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Best Practice Methods for Biological Resource Centres

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Abstract

Biological Resource Centres have been defined by the OECD as next generation culture collections focussed on supplying high quality resources into biotechnology research and development. In the context of EMBRIC these hold biodiversity specific to the marine environment. Two key Research Infrastructures in the EMBRIC consortium are responsible for maintaining and supplying marine organisms, the Microbial Resources Research Infrastructure (MIRRI), specifically groups microbial domain Biological Resource Centres (mBRCs) and the European Marine Biological Resource Centre (EMBRC) involves BRCs offering access to a wide variety of marine organisms. In order to meet user quality demands, culture collections have established quality management systems based on best practice (for example the OECD guidelines). These systems are designed to facilitate the provision of common basic requirements to provide authentic, well-preserved biological material(s) that is/are reproducible in properties for the long-term with associated data to facilitate their use. This deliverable brings together different approaches to recommend a common way forward for EMBRIC.

Table of Contents

1 Introduction

Living organisms, their cells or their replicable parts (e.g. genomes, plasmids, viruses, cDNAs,) are the basic elements of the life sciences and biotechnology. They are utilised as living reference materials for testing, screening, identification, as well as production of compounds, fuel and food. They are tools for knowledge generation and biodiversity conservation. They are grown, maintained and utilised around the world and are key to many research programmes, industrial processes and training courses. These biological resources must be maintained in a stable state to ensure reproducibility and sustainability. **This report brings together the key principles from available best practice and international standards to form the basis for best practices in the management of Biological Resource Centres (BRCs) that hold and supply marine microorganisms.** Most of the principles and procedures also apply to BRCs that supply marine macroorganisms (animals, seaweed).

Microorganism collections are intrinsically linked to data (databases) that are directly associated to biological resources. **It is the policy of EMBRIC BRCs to provide their users on every occasion with the products and services they require; these products and services must be of consistently high quality and fulfil product claims as defined in the BRC catalogues. At all times appropriate techniques and procedures that comply with relevant national law, regulations and policies must be in operation.** The EMBRIC consortium recommends that regular independent audits should be performed to ensure that these procedures are followed and are effective. Guidance is given in this document in order to achieve best practice for managing microorganism BRCs. Procedures for acquisition, propagation, maintenance and provision of marine organisms are described. These help put into practice procedures that comply with relevant national law, regulations and policies. There are a number of best practice and procedural guidance documents available for guidance in establishing appropriate operational practice (see Table 1).

The present guidelines define general best practice for the acquisition, maintenance and provision of biological materials and for the management of Biological Resource Centres as defined by the OECD (see definition below). The purpose of this report on best practice guidelines is to help ensure that biological materials are of the highest standard and authentic. The preservation techniques used must ensure the retention of the key features of the biological material to ensure consistency between centres supplying it. This will help to provide a reliable basis for research and development in different laboratories and to contribute towards protection of the health of laboratory personnel, the public and the environment.

There have been several initiatives to design quality management systems for microbial and cell culture collections [1]. The first community-developed system was the WFCC Guidelines, but national culture collection organizations also chose to design their own standards, for example the UK National Culture Collection (UKNCC) quality management system (www.ukncc.co.uk) and project consortia such as the Common Access to Biological Resources and Information (CABRI) guidelines

(www.cabri.org). There are also general standards that can be applied to microbiology laboratories such as Good Laboratory Practice (GLP) and several International Standards Organization (ISO) norms e.g. ISO 17025, ISO Guide 34 and the ISO 9000 series. There are several publications on collection management and methodology that provide information on protocols and procedures [2-6], but for infrastructures providing a common service it was considered that a set of at least minimum standards are required.

Table 1 Example best practices and standards

Guidance or standard	Reference or link
OECD Best Practice Guidelines for Biological Resource Centers (2007)	http://www.oecd.org/sti/biotech/38777417.pdf
Common Access to Biological Resources and Information (CABRI) guidelines	http://www.cabri.org
World Federation for Culture Collections (WFCC) recommendations	http://www.wfcc.info/pdf/WFCC_Guidelines_Version_Third_Edition.pdf
ISO 17025:2005, General requirements for the competence of testing and calibration laboratories	https://www.iso.org/standard/39883.html
ISO 9001:2015(en) Quality Management Systems – Requirements	https://www.iso.org/obp/ui/#iso:std:iso:9001:ed-5:v1:en
ISBER Best Practices for Repositories: Collection, Storage, Retrieval, and Distribution of Biological Materials for Research	http://www.isber.org/?page=BPR
A BRC operational standard based on the OECD best practice guidelines for Biological Resource Centres as a working draft for an ISO Standard	http://www.embarc.eu/deliverables/EMbaRC_D.NA1.2.1_2.28_BRC_standard.pdf
AFNOR. French Standard NF S96-900 "Quality of biological resource centers (BRCs) - Management system of a BRC and quality of biological resources from human or micro-organism origin" (2008)	http://www.p3gobservatory.org/download/projet+norme+Biobanque+Eng.pdf

OECD definition of Biological Resource Centres (BRCs)

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

The German Government through the Bundes Ministerium für Bildung und Forschung (BMBF), i.e. the German Federal Ministry of Research and Education supported a

small Secretariat to draw national efforts together in developing tools for the establishment of the Global Biological Resource Centre Network (GBRCN). The report of these activities demonstrated the importance of establishing common approaches and standards [7]. A basic requirement of any distributed network is common practice for operation and delivery of reproducible resources. Additionally, operation to international standards can improve the science based on such resources. The GBRCN is being established on a regional basis and in Europe, the Microbial Resources Research Infrastructure (MIRRI) was designed to first improve the quality management of BRCs and then, as a result, improve research and biotechnology through the authenticated material(s) they provide. The regional efforts are moving at their own pace and are sharing ideas, concepts and practice. In Europe, the pan-European ESFRI project 'MIRRI' recommends the adoption of quality management systems for its members [8]. The OECD best practice covers critical elements in the handling, storage, characterization and distribution of microorganisms and cell cultures, as well as the management of their associated information and sets the current "gold standard" [9]. However, it is not absolutely essential that all elements are introduced at one time and a process that sets a minimal level to ensure that resources are authentic, preserved in a stable condition for the long-term and that associated information is validated provides the ideal gateway to an environment of improvement and progress towards excellence. MIRRI sought to introduce such a system.

Historically, many businesses, research institutions and culture collections have introduced ISO 9001 series (latest ISO 9001:2015) certification as a benchmark for quality in order to achieve preferred supplier status. This standard is based upon the concept of process management developing an evidence-based system giving management system effectiveness through process performance measures and has developed with business needs over the years. Basically, it works on the principle of systematic control of activities to ensure that the needs and expectations of customers are met. However, a comparison with OECD best practice demonstrates that ISO 9001: 2015 does not adequately cover BRC specific operations thoroughly. It helps put in place good management systems, but it does not address the output of BRCs or the competence to deliver cultures and associated services. In most cases, standards are designed with specific purposes in mind and need adjustment to address some of the specific operational requirements of a BRC. Some critical elements often not covered are:

1. Compliance with various legal requirements in association with the handling and shipping of biological materials;
2. The use and preparation of reagents, media and other supplies;
3. A strategic plan for BRC future sustainability in order to avoid the loss of biological resources; or
4. Data management and staff qualifications and competence.

There are a number of ISO standards that go beyond the management of processes to cover the additional competence requirements for example ISO/IEC 17025, *General requirements for the competence of testing and calibration laboratories is a standard used by testing and calibration laboratories*. There are many commonalities with the ISO 9000 standard, but the former is more specific in requirements for

competence. The ISO/IEC 17025 standard comprises five elements that are: Scope, Normative References, Terms and Definitions, Management Requirements and Technical Requirements. Management requirements are primarily related to the operation and effectiveness of the quality management system within the laboratory. Technical requirements include factors that determine the correctness and reliability of the tests and calibrations performed in the laboratory. ISO/IEC 17025 is used to improve ability to consistently produce valid results. In contrast to ISO 9001: 2015, it is accreditation and not a certification process. The accreditation is a formal recognition of a demonstration of competence. A number of culture collections currently employ ISO 17025 for specific activities or processes essential to their operations. For example, CABI is accredited for its molecular identification services for fungi and bacteria and its methods for sampling and testing mould resistance of materials.

Other standards have been adopted to a lesser degree such as ISO Guide 34, *General requirements for the competence of reference material producers*. However, this guide was specifically written for reference material producers and it is used for the calibration of measuring equipment and for the evaluation or validation of measurement procedures. These include: pharmacopoeia standards and substances. Property values and their uncertainties are difficult to apply to living materials and many measurement principles are inappropriate. Furthermore, most BRCs do not work with reference material(s), as defined for ISO Guide 34, but mostly with type strains. These are references for the species, but not reference material as defined for the production of a specific metabolite etc.

This failure to address exactly the operation and needs of the BRC and its users has led individual collections, or collection communities, to design their own systems. The French culture collection community worked with the French national organization for standardization, the Association Française de Normalisation (AFNOR), to develop the French standard NF S96-900 “Quality of biological resource centers (BRCs) – Management system of a BRC and quality of biological resources from human or micro-organism origin” [10]. The Brazilian network of collections worked with their accreditation bodies led by IMMETRO - National Institute of Metrology, Quality and Technology to design and publish the standard NIT-Dicla061 *Aplicações e Requisitos Adicionais Acreditação ABNT NBR ISO/IEC 17025 dos Centros de Recursos Biológicos* for the accreditation of BRCs [1].

Whatever the authoritative document, standard, certification or accreditation process that is selected, a BRC quality management system must address several specific areas:

1. Organizational requirements
2. Equipment use, calibration, testing and maintenance records
3. Documentation management
4. Data management, processing and publication
5. Preparation of media and reagents
6. Accession of deposits to the BRC
7. Preservation and maintenance

[1] www.inmetro.gov.br/credenciamento/pdf/nit_dicla_061.pdf

8. Supply
9. Quality audit and quality review

Amongst the microorganism domain criteria set down by the OECD Best Practice Guidelines are recommendations on the following:

1. Staff-qualifications and training
2. Hygiene and biosafety
3. Equipment use, calibration, testing and maintenance records
4. Preparation of samples
5. Information provided with the biological material supplied

Essentially, the key actions in the transition to a BRC are implementing international operational standards to ensure the preservation and supply of authentic materials, employing the best practice in preservation and practices for the confirmation and validation of associated information. Additionally, BRCs must put in place mechanisms to keep pace with technological demands and perform research to add value to strain holdings. They need to work with national authorities and partners to implement national plans in the conservation of biodiversity, establish themselves as repositories for protection of intellectual property and be compliant with national law, regulations, and policies. This requires more than a quality management system. The need to manage its roles in science, in an appropriate regulatory environment needs inbuilt management procedures that do not add unnecessary burden and be part of a BRCs normal business operations.

Users of biological and genetic resources have responsibilities in access and the fair and equitable utilisation of them. In Europe, the EU Regulation on ABS (EU) No 511/2014[2] was enacted simultaneously with the coming into force of the Nagoya Protocol and this will be followed by the European Member states putting in place local implementing practices or instruments. In some countries this will be a balance between regulatory control and due diligence. Each country signatory to the CBD and the Nagoya Protocol will implement its own controls, ensuring compliance with the Protocol's requirements. All genetic resource users, not just mBRCs, must align their practices in the conservation and use of genetic resources in their work to comply globally with the Nagoya Protocol on ABS requirements, as well as working within the spirit of the CBD and ensuring compliance with national laws and regulations of all countries within which they work [11]. Publications on how practitioners can adapt their practices in compliance are available, for example, microbiologists need to ensure they understand when their work with genetic resources is in the scope of the regulation [12].

MIRRI's common understanding on Quality Management System (QMS), appropriate standards and best practice models

MIRRI has established a common understanding on biological resource management that includes quality management systems utilising appropriate standards and best practice models. Providing authentic high quality resources presupposes that BRCs optimise their processes and continually improve the skills necessary to perform their duties. The goal is to optimise operation through an on-going cyclic improvement

[2] http://eur-lex.europa.eu/legal-content/EN/TXT/?uri=CELEX:32014R0511

processes. Improving the competence and assessing the expertise of an organization in its field of activity. Raising the reliability of biological resources and related information to meet the expectation of the stakeholders concerning the requirements for basic research, R&D or commercial production purposes is crucial. MIRRI will help microbial domain BRCs (mBRCs) adopt scientific/technical evaluation and improvement processes, to adapt to progress in science and business management in general. This requires the alignment of the demands and the reduction of the discrepancies between collections.

To date the origin of the harmonized quality management system for BRCs has focussed on the biological material held and the BRCs range of services. The other most relevant factors determining the quality management of a BRC have concerned data sets, standard operating procedures and regulatory standards.

The conflict in finding an appropriate and harmonized quality management system on this basis is inherent to the system because it ignores the influence of parameters like collecting biodiversity, offering of various services, different funding strategies, different organizational structures, and different infrastructures within the organizations or different national regulations amongst the MIRRI member states. In addition, the various and changing user demands as well as the need for establishing specialized BRCs are not covered by the system strategy so far. A common quality management system with shared procedures at the detailed level is not achievable given all these differences and thus would not be beneficial.

Additionally, external drivers have a strong impact on the definition of any future system of managing quality in BRCs. Besides globalization, rapid changes and progress in science, product development, technology, logistics, lifestyle, customer needs and demands together with increased regulatory requirements will lead to even greater needs for system-level thinking and practice in quality management rather than the fragmentary micro-management activities in this sector in the past.

MIRRI has made the commitment of placing sound quality management at its core in its partner charter. This charter defines criteria for the participation of mBRCs, institutions or individuals providing resources, services, training and expertise or participating in joint projects within the framework of MIRRI. In its general principles it requires partner mBRCs to ensure they provide a high quality resources, services, training and expertise, and to commit to implement a quality management system and/or quality assurance procedures following appropriate international standards.. Partners are required to allow external audits by MIRRI-ERIC to provide an evaluation of their knowledge, competence, experience and compliance. They are also required to implement MIRRI Policies, specifically to fulfil the MIRRI-ERIC Data Management Policy and provide relevant and predetermined data to the MIRRI-ERIC catalogues following the FAIR (Findable, Accessible, Interoperable and Reusable) Data approach. Additionally, they must implement MIRRI policy on compliance with the Convention on Biological Diversity (CBD), the Nagoya Protocol and subsequent regional and national laws and on bio-risk assessment and biosecurity measures.

MIRRI's definition of quality management is no longer restricted to the biological material, but to the organization's policy and the governance of different compliance needs, regardless of where they impact. This includes IT systems, social

responsibility, laboratory processes and network membership criteria. The initial step is network driven and involves offering managerial solutions thus empowering a BRC to be a valuable partner in the MIRRI infrastructure. This essential shift incorporates the facts that BRCs are facing an increasingly complex regulatory environment, as well as more challenging requirements demanded by user communities and an increased focus on accountability. Hence, a broad range of governance, risk, quality and compliance initiatives across the organization of a BRC are necessary to cope with global development.

The MIRRI strategy needs to substitute the traditional BRC management approach, which has largely employed uncoordinated, independently planned and managed initiatives. Such approaches increase the overall risk for the organization. In addition, parallel compliance, quality and risk initiatives invariably lead to duplication of effort and may cause costs to spiral out of control. The BRC managerial strategy must master the situation accommodating the fact that governance, quality, risk, and compliance can be steered by similar processes. Through centrally managed control, definition, enforcement and monitoring a BRC has the ability to coordinate and integrate all these initiatives, that to date are managed independently and not mutual harmonized. MIRRI anticipates that its partners adopt this integrated approach of Quality Management and utilise the more procedural encompassing "Policy Compliance Management System" (Fig 1).

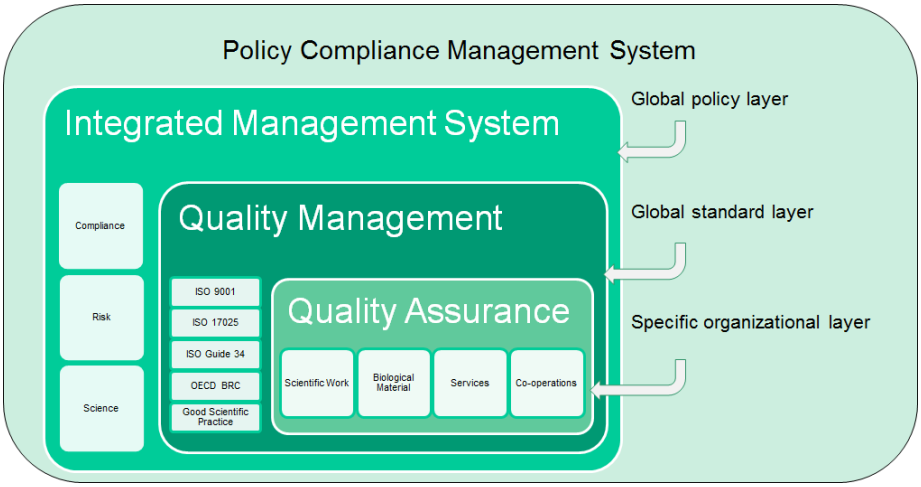

Figure 1. Layered system structure Policy Compliance Management System

Due to the linkage between BRCs and biotechnology a strong, internationally acknowledged and far-reaching ISO standard has been developed since 2013 ISO/TC 276 "Biotechnology" has been coordinating the establishment of a new ISO standard in liaison with other technical committees to avoid conflicts and/or duplication. The founding meeting of the international Technical Committee ISO/TC 276 took place in December 2013 in Berlin/Germany. The creation of the Technical Committee was preceded by a period of intensive preparation and different approaches to create appropriate standards or guidelines. The German DIN

(Deutsches Institut für Normung) took the initiative and formally submitted a proposal for the creation of ISO/TC Biotechnology. In February 2013, this was approved and DIN was entrusted with the secretariat. The focus of ISO/TC 276 is to find standardization needs and gaps in the field of biotechnology. The scope of ISO/TC 276 is "Standardization in the field of biotechnology processes that includes the following topics: 1) terms and definitions; 2) biobanks and bioresources; 3) analytical methods; 4) bioprocessing; 5) data processing including annotation, analysis, validation, comparability and integration; 6) metrology.

Within the next three years, ISO/TC 276 Biotechnology will work closely with related committees in order to identify standardization needs and gaps, and collaborate with other organizations to avoid duplication and overlapping standardization activities. Some MIRRI partners, including representatives from France and Germany have taken an active role in defining this new standard. The work on the new standard is ongoing. However although the above approach will develop a clear pathway towards enhanced quality, MIRRI does not specifically require BRCs to take the ISO route. Partners are free to utilise any quality management system but it must ensure the key principles of implementing international operational standards to ensure the preservation and supply of authentic materials, employing the best practice in preservation and practices for the confirmation and validation of associated information. Furthermore, this compliance must be demonstrated through independent audit.

EMBRC policy on standards and best practices

EMBRC is fully committed to providing high quality biological resources and associated logistical and analytical services and data. Until the present point in time, the development of common practises within EMBRC has focussed on (1) providing guidelines for a harmonized approach to organism access and use in compliance with the new EU regulation on Access and Benefit Sharing to genetic resources, and (2) developing common guidelines for data management.

Best Practice Guidelines (BPGs) have been drawn up for EMBRC culture collections to comply with the applicable international framework for accessing and using marine bioresources (UN Convention on the Law of the Sea, Convention on Biological Diversity and its Instrument - Nagoya Protocol on Access to Genetic Resources & Benefit Sharing, as well as the EU ABS regulation) for approval by the European Commission under the EU ABS Regulation (Regulation (EU) N° 511/2014. EMBRC BPGs for culture collections cover Material Accession Forms, terms and conditions for supplying materials to third parties, and tracking of resources. BPGs for accessing material (EMBRC BPGs for users) deal with accessing genetic material in situ, due diligence, and what information must be retained by the user prior to collection and to the transfer procedure. As a provider/supplier of marine genetic resources and a European research infrastructure, it is of utmost importance to EMBRC to comply with the EU ABS Regulation, and with national and international legal frameworks for accessing and utilizing marine genetic resources. Having its practices recognized at the European level will facilitate its mission as a provider of MGRs and aim to ensure user compliance with the due diligence obligations of the EU ABS Regulation.

EMBRC-ERIC acknowledges the importance of good data management of research data and has thus developed a Data Management Plan in anticipation of planned

research activities. Data often have a significantly longer lifespan than the research project that creates them. Researchers may continue to work on data after funding has ceased, follow-up projects may analyse or add to the data, and data may be re-used or synthesized by other researchers. Well-organized, well-documented, preserved and shared data are invaluable to advance scientific inquiry and to increase opportunities for learning and innovation. The EMBRC Data Management Plan covers all aspects of handling, organizing, documenting and enhancing research data, and enabling their sustainability and sharing.

On local and/or national-node scales, most EMBRC BRCs already implement some form of quality management system (although few are currently certified) and adhere (more or less officially) to BRC operational guidelines, usually based on those of the OECD. The EMBRC-ERIC business plan sets the adoption of common standard quality practices as a medium-term objective (first three years of the ERIC operational phase, i.e. 2018-2020).

2 Organisational requirements

A BRC must put in place organisational practices to ensure that it is able to provide resources to its users reliably and reproducibly. This includes being able to demonstrate that it is sustainable and will not suddenly stop operating without a contingency plan. The BRC should ensure biological materials will continue to be available for use and the materials provided safe and consistent. Section 2 and the following sections to section 13 are based upon the implementation of the OECD *Best Practice Guidelines on Biosecurity for BRCs*.

The BRC needs a strategy for its long-term sustainability. Adequate and reliable sources of funding vary from government support, income from products and services and private support.

If its future is threatened, the BRC shall have a plan to ensure that its unique holdings remain available.

2.1 Responsibilities of management

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

The Senior Management of each individual BRC must ensure that appropriate resources are available for staff members to discharge its responsibility towards this policy. The BRC should designate a Quality Manager whose duties include:

- Administering and monitoring an efficient up-to-date quality management system.
- Reporting and advising on quality matters.
- Representing the BRC on quality matters when dealing with users, suppliers and outside bodies.

Where possible a deputy should be appointed to serve in the absence of the quality manager. The Quality Manager should have direct access to the Senior Management of the BRC on matters concerning quality.

The BRC must designate a biosecurity officer, at operational level within the BRC, with the responsibility to ensure internal compliance with *Best Practice Guidelines on Biosecurity for BRCs*.

2.2 Staff - qualifications and training

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

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

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

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

It is the responsibility of all staff to familiarise themselves with documented protocols and comply with the policies and procedures laid down in the BRC Standard Operating Procedures and associated documentation at all times. It is the management's responsibility to ensure that staff have access to Quality Manuals and that they understand them and they are kept informed of any amendments.

2.3 Health and safety (biosafety)

All staff must follow the procedures laid down under the appropriate level of containment for the microorganisms being handled, as defined by the World Health Organisation (WHO, 2004) and as interpreted by national law, regulations and policies, to avoid contaminating samples, risk of infection and environmental dispersion.

2.4 Premises

The BRC environment must be conducive to handling the organisms held in the BRC. The premises must facilitate the acquisition, maintenance and provision of biological materials and the associated BRC services.

It is the responsibility of the member of staff allocated to a task to check that the accommodation is clean, appropriately illuminated and in the case of microorganisms that aseptic techniques are employed. Appropriate protective clothing worn and safety procedures followed.

Appropriate arrangements, in accordance with national and international regulations, for site security must be in place to ensure hazardous organisms cannot be released to unauthorised users.

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

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

3 Biological Resource Centre operations

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

- Receipt and storage of the initial sample.
- Preparation, regeneration, handling and processing of samples.
- Biological material storage area and back-up or safety duplicate collection. Duplicate collection shall be preferably in a remote building or alternative site.
- Supply, delivery/sales (kept separate from incoming accessions).
- Decontamination and cleaning of equipment and processing of wastes.

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.

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

3.1 Construction and operation

Construction must be appropriate for the work and in case of microorganisms, respect the containment level appropriate for the risk group of those worked with and must meet appropriate national law, regulations and policies. If major building, renovation or repair work, or other work that is likely to compromise containment or clean conditions, is necessary in Biological Resource Centres, normal activities must be suspended until the building renovation or repair work is completed.

3.2 Access

The minimal requirement is to restrict access to the BRC to authorised staff or those accompanied by them. BRCs housing hazardous biological materials must pay particular attention to security and where appropriate be fitted with security devices (see Best Practice Guidelines on Biosecurity for BRCs [9, 13]).

3.3 Maintenance and inspection

Cleaning of laboratory benching and equipment must be performed by authorised and trained staff using appropriate personal protection equipment and following documented procedures. A contamination-monitoring programme must be in place to include environmental monitoring of laboratory air and surfaces. If a major contamination problem arises in the BRC, the BRC manager is responsible for implementing a cleaning programme and an investigation of the source of contamination. Details of decontamination procedures shall be located in a

Procedures Manual or relevant Standard Operating Procedures (SOPs). Quality audit and quality review must be carried out.

3.4 Outside support services and supplies

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

4 Equipment use, calibration, testing and maintenance records

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

Appropriate maintenance and calibration procedures for common items of equipment used in microbial domain BRCs are summarised in Table 1 of Annexe 17.1.

5 Documentation management

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

5.1 Compliance with internal documentation

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

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

6 Data and informatics

The BRC must manage and store data and produce electronic catalogues based on authenticated and validated information.

6.1 Data management

It is critical to ensure that only competent, designated personnel have editing rights on master files of BRC data. Depositors are responsible for assuring the quality of data associated with the biological material. The BRC may require evidence to assure the validity of the data.

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

- Provide traceability of data through a history of modifications (dates and signatures of inputs, validations, modifications and deletions – including electronic means).
- Give signature for data entry, validation, modification or deletion (including electronic means).

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

a. Select data format, data representation and data transportation taking into consideration existing standards for data processing, e.g. DarwinCore/DiGIR, ABCD schema/BioCASE and/or the CABRI guidelines on catalogue production for strain data, CCINFO for the organizational information of BRCs.
b. Check vocabulary against standard reference lists or thesauri.
c. Keep consistency among BRCs for searching and retrieving of information from catalogues and databases:
d. There should be a minimum amount of information available for each accession in the collection (Minimum Data Set (MDS). Additional data may be included in the Recommended Data Set (RDS) and Full Data Set (FDS). The MDS and RDS are listed in Table 2, Appendix 1. The MDS comprises essential information to identify a unique item in the BRC. 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 shall always be recorded and made available whereas the RDS is recommended, and the FDS is additional optional information.
e. Spell checking for every field shall be a basic requirement.
f. International English should be chosen as a preferred language of data (in addition to local language if different).
g. A standardised approach should be adopted to certain scientific symbols (to avoid any errors due to incorrect reading of a character set, standard ASCII alternatives to symbols shall be used: e.g. Greek letters cannot be used, they shall be fully spelled (write alpha, gamma, beta...); the °symbol for

temperature is to be omitted entirely (e.g. 37C replaces 37°C); no subscripts or superscripts are allowed (e.g. cm3 replaces cm3 and CO2 replaces CO2).

h. BRCs should adopt procedures to detect errors in data to improve their quality and consistency. This is an essential part of information management and shall be both applied to the input of new data as well as to pre-existing information in current databases:
i. For existing data, a series of checks should be carried out to ascertain their validity and completeness. As more BRCs become associated, more searches should be made for common classes of error to allow more efficient error correction.
j. For new data, wherever possible, inputting must be checked against authorised lists of not only scientific names but also thesaurus/ontology to prevent errors such as mistyping.
k. BRCs must present evidence that they have applied a recognised protocol appropriate for each data element.[3]

6.2 Data processing

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

The databases should contain either information relating to strains held by a BRC (which at least, shall be retained as long as a strain remains viable), or other relevant data items or composite data needed by the BRC (e.g. users records). On the loss of a strain, the database record must be either printed and stored on file or copied to a digital archive before the entry is removed from the working database, placed in reserve or annotated to indicate that it is no longer available as living material.

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

The informatics system must ensure regular data back-up. Off-site storage of data is desirable. Data archives should be maintained in accordance with the maintenance of the biological resource storage policy. The support of these archives must be regularly updated according to its physical characteristics (obsolescence) and to software compatibility.

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

3 . A comprehensive treatment of Data Cleaning can be found in Chapman, A.D., *Principles and Methods of Data Cleaning – Primary Species and Species-Occurrence Data,* Version 1.0, Publisher - Global Biodiversity Information Facility (GBIF), 2005.

6.3 Access to data and publication

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

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

BRCs should ensure the quality and consistency of data sets and provide data to users while ensuring information security, bio-security, protection of IPR, client information and human dignity. National data protection regulations must be adhered to.

Exchange of information should be in line with the OECD Guidelines on the Protection of Privacy and Trans border Flows of Personal data.

BRCs must restrict access with editing rights to the electronic catalogues to competent, designated personnel.

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

7 Preparation of media and reagents

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

Accurate preparation and storage conditions of culture media, one of the fundamental steps in the growth and maintenance of biological materials, must be given special attention. The BRC should have defined standards for all preparations; media formulae must be documented and procedures put in place to make changes to procedures and for their approval and adoption. Media batches must be clearly labelled and expiry dates (date after which media and reagents are not to be used) defined and clearly indicated.

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

8 Accession of deposits to the BRC

8.1 Receipt and handling of biological materials

The BRC must document and implement safe procedures for receipt and storage appropriate to the type of biological materials handled. All incoming parcels that contain known or unknown organisms must be opened in a suitable containment laboratory or appropriate safety cabinet with local facilities for the safe handling and disposal of biological materials.

The depositor shall provide assurance that biological materials were obtained legitimately. Conditions of deposit shall be determined and agreed e.g. laid down in a material transfer agreement (MTA), for example to protect assigned intellectual property rights (IPR). Where deposits are outside the expertise of the BRC, alternative suitable BRCs should be recommended.

Quality control procedures must be carried out upon receipt of biological material to confirm its purity, identity and viability. The recommended procedures that should be carried out are in Table 3, Annexe 17.1.

Before accepting a deposit, the BRC must check against risk group lists and other lists to make sure that the biological material does not exceed the laboratory's biological safety containment level.

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

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

8.2 Accession

The BRC shall document its acquisition policy defining the biological material to be maintained and the criteria on which the acceptance of new biological material offered to the collection is based. This policy shall balance capability, capacity with scientific and user's needs.

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

The biological material received shall have the following information:

a. Name (where one can be applied), other identifier or cell culture description.
b. Depositor's name and address.
c. Source, substrate or host from which the biological material was isolated or derived (where identified) and date of isolation.
d. Geographical origin of material (the minimum requirement is the country of origin or the furnisher of the source, substrate or host).

e. Depositor's biological material number or other collection number(s), if deposited elsewhere.
f. Growth media and conditions, cell preservation or storage conditions where known.
g. Hazard information e.g. in the form of a safety data sheet.

8.3 Quality checks on the biological material

The BRC must employ a due diligence approach to performing authentication tests as well as determine the stability of some key features, growth requirements, and methods of maintenance and/or preservation as appropriate to the biological material maintained. This information must be recorded. These records must be retained and can be used as a base line when in-storage maintenance checks are performed or for validation after preservation restocking.

Where possible the identity/authenticity of the biological material must be confirmed after receipt by a competent person (employed or contracted by the BRC or its parental organisation). The biological material must be checked again by these competent persons before (if there are additional transfers of the biological material before it is preserved) and after preservation "(where appropriate for the organism type i.e. sometimes not necessary e.g. post cryopreservation of plasmids). This step may include identity, purity or property check of the biological material performed by the depositor.

A "maintenance plan" (i.e. a scheme for periodic control of the preserved material) is recommended for each item stored. Several aspects determine the frequency of the maintenance checks (e.g. the type of biological material, the preservation method, turnover of the material, etc.). The maintenance check must be appropriate to the biological material and be laid down in the domain specific criteria (details of quality controls can be found in Table 3, Annexe 17.1).

9 Preservation and maintenance

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

Where practicable and technically achievable microorganisms must be preserved by at least two methods; where two distinct methods are not applicable to the biological material, stocks, preferably cryopreserved stocks, must be maintained in separate locations and as master cell banks and as stocks for distribution. The labels shall include at least the batch date or number and the BRC accession number. Where possible an indication of expiry date must be provided to the user of the biological material. Biological materials with specific hazards must be clearly differentiated.

9.1 Long-term preservation

The commonly used approach for sustainable preservation of microbial cultures is long-term preservation employing liquid nitrogen [14], deep freezing, freeze-drying or L-drying methods. These methods allow high quality long-term storage, recovery and use of the microorganism. For each microorganism culture, an appropriate preservation method(s) should be chosen by the BRC based on its own experience or on the recommendations of the depositor. The methods used MUST be equivalent to those cited above and MUST ensure:

- High viability/recovery of the preserved culture;
- No contaminant in the preserved culture (see comments below, this does not include any recognised co-culture e.g. symbiotic microorganisms), which are not regarded as contaminants so 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.

The majority of microorganisms are yet to be grown in culture and often function together in an ecosystem; it is therefore becoming common practice to conserve consortia. In such cases, mBRCs should employ appropriate means to characterise the multiple partners to facilitate the monitoring of stability of the consortium following preservation and storage. The recommended methods for the storage and preservation of biological materials and the form in which it is distributed are set out in Table 4, Annexe 17.1.

9.2 Validation of methods and procedures

Validation of the methods and procedures used for preservation must be carried out to ensure their reproducibility and reliability, and general compliance during the quality control of biological material. Performance of the method(s) must correspond

to the criteria listed in Table 3 Annexe 17.1 (= viability, purity and identity/authenticity).

In addition to the requirements laid out in the General Best Practice Guidelines for all BRCs, the validation of quality check, characterisation and preservation methods is recommended using at least one of the following approaches:

- Performing blind tests;
- Comparing the results of the same method performed at different times (reproducibility).
- Comparing results obtained with different methods (reliability).
- Comparing the results obtained for the same method performed by different persons.

The results of quality checks and the procedure used must be recorded.

9.3 Stock control of the preserved biological materials

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

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

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

9.4 Storage of preserved biological materials

The biological material must be stored under environmental parameters that assure the stability of its properties (see Table 4, Annexe 17.1).

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

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

10 Supply

10.1 Order placement

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

To the extent that it can be determined, BRCs must supply microorganisms only to laboratories and only to those individuals who are trained in microbiology and have access to properly equipped laboratories, unless otherwise justified and documented. The recipient's facilities must meet the specific requirements as required by relevant national and international regulations and policies.

First orders from new clients must be received on an order form with the client's official letterhead and be signed by an authorised person. The BRC should accept fax and mail orders with an official user order number unless signature and/or permits are required for release of particular biological materials. E-mail orders can be accepted from known or registered users where signatures of authority are not required.

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

10.2 User validation

To ensure that only authorised users may access biological material that is pathogenic or toxic to humans, animals and plants, the BRC must implement national and international requirements and, as applicable, the following measures for the respective hazardous material:

- Comply with the measures set out in Best Practice Guidelines on Biosecurity for BRCs (see Annexe 17.2).
- Check that the name and signature of the head of department/division match against those registered in the BRC's list of authorised institutions.
- Check that the name and signature of the user match against those registered in the BRC's list of authorised users.
- Have written and signed documentation proving that the user has the appropriate containment facilities and the authorisation to import and handle such biological material.

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

10.3 Availability of the biological material ordered

Freeze-dried or cryopreserved (when supplied frozen) microorganisms should be dispatched as soon as possible once necessary licenses and/or documentation are

provided. Dispatch for such materials should be according to the laid down procedures and conditions. Where there is a delay foreseen in delivery of materials (e.g. actively growing cultures), then the client should be informed of this delay.

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

10.4 Packaging and Transport

The packaging of biological material and its transport by postal and other transport services is controlled by international and regional agreements and national laws.

To ensure safe and secure packaging and transportation of biological material, the BRC must follow the WHO Guidelines on International Regulations for the Packaging and Transport of Infectious Substances.[4] These best practice guidelines provide practical guidance to facilitate compliance with current international regulations for the transport of infectious substances by all modes of transport, both nationally and internationally.

Those materials exempt from the WHO guidelines (non-infectious microorganisms allocated to Risk Group 1) may be sent by (air) mail or other means of transport according to the Universal Postal Union (UPU) requirements.[5]

The International Air Transport Association (IATA) Dangerous Goods Regulations (DGR) 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. BRCs must 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.[6]

BRCs must ensure that staff responsible for the distribution of biological material have the necessary knowledge and training.

Staff responsible for the distribution of dangerous goods (including infectious substances) via air should have the shipper's training certificate as required by IATA.

10.5 Traceability of hazardous biological materials

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

4. www.unece.org/trans/danger/publi/unrec/rev13/
5. http://ibis.ib.upu.org
6. http://www.IATA.org/cargo/dg

10.6 Information provided with the biological material supplied

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

- The unique identifier of the biological material, accession number and batch number.
- An estimate of shelf-life, storage conditions, storage instructions and if appropriate, conditions of growth.
- Instructions for opening ampoules or vials (when appropriate and in all cases where materials are being provided to new users).
- A safety data sheet including the containment level required for handling the biological material, disposal measures and measures to take in case of spillage (see 11.4 below).
- A Material Transfer Agreement: an essential requirement to protect IPR and mandatory where they are required by national law. They are used to relay the depositor's and/or country of origin requirements on use of the biological material.[7]

An email return sheet to acknowledge receipt of materials may be desirable.

10.7 Invoicing for supply charges

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

10.8 Handling complaints and anomalies

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

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

Records of responses/solutions should be stored.

10.9 Refunds

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

7. Examples of MTA content can be found as an annex to the Bonn Guidelines (http://www.biodiv.org) and as an output of the MOSAICC project (http://www.belspo.be/bccm/mosaicc) - both voluntary codes of practice.

10.10 Confidentiality

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

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

11 Microorganism Biological Resource Centres compliance with national and international law

Microorganisms are isolated, grown, characterised, preserved for the long-term, stored and transported between laboratories. They are shipped by various means, by postal mail or by courier service, from one laboratory to another within countries, and often across borders or continents. They are sent for identification, reference, research or for production purposes from colleague to colleague, from and to culture collections. All these actions must be carried out safely and in compliance with the various legislation and regulations that control these matters. The BRC must ensure that any changes to applicable legislation and regulations are implemented in their procedures.

The importance of a laboratory's health and safety procedures extend beyond the laboratory to all those who come in contact with substances and products from that laboratory. A microorganism in transit might put carriers, postal staff, freight operators and recipients at risk, some organisms being relatively hazard free whilst others can be quite dangerous. Safety and shipping regulations must be followed to ensure safe transit. The BRC must adhere to regulations relevant to the distribution of microorganisms.

A Biological Resource Centre (BRC) shall, for example, comply with:

- Applicable health and safety requirements.
- Classification of microorganisms on the basis of risk.
- Applicable quarantine regulations.
- Intellectual property rights (IPR).
- Requirement that safety information is provided to the recipient of microorganisms.
- Applicable regulations governing shipping of cultures.
- Control of distribution of biological material (see paragraph 11.5 addressing biosecurity).
- Provision of appropriate safety information to the recipient of microorganisms.

In the process of isolation, handling, storage and distribution of microorganisms, there are many stages where compliance with the law, regulations or voluntary international conventions is required. Table 5, Annexe 17.1 lists some examples of these.

Whether it is compliance with the law, or duties of a caring employer, essential components for a safe workplace are:

- Adequate assessment of risks.
- Provision of adequate control measures.
- Provision of health and safety information.
- Provision of appropriate training.
- Establishment of record systems to allow safety audits to be carried out.
- Implementation of good working procedures.

Best practice requires BRCs to have and implement a sound health and safety plan.

11.1 Classification of microorganisms according to risk groups

Various classification systems exist and are implemented nationally. The key references are the definitions for classification made by the World Health Organisation (WHO). The definition and minimum handling procedures of pathogenic organisms are set by appropriate authorities in each country.

The WHO classifies microorganisms into four groups according to the risk they impose to humans:

Risk group 1: (no or low individual and community risk); A microorganism that is unlikely to cause human or animal disease.

Risk group 2: (moderate individual risk, low community risk); A pathogen that can cause human or animal disease but is unlikely to be a serious hazard to laboratory workers, the community, livestock or the environment. Laboratory exposures may cause serious infection, but effective treatment and preventive measures are available and the risk of spread of infection is limited.

Risk group 3: (high individual risk, low community risk); A pathogen that usually causes serious human or animal disease but does not ordinarily spread from one infected individual to another. Effective treatment and preventive measures are available.

Risk group 4: (high individual and community risk); A pathogen that usually causes serious human or animal disease and that can be readily transmitted from one individual to another, directly or indirectly. Effective treatment and preventive measures are not usually available.

A BRC must 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 must be recorded and made available to recipients of biological material.

11.2 Quarantine regulations

Clients, 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 licence the shipper is required to see a copy of a permit before such strains can be supplied.

Plant pathogens handled by BRCs that are subject to quarantine regulations must be registered by an appropriate governmental office. Import and transfer of such pathogens within the country must be carried out according to relevant law.

11.3 Intellectual Property Rights (IPRs)

On deposit of a microorganism, BRCs must record terms and conditions for its further distribution.

Transparency, retaining the link between the source and all recipients of biological materials, is the preferred practice. Where appropriate, material transfer agreements should be put in place (see 10.6).

11.4 Safety information provided to the recipient of microorganisms

Safety information must be dispatched with a microorganism indicating which risk group it belongs to and what containment and disposal procedures are necessary (as referred to in 10.6). For a microorganism, a safety data sheet shall include:

- The risk group of the organism being dispatched;
- A definition of the risks and assessment of the risks involved in handling the organism;
- Requirements for the safe handling and disposal of the microorganism;
- Containment level;
- Opening procedure for cultures and ampoules;
- Appropriate transportation of the microorganism;
- Procedures in case of spillage.

11.5 Control of Distribution of Hazardous Microorganisms

Microbial domain BRCs must follow the Code of Conduct on Biosecurity for BRCs and where appropriate implement the Best Practice Guidelines on Biosecurity for BRCs (see Annexe 17.2), to reduce the probability that dangerous biological material could be obtained by unauthorised persons and deployed to cause harm, without unduly hindering research, or being financially burdensome [15].

There is considerable concern over the transfer of certain infectious agents capable of causing substantial harm to human health. There is potential for such organisms to be passed to parties not equipped to handle them or to people who may make illegitimate use of them. To reduce the risk a BRC must have procedures in place, which meet national requirements to check the validity of customers that wish to receive hazardous organisms.

12 Code of Conduct on Biosecurity for Biological Resource Centres (BRCs)

Accumulated and advancing knowledge on biological systems offers substantial benefits to mankind, to research and to development in all areas of basic and applied bio-medical and bio-technological sciences. However, this improved knowledge is intrinsically associated with the potential for dual application: for beneficial or malicious purpose. The possibility of using scientific knowledge for peaceful or non-peaceful purposes reflects the dual-use dilemma and confers a responsibility on both those with the knowledge and with the biological resources. The responsibilities of those engaged in the life sciences have an increasing role for in-depth implementation of the Biological and Toxin Weapons Convention (BTWC). This Code of Conduct on Biosecurity is to help microbial Biological Resource Centres (BRCs) promote a basic ethical understanding of science compliant with the BTWC and raise awareness to prevent misuse in the life-sciences context. It is meant to complement legislative procedures. This Code intends to raise awareness within the BRCs and outside and to clearly demonstrate that BRCs are fully compliant with national and international legislation and support the BTWC as an international norm prohibiting biological weapons. The aim of this Code of Conduct is to prevent microbial BRCs from directly or indirectly contributing to the development or production of biological weapons or to any other malicious misuse of biological agents and toxins.

Many BRCs are entrusted with the collection and controlled supply of potentially hazardous bio-resources. This requires high responsibility, well-established risk analyses and appropriate BRC internal infrastructures, profound knowledge of relevant bio-legislation including export control and respective protective measures. This Code calls for implementation and compliance of awareness, accountability and oversight and targets all those engaged in life sciences activities, laboratory workers, managers, stakeholders and others.

12.1 Biorisk management

- Integrate biorisk management throughout the organization, provide adequate resources and identify opportunities for improvement and prevention.
- Assign responsibility to guarantee compliance with legal requirements, communication to staff and relevant third parties, and carry out reliable and appropriate risk assessment.

12.2 Raising awareness

- Devote specific attention in the education and further training of all staff to the risks of misuse of biological material, information and life sciences research and the requirements of regulations in this context.

- Maintain attention for and update knowledge on biosecurity by regular training and auditing.
- Raising awareness of related third parties on their responsibilities.

12.3 Accountability

- Report any finding or suspicion of misuse of biological material, information and technology directly to competent persons or commissions.
- Protect persons reporting on misuse and ensure that they do not suffer any adverse effects from their actions.

12.4 Internal and external communication

- Prevent access for unauthorised persons to internal and external e-mails, post, telephone calls and data storage concerning information about potential dual-use research or potential dual-use materials.
- Regulate the communication of sensitive information.

12.5 Research and sharing knowledge

- Screen for possible dual-use aspects during assessment or application procedures and during the execution of research projects.
- Minimize the risk that publication of results on potential dual-use organisms will contribute to misuse of that knowledge.
- Consider biosecurity implications when sharing knowledge.

12.6 Accessibility

- Screen staff and visitors where potential dual-use biological materials are stored or used.
- Ensure physical security of and access control to stored potential dual-use material in accordance with its risk classification.

12.7 Shipment and transport

- Screen recipients and transporters of potential dual-use biological materials, in consultation with the relevant authorities and parties.
- Perform export control in accordance with applicable regulations.
- Dispatch cultures in appropriate packaging and in accordance with IATA and/or relevant regulations for other means of transport

13 Quality audit and quality review

13.1 Purpose

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

13.2 Responsibility

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

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

13.3 Implementation

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

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

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

13.4 Method and procedure for quality checks

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

14 The future roles of the BRCs

A large fraction of the bacterial diversity remains uncharted. Of 90 known bacterial phyla, 40 are not yet cultured and 20 show very few cultured representatives [16]. Of almost a million of bacterial cultures, only about 11,000 are validly described species (Global Catalogue of Microorganisms). There is a need to access this untapped diversity and put the not-yet cultured microorganisms into culture. This is of particular relevance for the discovery of novel molecules that has been steadily declining within the last decades [17], for bioremediation and contamination. The discovery of novel microbial functions and applications is one of the biggest challenges of the 21st century [18]. A prime role of BRCs will be to facilitate the cultivation of novel types of microorganisms and promote the discovery, maintenance and safeguarding of the corresponding biomolecules.

14.1 The need for collection-related research

BRCs should not only supply high quality resources but should also provide expert knowledge regarding, and develop, innovative cultivation methods. This is particularly relevant for EMBRC as the marine environment represents one of the largest untapped sources of microorganisms [19]. These future demands will best be met by an own research department being established in BRCs.

14.2 Novel cultivation techniques

To access not-yet-cultured microorganisms their ecology first needs to be analysed and exploited for enrichment and isolation in the laboratory. Understanding the ecological function of metabolites is the best guide to their discovery knowing that natural products are carrier of the biological information. The study of the genome of *Streptomyces* MAR4 clade showed that they were able to produce prenyltransferases, which have a potential ecological role and are known to be of interest for pharmaceutical industries [20, 21]. In addition, certain *Streptomyces* strains are able to produce 8-aminofavolin (anti-cancer) molecules to survive in microaerobic conditions [22]. These results raise some questions: Who is using those metabolites? Against what are they produced? What do bacteria need for survival given their environmental conditions? The value and the discovery of novel molecules can be significantly increased if their composition, their biosynthetic pathway and their function are understood. One important basis for the development of new cultivation methods is a database or a library of conditions and ecological implications listing the current knowledge on each curated strain. As a supplier of high quality resources, the BRC could build and maintain such a database on strain-associated information.

“Classical” isolation methods often yield well-known taxa. Only few new isolation techniques have been developed in the past ten years like the iChip, the diffusion

chambers, the high-throughput single dilution, the dilution to extinction or the biofilm enrichment methods [23, 24, 25, 26, 27]. Although those techniques permitted the isolation of unknown microorganisms [23, 25, 26] additional efforts are required to bring the 60 underrepresented bacterial phyla into culture. BRCs must play a key role in resolving these challenges through their expertise in microbial cultivation, especially by following ecological concepts (e.g., R-strategists against K-strategists). *Acidobacteria* for example are known to be slow growers, which may be an adaptation to oligotrophic conditions. Applying low nutrient medium combined with long incubation time lead to the isolation of numerous novel strains of a previously uncultured subdivision of *Acidobacteria* [28]. Cultivation trials using extreme conditions (starvation, light intensity, high or low temperature, high pressure, oxygen limitations, very long incubation time) seem to be highly rewarding. BRCs must maintain the key expertise needed to develop and apply these concepts in the future.

14.3 Novel molecules screening pipelines

Next Generation Sequencing (NGS) technologies help to select organisms for subsequent studies. While biosynthesis gene clusters can be detected, the expression of silent or orphan genes, which potentially code for unknown products of interest, has remained a major challenge for product discovery. Another problem is the interpretation of functions of genes with insufficient sequence similarity to known genes. BRCs can provide expert knowledge for designing the appropriate experiments and finding suitable stimuli for the expression of silent genes.

In the future, it would be desirable to characterize the available strains more in depth with regard to their metabolism. However, actual screening techniques are not high throughput and require high biomass samples. In addition, new technology will be essential to discover more new biomolecules. As a future goal, BRCs could support screening efforts providing strain collectives and associated information. Existing initiatives like EU OPENSCREEN provide a suitable starting point.

14.4 Key strain concept

Only a limited number of strains that are isolated and published per year can be deposit due to the considerable costs of handling and limited storage capacity. BRCs have established a key strain concept, which provides suitable criteria to select strains that should be deposited. These criteria include taxonomic relevance, production of metabolite, model strain, type strain, unusual source of isolation, strains with sequenced genomes, or strains with well-characterized physiology/molecular traits [29].

15 Recommendations

EMBRIC endorses the implementation of appropriate quality management systems but remains flexible on the practices and procedures to deliver them. EMBRIC is defined length project clustering Biological and Medical Science Research Infrastructures to facilitate the adoption of common approaches and to take advantage of cross RI facilities, resources and expertise. It is important that the legacy relating to quality management is adopted broadly across the BMS RI's. CORBEL a similar H2020 cluster of RI's have adopted key principles on quality management and those adopted by EMBRIC reflect these. The following are recommendations following the analysis in this EMBRIC deliverable for all BRCs to follow.

Common BMS RI principles for quality management

The BMS RIs offer a wide portfolio of resources and services, ranging from access to biomaterials, technological platforms, databases, data analysis, expertise and consulting. Therefore, there is no one-size-fits-all solution for quality assurance and control that is applied by all BMS RIs. However, they all share a core set of principles:

- The BMS RIs recognize that standardisation is the basis for reproducible and traceable results in science. They therefore acknowledge and actively pursue their important role in cataloguing, developing, improving and widely disseminating community standards.
- The BMS RIs strive to apply quality management methodology to all of their core activities, thus ensuring highest-quality services and data to enable highest-quality science.
- The BMS RIs acknowledge that open access to research data is an important quality measure.
- The BMS RIs acknowledge that an independent third assessment by a competent authority is the gold standard for quality assurance.
- The BMS RIs strive to use internationally recognised standards (e.g. ISO, CEN) and best practices (e.g. OECD Best Practice Guidelines for Biological Centres) where applicable. They are also committed to actively engage in the development of internationally recognised standards where appropriate.
- The BMS RIs represent a wide area of expertise in the biomedical sciences. They recognize that pooling all their best-practice examples and guidelines in a shared resource provides great value for further improving the quality control in each individual BMS RI.
- The BMS RIs acknowledge the importance of training of quality management methodology for research infrastructure operators, managers and their users both from academia and from the private sector. They therefore include the topic of quality management into their training activities wherever appropriate.
- The BMS RIs recognize the importance of actively engaging with all other stakeholders (e.g. public funders, journals or users) to create awareness and appraisal for quality control as a central tenet in biomedical research. This is best

done by clearly communicating how the application of quality measures by the BMS RIs contributes to improving the biomedical research outputs.

16 Conclusion

mBRCs have a role to provide high quality resources to facilitate innovation and discovery in biotechnology. It is imperative that the resources they supply meet the requirements of the user and are provided with legal certainty for use. As countries are deciding how to implement the Nagoya Protocol for Access and Benefit Sharing and in light of concerns of biosecurity the community of microbial resource centres is responding. The development of common quality management systems with the ethos of development of excellence is an integral part of EMBRIC's activities. This complex operational environment must be addressed and an integrated overarching Policy Compliance Management System is needed for BRCs. It is not only the mBRCs that face this complex environment of legal requirements impacting on science but the scientists themselves. It is essential that we all work together to ensure the compliance of science. EMBRIC is collaborating with the international community to develop and differentiate appropriate standards and to develop best practice. The Research Infrastructures in EMBRIC are the places to come for advice on implementing BRC management standards, for the marine organisms and expertise to support research and development.

The future role of BRCs is a complex one with the majority of microorganisms yet to be cultured and huge areas of the ocean yielding new species there is much work to do. Not only are the species to found, isolated and grown there is a huge amount of effort needed to release their full potential. Coordination of effort and focus on the key challenges and bottlenecks through partnership in Research Infrastructures and the multidisciplinary clusters such as EMBRIC, is essential to reduce duplication and take advantage of synergies and the full extent of the available resources and expertise.

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18 Annex

The following tables of requirements and recommendations are based on those from the OECD Best Practice Guidelines for BRCs and adopted by the EMbaRC project consortium; there are other approaches for specific consortia or addressing organism groups available. The following data set recommendations for example have been utilised to enable harmonisation of biosample data for example behind sequence date see EMBRIC Deliverable D4.1 Development of data standards for the marine domain.

18.1 Table 1. Maintenance and Calibration Requirements for Equipment Commonly Used in BRCs

Item	Maintenance required	Verification of function
Autoclaves	Cleaning, pressure vessel, system of surveillance, maintenance contract as required; run with indicators	As recommended by manufacturer
Incubators	Cleaning, system of surveillance, maintenance contract as required	Manufacturers' standard on service
Liquid nitrogen storage vessels	Cleaning, leakage, pressure	Once yearly Manufacturers' Test
Centrifuges	Cleaning, system of surveillance, maintenance contract as required	Regular cleaning Manufacturers' service
Cryo-storage tanks	Removal of condensation and ice	
LN_2 store oxygen level alarm	System of surveillance, maintenance contract as required	Manufacturers' standard on service
LN_2 level alarms	Look for malfunction	None
Programmed Cooler	System of surveillance, maintenance contract as required	None
Cryomicroscope	Clean after use, Temperature calibration	Calibration equipment provided for test at each time of use
Spin and shelf freeze-drier	System of surveillance, maintenance contract as required	Calibration of the vacuum gauge
Microscopes	Clean after use, System of surveillance, maintenance contract as required	
Laminar Flow Cabinet	Clean after use, airflow	Annual functionality test
Class II Microbiological Safety Cabinet	Clean after use System of surveillance, maintenance contract as required	Manufacturers' standard on service
-20 °C Freezer	Temperature check	None
-80°C Freezer	Temperature check and registration System of surveillance, maintenance contract as required Security advices	
Media Preparation equipment	Clean after use	
Balance	System of surveillance, maintenance contract as required Clean after use	Manufacturers' standard on service

pH Meter	Clean after use	Test against Manufacturers' standard

LN_2 = Liquid Nitrogen

18.2 Table 2. Minimum Data Sets (MDS) and Recommended Data Sets (RDS) for Microbial Accessions to BRCs

Filamentous fungi	**Filamentous fungi**
Minimum Data Set (MDS)	**Recommended Data Set (RDS)**
Accession number	Misapplied names
Other collection numbers	Isolated from
Name	Mutant
Organism type	Literature
Restrictions	Sexual state
Status	Race
History of deposit	
Conditions for growth	
Form of supply	
Geographic origin	
Yeasts	**Yeasts**
Minimum Data Set (MDS)	**Recommended Data Set (RDS)**
Accession number	Isolated from
Other collection numbers	Mutant
Name	Sexual state
Organism type	Literature
Restrictions on distribution	Misapplied names
Status	Race
History of deposit	
Geographic origin	
Conditions for growth	
Form of supply	
Microalgae	**Microalgae**
Minimum Data Set (MDS)	**Recommended Data Set (RDS)**
Accession number	Literature
Other collection number	Conditions for storage
Name and taxonomy	Isolate history
History of deposit	
Isolate history	
Form of supply	
Geographic origin	
Conditions for growth	
Bacteria	**Bacteria**
Minimum Data Set (MDS)	**Recommended Data Set (RDS)**
Accession number	Serovar
Other collection numbers	Other names
Name	Isolated from
Infrasubspecific names	Mutant
Organism type	Genotype
Restrictions on distribution	Literature
Status	
History of deposit	
Geographic origin	
Conditions for growth	
Form of supply	

18.3 Table 2. Minimum (MDS) Data Sets and Recommended (RDS) for Microbial Accessions to BRCs (*cont.*)

Cyanobacteria	**Cyanobacteria**
Minimum Data Set (MDS)	**Recommended Data Set (RDS)**
Accession number	Other names
Other collection numbers	Isolated from
Name and taxonomy	Mutant
Infrasubspecific names	Genotype
Organism type	Literature
Restrictions on distribution	
Status	
History of deposit	
Conditions for growth	
Form of supply	
Geographic origin	
Archaea	**Archaea**
Minimum Data Set (MDS)	**Recommended Data Set (RDS)**
Accession number	Other names
Other collection numbers	Isolated from
Name	Mutant
Infrasubspecific names	Genotype
Organism type	Literature
Restrictions on distribution	
Status	
History of deposit	
Geographic origin	
Conditions for growth	
Form of supply	
Plasmids	**Plasmids**
Minimum Data Set (MDS)	**Full Data Set (FDS); RDS is not applicable**
Accession number	Constructed from
Name	Incompatibility group
Other culture collection numbers	Transfer ability
Type	Helper
Class	Copy number
Literature	Molecular weight
History of deposit	Cloned gene
Restricted distribution	Transposable element
Host for distribution	Promoter
Medium	Ribosome binding site
Selectable phenotype	Start codon
Replicon	Terminator
Host range	Further information (Remarks on propagation and/or on properties and/or on history, other name(s), etc)
	Restriction sites
	Sequence detail
	Price code
	Properties and application

18.4 Table 2. Minimum (MDS) Data Sets and Recommended (RDS) for Microbial Accessions to BRCs (*cont.*)

Protozoa	**Protozoa**
Minimum Data Set (MDS)	**Recommended Data Set (RDS)**
Accession number	Biochemical or molecular characteristics
Other collection numbers	Other name
Name	Substrate or host
Organism type	Year of isolation
Stage	Literature
History of deposit	
Status	
Restriction on distribution	
Conditions for growth	
Form of supply	
Geographic origin	
Phages	**Phages**
Minimum Data Set (MDS)	**Recommended Data Set (RDS)**
Accession number	Cell surface receptor
Element name	
Element type	
Other culture collection numbers	
Restricted distribution	
Literature	
History of deposit	
Host for propagation	
Host used for propagation	
Lysogenicity	
Virus used for	
Viruses	**Viruses FDS = MDS**
Minimum Data Set (MDS) = Full Data Set (FDS)	
Accession number	
Virus name	
Virus name abbreviation	
Former name	
Genus	
Pathotype, serotype, strain	
Original host	
Geographic origin	
Isolate history	
Reference isolate	
Quarantine regulations	
Remarks	
cDNA and gDNA Libraries	**cDNA and gDNA Libraries, MDS = RDS**
Minimum Data Set (MDS)	
Library Name	
Organism	
Type (cDNA or gDNA)	
Vector	
Insert Size	
Library Coverage	

18.5 Table 3. Quality control procedures recommended for microorganisms upon receipt

Microorganism	Viability	Purity	Identity/Authenticity	Stability
Plasmids	Confirm presence by growing the host/plasmid combination on appropriate selective medium.	Check the texture, the size and the opacity of the colonies grown on selective medium. Check also for homogeneity of the colonies and for absence of contaminants.	Check plasmid length by determination of the molecular weight of the covalently closed circle (ccc) DNA or by analysis of the restriction site pattern.	Confirm presence by growing the host/plasmid combination on appropriate selective medium. Confirm presence by PCR for cryptic plasmid.
Yeasts and Filamentous fungi	Check growth on appropriate medium.	Check for absence of contaminants using macro- and microscopic observations on the culture grown on appropriate medium.	Identify to species level using morphological (macroscopic and microscopic) and physiological features, where appropriate use biochemical features and molecular tools dependant on the taxa.	Check viability and purity. Confirm identity.
Bacteria	Check growth on appropriate medium.	Check for absence of contaminants using macro- and microscopic observations on the culture grown on appropriate medium.	Identify to species level using morphological (macroscopic and microscopic), and physiological tools, where appropriate, use molecular tools.	Check viability and purity. Confirm identity.
Cyanobacteria	Check growth on appropriate medium.	Check for absence of contaminants using macro- and microscopic observations on the culture grown on appropriate medium or specific contaminant medium.	Identify to genus level using morphological (macroscopic and microscopic), and physiological tools, where appropriate, use molecular tools.	Check viability and purity. Confirm identity.

Table 3. Quality control procedures recommended for microorganisms upon receipt (*cont.*)

Archaea	Check growth on appropriate medium.	Check for absence of contaminants using macro- and microscopic observations on the culture grown on appropriate medium.	Identify to species level using morphological (macroscopic and microscopic), and physiological tools, where appropriate, use molecular tools.	Check viability and purity. Confirm identity.
Viruses	Test infectivity to indicator hosts and propagation hosts.	Use electron microscopic observations.	Combine host reaction, electron microscopic observations and reaction with specific antisera. Where appropriate, use molecular tools.	
Phages	Test infectivity to indicator propagation host.	Test plaque morphology, use electron microscopic observations, test host spectrum.	Test plaque morphology, use electron microscopic observations, test host spectrum.	Test phage titre (pfu/mL)
Microalgae	Check growth on appropriate medium.	Check for absence of contaminants using macro- and microscopic observations on the culture grown on appropriate medium.	Identify to species level using morphological (macro- and microscopic) features and where appropriate use physiological and molecular tools dependant on the taxa.	Check viability and purity. Confirm identity.
Protozoa	Check growth on appropriate medium.	Check for absence of contaminants using macro- and microscopic observations on the culture grown on appropriate medium or specific contaminant medium.	Identify up to species level using morphological (macroscopic and microscopic), and/or where appropriate use biochemical features and molecular tools dependant on the taxa.	Check viability and purity. Confirm identity.
DNA libraries			For DNA libraries, analysis of the restriction site patterns. For individual clones of ordered DNA libraries, identity done by sequencing.	

18.6 Table 4. Recommended preservation methods and distribution forms

	Preservation	Distribution forms	Useful information
Plasmids	Two of the following methods : Cryopreservation of the H/P below -70°C. Cryopreservation of the H/P in LN_2. Freeze-drying of the H/P. Preservation of the plasmid DNA (preferably precipitated under ethanol) can also be applied as a preservation method.	Actively growing H/P on agar slant Actively growing H/P in liquid medium Cryopreserved H/P in dry ice Freeze-dried H/P Pure DNA	Plasmids containing genes that may tend to destabilise the physical and/or functional integrity (either by insertion, deletion or point mutation) shall preferably be deposited, maintained, tested and delivered as pure DNA.
Yeasts and Filamentous fungi	Two of the following methods : Cryopreservation below –140°C is preferred Cryopreservation below –80°C is accepted Freeze-drying or L-drying of the strain Sporulating-strains shall be maintained by at least two of the four different preservation methods listed, one of which shall be cryopreservation or freeze drying Non-sporulating strains will be maintained under oil or water or freeze drying and cryopreservation.	Actively growing strain on agar slant Freeze-dried or L-dried material in vials sealed under vacuum or inert gas Cryopreserved material in dry ice. Suspensions in liquid Liquid suspension deposited on filter paper	-
Bacteria	Two of the following methods : <u>Cryopreservation</u> below -140°C is preferred in a freezer below -80°C is accepted <u>Drying:</u> L-drying Shelf-freeze-drying Vacuum drying Spin-freeze drying	Actively growing strain on agar slant Freeze-dried or L-dried material in sealed vials Cryopreserved material in dry ice	-

Table 4. Recommended preservation methods and distribution forms (*cont.*)

Cyanobacteria	Two of the following methods : L-drying Cryopreservation in or above liquid nitrogen, in ultra low temperature (below -140°C) or on agar slant Freeze drying Serial transfer (if long term preservation is not possible)	Actively growing strain on agar slant Actively growing strain on liquid medium Cryo-preserved material in dried ice Freeze-dried material in sealed vials	-
Archaea	Two of the following methods : Cryopreservation below -140°C is preferred below -80°C is accepted L-drying Freeze-drying	Actively growing strain Freeze-dried or L-dried material in sealed vials Cryopreserved material in dry ice	-
Viruses	Two of the following methods : Virus maintenance in situ LN2 Freeze-drying	Freeze-dried material in sealed vials Cryopreserved material in dry ice	-
Phages	Two of the following methods: LN2 L-drying on filter paper in glass ampoule Storage of aliquots at -4°C	LN2-aliquots at ambient temperature or in dry ice Freeze-dried material is sealed ampoule Liquid aliquot (refrigerator)	-
Microalgae	Two of the following methods : Sterile liquid medium Sterile semi-solid medium (agar, alginate beads) Cryopreservation below – 140°C	Actively growing in liquid/semi-solid medium Cryopreserved material in dry ice is an option that can be pursued	-
Protozoa	Cryopreservation in or above liquid nitrogen below –140°C	Actively growing strain on liquid medium, or in animal biological liquid. Cryopreserved material in dry ice	-
DNA libraries	Two of the following methods: Cryopreservation of the H/P below -70°C Cryopreservation of the H/P in LN2 Freeze-drying or L-drying Preservation of the DNA precipitated under ethanol	Pure DNA Actively growing H/P Cryopreserved H/P in dry ice Freeze-dried H/P	-

H/P = host/plasmid combination; LN_2 = liquid nitrogen

18.7 Table 5. Summary of key elements of national and international regulatory controls related to microorganism domain BRCs

Action	Requirement	Law, Regulation, Convention	Further information
Collecting in the field	Prior Informed consent from a recognised authority	Convention on Biological Diversity	http://www.biodiv.org
	Mutually agreed terms on use	Convention on Biological Diversity	http://www.biodiv.org
	Consent from the land owner	Property law	
Import	Non-indigenous plant pathogens require licenses from country authority	Quarantine regulations	
	Human, animal and plant pathogens can often only be imported to specified laboratories	Health and Safety	
Handling: Manipulation; Growth	Containment dependent on hazard	Control of Biological Agents - Health and Safety EC Directive 2000/54/EEC on Biological Agents	http://www.brad.ac.uk/acad/sbtwc/btwc/nat_imp/leg_reg/uk/ec_com_2000_54.pdf#search='EC%20Directive%202000/54/EEC%20on%20Biological%20Agents
Genetic manipulation	Containment of manipulated organisms	Council Directive 98/81/EC from October 26th amending Directive 90/219/EEC on the contained use of genetically modified microorganisms Directive 2001/18/EC of the European Parliament and of the Council on the deliberate release into the environment of genetically modified organisms and repealing Council Directive 90/220/EEC Cartagena Protocol on Biosafety	http://www.biodiv.org/biosafety/protocol.asp http://www.biosafety.be/GB/Dir.Eur.GB/Cont.Use/90.219/TC.html http://www.biosafety.be/GB/Dir.Eur.GB/Cont.Use/98_81/98_81_TC.html
Deposit as part of a patent process	Long-term storage and compliance with the Budapest Treaty	Budapest Treaty on the International Recognition of the Deposit of Microorganisms for the Purposes of Patent Procedures	http://www.wipo.int/treaties/en/registration/budapest/

Table 5. Summary of key elements of national and international regulatory controls posting to microorganism domain BRCs (*cont.*)

Storage	Appropriate containment	Health and Safety Licence to hold pathogens Security	
Export to another country	Some plant and animal pathogens require export licences	Quarantine regulations	
	Dangerous organisms with potential for dual use	Export Licences for dangerous organisms, Biological and Toxin Weapons Convention (BTWC)	http://binas.unido.org/binas/regs.php http://www.opbw.org/convention/documents/btwctext.pdf http://www.dfat.gov.au/isecurity/pd/pd_4_96/pd9.html
Distribution	Packaging and transport considerations	IATA Dangerous Goods Regulations (DGR), Universal Postal Union (UPU) United Nations Committee of Experts on the Transport of dangerous goods	http://www.iata.org/cargo/dg/dgr.htm http://www.upu.int/ http://www.unece.org/trans/danger/danger.htm
	Sovereign rights over the strains	Convention on Biological Diversity	http://www.biodiv.org
	Access and benefit sharing	Bonn Guidelines	http://www.biodiv.org
	Intellectual Property Right	Patent Cooperation Treaty (PCT) The Budapest Treaty (BT)	http://www.wipo.int/treaties/en/registration/pct http://www.wipo.int/treaties/en/registration/budapest
	Customer licensed to receive organism	National regulations	
	Dangerous organisms	EU Council Regulation No 1334/2000 of the 22 June 2000 setting up a Community regime for the control of exports of dual-use items and technology	http://europa.eu.int/eur-lex/en/consleg/pdf/2000/en_2000R1334_do_001.pdf#search='EU%20Council%20Regulation%20No%201334%2F2000'