increased knowledge and understanding from changes.

Figure 35. Final draft excerpt.

Whenever major changes were made, the version of the working draft was changed. Major changes included new or deleted clauses and changes in more than approximately eight pages. Obsolete versions were retained and properly identified.

The several versions were listed in the form presented in Fig. 36. It was continually updated with the different Index versions to maintain traceability.

Version	Date	Description of changes

Figure 36. Template used to record the different versions of the draft and the draft's Index.

Some provisions of the OECD BPG were not considered. When relevant, a justification was maintained - the rational for "not-inclusion" was recorded in the template presented in (Fig. 37).

Clause	Provision	Rational

Figure 37. Template used to record OECD BPG provisions not included in the standard.

The rational for the most of the added new provisions is recorded in the template presented in Fig. 38.

Clause	New requirement	Rational

Figure 38. Template used to record new provisions included in the WD.

4.6.5 STRUCTURE

The structure of a standard depends on the recognition scheme in which it will be included.
A diagram summarising the procedure to establish the standard's structure (main clauses) is presented in Fig. 39.

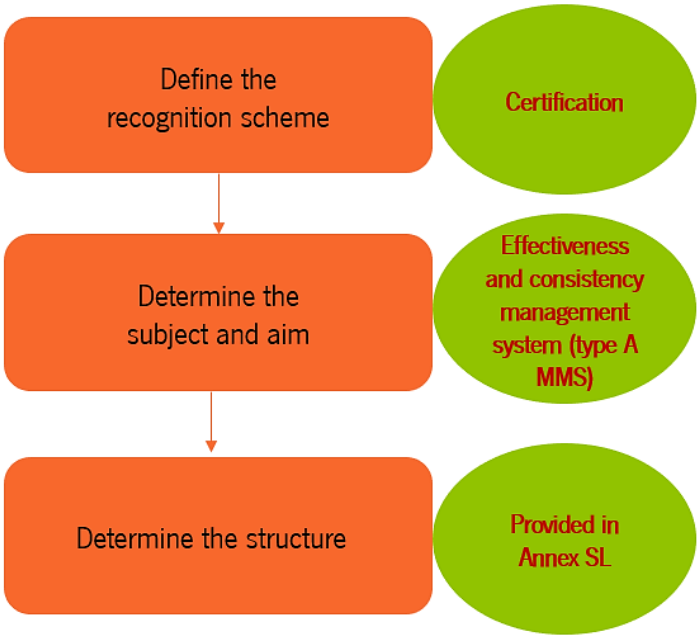


Figure 39. Procedure to establish the structure of the standard.

All the management system standards have a common structure – its main clauses –, the high-level structure (HLS) as determined by the ISO/IEC Directives (ISO/IEC, 2020c) Additional sub-clauses were added to address specific elements from the microbial biobanking.

4.6.6 DISCUSSION

The stage "*control of drafting*" was added to the SSS as, to our knowledge, neither ISO or ISEAL have procedures to control the drafting of standards.

The advantages are the: (1) identification of the ongoing version of the working draft at all moments, (2) identification of changes between different versions - knowledge about what changes were implemented, why, when and by who, and (3) identification of the origin of each provision in the working draft, (4) identification of the author/s of actions, by keeping traceability of decisions and changes.

It makes possible to support comment-discussion during the public consultation and to prevent discussions between developers repeated over time about the same issues. In fact, the development of a standard can take years and it is difficult for the developers to remember where the requirements came from, why and by whom a certain decision was made and why some requirement was added or deleted. It is important then, to keep traceability of decisions.

Decision on the structure is linked to the assessment scheme foreseen. It's our believe that awareness of this fact is very low among experts in technical committees and the risk of developing standards that

do not fit the interested parties' expectations is probably high compromising the standard setting principles such as Transparency, Impartiality, Consensus and eventually promoting technical barriers to trade.
The chosen structure enables alignment with other MSS greatly simplifying integration with other standards such as ISO 14001-Environmental management and ISO 26000-Social responsibility.

The content of the standard encompasses the relevant provisions selected from different reference documents and is aligned with the biobanking principles. The requirements are expressed in terms of process management and performance criteria. So, all the requirements convey criteria and the method to evaluate the fulfilment of the criteria is identified. Besides making the standard easy to understand and facilitating the translation to other languages, it will lead to a greater objectivity in conformity assessment leading to reliable results and improved reproducibility.

To write a standard demands a specific way of communication that experts in technical committees' experts may not master as they have, in principle, expertise in the field of standardisation, not in the standardisation practice.
Additional research to develop full guidance on how-to-write-requirements, could be interesting to achieve higher consistency in standards.

Besides the common text from annex SL, the provisions in the project-standard came mainly from the OECD BPG and ISO 9001. Nonetheless, all the other standards were a valuable source of provisions as, together, they cover the most important issues for mBiobanks.

4.7 THE STANDARD VALIDATION

The validation of the standard was done in order to ensure that (1) all the requirements clearly contribute to the attainment of the standard's goals, (2) only requirements that are relevant to meet these outcomes are included and (3) all the necessary requirements to address the defined goals are included.
Provisions' validation was done by (1) identifying the link between each requirement, the leading objective and the related biobanking-principle, (2) confirming that the provisions on the standard tackle all the objectives and (3) confirming that all mitigation measures established from the risk assessment were implemented.

To facilitate the link between the requirement and the appropriate objective, an intention declaration was made for each requirement or set of requirements, defining the desired outcome.
The results are presented below.

Context of the organization

Understanding the mBiobank and its context

Provision	Objective	Principle
The mBiobank shall determine external and internal issues that are relevant to its purpose and strategic direction and that affect its ability to achieve the intended result(s) of its C&EMS.	Ensure consistent and effective preservation and supply, biosecurity, biosafety and law compliance	All
The mBiobank shall monitor and review information about these external and internal issues.	Ensure that a consistent and effective preservation and supply, biosecurity, biosafety and law compliance is maintained.	All

Understanding the needs and expectations of interested parties

Provision	Objective	Principle
Due to their effect or potential effect on the mBiobank's ability to consistently and effectively preserve and supply authentic microorganisms meeting the interested parties and applicable statutory and regulatory requirements, the mBiobank shall determine: - the interested parties that are relevant to the C&EMS, and - the requirements of these interested parties that are relevant to the C&EMS.	Ensure consistent and effective preservation and supply, biosecurity, biosafety and law compliance.	All
The organization shall monitor and review information about these interested parties and their relevant requirements.	Ensure that a consistent and effective preservation and supply, biosecurity, biosafety and law compliance is maintained.	All

Determining the scope of the C&E management system

Provision	Objective	Principle
The mBiobank shall determine the boundaries and applicability of the C&EMS to establish its scope.	Ensure consistent and effective preservation and supply, biosecurity, biosafety and law compliance.	Rigor Law compliance

When determining the scope, the mBiobank shall consider: - the external and internal issues referred to in 4.1, - the requirements of relevant interested parties referred to in 4.2. - the microbiological domain it operates; - the nature of the microorganism preserved; - the safe operational level or safety limit for the handled microorganism; - the technical capacity for the intended-to-preserve microorganism.		
The mBiobank shall apply all the requirements of this standard if they are applicable within the determined scope of its C&E management system.		Rigor
The scope of the Biobank's C&MS shall be available to interested parties and be maintained as documented information. The scope shall state the nature of the biological material preserved and provide justification for any requirement of this standard that the Biobank determines is not applicable to the scope of its C&EMS. Conformity to this Standard may only be claimed if the requirements determined as not being applicable do not affect the Biobank's ability to ensure and demonstrate the effectiveness and consistency in microorganism preservation.	The main objective of the present standard is to provide general and specific requirements for the microbial biobank C&E management system in order to meet the mBb's interested parties' requirements. This standard also provides the necessary reference for certification/accreditation of microbial biobanks by competent bodies.	All
The BB has the responsibility to ensure that if it is in risk of closing down the BM is preserved.	Meet the interested parties' requirements.	Halt of biodiversity loss

C&E management system

Provision	Requirement	Principle
The MBiobank shall establish, implement, maintain and continually improve a C&MS, including the processes needed for microorganism reception, preservation, authentication and supply and their interactions, and biosafety and biosecurity procedures, in accordance with the provisions of this Standard.	Ensure consistent and effective preservation and supply, biosecurity, biosafety and law compliance.	All
The Biobank shall determine the processes needed for the C&EMS and their application throughout the Biobank, and shall:	Ensure consistent and effective preservation and supply, biosecurity, biosafety and law compliance.	All

a) determine the inputs required and the outputs expected from these processes; b) determine the sequence and interaction of these processes; c) assign the responsibilities and authorities for these processes; d) determine and apply the criteria and methods (including monitoring, measurements and related performance indicators) needed to ensure the affective operation and control of these processes; e) evaluate these processes and implement any changes needed to ensure that these processes achieve their intended results; f) scientifically justify any change in defined criteria arising from non-conformity identification; g) determine the resources needed for these processes and ensure their availability; h) determine and document the requirements to qualify the equipment and infrastructure; i) address the risks and opportunities as determined in accordance with the requirements of 6.1; j) improve the processes and the C&EMS.		
To the extent necessary, the mBiobank shall: a) maintain documented information to support the operation of its processes; b) retain documented information to have confidence that the processes are being carried out as planned.	Have confidence in process results. Objective evidence needed for conformity assessment.	Rigor

Leadership | Leadership and commitment | General

Provision	Objective	Principle
Top management shall demonstrate leadership and commitment with respect to the C&EMS by:		
a) taking accountability for the management of the C&EMS;	To meet the interested parties' requirements.	Rigor, Halt biodiversity loss
b) ensuring that the deposit, supply and C&E policies and the quality	To meet the interested parties' requirements.	All

objectives are established for the C&EMS and are compatible with the context, the mBiobanking principles the and its strategic direction;		
c) ensuring the Biobank or the organization of which the Biobank is a part shall be an entity that can be held legally responsible for its activities,	To meet the interested parties' requirements.	All
d) promoting the use of the process approach and risk-based thinking;	To meet the interested parties' requirements.	Rigor, Halt biodiversity loss, Security, Safety
e) ensuring that the resources needed for the Q &C management system are available;	Ensure effectiveness and consistency in preservation and supply	All
f) communicating the importance of conforming to the C&EMS requirements;	To meet the interested parties' requirements.	Rigor
g) ensuring that the C&EMS achieves its intended results;	Ensure effectiveness and consistency in preservation and supply	Rigor
h) engaging, directing and supporting persons to contribute to the C&EMS management;	To meet the interested parties' requirements.	Rigor
i) promoting improvement;	To meet the interested parties' requirements.	Rigor
j) supporting other relevant management roles to demonstrate their leadership as it applies to their areas of responsibility;	To meet the interested parties' requirements.	Rigor
k) ensuring that the mBiobank shall not operate beyond the established safe operational level or safety limit (see 4.3 scope).	Procedures on biosafety are in place	Biosafety

Customer and key interested parties focus

Provision	Objective	Principle
Top management shall demonstrate leadership and commitment with respect to the customer and key interested parties focus by ensuring that:	To meet the interested parties' requirements.	Rigor
a) customer and key interested parties and applicable statutory and regulatory requirements are determined, understood and met;	Ensure effectiveness and consistency in preservation and supply.	Rigor
b) the risks and opportunities that can affect conformity of the preserved microorganisms and the ability of the mBiobank to consistently and effectively preserve the microorganisms are determined and addressed;	Ensure effectiveness and consistency in preservation and supply. To meet the interested parties' requirements.	All

c) the focus on enhancing customer and key interested parties' satisfaction is maintained.	Ensure effectiveness and consistency in preservation and supply.	All

Competence focus

Provision	Objective	Principle
Top management shall demonstrate leadership and commitment with respect to the personnel competence ensuring that:	Ensure effectiveness and consistency in preservation and supply.	Rigor
a) competence requirements are determined, understood and consistently met;	Ensure effectiveness and consistency in preservation and supply.	Rigor
b) the risks and opportunities for the C&EMS efficiency that can affect competence of person(s) doing work under its control that affects efficiency of the C&E MS are determined and addressed.	Ensure effectiveness and consistency in preservation and supply.	Rigor

Policies

Establishing the C&E policy

Provision	Objective	Principle
Top management shall establish, implement and maintain a C&E policy that:	Ensure effectiveness and consistency in preservation and supply.	All
- is appropriate to the purpose and the context of the mBiobank and supports its strategic direction;	Ensure effectiveness and consistency in preservation and supply. To meet the interested parties' requirements.	All
- provides a framework for setting C&E objectives;	To meet the interested parties' requirements.	All
- provides a framework for the process validation;	Ensure effectiveness and consistency in preservation and supply.	Rigor, Technological updating
- includes a commitment to avoid any involvement in activities that could lessen the reliability of the interested parties;	To meet the interested parties' requirements.	Law compliance

- includes a commitment to comply with the laboratory best practice;	Ensure effectiveness and consistency in preservation and supply.	Rigor
- includes a commitment to ensure that person(s) participating in business processes know and apply the policies and procedures in their work	Ensure effectiveness and consistency in preservation and supply. To meet the interested parties' requirements.	Rigor
- includes a commitment to satisfy applicable requirements;		Rigor
- includes a commitment to continual improvement of the C&EMS;	Ensure effectiveness and consistency in preservation and supply.	Rigor
- shall not contradict the mBiobanking Principles.	To meet the interested parties' requirements.	Rigor

Biological material accession/acquisition/deposit /admission/acceptance policy

Provision	Objective	Principle
Top management shall establish, implement and maintain a biological material accession policy that:	To meet the interested parties' requirements.	Law compliance, Origin respect
- includes the identification of the biological material to be preserved;	To meet the interested parties' requirements.	Rigor
- is appropriate to the specific domain of the Biobank;	To meet the interested parties' requirements.	Rigor
- fulfils the OECD Guidelines and statutory and regulatory requirements;	To meet the interested parties' requirements.	Rigor, Law compliance
- includes the criteria on which the acceptance of new biological material intended to integrate the collection is based;	To meet the interested parties' requirements.	Rigor
- includes a commitment of treating all information related to the clients strictly confidential, unless national requirements apply,	To meet the interested parties' requirements.	Confidentiality
- includes a commitment to only accept deposits of biological material that meets the here present access criteria and fall into the groups of its specialist expertise,	To meet the interested parties' requirements.	Rigor
- includes a commitment to only accept deposits which are proven to be obtained legitimately,	To meet the interested parties' requirements.	Law compliance, Origin respect
- includes a disclaimer of responsibility of all information about the biological material provided by the depositor;	Ensure effectiveness and consistency in preservation and supply.	Rigor

Biological material supply policy

Provision	Objective	Principle
Top management shall establish, implement and maintain a microorganism supply policy that:	To meet the interested parties' requirements.	
- meets the specific requirements for supply as required by national and international statutory and regulatory requirements and relevant sectorial policies;	Fundamental procedures on biosafety and biosecurity are in place. To meet the interested parties' requirements.	Security, Safety, Law compliance
- includes the criteria upon which the material biological supply is based;	Fundamental procedures on biosafety and biosecurity are in place. To meet the interested parties' requirements.	Security, Safety, Law compliance
The mBiobank microorganism supply policy shall include, at least a commitment to:		
- only supply to users who have the appropriate facilities,	To meet the interested parties' requirements.	Security, Safety, Law compliance
- treat all information related to the clients strictly confidential, unless national requirements apply,	To meet the interested parties' requirements.	Confidentiality
- only supply micro-organisms to laboratories trained in microbiology and having access to properly equipped laboratories, with exceptions properly justified in documented information.	To meet the interested parties' requirements.	Safety

Communicating the policies

Provision	Objective	Principle
The mBiobank policies shall		
- be available as documented information, - be communicated and applied within the organization, - be available to relevant interested parties, as appropriate, - be reviewed for continuing suitability.	To meet the interested parties' requirements.	Rigor

Organizational roles, responsibilities and authorities

Provision	Objective	Principle
Top management shall ensure that the responsibilities and authorities for relevant roles are assigned, communicated, understood and made available as documented information within the organization.	Ensure effectiveness and consistency in preservation and supply.	Rigor
Responsibility and authority assigned shall include but not be limited to:		
- microorganism testing; - method amendments; - process validation master plan definition and implementation;	Ensure effectiveness and consistency in preservation and supply.	Rigor, Technological updating
- grant permission to visitors; - grant access to security areas; - grant access to microorganism stored within the security areas;	Procedures on biosafety and biosecurity are in place	Safety, Security
- competence requirements for person(s) doing work under its control; - accountability for the C&EMS compliance with the requirements of this Standard; - ensure that the processes are designed to delivering their intended outputs; - reporting and advising on the performance of the C&EMS and on opportunities for improvement (see 10.1) in particular to top management; - ensure that the integrity of the C&EMS is maintained when changes to the system are planned and implemented	Ensure effectiveness and consistency in preservation and supply.	Rigor
- ensure overall operation and administration of the mBiobank including budget planning and financial management;	To meet the interested parties' requirements.	Biodiversity preservation
- relate with regulatory agencies, the community, users, suppliers and providers of formal agreements; - ensure that there are appropriate numbers of staff with the required competence; - ensure the implementation of the quality policy;	To meet the interested parties' requirements.	Rigor
- implement a safe laboratory environment in compliance with OCDE BPG, laboratory best practice and applicable requirements;	Procedures on biosafety are in place	Safety, Law compliance

- implement the security measures in compliance with OCDE BPG and applicable laws and regulations;	Procedures on biosecurity are in place	Security, law compliance
- establish, implement and maintain up-to-date a contingency plan to ensure that preserved microorganisms are maintained during emergency situations or other conditions when laboratory services are limited or unavailable (see also 6.1);	To meet the interested parties' requirements.	Biodiversity preservation
- ensure compliance with this standard and biosecurity and biosafety provisions.	All	All

Planning

Actions to address risks and opportunities

Provision	Objective	Principle
When planning for the C&EMS, the mBiobank shall consider the issues referred to in 4.1 and the requirements referred to in 4.2 and determine the risks and opportunities that need to be addressed to:		
- to identify processes sources of variation;	Consistency	Rigor
- prevent or reduce undesired effects;	Effectiveness, consistency	Rigor
- achieve improvement;	Effectiveness, consistency	Rigor
- ensure the C&EMS can achieve its intended result(s);	Effectiveness, consistency	Rigor
- to enhance desirable effects;	Effectiveness, consistency	Rigor
- ensure the existence of the necessary capacity building.	to meet the interested parties' requirements and expectations	Preserve biodiversity

Provision	Objective	Principle
The risk assessment shall include, but not be limited to:		
- infrastructure, equipment and processes;	Effectiveness, consistency	Rigor
- information system,	Effectiveness, consistency	Confidentiality, rigor, security

- microorganism potential to cause harm to the health of humans, crops, livestock or infrastructure;	Biosafety	Safety
- the nature of the microorganisms in the Biobank inventory in order to assign it to the appropriate biosecurity risk levels;	Biosecurity	Security
- the mBiobanks's information security and customer's property;	Biosecurity	Security
- the Biobank's sustainability;	to meet the interested parties' requirements and expectations	Preserve biodiversity
- improper influence on staff that may negatively affect the safety and security of the mBiobank;	Biosecurity	Security
- externally provided processes (prior to determine the type and extent of control to apply);	Ensure effectiveness and consistency	Rigor
- integrity of the system when alterations are planned and implemented;	Ensure effectiveness and consistency	Rigor
- the potential misuse of the microorganisms in the mBiobank repository.	Biosecurity	Security

Provision	Objective	Principle
When doubts exist, the microorganism shall be assigned to the higher of two possible levels.	Biosecurity, biosafety	Security, safety
The risk assessment shall be reviewed at planned intervals, at least on an annual basis. The results shall be retained as documented information.	Biosecurity, biosafety	Security, safety
The mBiobank shall plan:		
a) actions to address identified risks, including but not limited to:		
i. biosafety and biosecurity assurance;	Biosecurity, biosafety	Security, safety
ii. control sources of variability;	Consistency	Rigor
iii. integrity of the key holdings in case of planned changes or if the mBiobanks future is threatened;	To meet the interested parties' requirements and expectations	Preserve biodiversity
iv. control of external provided processes;	Ensure effectiveness and consistency	Rigor
v. protect customer's property.	To meet the interested parties' requirements and expectations	Preserve biodiversity, Confidentiality

b) actions to address identified opportunities;	To meet the interested parties' requirements and expectations	Continual improvement
c) how to		
i. integrate and implement the actions into its C&EMS processes (see 4.4)	Ensure effectiveness and consistency	Rigor
ii. evaluate the effectiveness of these actions.	Ensure effectiveness and consistency	Rigor

C&E objectives and planning to achieve them

Provision	Objective	Principle
The organization shall establish the C&E objectives at relevant functions, levels and processes needed for the C&EMS.	To meet the interested parties' requirements and expectations	All
The C&EMS objectives shall:		
- be measurable;	Ensure effectiveness and consistency	Rigor
- take into account applicable requirements;	Ensure effectiveness and consistency	Rigor
- be relevant to the conformity of the biological material and preservation performance, to the competence of the Biobank and to the enhancement of customer and relevant interested parties' satisfaction;	Ensure effectiveness and consistency	Rigor
- be monitored;	Ensure effectiveness and consistency	Rigor
- be communicated;	Ensure effectiveness and consistency	Rigor
- be updated as appropriate;	Ensure effectiveness and consistency	Rigor, continual improvement
The organization shall maintain documented information on the C&E objectives and its results.	Ensure effectiveness and consistency	Rigor
When planning how to achieve its C&E objectives, the mBiobank shall determine:	Ensure effectiveness and consistency	Rigor
i. what will be done;		
ii. what resources will be required;		
iii. who will be responsible;		

iv. when it will be completed;		
v. how the results will be evaluated.		

Planning of changes

Provision	Objective	Principle
When the mBiobank determines the need for changes to the C&EMS, the changes shall be carried out in a planned manner (see 4.4).	Ensure effectiveness and consistency	Rigor
The mBiobank shall consider:		
- the purpose of the changes and their potential consequences (see 6.1);		
- the integrity of the Q&CMS management system;		
- the availability of resources;		
- the allocation or reallocation of responsibilities and authorities.		

Biosafety

Provision	Objective	Principle
The Biobank shall ensure that all biological materials are assigned to appropriate risk groups; this includes a positive assignment to Risk Group 1 unless otherwise considered hazardous. Risk group information shall be recorded and made available to recipients of the microorganisms.	Procedures on biosafety are in place	Safety
The Biobank shall establish and document safe procedures appropriate to the type of biological materials handled and according to definition as minimum handling procedures for pathogenic microorganisms as established by appropriate authorities at national level (see Note 1).	Procedures on biosafety are in place	Safety

Biosecurity

Internal access to hazardous BM

Provision	Objective	Principle
The Biobank shall ensure that microorganisms assigned to a high biosecurity risk are stored and handled within the high security area, by authorized person(s). A chain custody for the biological material that presents a moderate or high biosecurity risk movement from outside the high security or restricted area (see 7.3) shall be established, documented and implemented.	Procedures on biosecurity are in place	Security
The Biobank shall determine the requirements for security screening of person(s) doing work under its control, in line with national privacy law, before the granting of access to a higher security level.	Procedures on biosecurity are in place	Security
The Biobank shall control the access of visitors and persons doing work under the Biobank control, to the security areas (see 6.1) ensuring that only authorized person(s) have access to microorganisms that are pathogenic or toxic to human, animals and plants; security devices should be used. All persons in the mBiobank shall carry, except in circumstances where doing so would present a health and safety risk, an identification item indicating the maximum level of security access (see Note 1).	Procedures on biosecurity are in place	Security
The Biobank shall capture the identification item upon termination of employment or work under its control and retain information about the person. Identification items from visitors shall be retain when exiting. Records from visitors shall be retained by the Biobank.	Procedures on biosecurity are in place	Security

Supply

Provision	Objective	Principle
The Biobank shall identify the institutions and/or person(s) authorised to be supplied with pathogenic or toxic to humans animals and plants microorganisms and shall ensure that those microorganisms are only supplied to these authorised institutions or persons by verifying their validity.	Procedures on biosecurity are in place	Security

Documented information proving that the user has the appropriate containment means and the authorisation to import and handle such biological material shall be obtained and retained.	Procedures on biosecurity are in place	Security

Inventory

Provision	Objective	Principle
The mBiobank shall maintain as documented information the identification of all preserved microorganisms.	Procedures on biosecurity are in place	Security

Support | Resources | General

Provision	Objective	Principle
The mBiobank shall determine and provide the resources needed for the establishment, implementation, maintenance and continual improvement of the C&EMS.	Ensure effectiveness and consistency	Rigor, Competence, Continual improvement
The mBiobank shall consider: i. the capabilities of, and constraints on, existing internal resources; ii. what needs to be obtained from external providers.	Ensure effectiveness and consistency	Rigor, Competence, Continual improvement

People

Provision	Objective	Principle
The mBiobank shall determine and provide the persons necessary for the effective implementation of its C&EMS and for the operation and control of its processes.	Ensure effectiveness and consistency	Rigor, Competence,

Infrastructure

Provision	Objective	Principle
The mBiobank shall determine, provide and maintain the infrastructure necessary for the operation of its processes and to achieve conformity with biosafety, biosecurity and microorganism's preservation requirements (see Note 1).	Ensure effectiveness and consistency	All
The mBiobank shall have its infrastructure (including all areas under its responsibility):		
- in conformity with the containment level appropriate for the risk group of the preserved microorganisms;	Biosafety procedures are in place	Safety
- qualified according to the validation requirements and reflecting any seasonal variation;	Consistency	Rigor
- described and maintained as documented information.	Ensure effectiveness and consistency	Rigor

Provision	Objective	Principle
The mBiobank shall determine the appropriate areas to accommodate its activities, with an effective separation between nearby areas where incompatible activities are carried out including, but not limited to:	Ensure effectiveness and consistency, biosecurity and biosafety procedures.	Rigor, Security, Safety
- receipt and storage of the initial microorganisms;		
- preparation, regeneration, handling and processing microorganisms;		
- microorganisms storage area and back-up or safety duplicate collection (see Note 3).		
- supply, delivery/sales kept separated from incoming accessions;		
- decontamination and cleaning of equipment and processing of wastes.		

Provision	Objective	Principle
The mBiobank building and other associated areas shall:		

i. respect the containment level appropriate for the risk group of the microorganisms worked with;	Biosafety procedures.	Safety
ii. be classified and identified according to the risk level associated to the nature of the held biological material (“high”, “restricted” and “general” security areas, as appropriate (see 6.1, 7.6 and 7.7);	Biosafety procedures.	Safety
iii. be structurally sound;	Ensure effectiveness and consistency, biosecurity and biosafety procedures.	Safety, security, rigor
iv. be unobstructed, clean and free from laboratory materials.	Ensure effectiveness and consistency, biosecurity and biosafety procedures.	Safety, security, rigor

Provision	Objective	Principle
The procedures for the management of the mBiobank’s equipment shall:		
i. include the necessary information for use, control of performance and maintenance (see 7.1.4);	Ensure effectiveness and consistency	Rigor
- be available to the authorised users;		
- be maintained as documented information.		

Environment for the operation of processes

Provision	Objective	Principle
The mBiobank shall determine provide and maintain the environment necessary for the operation of its processes and to consistently achieve conformity in microorganism preservation.	Ensure effectiveness and consistency	Rigor

Monitoring and measuring resources

General

Provision	Objective	Principle
The mBiobank shall determine and provide the resources needed to ensure valid and reliable results when monitoring or measuring is used to process control and to microorganism testing and activities having a significant impact on the mBb's objectives.	Ensure consistent and effective preservation	Rigor
The mBiobank shall ensure that the provided resources are:		
- suitable for the specific type of monitoring and measurement activities being undertaken;	Ensure consistent and effective preservation	Rigor
- qualified for operation including at least:	Ensure consistent and effective preservation	Rigor
i. confirmation of the correct installation;		
ii. ensuring the access to all the relevant information about operation and maintenance;		
iii. calibration, if appropriate;		
iv. testes to confirm the upper and lower operating limits and/or worst case conditions;		
v. qualified for performance, including but not limited to performing tests covering the operating range of the intended process in order to confirm compliance with requirements;		
- re-qualified at planned intervals, to confirm the state of control;		
- are maintained to ensure their fitness for purpose.		

Measurement traceability

Provision	Objective	Principle
When measurement traceability is a requirement or is considered by the mBiobank to be an essential part of providing confidence in the validity of measurement results measuring equipment shall be:	Ensure consistent and effective preservation	Rigor
- calibrated and/or verified at planned intervals, and prior to use, against measurement standards traceable to international or national measurement standards; when no such standards exist, the basis used for calibration or verification shall be retained as documented information;		
- identified in order to determine their status and, when relevant, its usual location;		
- safeguarded from adjustments damage or deterioration that would invalidate the calibration status and subsequent measurement results.		
The mBiobank shall determine if the validity of previous measurement results has been adversely affected when measuring equipment is found to be unfit for its intended purpose and shall take appropriate action as necessary.		

Organizational knowledge and process understanding

Provision	Objective	Principle
The mBiobank shall determine the knowledge and understanding necessary for the operation of its processes and to achieve a consistent effectiveness in process results. This knowledge and understanding shall be maintained and be made available to the extent necessary.	Ensure consistent and effective preservation	Rigor
When addressing changing needs and process understanding the mBiobank shall consider its current knowledge and determine how to acquire or access any necessary additional knowledge and required updates.	Ensure consistent and effective preservation	Rigor

Provision	Objective	Principle
The mBiobank shall continually update knowledge relevant to the taxonomy, handling, preservation/processing and distribution of micro-organisms. A procedure shall be established and implemented for the:	Ensure consistent and effective preservation	Continual improvement
- identification of key literature and legal requirements;		
- communication inside de mBiobank;		
- periodicity for analysis.		

Competence

Provision	Objective	Principle
The mBiobank shall		
- determine the necessary competence of person(s) doing work under its control that affects the performance and effectiveness of the C&EMS.	Ensure consistent and effective preservation	Competence
- ensure that these persons are competent on the basis of appropriate education, training, or experience;		
- where applicable, take actions to acquire the necessary competence, and evaluate the effectiveness of the actions taken;		
- retain appropriate documented information as evidence of competence, including authorisation to use specialist equipment, perform special tasks.		

Awareness

Provision	Objective	Principle
The mBiobank shall ensure that persons doing work under its control are aware of:		
- the system policies;	To meet the interested parties' requirements	All

- relevant objectives;	Ensure consistent and effective preservation; To meet the interested parties' requirements	All
- the importance to comply with the procedures related the appropriate level of containment for the organisms being handled to avoid sample contamination, risk of infection and environmental dispersion;	Biosafety procedures in place.	Safety
- the importance to comply with biosecurity procedures;	Biosecurity procedures in place.	Security
- their contribution to the effectiveness of the C&EMS, including the benefits of improved performance;		
- the risks arising from breaches on biosafety and biosecurity procedures;	Biosecurity and biosafety procedures in place.	Security, Safety
- the implications of not conforming with the C&EMS requirements.	Ensure consistent and effective preservation; To meet the interested parties' requirements	All

4.8 COMMUNICATION

Provision	Objective	Principle
The mBiobank shall determine the internal and external communications relevant to the C&EMS, including:	Ensure consistent and effective preservation; To meet the interested parties' requirements.	All
- on what it will communicate;		
- when to communicate;		
- with whom to communicate;		
- how to communicate;		
- who communicates.		
On communicating with customers and interested parties the mBiobank shall:		
- make available data describing the biological material (Minimum Data Set shall be available – see Note 1);		

- make available data describing the biological material origin;	Law compliance	Origin respect
- provide user with electronic catalogues (see note3)		
- ensure information security, protection of IPRs and client information, while providing data to users;		
- comply with the Protection of Privacy and Transborder Flows of Personal data;		

Provision	Objective	Principle
The Biobank shall establish the criteria to apply when deciding which information related to the microorganisms held will enter the public domain.	To meet the interested parties' requirements; Ensure consistent and effective preservation	Security, Origin respect, Law compliance, Confidentiality

Documented information

General

Provision	Objective	Principle
The mBiobank's C&EMS shall include:		
- documented information required by this Standard;	Ensure consistent and effective preservation	Rigor
- documented information determined by the mBiobank as being necessary for the effectiveness of the C&EMS;	Ensure consistent and effective preservation	Rigor
- documented information necessary for legal purposes;	To meet the interested parties' requirements	Rigor, law compliance
- a description of the mBiobank's C&EMS, the identification of the biobanking domain and, the processes of the C&EMS and its interactions.	To meet the interested parties' requirements	All

The mBiobank's documented information shall be communicated to relevant person(s) doing work under its control. The Biobank shall ensure that this information is understood and that is easily available to relevant persons.	Ensure consistent and effective preservation	Rigor

Creating and updating

Provision	Objective	Principle
When creating and updating documented information the mBiobank shall ensure:		
- Appropriate format	Ensure consistent and effective preservation	Rigor
- The availability of media to immediate record of observations, data and calculations (temporary records);	Ensure consistent and effective preservation	Rigor
- Review and approval for reliability and accuracy;	Ensure consistent and effective preservation; To meet the interested parties' requirements	Rigor, continual improvement
- Identification of authorized reference documents against which new data shall be introduced to prevent errors such as mistyping;	Ensure consistent and effective preservation; To meet the interested parties' requirements	Rigor, continual improvement
- Procedures to detect errors in data in order to improve their quality and consistency.	Ensure consistent and effective preservation; To meet the interested parties' requirements	Rigor, continual improvement

Control of documented information

Provision	Objective	Principle
Documented information required by the C&EMS and by this standard shall be controlled to ensure:		
- it is available and suitable for use, where and when it is needed;	Ensure consistent and effective preservation	Rigor
- it is adequately protected;	To meet the interested parties' requirements	Rigor, security, law compliance
For the control of documented information, the organization shall address the following activities, as applicable:		

- distribution, access, retrieval and use (see note 2);	To meet the interested parties' requirements; Ensure consistent and effective preservation	Rigor, security, law compliance
- storage and preservation, including preservation of legibility		
- control of changes		
- retention and disposition		

Provision	Objective	Principle
Documented information of external origin determined by the organization to be necessary for the planning and operation of the C&EMS shall be identified as appropriate, and be controlled.	To meet the interested parties' requirements; Ensure consistent and effective preservation	Rigor, security, law compliance
Documented information retained as evidence of conformity shall be protected from unintended alterations.	To meet the interested parties' requirements; Ensure consistent and effective preservation	Rigor, security, law compliance

Information system

Provision	Objective	Principle
The Biobank shall maintain and continually update:		
- a data base for internal use of the held microorganisms and related information;	Ensure consistent and effective preservation	Rigor, security, law compliance
- an electronic catalogue providing information to users about the microorganism held.	To meet the interested parties' requirements	
The data base and information system shall:		
- enable restricted access and information classified with different access levels (see note 1);	To meet the interested parties' requirements	Security, confidentiality, law compliance
- protection for confidential data;	To meet the interested parties' requirements	Security, confidentiality, law compliance
- request user authentication and check identifiers and password validity;	To meet the interested parties' requirements	Security, confidentiality, law compliance
- have mechanisms in place to avoid the loss of data and ensure its	To meet the interested parties' requirements	Rigor, Security, confidentiality

integrity.	Ensure consistent and effective preservation	
The Biobank shall maintain data relating to lost strains; this data shall be identified as no longer available as living material.	To meet the interested parties' requirements	Rigor, biodiversity preservation

Operation | Operational planning, development and maintenance

Provision	Objective	Principle
The mBiobank shall plan, develop, qualify, implement, maintain and control the process(es) (see 4.4) need(ed) to:		
• meet the requirements for the effective and consistent preservation of microorganisms, assuring biosafety and biosecurity, and to implement the actions determined to address risks and opportunities, by:	To meet the interested parties' requirements; Ensure consistent and effective preservation	All
• determining the process(es) inputs and outputs;	Ensure consistent and effective preservation	Rigor
• determining the requirements for the:		
- an effective and consistent microorganism preservation;	Ensure consistent and effective preservation; To meet the interested parties' requirements;	Rigor
- performance qualification;	Ensure consistent and effective preservation;	Rigor
- biosafety assurance;	To meet the interested parties' requirements;	Safety
- biosecurity assurance;	To meet the interested parties' requirements;	Security
• establishing the normal operating range for preservation process operation;	Ensure consistent and effective preservation;	Rigor
• establishing the strategy for the preservation process control;	Ensure consistent and effective preservation;	Rigor
• determining the resources needed to achieve:		
- effectiveness and consistency in microorganism preservation and testing	Ensure consistent and effective preservation;	Rigor
- conformity to the biosafety and biosecurity requirements.	Procedures in biosafety and biosecurity; To meet the interested parties' requirements;	Safety, security

The o mBiobank shall control planned changes and review the consequences of unintended changes, taking actions to mitigate any adverse effects, as necessary. Changes to the approved procedures, acceptance criteria or operating parameters, shall be documented and scientifically justified.	Ensure consistent and effective preservation	Rigor
The mBiobank shall ensure that outsourced processes are controlled (see 8.4).	Ensure consistent and effective preservation	Rigor

Control of externally provided processes, products and services | General

Provision	Objective	Principle
The Biobank shall determine and document the requirements for the externally provided processes, products and services, communicate these requirements to the external provider and ensure that the externally provided processes, products and services conform to requirements.	Ensure consistent and effective preservation	Rigor
The Biobank shall determine the controls to be applied to externally provided processes, products and services when:		
- products and services from external providers are intended for the microorganism preservation, authentication and/or transport;	Ensure consistent and effective preservation	Rigor
- services from external providers are intended for validation purposes;	Ensure consistent and effective preservation	Rigor
- microorganism is supplied directly to the customer by external providers on behalf of the mBiobank;	Ensure consistent and effective preservation	Rigor
- microorganism intended to preserve is received from the customer by an external provider under the responsibility of the mBiobank;	Ensure consistent and effective preservation	Rigor
- a process, or part of a process, is provided by an external provider as a result of a decision by the mBiobank.	Ensure consistent and effective preservation	Rigor
The mBiobank shall determine and apply criteria for the selection, evaluation, monitoring and re-evaluation of performance of external providers based on	Ensure consistent and effective preservation	Rigor

their ability to provide processes or products and services in accordance with requirements. The mBiobank shall retain documented information of these activities and any necessary actions arising from the evaluations.		
When the Biobank decides to externally provide the preservation and /or authentication process, or part of these, the Biobank shall ensure that this (these) process(es), and all the inter-related processes, are validated according to this International Standard provisions.	Ensure consistent and effective preservation	Rigor
The Biobank shall determine which external provided processes, or part of these, shall be communicated to the customers. When storage of the preserved microorganisms is externally provided customers shall be informed.	To meet the interested parties' requirements;	Rigor

Type and extent of control

Provision	Objective	Principle
The Biobank shall ensure that externally provided processes, products and services do not adversely affect the mBiobank's ability to consistently preserve and supply authenticated microorganisms. The mBiobank shall determine the risks of externally provided processes, products and services to the effectiveness and consistency of the preservation process and microorganism authentication and, when necessary, take measures to avoid negative effects.	Ensure consistent and effective preservation; To meet the interested parties' requirements;	All
The Biobank shall:		
a) ensure that externally provided processes remain within the control of its C&EMS;	Ensure consistent and effective preservation; To meet the interested parties' requirements;	All
b) define both the controls that it intends to apply to an external provider and those it intends to apply to the resulting output;	Ensure consistent and effective preservation; To meet the interested parties' requirements;	All
c) take into consideration:		

- the potential impact of the externally provided processes, products and services on the Biobanks's ability to consistently meet customer and applicable statutory and regulatory requirements;	Ensure consistent and effective preservation; To meet the interested parties' requirements;	All
- the effectiveness of the controls applied by the external provider;	Ensure consistent and effective preservation; To meet the interested parties' requirements;	All
d) determine the verification, qualification or other activities, necessary to ensure that the externally provided processes, products and services meet requirements.	Ensure consistent and effective preservation; To meet the interested parties' requirements;	All
When the Biobank decides to externally provide microorganism processing intended for preservation the process shall be validated according to the provisions of this International Standard, and the related activities, equipment and infrastructure are qualified for performance. Documented information shall be retained for evidence.	Ensure consistent and effective preservation	Rigor
When the mBiobank decides to externally provide microorganism processing and storing, first part audits shall be carried out to externally provided processes, at planned intervals commensurate to risk. Documented information shall be retained.	Ensure consistent and effective preservation; To meet the interested parties' requirements;	All

Information for external providers

Provision	Objective	Principle
The mBiobank shall communicate to external providers its requirements for:		
a) the processes, products and services to be provided;	Ensure consistent and effective preservation and supply	Rigor
b) the approval of:		
- products and services;	Ensure consistent and effective preservation and supply	Rigor
- methods, processes and equipment;	Ensure consistent and effective preservation and supply	Rigor

- the release of products and services;	Ensure consistent and effective preservation and supply	Rigor
c) competence, including any required qualification of persons;	Ensure consistent and effective preservation and supply	Rigor
d) the external providers' interactions with the organization;	Ensure consistent and effective preservation and supply	Rigor
e) control and monitoring of the external providers' performance to be applied by the organization;	Ensure consistent and effective preservation; To meet the interested parties' requirements;	All
f) verification or validation activities that the organization, or its customer, intends to perform at the external providers' premises.	Ensure consistent and effective preservation and supply	Rigor

Production and service provision | Control of production and service provision

Provision	Objective	Principle
The mBiobank shall implement preservation and supply of microorganisms under controlled conditions.	Ensure consistent and effective preservation and supply	Rigor
Controlled conditions shall include, as applicable:		
a) the availability of documented information that defines:	Ensure consistent and effective preservation and supply	
- the required activities to perform biological material preservation, testing and supply;		Rigor
- the results to be achieved;		
b) the availability and use of suitable monitoring and measuring resources;		
c) the implementation of monitoring and measurement activities at appropriate stages to confirm that criteria for control of processes or outputs, and acceptance criteria have been met;		
d) the use of suitable infrastructure and environment for the operation of processes taking into account the biosecurity and biosafety risk level; suitable infrastructure shall include measures to prevent direct		Rigor, safety, security

access of persons to areas where its presence can influence the conformity of the biological material.		
e) the appointment of competent personnel	Ensure consistent and effective preservation; To meet the interested parties' requirements.	All
f) the implementation of actions to prevent error and decrease variability in process results;	Ensure consistent and effective preservation and supply; To meet the interested parties' requirements.	All
g) the implementation of release, delivery and post-delivery activities;	Ensure consistent and effective preservation and supply; To meet the interested parties' requirements.	All
h) the conduction of all activities with biological material in areas corresponding to the appropriate biosecurity risk level resulting from the application of the biosecurity risk assessment (see 6.1).	Biosecurity procedures are in place.	Security
i) the implementation of measures to restrict the access to areas liable of influence the quality of in-process-microorganisms.	Ensure consistent and effective preservation;	Rigor

Accession to Deposit

Provision	Objective	Principle
The Biobank shall establish, document and maintain procedures for the reception, acceptance or denial of requests for microorganism preservation.	Ensure consistent and effective preservation and supply; To meet the interested parties' requirements.	All
The Biobank shall communicate to the customer the conditions for the microorganism deposit. Transparency regarding intellectual property rights shall be provided.	Ensure consistent and effective preservation and supply; To meet the interested parties' requirements.	All

Provision	Objective	Principle
Before accepting a request for biological material deposit, the Biobank shall		

- ensure the authenticity (legitimacy) of the applicant; all biological material requests, including those refused, shall be documented and retained.	To meet the interested parties' requirements.	Origin respect, law compliance, biosafety, biosecurity
- perform a biosecurity risk assessment as established (see 6.3), unless biological material is being transferred from other mBiobank along with the respective risk assessment methodology and results and there are not new circumstances or information that can affect the results of the original assessment;	Biosecurity procedures are in place	Law compliance, biosecurity
- confirm the risk level of the biological material asked for deposit;	Biosecurity and biosafety procedures are in place	Law compliance, security, safety
- confirm the risk level of the biological material asked for deposit is within safety containment level of the mBiobank (see 6.2);	Biosecurity and biosafety procedures are in place	Law compliance, security, safety
- ensure the following information about the biological material is provided:		
a) name and other identifier or a culture description;	Ensure consistent and effective preservation and supply; Biosecurity and biosafety procedures are in place.	All
b) name and address of the applicant [depositor];	Biosecurity and biosafety procedures are in place. To meet the interested parties' requirements.	All
c) source, substrate or host from which the biological material was isolated or derived from (where identified) and date of isolation;	Biosecurity and biosafety procedures are in place. To meet the interested parties' requirements.	All
d) geographical origin of the biological material (the minimum requirement is the country of origin or the furnisher of the source, substrate or host);	To meet the interested parties' requirements.	Origin respect
e) depositor's biological material number or other collection number(s), if deposited elsewhere;	Biosecurity and biosafety procedures are in place. To meet the interested parties' requirements.	All
f) growth media and conditions;	Ensure consistent and effective preservation and supply;	Rigor
g) cell preservation or storage conditions, where known;	Ensure consistent and effective preservation and supply;	Rigor
h) risk information.	Biosecurity and biosafety procedures are in place	Law compliance, security, safety

Provision	Objective	Principle
The mBiobank shall require documented evidence to assure the validity of the provided information. This information shall be maintained.	Biosecurity and biosafety procedures are in place. To meet the interested parties' requirements.	All
Alternative mBiobanks shall be recommended when request is outside the Biobank's expertise.	To meet the interested parties' requirements.	Biodiversity preservation

4.8.1 MATERIAL RECEPTION

Provision	Objective	Principle
The Biobank shall establish, document and implement procedures for the biological material reception, including but not limited to:	Ensure a consistent and effective preservation and supply; Biosafety and biosecurity procedures in place.	Biodiversity preservation, rigor, safety, security, origin respect, law compliance, confidentiality
a) identification;	Ensure a consistent and effective preservation and supply; Biosafety and biosecurity procedures in place.	Biodiversity preservation, rigor, safety, security, origin respect, law compliance, confidentiality
b) quarantine requirements;	To meet the interested parties' requirements. Biosafety and biosecurity procedures in place.	Biodiversity preservation, rigor, safety, security, origin respect, law compliance, confidentiality
c) appropriate contention conditions for opening the package received, in order to assure its safe handling and disposal;	To meet the interested parties' requirements. Biosafety and biosecurity procedures in place.	Biodiversity preservation, rigor, safety, security, origin respect, law compliance, confidentiality
d) the tests to perform in order to confirm:	Ensure a consistent and effective preservation and supply	Rigor
- purity,		
- identity,		
- viability,		
- stability of key features,		

- growth requirements.		

Provision	Objective	Principle
The results from the confirmation procedures shall be documented and maintained they shall be used as base line when in-storage maintenance checks are performed and for testing after preservation.	Ensure a consistent and effective preservation and supply	Rigor

Material preservation

Provision	Objective	Principle
In order to ensure a minimum number of transfers of generations from the original biological material for each biological material the Biobank shall maintain a master cell bank and a stock for distribution for each type of biological material preserved. Master stock shall be produced from the original biological material and shall be used to generate the distribution stock.	Ensure a consistent and effective preservation and supply	Rigor, biodiversity preservation
The distribution stock shall be used to supply purposes.	Ensure a consistent and effective preservation and supply	Rigor, biodiversity preservation
The mBiobank shall give a unique identifier to the biological material preserved which shall never be re-used even when the biological material is eliminated from the mBiobank.	Ensure a consistent and effective preservation and supply. Biosecurity and biosafety procedures are in place.	Rigor, biodiversity preservation, safety, security

Provision	Objective	Principle
The Biobank shall establish, document and maintain procedures for the biological material preservation including, but not limited to:	Ensure a consistent and effective preservation and supply	Rigor, biodiversity preservation
- the type of container for the microorganism (tubes, vials, ampoules);	Ensure a consistent and effective preservation and supply	Rigor, Biodiversity preservation

- storage conditions;	Ensure a consistent and effective preservation and supply	Rigor, Biodiversity preservation,
- method for the assignment of a unique identifier;	Ensure a consistent and effective preservation and supply	Rigor, Biodiversity preservation,
- method for the assignment of the expiry date;	Ensure a consistent and effective preservation and supply;	Rigor, Biodiversity preservation,
- labelling requirements which shall include, at least, the unique identifier, preparation date and expire date;	Ensure a consistent and effective preservation and supply; meet interested parties' requirements	Rigor, Biodiversity preservation,
- the storage site of each item;	Ensure a consistent and effective preservation and supply; Biosecurity and biosafety measures in place; meet interested parties' requirements	Rigor, Biodiversity preservation, safety, security
- the method to identify master cell banks and stock for distribution;	Ensure a consistent and effective preservation and supply; meet interested parties' requirements	Rigor, Biodiversity preservation
- the established re-stocking practices;	Ensure a consistent and effective preservation and supply; meet interested parties' requirements	Rigor, Biodiversity preservation
- the method for the preserved microorganisms control (quality-checks);	Ensure a consistent and effective preservation and supply; meet interested parties' requirements	Rigor, Biodiversity preservation
- levels of access;	Ensure a consistent and effective preservation and supply; Biosecurity and biosafety measures in place; meet interested parties' requirements	Rigor, Biodiversity preservation, safety, security
- the records to maintain.	Ensure a consistent and effective preservation and supply; meet interested parties' requirements	Rigor, Biodiversity preservation

Provision	Objectives	Principle
The biological material shall be preserved by at least two methods, under environmental parameters that ensure the stability of its properties. The methods for preservation shall be selected according to recommendations from the depositor (if appropriate) and previous experience of the mBiobank. These shall ensure:	Ensure a consistent and effective preservation and supply; meet interested parties' requirements	Rigor, Biodiversity preservation

- high viability/recovery of the preserved culture;		
- absence of contaminant in the preserved culture (this does not include any recognised co-culture e.g. symbiotic micro-organisms, which are not regarded as contaminants as long as the constituents are correctly specified and checked by microbiological and molecular analysis, as applicable).		
- authenticity of the preserved culture and genome integrity (molecular, phenotypic analysis), where applicable.		
Where two distinct methods are not applicable, cryopreserved stocks shall be maintained in separate locations. A duplicate collection of relevant biological material shall be maintained, preferably on another site as a 'disaster' protection measure and to avoid accidental loss.		
The size of the masters and distribution stocks shall be established according to the anticipated distribution rate.	Meet interested parties' requirements	Rigor (achieve planned results for the activity)
Key parameters of the preservation procedure shall be monitored and retained.	Ensure a consistent and effective preservation and supply;	Rigor

Microorganism supply (distribution)

Provision	Objectives	Principle
The mBiobank shall implement control activities to verify that the microorganism to supply complies with requirements, and retain the related information. It shall include, but not be limited, to:		
a) evidence of conformity with the acceptance criteria;	Ensure a consistent and effective preservation and supply;	Rigor
b) traceability to the person(s) authorising the release	Ensure a consistent and effective preservation and supply;	Rigor

Provision	Objective	Principle
The mBiobank shall identify, establish and document the requirements for the biological material supply, including but not limited to:		
- approval of customers (e.g. confirm requester's identity, confirm whether it is an authorised requester, confirm that possesses the required skills and infrastructure);	Meet interested parties' requirements, laws and regulations, biosafety, biosecurity	Law compliance, safety, security
- approval of requests, including requests of hazardous microorganisms;	Meet interested parties' requirements, laws and regulations, biosafety, biosecurity	Law compliance, safety, security
- the information to be provided along with the material;	Meet interested parties' requirements, laws and regulations, biosafety, biosecurity, effectiveness in supply	Law compliance, safety, security, rigor
- transport requirements (see Notes 1, 2, 3) including measures to ensure the safe and secure packaging and transportation;	Meet interested parties' requirements, laws and regulations, biosafety, biosecurity, effectiveness in supply	Law compliance, safety, security, rigor
- legal requirements;	Meet interested parties' requirements, laws and regulations, biosafety, biosecurity	Law compliance, safety, security
- the documented information to be retain.	Meet interested parties' requirements, laws and regulations, biosafety, biosecurity, effectiveness in supply	Law compliance, safety, security, rigor

Provision	Objective	Principle
The mBiobank shall retain at least the following information:		
- the supplied microorganism identification;	Meet interested parties' requirements, laws and regulations, biosafety, biosecurity, effectiveness in supply	Law compliance, safety, security, rigor
- method and date of shipment;		
- name and address of the person to whom sent.		

Provision	Objective	Principle
The mBiobank shall provide the following information to the customer:		
- the unique identifier of the supplied microorganism and batch number;	Meet interested parties' requirements, laws and regulations, biosafety, biosecurity, Ensure a consistent and effective supply	Law compliance, safety, security, rigor
- an estimate of shelf-life;	Ensure a consistent and effective supply	Rigor
- storage conditions;	Ensure a consistent and effective supply	Rigor
- storage instructions and (if appropriate), conditions of growth;	Ensure a consistent and effective supply	Rigor
- the risk group of the microorganism;	Biosafety and biosecurity procedures	Safety, security
- the containment level required for handling the microorganism;	Biosafety and biosecurity procedures	Safety, security
- the results of the risk assessment;	Biosafety and biosecurity procedures	Safety, security
- requirements for the safe handling and disposal of the microorganism;	Biosafety and biosecurity procedures	Safety, security
- disposal measures;	Biosafety and biosecurity procedures	Safety, security
- measures to take in case of spillage;	Biosafety procedures	Safety
- instructions for opening culture container (e.g ampoules and vials)	Ensure an effective supply, Biosafety procedures	Rigor, Safety
- transportation conditions of the microorganism.	Meet interested parties' requirements, laws and regulations, biosafety, biosecurity, Ensure a consistent and effective supply	Law compliance, safety, security, rigor

Provision	Objective	Principle
The mBiobank shall provide the user with a Material Transfer Agreement, or an equivalent document, requesting acknowledge receipt of the received materials and documents.	Meet interested parties' requirements, laws and regulations, biosafety, biosecurity, Ensure a consistent and effective supply	Law compliance, safety, security, rigor

All requests for biological materials shall be documented.	Meet interested parties' requirements, laws and regulations, biosafety, biosecurity, Ensure a consistent and effective supply	Law compliance, safety, security, rigor
Information about supplied microorganisms shall include:		
- the biological material identification;	Meet interested parties' requirements, laws and regulations, biosafety, biosecurity, Ensure a consistent and effective supply	Law compliance, safety, security, rigor
- method and date of shipment;		
- name and address of the person to whom sent.		

Maintenance checks (viability tests)

Provision	Objective	Principle
The Biobank shall determine the viability testes to perform for each item preserved.	Ensure a consistent and effective preservation and supply	Rigor
The testes shall be performed at planned intervals, and shall include, at least:		
- viability (counting the number of cells or equivalent method);	Ensure a consistent and effective preservation and supply	Rigor
- check growth on appropriate medium;		
- check contamination from mycoplasma, bacteria, fungi and virus;		
- authentication of the cell line by appropriate tests (PCR, immuno-phenotypic tests, microsatelite tests).		

Microorganism testing

Provision	Objective	Principle
The mBiobank shall establish and document the methods used for the microorganism testing, including but not limited to viability, identity, purity.	Ensure an effective preservation and supply	Rigor
Testing methods shall be qualified for performance and the qualification results shall be retained.	Ensure a consistent and effective preservation and supply	Rigor

Cleaning / sterilisation

Provision	Objective	Principle
The Biobank shall establish, document and implement cleaning and decontaminating procedures on the material and areas liable to influence microorganism quality.	Ensure a consistent and effective preservation and supply	Rigor
Cleaning and sterilization procedures shall be qualified for performance.	Ensure a consistent and effective preservation and supply	Rigor
A contamination monitoring program shall be established and implemented. It shall include but not be limited to:		
- equipment,	Ensure a consistent and effective preservation and supply	Rigor
- benches surfaces,		
- material,		
- all microorganism containment areas,		
- a contamination monitoring program.		

Media and reagent preparation

Provision	Objective	Principle
Accurate preparation, storage and preservation of culture media is one of the fundamental steps in the growth and maintenance of biological materials.		
The Biobank shall establish, document, implement and qualify procedures to prepare culture media for the growth and/or maintenance of the living biological materials held.	Ensure a consistent preservation	Rigor
The results from qualification shall be retained.	Ensure a consistent preservation	Rigor

The procedures used for the preparation of culture media shall be maintained as documented information and shall include, at least:		
- media formula;	Ensure a consistent and effective preservation and supply	Rigor
- criteria for reagents acceptance;		
- sterilization;		
- storage conditions;		
- method to estimate the expiry date;		
- method for the microorganism identification (e.g by labeling).		

Preservation process validation

Provision	Objective	Principle
Before performing routine preservation, the mBiobank shall establish, document, and implement a procedure for the validation of the processes included in the microorganism preservation lifecycle, in order to ensure effectiveness and consistency in preservation and supply (see Note 1).	Ensure a consistent and effective preservation and supply	Rigor
It shall include, but not be limited to:		
- the scope of validation and extent of performance qualification (see Note 2) and its rational;	Ensure a consistent and effective preservation and supply	Rigor
- the use of scientific approaches to achieve enhanced knowledge about process factors and its influence on microorganism quality attributes (see Note 3);		
- the sampling plan for process development and design and the rationale behind it;		
- statistical methods for data analysis;		
- the approach for qualification procedures;		
- the rational for the comprehensiveness of the qualification procedures (e.g. equipment, infrastructure, bio-analytical methods and other processes);		

- strategy to maintain the process in a state of control providing assurance of continued suitability and capability;		
- strategy to continually improve process knowledge and understanding;		
- the methods for recording and evaluating results, including, where appropriate, statistical tools to support any conclusions with regard to the variability and capability of processes.		
The validation activities shall be planed (see Note 4).		
Evidence of preservation process effectiveness and consistency shall be retained.		

Identification and traceability

Provision	Objective	Principle
The mBiobank shall use suitable means to obtain, identify and retain outputs when it is necessary to ensure the conformity.	Ensure a consistent and effective preservation and supply	Rigor
The mBiobank shall identify the status of outputs with respect to monitoring and measurement requirements throughout the microorganism preservation lifecycle.	Ensure a consistent and effective preservation and supply	Rigor
The mBiobank shall ensure and control the unique identification of the outputs when traceability is a requirement, and shall retain the documented information necessary to enable traceability.	Ensure a consistent and effective preservation and supply	Rigor
The mBiobank shall control microorganisms belonging to the customer while they are under the mBiobank's responsibility. The mBiobank shall identify, verify, protect and safeguard the customer's microorganism.	Ensure a consistent and effective preservation	Rigor
When microorganism belonging to the customer is lost or otherwise found to be unsuitable for use, the mBiobank shall report this to the customer.	Meet the interested parties' requirements	Rigor

Post-delivery activities

Provision	Objective	Principle
The mBiobank shall meet the requirements for post-delivery activities associated with the supplied microorganism. In determining the extent of post-delivery activities that are required, the mBiobank shall consider:	Meet the interested parties' requirements	Rigor
- statutory and regulatory requirements;	Meet the interested parties' requirements	Rigor
- the potential undesired consequences associated with the microorganism handling;	Meet the interested parties' requirements	Rigor
- the nature of the biological material;	Meet the interested parties' requirements	Rigor
- customer feedback.	Meet the interested parties' requirements	Rigor

Control of changes

Provision	Objective	Principle
The mBiobank shall review and control changes to implement throughout the microorganism preservation lifecycle to the extent necessary to ensure continuing conformity with requirements. The mBiobank shall retain documented information describing the results of the review of changes the person (s) authorising the change and any necessary actions from the review.	Ensure a consistent and effective preservation, biosafety and biosecurity procedures are in place	Rigor, safety, security

Control of nonconforming process outputs, products and services

Provision	Objective	Principle
The mBiobank shall ensure that outputs that do not conform to their requirements are identified and controlled to prevent their unintended use or delivery.	Ensure a consistent and effective preservation; Meet the interested parties' requirements	Rigor, continual improvement

The mBiobank shall take appropriate actions based on the nature of the nonconformity and its effect on the conformity of the held microorganisms. This shall also apply to nonconforming microorganism detected after supply.	Ensure a consistent and effective preservation; Meet the interested parties' requirements	Rigor, continual improvement
The organization shall deal with nonconforming outputs in one or more of the following ways:		
- correction;	Ensure a consistent and effective preservation; Meet the interested parties' requirements	Rigor, continual improvement
- segregation, containment, return or suspension of provision of microorganisms;		
- informing the customer.		
Conformity to the requirements shall be verified when nonconforming outputs are corrected.	Ensure a consistent and effective preservation; Meet the interested parties' requirements	Rigor, continual improvement
The organization shall retain documented information that:		
- describes the nonconformity;	Ensure a consistent and effective preservation; Meet the interested parties' requirements	Rigor, continual improvement
- describes the actions taken;		
- describes any concessions obtained;		
- identifies the authority deciding the action in respect of the nonconformity.		

Performance Evaluation | Monitoring, measurement, analysis and evaluation | General

Provision	Objective	Principle
The mBiobank shall determine:		
- what needs to be monitored and measured;	Ensure a consistent and effective preservation and supply	Rigor
- the methods for monitoring, measurement, analysis and evaluation needed to ensure valid results;	Ensure a consistent and effective preservation and supply	Rigor

- when the monitoring and measuring shall be performed;	Ensure a consistent and effective preservation and supply	Rigor
- when the results from monitoring and measurement shall be analysed and evaluated.	Ensure a consistent and effective preservation and supply	Rigor
The mBiobank shall evaluate the performance of the C&EMS and retain appropriate documented information as evidence of the results.	Ensure a consistent and effective preservation; Meet the interested parties' requirements	Rigor, continual improvement

4.8.2 CUSTOMER SATISFACTION

Provision	Objective	Principle
The mBiobank shall monitor customers' perceptions of the degree to which their needs and expectations related to the microorganism received or under preservation have been fulfilled.	Meet the interested parties' requirements	Continual improvement
The mBiobank shall determine the methods for obtaining, monitoring, analysing and take actions upon this information.	Meet the interested parties' requirements	Continual improvement

Analysis and evaluation

Provision	Objective	Principle
The mBiobank shall analyse and evaluate data and information arising from monitoring and measurement.	Ensure a consistent and effective preservation and supply	Rigor
The results of analysis shall be used to evaluate:		
- conformity of the biological material supplied;	Ensure an effective supply	Rigor
- process effectiveness and consistency;	Ensure a consistent and effective preservation and supply	Rigor
- the degree of customer satisfaction with the preservation service and the microorganism supply;	Meet the interested parties' requirements	Continual improvement

- the performance and effectiveness of the C&EMS;	Ensure a consistent and effective preservation and supply	Rigor
- if planning has been implemented effectively;	Ensure a consistent and effective preservation and supply	Rigor, continual improvement
- the effectiveness of actions taken to address risks and opportunities;	Meet the interested parties' requirements	Rigor, continual improvement
- the performance of external providers;	Ensure a consistent and effective preservation and supply	Rigor, continual improvement
- the need for improvements to the quality management system.	Ensure a consistent and effective preservation and supply	Continual improvement

Internal Audit

Provision	Objective	Principle
The mBiobank shall conduct internal audits at planned intervals, at least one per year, to provide information on whether the C&EMS:	Meet the interested parties' requirements	Continual improvement
a) conforms to:	Meet the interested parties' requirements	Continual improvement
- the mBiobank's own requirements for its C&EMS;		
- the requirements of this Standard;		
b) is effectively implemented and maintained.		
The mBiobank shall:		
- plan, establish, implement and maintain an audit programme(s) including the frequency, methods, responsibilities, planning requirements and reporting, which shall take into consideration the importance of the processes concerned, changes affecting the organization, and the results of previous audits. It shall include a microorganism deposit trail through to storage and supply trail from receipt of order to supply. These should be chosen at random.	Meet the interested parties' requirements	Continual improvement
- define the audit criteria and scope for each audit;		

- select auditors and conduct audits to ensure objectivity and the impartiality of the audit process;		
- ensure that the results of the audits are reported to relevant management;		
- take appropriate correction and corrective actions without undue delay;		
- retain documented information as evidence of the implementation of the audit programme and the audit results.		

Note: See ISO 19011 for guidance.

Management Review | General

Provision	Objective	Principle
Top management shall review the organization's C&EMS at planned intervals, to ensure its continuing suitability, adequacy, effectiveness and alignment with the strategic direction of the organization.	Meet the interested parties' requirements	Continual improvement

Management review inputs

Provision	Objective	Principle
The management review shall be planned and carried out taking into consideration:		
- the status of actions from previous management reviews;	Meet the interested parties' requirements	Continual improvement
- changes in external and internal issues that are relevant to the quality management system;	Ensure a consistent and effective preservation, biosafety and biosecurity procedures are in place	Rigor, safety, security
- information on the performance of the C&EMS, including trends in:		
- customer satisfaction and feedback from relevant interested parties;	Meet the interested parties' requirements	Continual improvement

- the extent to which quality objectives have been met;	Ensure a consistent and effective preservation, biosafety and biosecurity procedures are in place, Meet the interested parties' requirements	Rigor, safety, security, Continual improvement
- process effectiveness and consistency;	Ensure a consistent and effective preservation	Rigor
- nonconformities and corrective actions;	Meet the interested parties' requirements	Continual improvement
- monitoring and measurement results;	Meet the interested parties' requirements	Continual improvement
- audit results;	Meet the interested parties' requirements	Continual improvement
- the performance of external providers;	Ensure a consistent and effective preservation; Meet the interested parties' requirements	Rigor, continual improvement
- the adequacy of resources;	Ensure a consistent and effective preservation; Meet the interested parties' requirements	Rigor, continual improvement, technological updating
- the effectiveness of actions taken to address risks and opportunities (see 6.1);	Ensure a consistent and effective preservation; Meet the interested parties' requirements	Rigor, continual improvement
- opportunities for improvement.	Meet the interested parties' requirements	Continual improvement

Management review outputs

Provision	Objective	Principle
The outputs of the management review shall include decisions and actions related to:		
- opportunities for improvement;	Meet the interested parties' requirements	Continual improvement
- any need for changes to the C&EMS;	Meet the interested parties' requirements	Continual improvement
- resource needs.	Meet the interested parties' requirements	Continual improvement, technological updating
The mBiobank shall retain documented information as evidence of the results of management reviews.	Meet the interested parties' requirements	Rigor

Improvement | General

Provision	Objective	Principle
The mBiobank shall determine and select opportunities for improvement by implementing any necessary actions to:		
- improve effectiveness and consistency of the processes	Ensure a consistent and effective preservation; Meet the interested parties' requirements	Rigor, continual improvement
- improve effectiveness of biosafety and biosecurity measures.	Meet the interested parties' requirements	Rigor, continual improvement

Nonconformity and corrective action

Provision	Objective	Principle
When a nonconformity occurs, including any arising from complaints or security breaches, the mBiobank shall (see Note 1):		
- react to the nonconformity and, as applicable:	Ensure a consistent and effective preservation; Meet the interested parties' requirements	Rigor, continual improvement, safety, security
- take action to control and correct it;		
- deal with the consequences;		
- evaluate the need for action to eliminate the cause(s) of the nonconformity, in order that it does not recur or occur elsewhere, by:		
- reviewing and analysing the nonconformity;		
- determining the causes of the nonconformity;		
- determining if similar nonconformities exist, or could potentially occur;		
- implement any action needed;		
- review the effectiveness of any corrective action taken;		
- update risks and opportunities determined during planning, if necessary;		

- make changes to the C&EMS, if necessary.		

Provision	Objective	Principle
Corrective actions shall be appropriate to the effects of the nonconformities encountered.	Ensure a consistent and effective preservation; Meet the interested parties' requirements, ensure procedures on biosafety and biosecurity	Rigor, continual improvement, safety, security
The organization shall retain documented information as evidence of:		
- the nature of the nonconformities and any subsequent actions taken;	Ensure a consistent and effective preservation; Meet the interested parties' requirements, ensure procedures on biosafety and biosecurity	Rigor, continual improvement
- the results of any corrective action.		

Continual improvement

Provision	Objective	Principle
The mBiobank shall continually improve the suitability, adequacy and effectiveness of the C&EMS.	Ensure a consistent and effective preservation; Meet the interested parties' requirements, ensure procedures on biosafety and biosecurity	Rigor, continual improvement, safety, security

4.9 PUBLIC CONSULTATION

During public consultation stage – which was not implemented as the standard is not intended to be published - the draft would be made available for scrutiny and comment to a widely-based group of organisations who have interest in the content and application of the standard – the interested parties. These include heads of culture collections, curators, quality managers of mBiobanks, bio-industry, microbiologists, governmental officers and auditors. This procedure provides appropriate opportunities for valuable contributions and make the process transparent.

Received comments should be registered, analysed and discussed within the assigned committee for decision; the content of the standard is decided by consensus - general agreement of as many as possible of the committee members, rather than by majority voting. The decision for accepting or not the comments would be justified and recorded. These records would be made available to participants.

4.10 LEVELS OF COMPLIANCE

The dimension, objectives and purpose of the CC can vary widely, and so the requirements needed to manage the CC's operation.

This standard intends to be inclusive. It was thought to serve all the collections regardless their dimension, purpose and means. To do so, different levels of compliance (with the requirements) were defined. They base on the risks for the microorganism authenticity, long-term deposit, safety and security.

The requirements in the standard were classified into three different levels according to their degree of importance towards the objectives. The standard is composed by a combination of baseline, medium and high-level requirements. To claim compliance with the standard within a given level, the BRC would apply for a conformity assessment for that level. The conformity assessment will be conducted to determine whether the MS complies with the requirements contained in the intended level.

The requirements for each level of assessment are presented in Table 12. Only CC working within a containment level 1-2 may apply for "Baseline compliance". Auditors should have relevant experience in the field and training and experience in auditing techniques. Guidance from ISO 19011 should be considered when auditing this standard.

Table 12. Levels of compliance for certification.

Level of compliance	Requirements to fulfil	Clause	Obs.
1	Context	4.3, 4.4	
	Leadership	5	
	Planning	6	
	Support	7	
	Operation	8.1-8.3, 8.5-8.7, 8.9, 8.10	mBb not performing process validation must ensure the effective microorganism deposit (preservation) by other means such as duplication of the collection
	Biosecurity	8.4	
	Performance Evaluation	9	
	Improvement	10	
2	Context	4.1, 4.2	
3	Operation – process validation	8.8	

CHAPTER 5. PROCESS VALIDATION: FROM THEORY TO PRACTICE

5.1 GENERAL

With a proactive approach, consistency is built throughout the microorganism preservation lifecycle through proper process design so that the forth coming failure (which could end in microorganism loss) can be avoided.

A three-stage process validation approach (similar to that used by PhI) is proposed. In theory, this approach, might be applied to all preservation techniques, such as cryopreservation, as well as to the associated procedures such as media preparation and sterilization.

It bases in detecting the process critical factors, evaluating their impact in the microorganism critical attributes (authenticity) and allowing variation within specified limits. Process inputs' variability can thus be reduced and allowed within a certain range proven to lead to the expected results.

The influence of process factors on microorganism attributes has long been studied (Goos et al., 1967; Simon & Whang, 1967; Hwang & Howells, 1968; Lange & Boyd, 1968; Yee et al., 1972; Cunningham, 1973) although, to our best knowledge, this process validation strategy has never been implemented in microbial Biobanks.

By embracing this new approach, microbial Biobanks would be challenged to better:

1. Identify and understand the sources of variation throughout the microorganism preservation lifecycle.
2. Detect the presence and degree of variation that is transferred from sources into the biological material.
3. Understand the impact of variation on microorganism quality attributes (authentication attributes).
4. Control variation based on the understanding of the sources of variation and the risk it represents to the authenticity (quality) of the preserved microorganism.

The general steps for the validation approach in mBb are presented in Fig. 40.

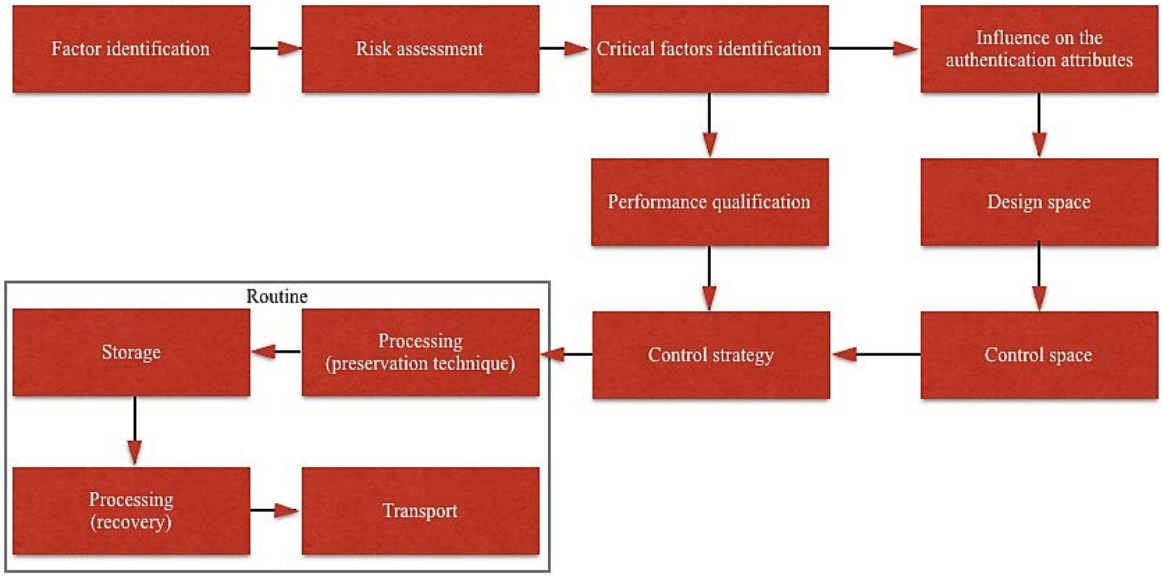


Figure 40. General overview of the activities involved in mBb process validation and routine operation.

Validation studies initiate with the identification of the microorganism-to-preserve critical quality attributes (mCQA), those characteristics intended to be maintained in the microorganisms aimed for long-term storage. mQCA will be the criteria to assess the microorganism authenticity before supply. These characteristics generally relate to the microorganism viability, purity and identity. They must be measurable or likely of qualitative assessment. Testing before preservation should encompass these attributes and the results must be retained.

The process factors are then identified. The most critical ones are selected for further statistical studies aiming to understand their impact on the mCQA - this relation becomes well understood, as well as the associated tolerances, by mathematical translation. By understanding the tolerances of these critical points, it is possible to establish a set of limits for operation (a space within which the integrity of cells during operation is assured) having in place a flexible and robust preservation process that can adapt over time. The design space – the set of maximum and minimum values for all the critical process parameters within which conformity has been proven - and the control space – a narrower "space" within the design space which will be the "space" allowed during routine preservation – might though be defined. A strategy to control the critical parameters is established based on gained knowledge. During this stage, while confirming that process and "product" requirements are met, the control system provides, in a continual basis, new information that is used (by integration in processes) to continual process improvement. This information results from the multiple measurement and monitoring systems. Tracking and trending of data leads to the detection of particular causes of variability providing opportunities to improve process consistency (by reducing inherent variability).

Determination of the state of control of the process in routine preservation should be calculated using appropriate statistics and based on appropriate confidence levels. These confidence levels should be based on risk factors, experience and attribute criticality. The level of control to apply will depend on the corresponding risk level: higher levels of control must be implemented for parameters associated with higher risk.

The diagram in Fig. 41 presents the validation approach, detailing the process qualification stage.

Green boxes represent the design and development stage – aiming to establish the control space and outline the control strategy -, blue boxes overarch the process qualification stage - aiming to ensure that all operations included in the preservation lifecycle are capable of effective and consistent operation -, and red boxes the improvement stage -where information is continuously collected and used to the process development., closing this way the cycle of validation activities.

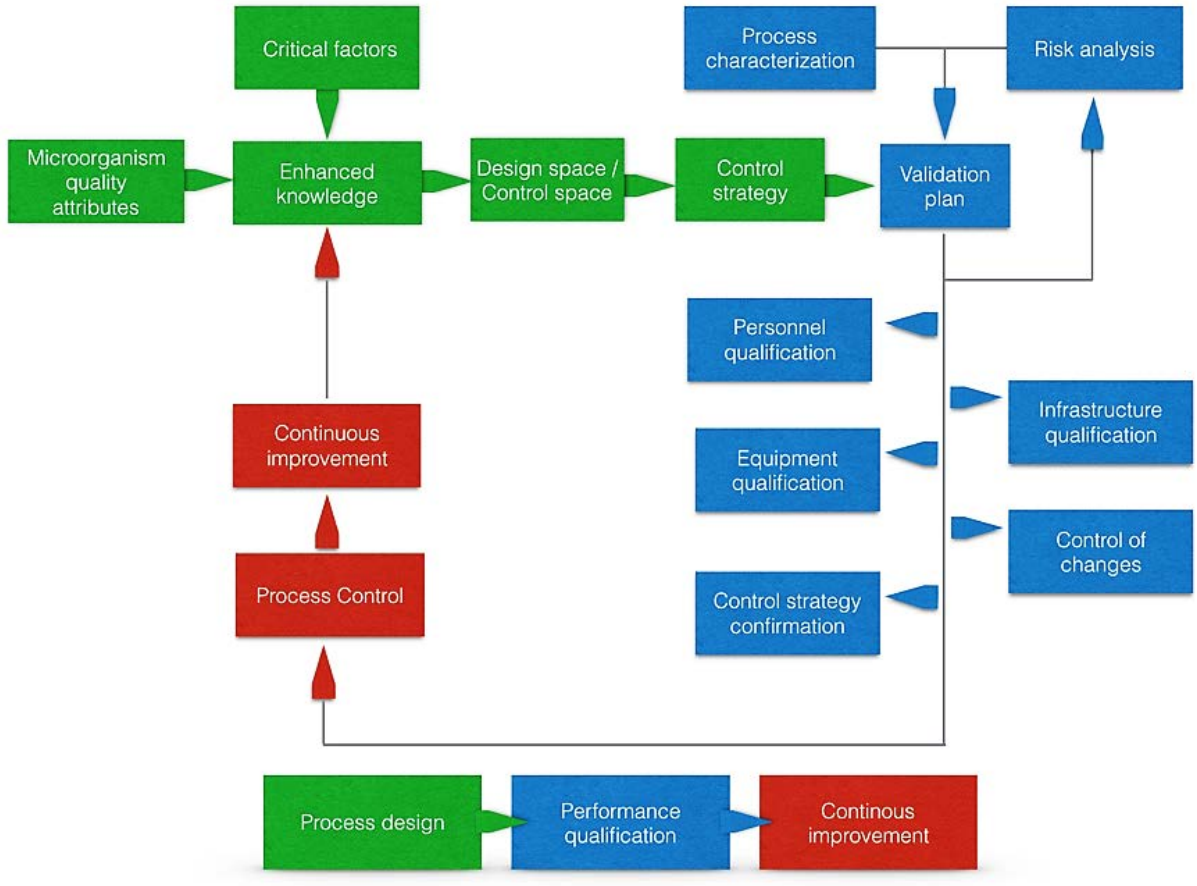


Figure 41. Diagram representing the three different stages for the process validation, according to a lifecycle-approach, detailing process qualification.

Process qualification is defined and implemented to assure all operations included in the preservation lifecycle are capable of effective and consistent operation. Qualification activities should include, at least, the following issues:

- Process parameters, process limits, raw material specifications
- How and what data should be collected and how should it be evaluated (interpreted)
- Testing methods to validate and acceptance criteria
- Sampling plan (including sampling points and number of samples)
- Confidence level (based on risk analysis)
- Criteria for a rational conclusion of whether the process is acceptable
- Statistical methods to use in data analysis
- Method to address non-conformities
- Design of facilities and qualification of equipment, utilities and facilities
- Personnel training and method to assess competence (qualification)
- Material qualification (such as vials and closures, ampoules, petri dishes)

Testing methods should yield results that ensure a reliable evaluation of the microorganism attributes. They must be verified and validated. Equipment used for these tests should be qualified as well as the measuring instruments used for the qualification. Qualification may include calibration.

The qualification stage can be considered complete when there is scientific evidence that (1) an appropriate level of assurance that the preservation process has been designed to effectively and consistently preserve microorganisms and (2) there is in place an effective measuring and monitoring system to control the preservation process. The routine preservation of microorganisms is performed under the same or equivalent conditions as demonstrated in process qualification.

The three-stage sequence for process validation - *understanding & designing, qualifying* and *maintaining the validated state* – is applicable (and desirable) for all processes and methods performed in a mBb such as cleaning, sterilising, packaging and testing.

5.2 VALIDATION EXERCISES FOR CRYOPRESERVATION

In order to provide mBbs with a basis for action we decided to give guidance in developing a validation plan (main issues to consider) and develop a risk analysis for cryopreservation.

The risk analysis studies were performed to identify the cryopreservation critical factors which would be subjected to further DOE studies. The general strategy is presented Fig. 42.

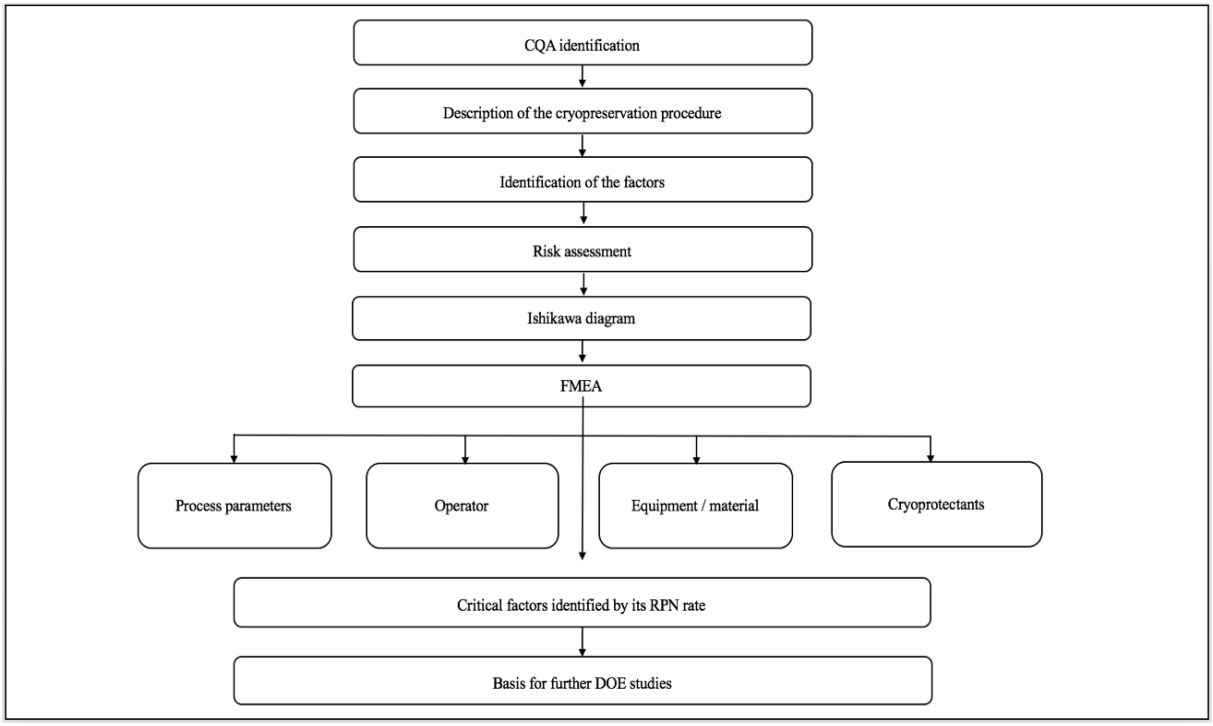


Figure 42. General procedure for the risk analysis steps in the validation of the cryopreservation process.

5.2.1 CRYOPRESERVATION PROCEDURE

An outline of the Cryopreservation Process (procedure) for fungi is presented in Table 13.

Table 13. Cryopreservation/recovery procedure (abridge description).

Preparation of the cryoprotectant solution (ex.: glycerol + distilled water)
This solution is distributed in aliquots in universal glass bottles
The cryoprotectant solution is sterilised by autoclave a day before its use, and maintained at 4°C
The cryoprotectant solution is tested for contamination
Samples to preserve are grown in slants, for the necessary time
1-2 mL of the cold glycerol solution is poured into the slant tubes with the grown and mature cultures
A suspension of mycelia and spores is prepared
Suspension is distributed into the cryovials with the glass beads
Cryovials are distributed in a freezing container
The freezing container is maintained at -80 °C for at least 4 hours
Cryovials are transferred into appropriate boxes in the deep-freezer
Storage at 80°
Thawing
Packaging
Transport

It is based in the MUM's cryopreservation process description, version 2013-04-09.

5.2.2 THE MICROORGANISM CQA

The studies begin by searching for and establishing of the microorganism critical attributes. Those have been a decades-old concern among mBb (Lessel, 1970) and include the microorganism VIP characteristics: viability, identity and purity (Becker et al., 2015).

5.2.3 RISK ANALYIS STUDIES

All process variables may directly or indirectly link to (affect) the fungi critical attributes. To reduce the variables to be investigated, by selecting the potential high impact factors (that will be targeted by the validation studies), a risk assessment must be performed.

The two basic elements of a risk assessment (ISO, 2018) are risk identification (risk recognition and description) and analysis (determining the nature of the risk and estimating its level). Several tools can be used with this purpose (IEC, 2019)[33].

This study used three different risk assessment techniques aiming to identify and hierarchically organise the cryopreservation factors:

a) Checklist – to identify and gather all the factors (these might be collected during a brainstorming);
b) Ishikawa diagram – to categorise the factors according to their role in the process, continuing the identification stage;
c) FMEA based studies - to rank the factors according to their criticality.

5.2.4 IDENTIYING THE FACTORS

Check-lists are a simple method for risk identification. They have several advantages: are easy to perform and its results can evolve over time through contribution of experts from different functional areas inside the organisations.

Based on the cryopreservation process description, main process inputs (factors) were listed and examined for symptoms of potential risks (Table 14). Having in mind further qualification needs, factors to be tested and qualified were also pointed.

[33] The IEC 31010:2009 standard supports ISO 31000 standard (ISO, 2018a) by providing guidance on selection and application of techniques for risk assessment. It doesn't deal specifically with safety as its references (to safety) are purely of an informative nature. Guidance on the introduction of safety aspects into IEC standards is laid down in ISO/IEC Guide 51 (ISO/IEC 2014).

Table 14. Identification of the factors (F), CQA, testing (T) and qualification needs (PQ) and needs for the fungi-cryopreservation process.

FACTORS	F	CQA	T	PQ
Cryoprotectant composition	☐	☐	☑	☐
Type of cryoprotectant	☐	☐	☐	☐
Cryoprotectant temperature	☑	☐	☑	☐
Aliquots mass	☑	☐	☐	☐
Sterilisation temperature	☑	☐	☐	☐
Seterilisation time	☑	☐	☐	☐
Type of growth media	☑	☐	☐	☐
Incubation temperature	☑	☐	☐	☐
Incubation time	☑	☐	☐	☐
Type of beads	☑	☐	☐	☐
Temperature decreasing rate (freezing container)	☑	☐	☐	☐
Time for freezing (freezing container)	☑	☐	☐	☐
Duration of transfer	☑	☐	☐	☐
Transfer conditions (temperature)	☑	☐	☐	☐
Storage temperature	☑	☐	☐	☐
Temperature increasing rate (recovery)	☑	☐	☐	☐
Packaging material	☑	☐	☐	☐
Transport temperataure	☑	☐	☐	☐
Transport time	☑	☐	☐	☐
Operator competence	☑	☐	☐	☑
Material and infrastructure sanitation/	☑	☐	☑	☑
Microorganism authenticity	☑	☑	☑	☐
Microorganism purity	☑	☑	☑	☐
Microorganism viability	☑	☑	☑	☐
Equipment fitness the purpose	☐	☐	☐	☑
Preventive maintenance	☐	☐	☐	☑
Infrastructure fitness the purpose	☐	☐	☐	☑

5.2.5 CATEGORISING THE FACTORS

An Ishikawa diagram, aiming to identify the factors that can negatively impact the microorganism identity, purity and viability, if they fail or fall outside control, was constructed. Factors were categorised in four different categories: (1) equipment and material, (2) operator, (3) process parameter, (4) additives (cryoprotectant). Results are presented in Fig. 43.

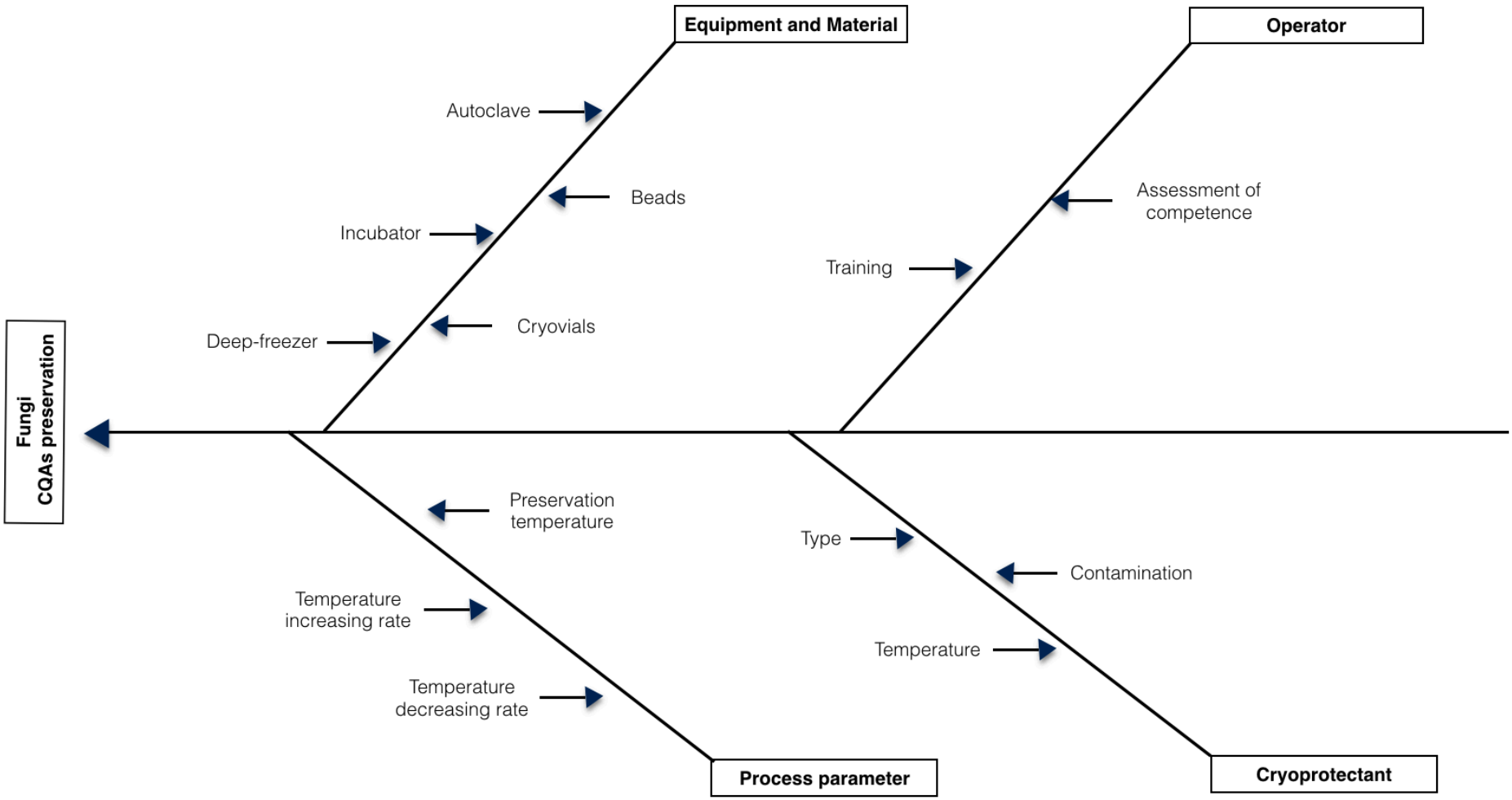


Figure 43. Ishikawa diagram for the cryopreservation fungi factors.

5.2.6 RANKING THE FACTORS

To hierarchically organise the factors pointed in the Ishikawa diagram, a FMEA based study was further performed.

FMEA study attempted to answer the following questions:

- Which are the potential failures in the cryopreservation process and what are the consequences for the preserved fungi?
- Why they might happen?
- Which is the likelihood of the failure to happen?
- Which is the risk level for each failure?

When initiating the FMEA, the failures were broken down into those input categories coming from:

- Process
- Operator,
- Equipment/material,
- Cryoprotectant.

5.2.6.1 Strategy

The factors were hierarchically organised according to their criticality; a risk priority number (RPN) was assigned to each of them.

The strategy used for the FMEA study is presented in Fig. 44.

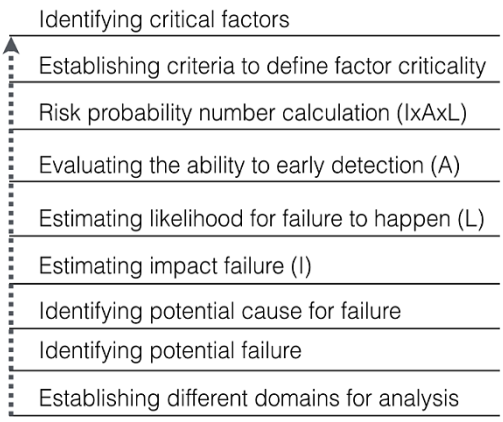


Figure 44. General strategy for the FMEA based studies.

Four domains were established:

- Process parameter;
- Operator;
- Additive (cryoprotectant);
- Equipment or material.

The potential failures and cause for failure - i.e, the way the parameter/ operator/ additive/ equipment or material can potentially fail in meeting the requirements - were identified as well as the potential effect of failure on the fungi CQA.

Each failure (resulting from a specific cause) was scored in terms of Impact, Likelihood and Ability to Detect according to the following criteria:

a) A ranking number, from 1 to 5, was given to each failure in order to measure its impact on the fungi CQA (potential consequences of the failure on the mCQA. Criteria are presented in Fig. 45.

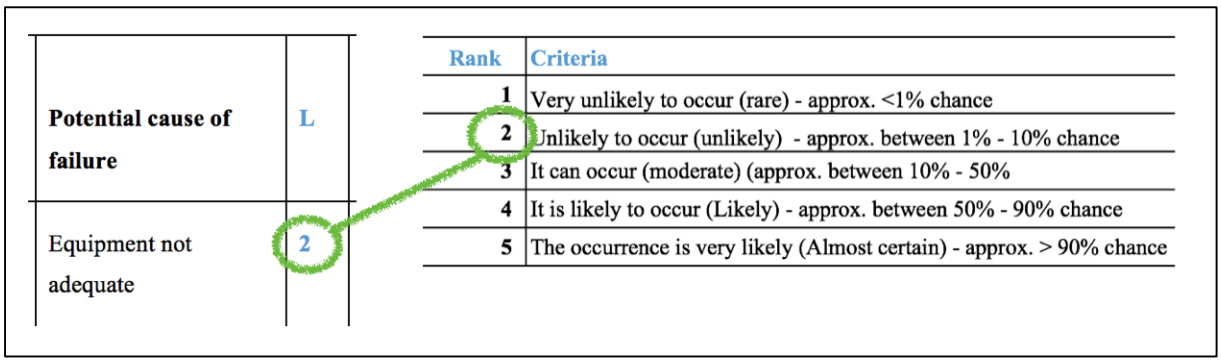
Rank	Impact of the effect on the fungi authenticity (criteria)
1	Minor problem with no consequences to BM authentication
2	Some disruption possible (problem that interrupt an activity or process)
3	Significant lost of time and resources
4	Problem having consequences on at least one of the authentication parameters
5	Major problem whose consequences are loss a BM

Process parameter	Potential failure	Potential effect of failure	I
Decreasing temperature rate	Measurable or likely to be estimated, but not adequate	Cell damage	5

Figure 45. Criteria and corresponding ranking number for the "impact" of the potential failure on fungi authentication (upper table); Excerpt of a FMEA table showing the ranking number "5" given to the potential failure in the "decreasing temperature rate" (bottom table).

b) The cause or causes - as there might be several causes - for the potential failure(s) was (were) determined. The likelihood for the potential failure to happen (according to the cause) was evaluated and translated in a ranking number from 1 to 5; the criteria underpinning the likelihood

scale are presented in Fig. 46.

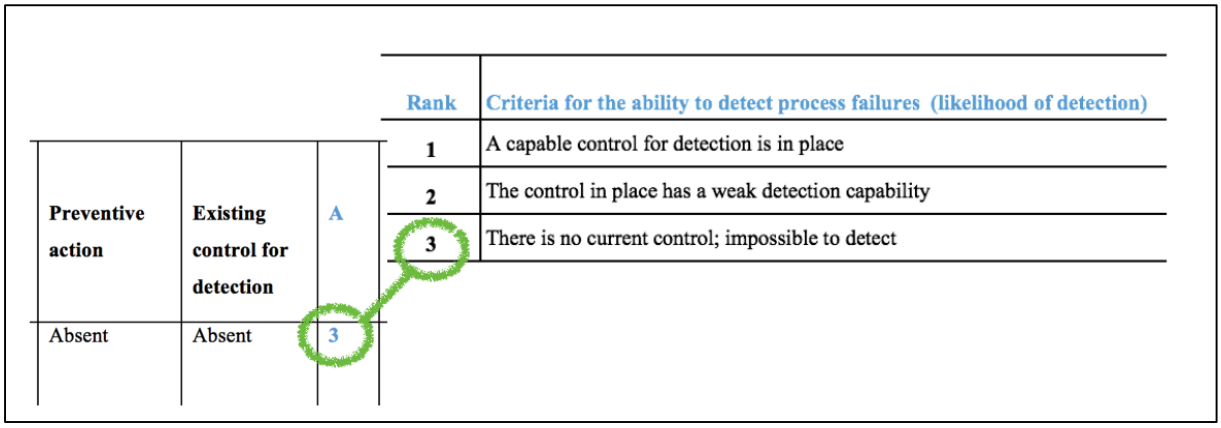


Potential cause of failure	L
Equipment not adequate	2

Rank	Criteria
1	Very unlikely to occur (rare) - approx. <1% chance
2	Unlikely to occur (unlikely) - approx. between 1% - 10% chance
3	It can occur (moderate) (approx. between 10% - 50%
4	It is likely to occur (Likely) - approx. between 50% - 90% chance
5	The occurrence is very likely (Almost certain) - approx. > 90% chance

Figure 46. Criteria for the raking number attributed to the "probability of occurrence" of a failure during the cryopreservation process (table in the right); the table in the left (FMEA excerpt) shows the ranking number "2" attributed to failure in the "decreasing temperature rate" caused by the equipment (equipment not adequate).

c) Control methods in place (to detect a failure or potential failure) which could enable the implementation of actions to eliminate or reduce the risk for a potential failure to happen were further identified. An "ability to detect" ranking number (from 1 to 3) measures the probability of detecting a failure or potential failure; criteria for estimate the "ability to detect" are presented in Fig. 47.



Preventive action	Existing control for detection	A
Absent	Absent	3

Rank	Criteria for the ability to detect process failures (likelihood of detection)
1	A capable control for detection is in place
2	The control in place has a weak detection capability
3	There is no current control; impossible to detect

Figure 47. Criteria underpinning the raking number for the "ability to detect" a failure in the cryopreservation process (table in the right); the table in the left (FMEA excerpt) shows the ranking number "3" attributed to "ability to detect" a certain failure" meaning that there is no control in place making the failure impossible to detect.

A "*Risk Priority Number*" (RPN) was attributed to each potential failure (according to the cause). It is a numerical ranking, representing the overall magnitude of the risk, that results from the arithmetic product of the "*Impact*", "*Likelihood*" and "*Ability to Detect*" scores (Fig. 48) A maximum RPN of 75 and a

minimum of RPN of 1 are possible. A RPN threshold of 10 was set. Factors above the defined threshold were regarded as potential critical factors. Those should be evaluated by subsequent process characterisation studies.

Process parameter	Potential failure	Potential effect of failure	I	Potential cause of failure	L	Preventive action	Existing control for detection	A	RPN
Decreasing temperature rate	Not adequate (to fast or to slow)	Cell damage	5	Equipment not adequate	2	Absent	Absent	3	30

Figure 48. Calculation of the "*Risk Priority Number"* for a potential failure and its cause, in the FMEA study (I x L x N = RPN).

5.2.6.2 FMEA results

The results from the FMEA study are presented in Annex II.

Table 15 presents the cryopreservation factors ranked according to their RPN. As can be observed, the storage temperature, as well as the temperature rate for freezing and thawing are crucial. The same happens with the sterilisation of materials and the composition of the raw material to add to the microorganism (as is the case of the cryoprotectant).

Further DOE studies, to select relevant factors, would be prioritised based on these RPN.

Table 15. Cryopreservation factors ordered by its RPN factors.

Factor	RPN
Decreasing temperature rate (freezing)	30
Decreasing temperature rate (freezing)	30
Increasing temperature rate (recovery)	30
Increasing temperature rate (recovery)	30
Temperature during storage	30
Autoclave effectiveness	30
Raw material composition	30
Laminar flow cabinet (EPA filter)	15
Cryovials characteristics	15
Beads characteristics	15
Type of cryoprotectant	15
Temperature of the cryoprotectant	15
Deep Freezer performance	10

Factor	RPN
Incubator (increase of temperature)	10
Operator failure in keeping records	8
Operator failure in authentication	5
Operator failure in interpreting results and decisions	5
Operator failure in raw material approval (presence of poison or lack of a crucial component)	5
Operator failure in the preparation of solutions / suspensions	5
Operator failure in microorganism labelling	5
Cryoprotectant composition	5
Incubator (decrease of temperature)	3

Further DOE studies to identify relevant factors that can impact the mCQA would be prioritised based in the RPN rates resulting from the FMEA study.

5.3 VALIDATION PLAN

Validation activities must be carefully planned and communicated to the organisation. A validation plan should though be developed early in the validation activities. It should include, at least (1) the embraced validation approach, (2) the scope of validation, (3) the procedures to develop, implement and document, (4) the information to retain.

Minimum details that should be included in a validation planning are presented in Table 16.

Table 16. Items to include in the Validation Plan.

Item	Detail
Validation approach	Rational and objectives to achieve
Scope of application	Identification of the processes to be validated; Identification of the activities, utilities, equipment and personnel to be qualified
Validation Schedule	Validation planning considering the three stages
Responsibilities / authorities	Encompassing tasks / decisions
Process description	Activities, responsibilities, resources
General acceptance criteria	Testing, operation
Documented information	Information to maintain and retain (documents and records)
Description of the infrastructure	Premises and utilities related to the cryopreservation process validation
Equipment inventory	Equipment used throughout all the fungi (cryo)preservation lifecycle

5.4 DISCUSSION

The developed standard contains a completely new clause dedicated to process validation. Process validation is a key-clause for the mBiobanks to achieve consistency in preserving microbial resources. Process validation could be more advantageous for mBiobanks (with gains in efficiency) when compared with the alternative strategy that is having a duplicate of the collection. Further research on process validation applied to microbial biobanking would be necessary to test and develop the here proposed validation approach. There is a major difference between pharmaceutical industry and mBiobanks: instead of products and formulas, mBiobanks deal with living beings. Instead of product design biobanks have a microorganism whose attributes must be maintained unchangeable during preservation. Considering the complexity of living systems, it is also expected from this validation approach an increased difficulty in establishing links between process variables and microorganism (or a group of microorganisms) attributes.

After the tests performed, it seems that risk analysis tools are adequate for the cryopreservation scrutiny and risk prioritisation. However, it must be noted that the RPN obtained from FMEA studies is not a perfect representation of the risk associated with a failure as it is subjective. In practice, high severity issues must always be considered regardless of RPN value.

CHAPTER 6. CONCLUSION

GENERAL CONCLUSIONS

Microbial biobanks are a key component of biotechnology, by providing microorganisms worldwide. A global biobanking network, facilitating access to high-quality microorganisms needs to be established. Many efforts have been done with that purpose but no concrete output has been seen so far. One of the difficulties is the absence of a standard providing the quality criteria to create a certification scheme that enables mutual recognition of quality. The purpose of this work was to develop such standard. The need for a new standard for microbial biobanks was assessed by a "justification study" according to which a new standard is needed. To ensure that the standard would fit the purpose - being the cornerstone to create a certification scheme – it would need to be accepted by a wide range of interested parties, at international level. To do so, the standard would need to fit an international standardisation scheme. To ensure that purpose, a standard-setting strategy, based in international standard development methods, was developed and followed. It helped to ensure transparency during the process, and credibility and relevance of the standard. Through a validation study (which, to our best knowledge, is not a normal procedure for standard-setting bodies) it was ensured that the standard fulfils its objectives: all the requirements clearly contribute to the attainment of the standard's goals, only requirements that are relevant to meet these goals are included and that all the necessary requirements to address the defined goals are included. The strategy is proactive in nature as the risks foreseen during the implementation were identified and assessed and mitigation measures were added, during the standard development. To our best knowledge, also this is not a normal procedure undertaken by standard-setting bodies. The likelihood of problems during the implementation was, this way, reduced. Committed with transparency and impartiality, the strategy ensures participation of a wide range of interested parties and absence of unnecessary barriers to trade giving, at the same time, the opportunity to gather valuable inputs from a wide range of interests, which increases robustness of the standard while building trust.

A management system standard providing the criteria for the mBiobanks' certification was developed. It is aligned with other MSS and includes all the relevant issues for mBiobanks. This was achieved by considering all the relevant standards in this domain with special on the OECD BPG.

The proposed standard would be able to integrate existing national recognition schemes. Audits to this standard would be performed under the ISO 19011 standard's guidance. Auditors with competence to

audit this standard would need to be competent for ISO9001 auditing and have relevant knowledge and experience in mBiobanking.

6.1 LIMITATIONS

Major limitations were:

- Not having the public consultation done, probably missing meaningful insights about the standard and its content
- The fact that we did not have feed-back from collections having standards implemented - such as ISO 9001, ISO/IEC 17025 or ISO 20387. This information could have enriched the risk assessment (ToR) preventing problems and difficulties in implementation, would contribute to identify gaps, and assess relevance of the provisions on the standard.
- The impossibility of having the standard implemented. That would give us the possibility of receiving information from mBiobanks about the feasibility, relevance and potential improvements.

6.2 FURTHER RESEARCH

Further research would be needed to evaluate the standards' fitness for purpose. The relevance of the standard's provisions, difficulties and problems in implementation. This type of information would bring precious insights to improve the standard's adequacy enabling the project consolidation.

The three-level assessment feasibility and impact would also need to be tested.

Regarding the new clause for process validation, it would be important to:

- assess the feasibility and effectiveness of process validation, and benefits at operational level;
- evaluate the costs of implementing this validation approach;
- evaluate process validation relevance and eventually conclude about its capacity to exclude the need of having a duplicate of the collection.
- test the process validation provisions (Sub-clause 8.8 on the standard) for the different processing methods and types of microorganisms.

6.3 FINAL REMARKS

Microbial biobanks are collections of microorganisms working worldwide. To be able to respond to the current challenges on the microbial diversity preservation and mBb's inter-(co)operation (such as establishing the so longed GBRCN), they need to achieve high-performance levels, ensuring an effective long-term preservation of their assets. It was clear that there is a need for a specific standard to drive mBb in this endeavour, as standards can provide the tools to upgrade performance and define the path to attain the desired goals.

This research intended to contribute to the establishment of a mBb network at international level, by developing a standard that can provide the criteria for an accredited certification. It harmonises procedures among mBb, sets the minimum quality criteria and creates a common language.

This research intended also to contribute to the standard-setting field by giving insights to the current standard-setting-strategies, especially with the contribution of the stages related to the control of drafting, the risk assessment (ToR), the management approach, and the standard validation.

To achieve de main goal (drafting a standard), several topics were studied and were key in the standard's development. Among these, we highlight the principles ruling the biobanking activity, the mBb's quality-management objectives and quality-management model currently in place.

Resulting from the present research, a change in the current quality-management approach has been proposed. Moreover, these results have triggered a lot of thinking inside the microbial biobanks about efficiency, calling into question the usefulness of the current approach to quality. Awareness of the benefits of proactive approaches, opened a breach for shifting the management paradigm.

This research coincided with the development of both ISO 20387 Biotechnology - Biobanking - General requirements for biobanking and the, yet under development, "WD ISO24088 - Biotechnology - Biobanking - The collection, processing, storage and transportation criteria for microbiological material". The ISO 20387 and our standard differ in purpose, management methodology and assessment scheme. The here proposed standard, provides a certifiable management system focused on consistency and effectiveness, valuing proactivity and conveying basic biosafety and biosecurity measures.

Beyond providing text for the above international standards, the developed standard may be used, as a working draft, by any standardisation body wishing to establish a certification scheme for microbial biobanks, a void as yet unsolved.

REFERENCES

AFNOR (2007), NF S96-900 - Qualité des Collections de Ressources Biologiques (CRB) – Système de management d'un CRB et qualité des ressources biologiques d'origine humaine et microbienne, Association Française de Normalisation, Paris, France.

Agrawal, A. M., Pandey, P. (2015), Scale Up of Pan Coating Process Using Quality by Design Principles, Journal of Pharmaceutical Sciences, Vol. 104, No 11, pp. 3589–3611.

Ahmed, A., Kayis, B., Amornsawadwatana, S. (2007), A review of techniques for risk management in projects, Benchmarking: An International Journal, Vol. 14, No. 1, pp. 22-36.

Allen, R., Sriram, R. (2000), The Role of Standards in Innovation, Technological Forecasting and Social Change, No. 64, pp. 171-181.

Alsmeyer, D., Pazhayattil, A., Chen,S., Munaretto, F., Hye,M., Sanghvi, P. (2015), Acceptance Probability (Pa) Analysis for Process Validation Lifecycle Stages, AAPS PharmSciTech.

Antony, J. (2014), Design of Experiments for Engineers and Scientists, 2nd Edition, Elsevier Ltd.

Badawy, S.I.F, Narang, Ajit S., LaMarche, Keirnan, Subramanian, Ganeshkumar, Varia, Sailesh A. (2012), Mechanistic basis for the effects of process parameters on quality attributes in high shear wet granulation. International Journal of Pharmaceutics, Vol. 439, pp. 324–333.

Becker P, Stubbe D, Claessens J, Roesems S, Bastin Y, Planard C, Cassagne C, Piarroux R, Hendrickx M (2015). Quality control in culture collections: Confirming identity of filamentous fungi by MALDI-TOF MS, Mycoscience, No 56, pp. 273-279. https://doi.org/10.1016/j.myc.2014.08.002

BIPM (2012), International Vocabulary of Metrology – Basic and general concepts and associated terms - JCGM 200:2012 (VIM 3rd edition), Bureau International de Poids et Mesures, France.

Blind, K., Jungmittag, A., Mangelsdorf, A. (2011), The economic benefits of standardization, DIN - German Institute for Standardization, Berlin.

Boundy-Mills K (2012), Yeast culture collections of the world: meeting the needs of industrial researchers, Journal of Industrial Microbiology, 39, pp 673-680. DOI:10.1007/s10295-011-1078-5

Boussès, C., Ferey, L., Vedrines, E., Gaudin, K. (2015), Using an innovative combination of quality-by-design and green analytical chemistry approaches for the development of a stability indicating UHPLC method in pharmaceutical products, Journal of Pharmaceutical and Biomedical Analysis, Vol 115, No 10, pp.114–122.

Carlson, C. S. (2015), Understanding and Applying the Fundamentals of FMEAs, 2014 Annual Reliability and Maintainability Symposium, ReliaSoft Corporation, USA.

CEN-CENLEC (2010), CEN-CENELEC Guide17 - Guidance for writing standards taking into account micro, small and medium-sized enterprises (SMEs) needs, European Committee for Standardization and European Committee for Electrotechnical Standardization, Brussels, Belgium.

CEN-CENLEC (2013), Standards and your business, European Committee for Standardization/European Committee for Electrotechnical Standardization, Brussels – Belgium, available at http://www.cencenelec .eu/News/Publications/Publications/Standards-and-your-business_2013-09.pdf (accessed 22.02.2021).

Chatterjee, B. & Wong, W. (2012), QbD and the New Process Validation Guidance, Vol. 115, pp. 114–122.

Cunningham, J. L. (1973), Longevity of Rust spores in Liquid Nitrogen, Plant Disease Reporter, Vol 57, No 9, pp. 793-795.

Dale, G., Wiele, T., Iwaarden, J. (2007), Managing Quality, Blackwell Publishing.

Debrus, B., Lebrun, P., Ceccato, A., Caliaro, G., Rozet, E., Nistor, I., Oprean, R., Rupérez, F.J., Barbas, C., Boulanger, B., Hubert, P. (2011), Application of new methodologies based on design of experiments, independent component analysis and design space for robust optimization in liquid chromatography, Analytica Chimica Acta, Vol. 691, pp. 33–42.

Domingues, P., Sampaio, P., Arezes, P. M. (2016), Integrated management systems assessment: a maturity model proposal, Journal of Cleaner Production, Vol. 124, pp. 164-174, available on line at: http://dx.doi.org/10.1016/j.jclepro.2016.02.103 (accessed 18.05.2021)

EMA (2016), Guideline on process validation for finished products - information and data to be provided in regulatory submissions, available at: http://www.ema.europa.eu/docs/en_GB/document_library/Scientific_guideline/2014/02/WC500162136.pdf (accessed 22.02.2021).

Ernst, D., Lee, H., Kwak, J. (2014). Standards, innovation, and latecomer economic development: Conceptual issues and policy challenges, Telecommunications Policy, Vol. 38, Issue 10, pp. 853-862, Elsevier, available at https://reader.elsevier.com/reader/sd/pii/S0308596114001359?token=B4A4A0B6DA43E0E81725D2DDE9800970F87B995C94B5D8CD6C44A65F5AEF934FDE371E77234FE83786DB38CF0F971FB8 (accessed at 22.02.2021).

European Commission (2015), EU Guidelines for Good Manufacturing Practice for Medicinal Products for Human and Veterinary Use, Annex 15: Qualification and Validation, available at: http://ec.europa.eu/health/documents/eudralex/vol-4/index_en.htm (accessed 13 June 2016).

FDA (2011), Process Validation: General Principles and Practices Current Good Manufacturing Practices, Rev 1, Guidance for Industry, US Food and Drug Administration, Rockville (MD) US, available at: http://www.fda.gov/downloads/Drugs/Guidances/ UCM070336.pdf (accessed 18 Apr 2019).

Forti, T., Souto A., Nascimento, C., Nishikawa, M., Hubner, M., Sabag F., Temporal, R., Rodrigues J., Silva M. (2016), Evaluation of a fungal collection as certified reference material producer and as a biological resource center, Brazilian Journal of Microbiology, Vol 47, p. 403-409.

Furuta, K. Schacter, B. (2015), Report on Status of ISO276/WG2 on Biobanks and Bioresources: International Standards for Biobanking, Biopreservation an Biobanking, Vol. 13, No.6, pp. 452-453.

Gijo, E. V. (2006), Improving Process Capability of Manufacturing Process by Application of Statistical Techniques, Quality Engineering, Vol. 17, pp. 309–315. http://dx.doi.org/10.1081/QEN-200056494

Girotra, P., Kumar, S. S., Kumar, G. (2016), Development of zolmitriptan loaded PLGA/poloxamer nanoparticles for migraine using quality by design approach, International Journal of Biological Macromolecules, Vol. 85, pp. 92–101.

Glodek M, Liebowitz S, McCarthy R, McNally G, Oksanen C, Schultz T, Sundararajen M, Vorkapich R, Vukovinsky k, Watts C, Millili G, (2006), Process Robustness - A PQRI White Paper, Pharmaceutical Engineering, Vol. 26, No. 6, available at: http://pqri.org/wp-content/uploads/2015/08/pdf/06ND-online_Glodek-PQRI.pdf (accessed 22.02.2021).

Goos, R., Davis, E. E., Butterfield, W. (1967), Effect of warming rates on the viability of frozen fungous spores, Mycologia, Vol. 59 No. 1, pp. 58-66.

Gasser, U., & Palfrey, J. (2013), Fostering innovation and trade in the Global Information Society: The different facets and roles of interoperability, Law, Policy & Economics of Technical Standards eJournal. Available online at https://papers.ssrn.com/sol3/papers.cfm?abstract_id=2192647#references-widget (accessed 18.05.2021).

Hallenbeck, P. C., Grogger, M., Mraz, M., Veverka, M. (2015), Building a better mousetrap I: Using Design of Experiments with unconfounded ions to discover superior media for growth and lipid production by Chlorella sp. EN1234, Bioresource Technology, Vol. 184, pp. 82–89. DOI: 10.1016/j.biortech.2014.10.144

Hosotani, K (1992), Japanese Quality Concepts, An Overview, Ed. Quality Resources, New York.

Hoyle, D. (2011), Quality Management Essentials, New York, USA, Routledge, Taylor & Francis Group. ISBN 13: 978-0-75-066786-9.

Hradesky, J. (1988), Productivity and Quality Improvement - A Practical Guide to Implement Statistical Process Control, McGraw-Hill Book Company.

Hwang, S., Howells, A. (1968), Investigation of Ultra-low Temperature for Fungal Cultures, Cryoprotection afforded by Glycerol and Dimethyl Sulfoxide to 8 Selected Fungal Cultures, Mycologia, Vol. 60, No. 3, pp. 622-626.

Hwang, R., Noack, R.M. (2011), Application of design of experiments to pharmaceutical formulation development, International Journal of Experimental Design and Process Optimisation, Vol. 2, No. 1, pp.58–65.

ICH (2005), International Conference on Harmonisation of Technical Requirements for Registration of Pharmaceuticals for Human use Q9 - Quality Risk Management, Current Step 4 version, Quality Guidelines, Harmonised Tripartite Guideline, EU, Japan, US. Available at: https://www.ich.org/page/quality-guidelines (accessed 22.02.2021).

ICH (2008), International Conference on Harmonisation of Technical Requirements for Registration of Pharmaceuticals for Human Use Q10 - Pharmaceutical Quality System, Harmonised Tripartite Guideline, EU, Japan, US. Available at: https://www.ich.org/page/quality-guidelines (accessed 22.02.2021).

ICH (2009), International Conference on Harmonisation of Technical Requirements for Registration of Pharmaceuticals for Human Use Q8 (R2) - Pharmaceutical Development, Harmonised Tripartite Guideline, EU, Japan, USA. Available at: https://www.ich.org/page/quality-guidelines (accessed 22.02.2021).

IEC (2019), IEC 31010:2019 - Risk management - Risk assessment techniques, International Electrotechnical Commission, Geneva, Switzerland.

ILAC, 2015. Rules for the Use of the ILAC MRA Mark, ILAC-R7:05/2015. Silverwater, Australia. (accessed 21.01.21).

ILAC (2019), Structure of the ILAC Mutual Recognition Arrangement and Procedure for Expansion of the Scope of the ILAC Arrangement, ILAC-R6:05/2019, Silverwater, Australia (available at https://ilac.org/publications-and-resources/ilac-rules-series/ (accessed 21.01.2021)

INMETRO (2020), NIT-DICLA-061, Rev.4, Requisitos sobre a acreditação dos laboratórios de ensaio e dos produtores de materiais de referência dos centros de recursos biológicos, Associação Brasileira de Normas Técnicas, Brasil.

IPQ (1999), NP EN 1619:1999 – Biotecnologia. Processos e produção em grande escala. Requisitos gerais para a gestão e organização dos procedimentos para conservação de estirpes. Instituto Português da Qualidade, Lisboa, Portugal.

ISEAL (2014), Setting Social and Environmental Standards, ISEAL Code of Good Practice, Version 6.0, ISEAL Alliance, London, United Kingdom.

ISEAL (date unknown), Assuring Compliance with Social and Environment Standards Code of Good Practice, version 1.0, ISEAL Alliance, London, United Kingdom. Withdrawn

ISO, 2006a, The future of ISO 9000 and ISO 14000, ISO Management Systems – January-February. International Organization for Standardization, Geneva, Switzerland (accessed 21.01.21).

ISO (2006b), ISO/TS 17665-1:2006 Sterilization of health care products — Moist heat — Part 1: Requirements for the development, validation and routine control of a sterilization process for medical devices, International Organization for Standardization, Geneva, Switzerland.

ISO (2009), ISO Guide 73:2009 - Risk management – Vocabulary, International Organization for Standardization, Geneva, Switzerland.

ISO (2012), 15189:2012 - Medical laboratories - Requirements for quality and competence, International Organization for Standardization, Geneva, Switzerland.

ISO (2013), ISO 16290:2013 - Space systems — Definition of the Technology Readiness Levels (TRLs) and their criteria of assessment, International Organization for Standardization, Geneva, Switzerland, Available at https://www.iso.org/obp/ui/#iso:std:iso:16290:ed-1:v1:en:term:2.17 (accessed 8 Mar 2017).

ISO (2014), ISO Guide 82 - Guidelines for addressing sustainability in standards, International Organization for Standardization, Geneva, Switzerland.

ISO, 2015a, ISO9000:2015 - Quality management systems – Fundamentals and vocabulary. International Organization for Standardization, Geneva, Switzerland.

ISO, 2015b, ISO9001:2015 - Quality management systems – Requirements. International Organization for Standardization, Geneva, Switzerland.

ISO (2018a), ISO 31000:2018 - Risk management - Guidelines, International Organization for Standardization, Geneva, Switzerland.

ISO (2018b), ISO20387 - General requirements for biobanking. International Organization for Standardization. Geneva, Switzerland.

ISO (2018c), ISO 19011 - Guidelines for auditing management systems, International Organization for Standardization, Geneva, Switzerland. Available at https://www.iso.org/standard/70017.html (accessed 18.05.2021).

ISO (2020a), ISO Committee on Conformity Assessment (CASCO) Structure, Process and Rules of Operation, QS-CAS-PROC01. International Organization for Standardization, Geneva, Switzerland.

ISO (2020b), CAS/PROC/33 Common Elements in ISO/CASCO Standards. International Organization for Standardization, Geneva, Switzerland.

ISO/IEC (1994), ISO/IEC Guide 59 - Code of good practice for standardization, International Organization for Standardization, Geneva, Switzerland. Withdrawn

ISO/IEC (2004a), ISO/IEC Guide 2 - Standardization and related activities - General vocabulary, 8th Edition. International Organization for Standardization, Geneva, Switzerland.

ISO/IEC (2004b), ISO/IEC 17000:2004 - Conformity assessment - Vocabulary and general principles, International Organization for Standardization and International Electrotechnical Commission, Geneva, Switzerland.

ISO/IEC (2005), ISO/IEC 17025:2005 - General requirements for the competence of testing and calibration laboratories, International Organization for Standardization, Geneva, Switzerland. [Withdrawn]

ISO/IEC (2014), ISO/IEC Directives, Part 1 - Consolidated ISO Supplement — Procedures specific to ISO, Fifth edition, International Organization for Standardization and International Electrotechnical Commission, Geneva, Switzerland. Withdrawn

ISO/IEC (2014), ISO/IEC Guide 51:2014 Safety aspects – Guidelines for their inclusion in standards, International Organization for Standardization, Geneva, Switzerland.

ISO/IEC (2017), ISO/IEC 17025 - General requirements for the competence of testing and calibration laboratories, International Organization for Standardization, Geneva, Switzerland.

ISO/IEC (2020c), ISO/IEC Directives, Part 1, Consolidated ISO Supplement, International Organization for Standardization, Geneva, Switzerland.

ISO/IEC (2021), ISO/IEC Directives Part 2 - Principles and rules for the structure and drafting of ISO and IEC documents, International Organization for Standardization, Geneva, Switzerland.

Juran, J. (1992), Juran on Quality by Design: The New Steps for Planning Quality into Goods and Services, The Free Press, USA.

Juran, J., Godfrey, A. (1999), Juran's Quality Handbook, McGraw-Hill.

Kan, S., Lu, J., Liu, J., Wang, J., Zhao, Y. (2014), A quality by design (QbD) case study on enteric-coated pellets: Screening of critical variables and establishment of design space at laboratory scale, Asian Journal of Pharmaceutical Sciences 9, 268- 278.

Kolaric, W. (1995), Creating Quality, McGraw-Hill International Editions, Singapore.

Kume, H. (1989), Métodos Estatísticos para Melhoria da Qualidade, Editora Gente, Sociedade S. Paulo AOTS Alumni, Rio de Janeiro, Brasil.

Lange, B. J., Boyd, W. J. (1968), Preservation of Fungal Spores by Drying on Porcelain Beads, Phytopathology, Vol. 58, pp. 1711-1712.

Largoni, M., Facco, P., Bernini, D, Bezzo, F., Barolo, M. (2015), Quality-by-Design approach to monitor the operation of a batch bioreactor in an industrial avian vaccine manufacturing process, Journal of Biotechnology , Vol. 211, pp. 87–96.

Leon, R., Shoemaker, A., Tsui, K.-L. (1993), Discussion on planning for a designed industrial experiment, Technometrics, Vol. 35, No. 1, pp. 21–24.

Lessel, E. F. (1970), Dilemmas of Curators of Culture Collections, Culture Collections os Microorganisms: Proceedings of International Conference, Oct. 7-11, pp. 63-67.

Lima, N. (2007), Centros de recursos biológicos: novos desafios para as coleções de culturas, M. L. Nunes and N.M. Bandarra (Eds.), Micologia, avanços no conhecimento, Ed. Universitária da UFPE, Recife, pp. 173-180, ISBN: 978-85-7315-444-3. Conferência Plenária Convidada apresentada no 5° Congresso Brasileiro de Micologia. 12 - 16 de Novembro de 2007, Recife, Brasil.

Lima, N. (2020), 1° Seminário Pernambucano de Excelência em SGI 68, Recife, Brasil.

Long, M., Henkels, W. D. & Baseman, H. (2011), FDA's New Process Validation Guidance: Industry Reaction, Questions, and Challenges, Pharmaceutical Technology, Vol. 35.

Mallik, R., Raman, S., Liang, X., Grobin, A., W.; Choudhury, D. (2015), Development and validation of a rapid ultra-high performance liquid chromatography method for the assay of benzalkonium chloride using a quality-by-design approach, Journal of Chromatography A, Vol. 1413, pp. 22–32.

Maropoulos, P., Ceglarek, D. (2010), Design verification and validation in product lifecycle, CIRP Annals - Manufacturing Technology, Vol. 59, pp. 740–759.

MCT (2002), Sistema de Avaliação da Conformidade de Material Biológico. Ministério da Ciência e Tecnologia, Brasília, Brasil. Available at: http://www.mct.gov.br/upd_blob/0001/1014.pdf (accessed 15 June 2016).

Moen, R., Nolan, T., Provost, L. (1991), Improving Quality Through Planned Experimentation, Singapore, MacGrow-Hill Book Co., ISBN 0-07-100837-3.

NASEM (2020), Biological Collections: Ensuring Critical Research and Education for the 21st Century. National Academies of Sciences, Engineering, and Medicine, Washington, DC: The National Academies Press, ISBN: 978-0-309-49853-1, available at https://doi.org/10.17226/25592 (accessed 18.05.2021).

OECD (2001), Biological Resource Centres - Underpinning the future of life sciences and biotechnology, OECD, Pari, ISBN 92-64-18690-5 93 2001 04 1 P.

OECD (2004), OECD Global Forum Knowledge Economy: biotechnology, Guidance for the operations of biological research centres, Certification and quality criteria for BRCS, Paris.

OECD (2007), OECD Best Practice Guidelines for Biological Resource Centres, OECD, Paris.

OECD (2010), Glossary of Key Terms in Evaluation and Results Based Management, OECD, Paris, available at https://www.oecd.org/dac/evaluation/2754804.pdf (accessed 23 .02.2021).

Parthasarathy, S. R., Krishna, P. K. (2012), Recent Trends in Validation, International Journal of Pharmaceutical, Chemical and Biological Sciences, Vol. 2, No. 1, pp. 29-37.

Patel, C., Desai, D. G., Seth, A. (2015), Process validation of artemether and lumefantrine 80/480 mg tablet, Pharma Science Monitor, Vol. 6, No. 1, pp. 233-243.

PharmOut (2016), website, available at: https://www.pharmout.net (accessed 22.02.2021).

Pluta, P. L. (2011), FDA Lifecycle Approach to Process Validation — What, Why, and How?, Journal of Validation Technology, Spring, pp. 51-61.

Rathore, A. S., Winkle, H. (2009), Quality by design for biopharmaceuticals, Nature Biotechnology, January, Vol. 27, No. 1.

Raven, M., Blind, K. (2017), The characteristics and impacts of scientific publications in biotechnology research referenced in standards, Technological Forecasting and Social Change, Vol. 115,

pp. 167-179, available at http://dx.doi.org/10.1016/j.techfore.2016.10.001 (accessed 21.01.21).

Rozet, E., Lebrun, P., Debrus, B., Boulanger,B., Hubert, P. (2013), Design Spaces for analytical methods, Trends in Analytical Chemistry, Vol. 42, pp. 157-167.

Simon, E. M., Whang, S. W. (1967), Tetrahymena: effect of freezing and subsequent thawing on breeding performance, Science, Vol. 155, No. 3763, pp. 694-696.

Sangshetti, J., Deshpande, M., Zaheer Z., Shinde, D., Arote, R. (2017), Quality by design approach: Regulatory need, Arabian Journal of Chemistry, Vol. 10, No. 2. doi.org/10.1016/j.arabjc.2014.01.025.

Santos I., Lima N. (2001), Criteria followed in the establishment of a filamentous fungal culture collection – Micoteca da Universidade do Minho, World Journal of Microbiology and Biotechnology, No. 17, pp. 215-220.

Skrdla, Peter J., Wang, T., Antonucci, V., Dowling, T., Ge, Z., Ellison, D., Curran, J., Mohan,G., Wyvratt, J. (2009), Use of a Quality-by-Design approach to justify removal of the HPLC weight % assay from routine API stability testing protocols. Journal of Pharmaceutical and Biomedical Analysis, Vol. 50, pp. 794-796.

Smith, D. and Ryan, M. (2012), "Implementing best practices and validation of cryopreservation techniques for microorganisms", The Scientific Workd Journal, Vol.2012, Article ID 805659, https://doi.org/10.1100/2012/805659

Tassey, G. (2000), Standardization in technology-based markets, Research Policy, No. 29, pp. 587–602.

UN (1997), E/1997/65/Add.3: Operational Activities of the United Nations for International Development Cooperation: Follow-Up to Policy Recommendations of the General Assembly Addendum Capacity-Building. Report of the Secretary-General. United Nations, Economic and Social Council, Geneva, 30 June-25 July: 1997.

UN (2015), Transforming our world: the 2030 Agenda for Sustainable Development - Resolution adopted by the General Assembly on 25 September 2015, United Nations. Available at https://sustainabledevelopment.un.org/post2015/transformingourworld (accessed 20.02 2021).

UNEP/SETAC (2005), Life Cycle Initiative, Life Cycle Approaches - The road from analysis to practice.

Verma, S., Lan, Y., Gokhale, R., Burgess, D. J. (2009), Quality by design approach to understand the process of nanosuspension preparation, International Journal of Pharmaceutics, Vol. 377, pp. 185–198.

WFCC (2010), WFCC Guidelines, 3rd Edition, World Federation of Culture Collections, ISBN 92 9109 043 3, available at http://www.wfcc.info/guidelines/ (accessed 22.02.2021).

WTO (2012), Agreement on Technical Barriers to Trade, Committee on Technical Barriers to Trade, World Trade Organisation, 29 November 2012, (available at http://www.wto.org/english/tratop_e/tbt_e/tbt_e.htm, accessed 22.02.2021).

WTO (2000), Second triennial review of the operation and implementation of the agreement on technical barriers to trade, G/TBT/9, (available at https://www.wto.org/english/tratop_e/tbt_e/tbt_triennial_reviews_e.htm, accessed 22.02.2021).

Wuchter, P. Bieback, K., Schrezenmeier, H., Bornhäuser, M., Müller, L.P., Bönig, H., Wagner, W., Meisel, R., Pavel, P., Tonn, T., Lang, P., Müller, I., Renner, M., Malcherek, R., Saffrich, R., Buss, E. C., Horn, P., Rojewski, M., Schmitt, A., Ho, A., Sanzenbacher, R., Schmitt, M. (2015), Standardization of good manufacturing practice compliant production of bone marrow derived human mesenchymal stromal cells for immunotherapeutic applications, Cytotherapy, Vol. 17, pp. 128 -139.

Yee, B., Tsuyumu, S., Adams, B. G. (1972), Biological Effects of Dimethylsulfoxide on Yeast, Biochemical and Biophysicaal Research Communications, Vol. 49, No. 5, pp. 1336-1342.

Yu, L. X. (2008), Pharmaceutical Quality by Design: Product and Process Development, Understanding, and Control, Pharmaceutical Research, Vol. 25, No. 4, pp. 781-791.

Zidan, A. S., Sammour, O. A., Hammad, M. A., Megrab, N. A., Habib, M.J., Khan, M. A. (2007), Quality by design approach to understand the process of nanosuspension preparation, International Journal of Pharmaceutics, Vol. 332, pp. 55–63.

ANNEXES

Annex 1

PROCEDURE FOR THE CONTROL OF THE STANDARDS'S DRAFTING

SCOPE: This procedure applies to the development of a standard for microbial biobanks.

OBJECTIVES: This procedure intends to ensure:
(1) that the working document is the last version of the document;
(2) that the source of all the provisions is known;
(3) traceability of changes (what was changed and why).

RELATED DOCUMENTS:

- Working document
- Version list_standard
- Version list_index
- Version list_goal
- Version list_scope
- List of sources&colors
- Provisions not included
- Notes and new requirements

PROCEDURE:

Create the template of the working document including a field to record: the **version No** and the **date**	Version numbers initiate in 1; the date has de following format: year/ month/day separated by one *space*; the document's name initiate with the date + working document's name; Example: **2016 08 01 BbDraft**
Give all the sources a color an record the correspondence	
When drafting the provisions, use the different colors (according to the respective source)	
When major changes are made to the document, make out a new version of the document	Changes in the body of the document are record in: "Version list_standard"; Changes in the index are record in: "Version list_index"; Changes in the "Goal" are record in: "Version list_goal"; Changes in the "Scope" are record in: "Version list_scope";
Identify and keep the obsolete version	Obsolete versions of the documents are kept in a folder identified as having obsolete documents; Example: "BbDraft v1 2016 01 10" is kept in a folder whose name is "BbDraft_obsolete"
When drafting, record the major changes in the correspondent Version list_standard	
Requirements on the OECD document not included in the standard are justified	The OECD provisions not included in the standard are record in the form "Provisions not included"; record the reason why they were not included.
Record new requirements and its rational	Relevant requirements added to the standard that were not included in the sources, or OECD provisions that were altered, are registered in "Notes and new requirements"

Annex II

Table 1AII – FMEA study on fungi cryopreservation for process factors presenting each factor's criticality by its Risk Priority Number (RPN)

Process parameter	Potential failure	Potential effect of failure	I	Potential cause of failure	L	Preventive action	Control for detection	A	RPN
Decreasing temperature rate	Not adequate (to fast or to slow)	Cell damage	5	Equipment not adequate	2	Absent	Absent	3	30
Decreasing temperature rate	Not adequate (to fast or to slow)	Cell damage	5	Lack of process knowledge	2	Absent	Absent	3	30
Increasing temperature rate	Measurable or likely to be estimated, but not adequate	Cell damage	5	Equipment not adequate	2	Absent	Absent	3	30
Increasing temperature rate	Measurable or likely to be estimated, but not adequate	Cell damage	5	Lack of process knowledge	2	Absent	Absent	3	30
Preservation temperature (during storage)	Temperature increase	Cell damage	5	Freezer breakdown	2	Freezer maintenance Alarm seting	Alarm	1	30

(I: Impact; L: Likelihood; A: Ability to detect)

Table 2AII - FMEA study on fungi cryopreservation for the operator presenting each factor's criticality by its Risk Priority Number (RPN)

Operator	Potential failure	Potential effect of failure	I	Potential cause of failure	L	Preventive action	Control for detection	A	RPN
Competence	Lack of competence for operations	Failure in authentication	5	Lack of training	1	Present	Present	1	5
			5	Lack of knowledge	1	Present	Present	1	5

Operator	Potential failure	Potential effect of failure	I	Potential cause of failure	L	Preventive action	Control for detection	A	RPN
		Failure in interpreting results and decisions	5	Lack of training		Present	Present	1	5
				Lack of knowledge	1	Present	Present	1	5
		Failure in raw material approval (presence of poison or lack of a crucial component)	5	Lack of training	1	Present	Present	1	5
			5	Lack of knowledge	1	Present	Present	1	5
		Failure in the preparation of solutions / suspensions	5	Lack of training	1	Present	Present	1	5
				Lack of knowledge	1	Present	Present	1	5
		Failure in labelling	5	Lack of training	1	Present	Present	1	5
				Lack of knowledge	1	Present	Present	1	5
		Failure in keeping records	4	Lack of training	1	Present	Absent	2	8

(I: Impact; L: Likelihood; A: Ability to detect).

Table 3AII - FMEA study on fungi cryopreservation for the operator presenting each factor's criticality by its Risk Priority Number (RPN) - FMEA study on fungi cryopreservation for equipment and material presenting each factor's criticality by its Risk Priority Number (RPN)

Equipment / Material	Potential failure	Potential effect of failure	I	Potential cause of failure	L	Preventive action	Existing control for detection	A	RPN
Deep Freezer	Increase in temperature	Cell damage	5	Breakdown	2	Set alarm Eq. maintenance	Present (alarm)	1	10
Incubator	Decrease of temperature	Irrelevant	1	Breakdown	2	Eq. maintenance	Present (alarm)	1	3
	Increase in temperature	Cell damage	5	Breakdown	2	Equipment maintenance	Present (alarm)	1	10
Autoclave	Problem during the sterilisation stages	Biological material contamination	5	Autoclave breakdown, presence of air, ...	2	Maintenance .Bowie&Dick test	Present (Records + Bowie&Dick results)	3	30
Laminar flow cabinet	Failure in EPA filter	Purity failure	5	Sample contamination	1	Eq.maintenance	Absent	3	15
Cryovials	Material not adequate	Cell damage	5	Liberation of poison	1	Absent	Absent	3	15
			5	Lack of resistance to very low temperatures	1	Absent	Absent	3	15
Beads	Material not adequate	Cell damage	5	Liberation of poison substance	1	Absent	Absent	3	15
Raw material	Presence of poison substance	Cell damage	5	Absent in the certificate of analysis	2	Absent	Absent	3	30

(I: Impact; L: Likelihood; A: Ability to detect)

Table 4AII - FMEA study on fungi cryopreservation for the operator presenting each factor's criticality by its Risk Priority Number (RPN) - FMEA study on fungi cryopreservation for equipment and material presenting each factor's criticality by its Risk Priority Number (RPN)

Cryoprotectant (CRY)	Potential failure	Potential effect of failure	I	Potential cause of failure	L	Preventive action	Existing control for detection	A	RPN
Type of CRY	CRY not adequate	Cell damage	5	State of the art Lack of testing	1	Absent	Absent	3	15
Temperature of the CRY	Temperature not adequate	Cell damage	5	State of the art Lack of testing	1	Absent	Absent	3	15
Contamination of the CRY	Failure in purity	Failure in authentication test	5	Failure in sterilisation	1	Present (sterilisation)	Present (contamination test)	1	5

(I: Impact; L: Likelihood; A: Ability to detect).