

Quality Manual

ISO 17025:2005

General requirements for the competence of
testing and calibration laboratories

ISO 9001:2015

Quality Management System – Requirements

NF S 96-900:2011

Quality of biological resource centres (BRCs) –
Management system of a BRC and quality of biological resources

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The Organization: IBBL

The *Integrated BioBank of Luxembourg (IBBL)* was founded in 2008 as part of the 'Health Sciences and Technology Action Plan' of the Luxembourg government. The premises of IBBL, located in 1, rue Louis Rech, 3555 Dudelange in Luxembourg, were constructed in 2017 and the activities of IBBL were transferred from its previous location in Luxembourg town to these premises in November 2017.

According to the law of 3rd December 2014 on the organization of public research, the IBBL has been integrated into the new *Luxembourg Institute of Health (L.I.H.)*. The law guarantees both the status of a clearly identified structure, the *IBBL Institute (IBBL)*, and management autonomy, allowing IBBL to fully assume its role as service provider on a national and international level. The Chief Executive Officer (CEO) of the IBBL Institute reports directly to the Board of Directors of the Luxembourg Institute of Health. This new organization reflects the willingness of the Government to reinforce the research structures in Luxembourg by creating synergies of people and technology in this fast-changing sector.

With over 300 staff, the Luxembourg Institute of Health henceforth continues the commitment of its predecessors, the CRP-Santé and the IBBL foundation, to the improvement of patients' lives, diagnosis and disease treatment.

IBBL has invested in laboratory facilities, technology platforms and a highly qualified and experienced staff – covered by a well-defined Quality Management System. This integrated infrastructure allows IBBL to offer high-quality biobanking and biotechnology services.

IBBL is focused on the collection, processing, qualification and storage of human biospecimens, samples and associated data, which are then made available to national and international research organizations investigating new diagnostics and treatments for diseases. Together with public and private partners, IBBL hopes to catalyze research that translates today's discoveries into tomorrow's "next generation" healthcare solutions.

IBBL also pursues biospecimen research activities dedicated to the identification, development and implementation of novel quality control methods aiming to determine the "fitness-for-purpose" of biological resources by focusing especially on pre-analytical variations.

Service Offers

The services offered by IBBL include:

Biobanking

This group of services includes:

- **Collection Kits**
 - Design and production of customized barcoded sample collection kits
 - Kit logistics and stock management
- **Sample Collection**
 - Collection of samples including blood, tissue, urine, saliva, cerebrospinal fluid (CSF) and stool from hospitals across Europe
 - Management of logistic chain from point of collection to storage
 - Prompt sample retrieval and distribution
 - Temperature monitoring throughout transport
- **Sample Catalogue**
 - Range of human samples in inventory (blood, tissue, urine, saliva, CSF, stool and derivatives)
 - Focus on cancer, diabetes, Parkinson's Disease and healthy controls
 - Extensive annotation with clinical data
- **Sample and Data Storage**
 - Sample storage for all sample types at a range of temperatures: controlled ambient, +4°C, -20°C, -80°C and -196°C (liquid nitrogen vapor)
 - Long-term storage of archived samples
 - Cryopreservation with controlled-rate freezing
 - Fully web-based eCRFs (electronic Case Report Forms) and LIMS (Laboratory Information Management System) validated for clinical trials.
- **Project Management**
 - Comprehensive management of all aspects of a research project, including preparation of study protocol, ethics committee submissions, budgets, strategic advice, progress reports, collaboration agreements, issue management and publications.

Sample Processing

In this category, we provide a full range of standardized, validated high-throughput processes for all types of biological samples, e.g.:

- Genomic and Circulating DNA Extraction
- miRNA / m RNA Extraction
- Protein Extraction
- Peripheral Blood Mononuclear Cell (PBMC) Extraction
- Cell Sorting
- Cell Culture
- Lymphoblastoid Cell Line Establishment
- Frozen Biospecimen Aliquoting
- Tissue Block Processing
- Slide and Image Processing
- Tissue Microarrays

We perform also customized sample processing based upon client requirements.

Sample Analysis & Quality Controls

The available testing methods include:

- **Quality Control of Fluid Biospecimens**

Immunoenzymatic and biochemical assays on serum, plasma, urine and cerebrospinal fluid samples, including

- sCD40L measurement
- Creatinine measurement
- Cystatin C measurement
- Hemoglobin measurement
- C-reactive Protein measurement
- Calprotectin measurement
- LacaScore Assay (Ascorbate/lactate ratio)

- **Quality Control of Nucleic Acids**

Spectroscopic and amplification assays, including:

- Total DNA quantification and purity (photometry)
- Double-stranded DNA quantification (fluorometry)
- RNA quantification and purity (photometry)
- RNA quantification (fluorometry)
- Quantification of human DNA (qPCR)
- Quantification of bacterial DNA (qPCR)
- DNA cross-linking assessment
- DNA fingerprinting
- Long-range PCR
- RNA integrity number (RIN) measurement
- Size-range PCR
- RT-PCR for mRNA/miRNA
- SPUD assay
- mRNA quality index
- cfDNA size measurement
- WGA Index
- Illumina FFPE QC Assay

- **Quality Control of Cells**

Flowcytometric and gene expression analysis assays, e.g.

- Cell viability, apoptosis
- qPCR gene expression analysis
- Purity of cell subpopulations

- **Quality Control of Tissue**

- Histological QC (Tumor/stroma/necrosis)
- Immunohistochemistry

- **Sample Annotations**

- Sequencing (16S rRNA, TruSeq genotyping, HLA genotyping)
- Methylation analysis
- miRNA & onco-mRNA profiling (using high throughput Wafergen SmartChip™)
- Bio-Plex (multiplex measurements of cytokines, inflammation proteins and phosphoproteins)

Biospecimen Proficiency Testing

IBBL offers the following schemes:

Sample Testing

- DNA quantification and purity
- RNA quantification and purity
- RNA Integrity
- Cell Viability
- Tissue Histology
- Serum CD40 Ligand Quantification
- Serum/Plasma Hemoglobin Quantification
- CSF Hemoglobin Quantification

Sample Processing

- DNA Extraction Efficiency from Whole Blood
- RNA Extraction Efficiency from Whole Blood
- DNA Extraction Efficiency from FFPE Cells
- RNA Extraction Efficiency from FFPE Cells
- Viable PBMC Isolation

Biomarker Validation

This service offer includes:

- Pre-analytical validation
- Analytical validation
- Clinical verification
- Method comparison
- Quality Control Material production and provision

University Biobanking Certificate

In an effort to share our biobanking expertise we have developed a learning course in collaboration with the University of Luxembourg that is endorsed by ISBER (International Society for Biological and Environmental Resources). The course uniquely combines environmental and clinical principles of biobanking into one transdisciplinary university certificate covering all technical, scientific and ethical/legal aspects.

This service is not covered by the certification or accreditation scope.

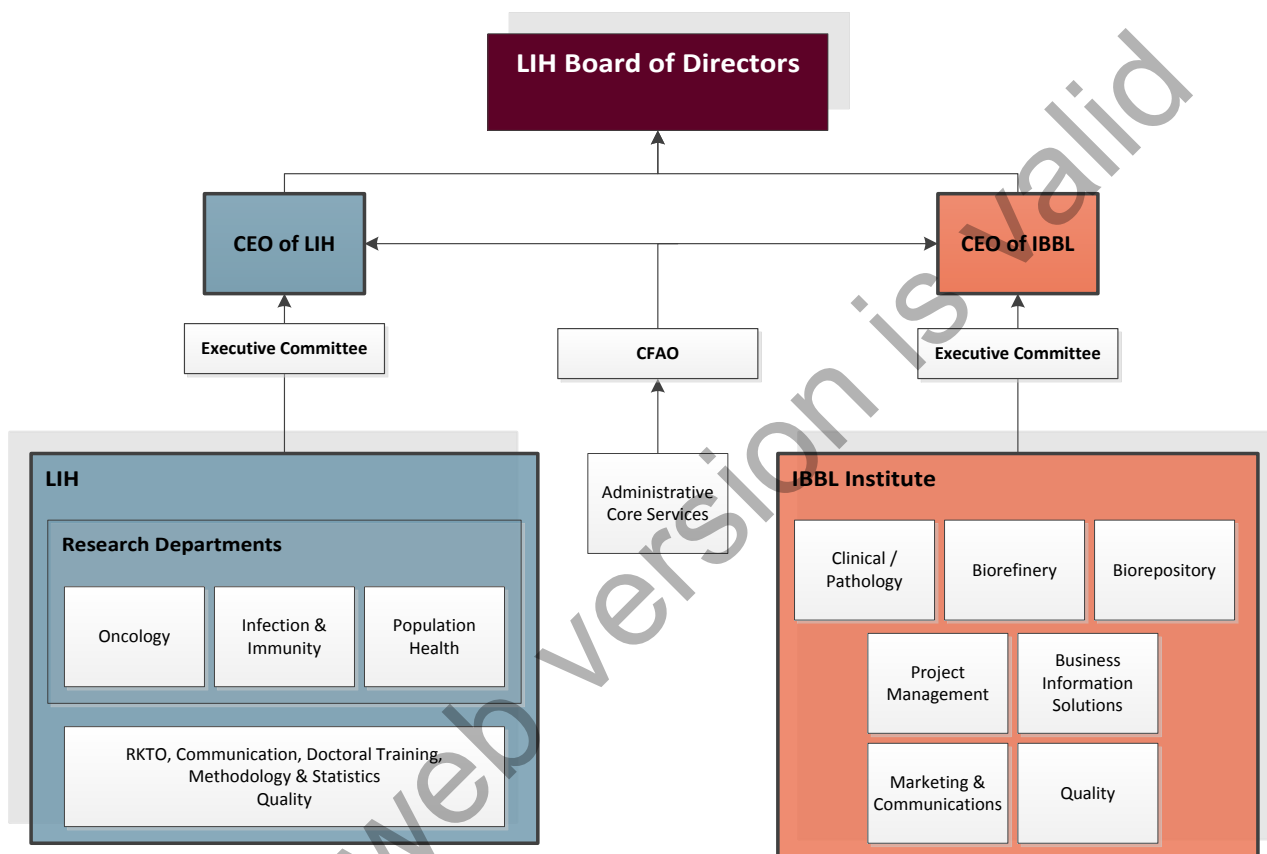
Services Types

Generally, IBBL distinguishes between the following service types, which combine one or more of the above-mentioned service offers:

- **Collaborative Collection Projects**
 - IBBL and one or more partners collaborate to establish and maintain a collection of biological resources for biomedical research. For these cases, the control of the samples is shared between the partner(s) and IBBL. An example workflow – based upon the use of collection kits provided by IBBL – is presented in Exhibit A.
- **Client Collection Projects**
 - IBBL stores and administers biological resources, for which IBBL does not have (co-) control over the subsequent use of the samples. Such a project may include only workflows for sample receipt, storage and distribution, but may also include sample processing and/or sample testing activities. An example workflow is shown in Exhibit B.
- **Service Contracts**
 - IBBL performs selected services such as processing and/or testing and storage of samples, e.g. in the scope of clinical trials.
 - The activities of IBBL as PT provider are managed by Service Contracts as well as IBBL's biomarker validation services.

Management Structure

The overall structure of the Luxembourg Institute of Health (L.I.H.), in which the IBBL exists as an autonomous institute is shown below:



The Board of Directors is responsible for the activities of the whole L.I.H., i.e. including those of the IBBL. It is composed of:

- | | |
|-----------------------|--|
| • Dr. Gregor BAERTZ | Orthopedic surgeon (Luxembourg), <i>President of the Board</i> |
| • Dr. Viviane BREMER | Robert Koch Institute (Germany) |
| • Stéphanie DAMGÉ | Jonk Entrepreneuren (Luxembourg) |
| • Patrizia LUCHETTA | VP Public Affairs – Boson Energy (Luxembourg) |
| • Dr. Hugues MALONNE | Federal agency for medicines and health products (Belgium) |
| • Dr. Nadine MARTIN | Swiss Institute for Translational and Entrepreneurial Medicine (Switzerland), <i>Vice-president of the Board</i> |
| • Dr. Robert MÜLLER | Medical doctor specialized in Urology (Luxembourg) |
| • Pierrot SCHILTZ | Lawyer (Luxembourg) |
| • Pr. Evelin SCHROECK | Uniklinikum Dresden (Germany) |

In addition, Xavier POOS, Ministry of Health, has been nominated as “Commissaire de Gouvernement”.

The internal IBBL organizational structure is available in the current IBBL Organizational Chart.

Quality Management System (QMS)

Rationale of the QMS

The use of standardized procedures for the collection, preparation, testing, storage at appropriate temperatures of biological materials and their distribution is necessary so that the samples can be used in an accurate and reproducible manner. The use of standardized procedures is a *sine qua non* condition to ensure the quality of the biomedical research results, by elimination of pre-analytical variations and by providing reliable test results. Therefore IBBL is committed to run its operations under the control of a well-defined Quality Management System (QMS).

The IBBL management delegates to the Quality Manager the task of coordinating, implementing and following-up the Quality Management System. The Chief Scientific Officer is responsible for directing the scientific activities of the biobank. In close collaboration, both functions ensure compliance of the organization with normative requirements as targeted by the QMS.

The QMS at IBBL has been conceived and is maintained by considering the requirements of the following laws, norms, guidelines and "Best Practices":

- Loi du 3 décembre 2014 – Organisation des centres de recherche
- ISO/IEC 17025:2005 General requirements for the competence of testing and calibration laboratories
- ISO 17025:2017 General requirements for the competence of testing and calibration laboratories
- ISO 9001:2015 Quality Management Systems – Requirements
- NF S 96-900:2011 Quality of biological resource centres (BRCs) – Management system of a BRC and quality of biological resources
- ISO/IEC 17043:2010 Conformity assessment – General requirements for proficiency testing
- Best Practices for Repositories: Collection, Storage, Retrieval and Distribution of Biological Materials for Research – International Society for Biological and Environmental Repositories (ISBER), Forth Edition 2018
- NCI Best Practices for Biospecimen Resources – US National Cancer Institute, 2016
- OECD Best Practice Guideline for Biological Resource Centres – General Practices for all BRC's, 2007
- Council of Europe, Recommendation Rec(2006)4 on Research on Biological Materials of Human Origin
- Good Clinical Laboratory Practice (GCLP) – World Health Organization (WHO), 2008
- ICH GCP – Guidelines for good clinical practice (ICH E6(R2)), Nov. 2016
- ISO 31000: 2018 – Risk Management – Guidelines
- ISO 45001: 2018 – Occupational health and safety management systems – Requirements with guidance for use
- ISO 19011:2011 Guidelines for auditing management systems
- ISO 10012:2003 Measurement management systems – Requirements for measurement processes and measuring equipment
- EU 2016/679 Regulation on the protection of natural persons with regard to the processing of personal data and on the free movement of such data (General Data Protection Regulation) – GDPR

Quality Manual – Scope of the QMS

The present Quality Manual summarizes the QMS implemented for the accreditation of IBBL according to:

- **ISO/IEC 17025:2005** General requirements for the competence of testing and calibration laboratories,

and for the certification of IBBL according to:

- **ISO EN DIN 9001:2015** Quality Management Systems – Requirements

The activities in the accreditation scope are:

- **Acquisition, validation, processing, storage, administration and distribution of biological material and associated data on which tests are done:**
 - **M007:** Nucleic acid quantification by Spectrophotometry (in-house developed)
 - **M005:** DNA quantification by Spectrofluorometry (in-house developed)
 - **M008:** RNA Integrity Measurement (in-house developed)
 - **M004:** Complete Blood Count with ABX Micros CRP 200 (in-house developed)
 - **M006:** DNA cross-linking assessment by PCR
 - **M017:** Long-range PCR
 - **M046:** Quantification of sCD40 Ligand in Serum
 - **M053:** 16S rRNA Gene Sequencing

The activities in the certification scope are:

- **Acquisition, validation, processing, storage, administration and distribution of biological material and associated data to public or private end-users / researchers**

The biospecimen research activities of IBBL and the organization and performance of the University Course in collaboration with the University of Luxembourg are excluded from the accreditation and certification scope.

The quality processes apply to activities executed by IBBL at its premises in 1, rue Louis Rech, 3555 Dudelange, Luxembourg.

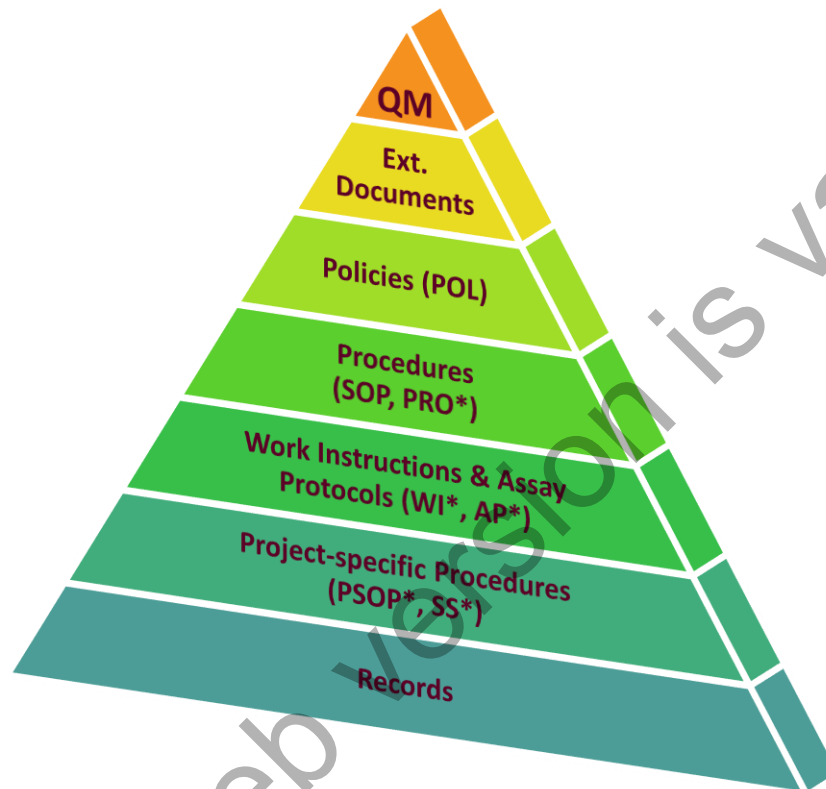
The Quality Manual is an integral part of the documented QMS of IBBL; it is created and maintained by the Quality Manager, reviewed and approved by the IBBL Management.

Internal publication follows the rules of *SOP QM-DC Document Control*.

IBBL promotes the accessibility of the Quality Manual to its partners, clients and other interested parties by providing the current version on its website. However, this version of the Quality Manual is an authorized, but uncontrolled copy. Only the electronic version is deemed valid and current.

Document Hierarchy

The QMS is planned and maintained via quality documents, which include:



Quality Manual

External Documents

- Regulatory texts, guidelines, publications...

Policies

- Intentions and directions of the organization, formally expressed by the top management

Procedures (SOPs, PROs)

- High-level process descriptions, including related process flowcharts (SOPs – IBBL only)
- Corporate quality procedures (for administrative core services) (PROs – Corporate only)

Work Instructions (WI) and Assay Protocols (AP) with associated forms (F), assay sheets (AS), templates (T), spreadsheets (S) and annexes (A)

- Detailed instructions for the execution of standard tasks including corporate work instructions (for administrative core services)
- Related forms, templates and spreadsheets for standardized record keeping

Project-specific Procedures with associated annexes, forms, templates and spreadsheets

- Detailed instructions for the execution of project-specific tasks with the associated forms, templates and spreadsheets
- Examples: Project-specific Standard Operating Procedures (PSOPs), Study Summaries (SS)

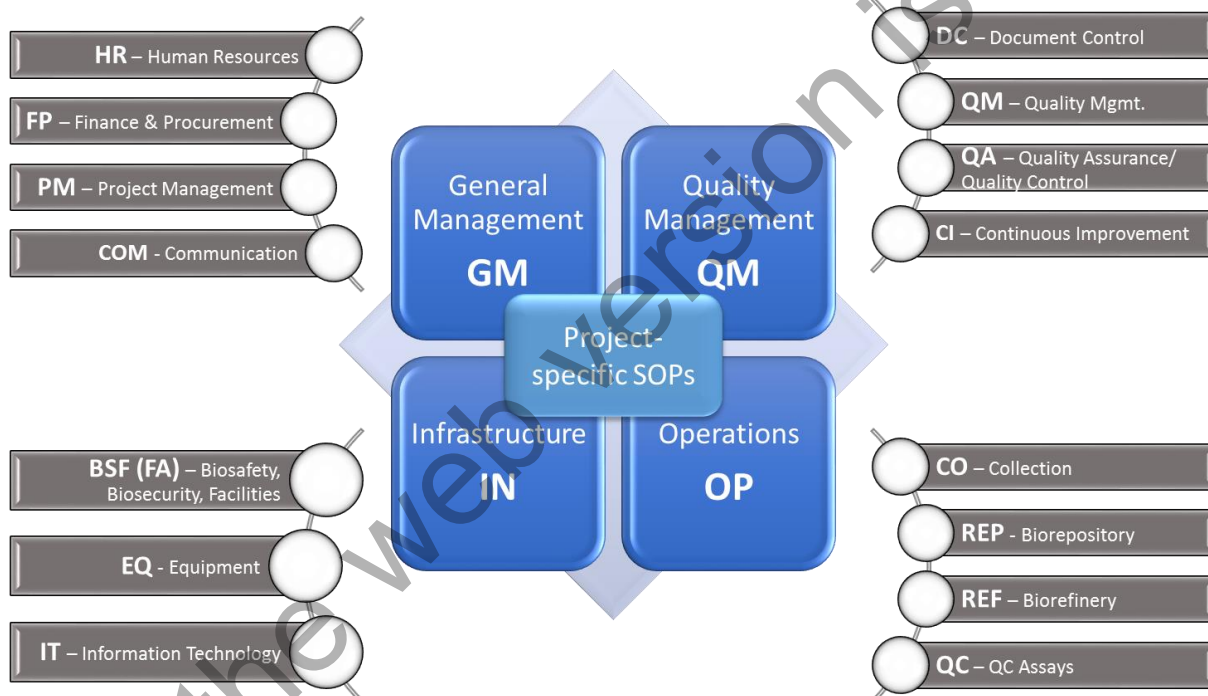
Records

- All types of quality records, resulting from the execution of tasks covered by the documents above.
- Examples: completed forms, tables, lists, databases, reports, logbooks, job descriptions, control charts, analytical raw data...

The principles of document and record control are summarized in *SOP QM-DC Document Control*.

QMS Structure

The documented QMS is structured in four chapters with related sub-chapters, constituting the four pillars on which the execution of IBBL's services is based:



The procedures defined in the QMS chapters “GM – General Management” and “IN – Infrastructure” are the backbone of the **“support processes”**, while the **“management processes”** are covered in the QMS chapter “QM – Quality Management”; both process types are essential to fulfill the services to the customers. The **“service or operational processes”** are described in the QMS chapter “OP”. A supplementary layer of “project-specific procedures” ensures the fulfillment of customer-specific needs, where needed. *SOP QM-DC Document Control* provides more details about the structure.

One Standard Operating Procedure (SOP) is established for each sub-chapter, summarizing IBBL's policies and processes relevant to this part of the QMS and their interactions with other QMS parts. The section below provides a snapshot of items covered in each subchapter.

IBBL, being an autonomous institute within the Luxembourg Institute of Health (LIH) and having its distinct quality management system, uses some administrative core service support provided by LIH entities, such as Human Resources, Finance, Procurement and IT.

Related procedures are documented in “Corporate Quality Documents” (refer to *WI DC-901 Corporate Quality Documents Administration*), which are fully integrated into the above-mentioned QMS structure of IBBL.

General Management

- Human Resources (SOP GM-HR)

This sub-chapter covers the principles and provisions for the administration of human resources at IBBL:

IBBL Management defines its human resource forecast in order to provide competent staff in sufficient number to execute all tasks within its mission.

IBBL ensures that IBBL's management and staff are free from any undue internal and external commercial, financial or other pressures that may adversely affect the quality of their work. IBBL adheres to stringent confidentiality rules in order to protect the privacy of donors, but also the intellectual property of IBBL and its collaboration partners, where needed.

Job Descriptions are used to define the job holders' responsibilities in relation to required skills, competencies and experience and hierarchical structures within IBBL. IBBL has processes in place, which ensure that hired staff is continuously trained in job-specific, regulatory, safety & health and quality matters. The appraisal process serves to determine the performance level of staff, identifying individual objectives and related development needs, and the effectiveness of training measures.

- Finance & Procurement (SOP GM-FP)

The "FP" section of the QMS describes purchasing of goods & services and includes provisions for the selection and evaluation of suppliers and subcontractors.

- Project Management (SOP GM-PM)

This subchapter addresses all phases of project management of a Project, covering Project Initiation and Approval, Project Set-Up, Project Operation, and Project Closing.

IBBL has established a Project Management structure in order to ensure that all types of research and biobanking-related Projects as well as Fee-for-Service contracts are handled in a responsible and consistent way, that Project planning is adequately performed, documentation is appropriately tracked, and that the responsibilities of the staff involved in the preparation and execution of Projects are clearly defined. Specific focus has been put on the structure and execution of the "Proficiency Testing" program.

In addition, provisions for sample and data access (such as governance, policies and procedures) are covered in this part of the QMS. This includes procedures for sample and data distribution and destruction.

Quality Management

- Document Control (SOP QM-DC)

This subchapter covers Document Management and Records Management processes.

A Document Hierarchy has been established to manage documents and records within the Quality Management System (QMS) of IBBL and those overlapping with the quality management system of LIH. Naming and coding systems, including version numbering, ensure unique identification of each internal and external document.

For internal documents, formalized review and approval processes are in place, related to the type of document. Controlled distribution and retraction of internal and external documents takes place and, where needed, access to obsolete versions is granted under controlled conditions. Listings of current documents and the documents themselves are easily accessible to the employees of IBBL.

The principles for archiving documents are defined. Rules related to periodic revisions are specified as well as processes for annotations, corrections or deviations, when needed.

- Quality Management (SOP QM-QM)

The "QM" subchapter covers the key Quality Management processes within the QMS of IBBL such as management of nonconformities, administration of corrective and preventive actions, customer complaints management and continuous improvement, including customer satisfaction surveys and management review.

- Quality Assurance / Quality Control (SOP QM-QA)

This subchapter contains the general principles for Quality Assurance (QA) and Quality Control (QC) at IBBL. QA and QC are vital monitoring methods, in addition to processes such as control of nonconforming work, customer complaints management and continuous improvement.

IBBL maintains a process for internal and external audits, performs quality control checks and quality assessments to verify process or product quality, and ensures that related findings are used to continuously improve the system.

- Continuous Improvement (CI)

This subchapter contains the risk management processes of IBBL and LIH. Other processes contributing to continuous improvement are – for historical reasons – covered in the subchapter “Quality Management” (see above).

Infrastructure

- Facilities (SOP IN-FA)

This subchapter covers the general provisions related to the IBBL facilities. Biobanking facilities are important to ensure biospecimen, sample and data integrity throughout the whole life cycle of samples, from reception until distribution, including processing and testing methods.

Therefore, IBBL ensures that the premises conform to legal and security requirements and are appropriately arranged for different process steps. IBBL controls access, maintains procedures for operational safety & hygiene, performs environmental monitoring and maintains a Disaster Recovery Plan.

- Equipment (SOP IN-EQ)

The “EQ” chapter consists of processes for the management of laboratory and storage equipment used for IBBL’s services.

The laboratory is furnished with all equipment, necessary for the correct performance of its services. A life cycle approach for equipment administration is applied to ensure that equipment is fit for purpose within the scope of IBBL’s services. This includes the execution of pre-defined qualifications or checks before an instrument is put into operation, a controlled phase of use as well as an organized retirement.

IBBL has defined responsibilities for the metrological function in job descriptions and procedures as applicable. IBBL has chosen to distribute responsibilities throughout the organization. Activities and requirements related to metrology (measurement processes and measuring equipment) are seamlessly integrated into the QMS, thus ensuring the establishment, documentation, maintenance and continuous improvement of the underlying measurement management system. Where required, related personnel at IBBL has the adequate competence; alternatively activities are outsourced.

- Information Technology (SOP IN-IT)

Here are summarized processes related to the information & communication technology (ICT) infrastructure and IBBL-specific processes of IBBL’s Business Information Solutions (BIS) department for the benefit of the whole organization.

Data management during the life-cycle of a Biospecimen is increasingly performed using computerized systems. Therefore, the administration of these data must ensure data integrity throughout collection, processing storage and transmission. IBBL puts specific emphasis on data protection, including the privacy of donor and sample-related data.

Operations

- Collection (SOP OP-CO)

The “CO” subchapter of the QMS contains general principles for specimen collection and data collection & management performed – including the administration of informed consent of the donors – under the responsibility of, or with support of IBBL.

The respect of legal and ethical principles for collecting biospecimens and related data is of utmost importance to ensure the rights, safety and well-being of the donors.

Biospecimen Science has demonstrated that the pre-analytical conditions of biological samples are relevant for the “fitness-for-purpose” of biospecimens and samples. In addition, the type and quality of associated data – sample and donor related – is important for providing useful and reliable input to biomedical research.

The implemented processes are intended to ensure these goals are achieved.

- *Biorepository (SOP OP-REP)*

This subchapter defines the general principles for reception, storage, internal and external distribution as well as destruction of biological material by the “Biorepository” department of IBBL. The collection kit production and administration process is also included in this QMS section.

- *Biorefinery (SOP OP-REF)*

Here are covered the general principles applied to “Sample Processing” performed at IBBL.

“Sample Processing” is defined as manual and/or automated manipulation of Specimens or Samples to produce Simple Derivatives, Complex Derivatives or Substantially Modified Derivatives (see Exhibit F for definitions).

Sample Processing is a crucial step in the life cycle of biological samples. Therefore, IBBL maintains Work Instructions to describe specifications and requirements of Sample Processing Methods, validates critical methods, executes Sample Processing Methods under controlled environmental conditions, using suitable equipment and software, and adequately trained personnel, and ensures traceability of the Sample Processing steps by relevant records.

- *QC Assays (SOP OP-QC)*

The “Quality Control (QC) Assays” section of the QMS covers the processes related to sample testing performed at IBBL.

“Sample Testing” is defined as manual and/or automated testing of Specimens or Samples to determine characteristics of Specimens and Samples. Output of a testing process is a result. Results can be quantitative or qualitative.

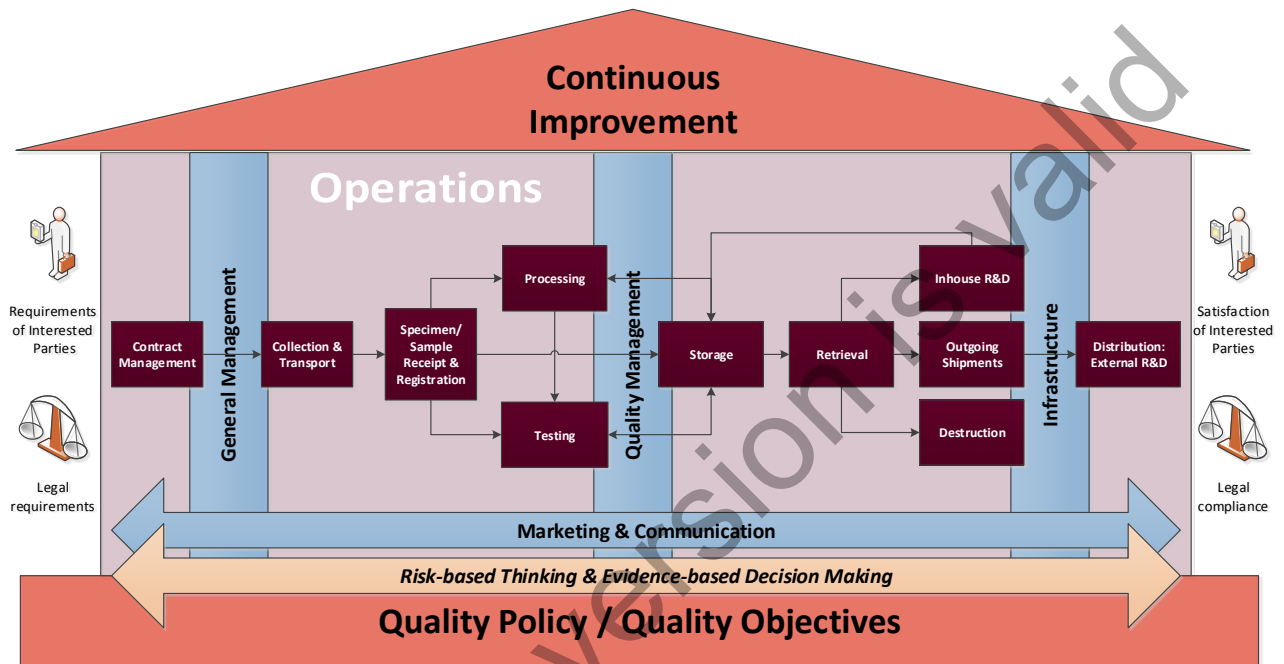
Sample Testing is an important step in the life cycle of biological samples, especially when Samples have been produced by “critical” methods (see *SOP OP-REF Biorefinery*) and in the scope of the “fitness-for-purpose” for any downstream use of the samples.

IBBL maintains Assay Protocols to describe specifications and requirements of Sample Testing Methods, validates important testing methods, executes Sample Testing under controlled environmental conditions, using suitable equipment and software, and adequately trained personnel, ensures traceability of the Sample Testing steps by relevant records, and communicates results to collaboration partners/clients only after formal approval and by official reports.

The submission of selected analytical methods for accreditation according to ISO 17025 demonstrates IBBL’s commitment to reliable test data for Biospecimens and Samples.

Process Overview

The following scheme provides a schematic overview of the way the Quality Management System interacts with the major components of IBBL's service processes.



The focus of providing services is the fulfillment of requirements of interested parties in compliance with applicable laws and regulations. The quality policy and the related quality objectives form the foundation of IBBL's service quality. These, in combination with the organization-wide application of the support processes "General Management", "Quality Management" and "Infrastructure" (as described before) are the measures implemented to ensure customer-oriented "Operations", i.e. the execution of services to the customers. Risk-based thinking and continuous monitoring of performance levels with respect to efficiency, compliance and customer satisfaction via the "QM" processes guarantees evidence-based decision making and the continuous improvement of the organization.

Furthermore, the Marketing & Communications Department ensures that IBBL's visions, missions, strategic plans and concrete projects are regularly and adequately communicated within the organization and to our interested parties including the general public. Examples are the annual report, internal and external newsletters, press releases and the websites: www.ibbl.lu, www.biobank.lu and www.lih.lu.

The key business process of IBBL is composed of the milestones of **acquisition, receipt, processing, testing, storage, administration and distribution** of biological material and associated data. These milestones are broken down into sub-processes (e.g. contract management, collection & transport...) depicted above, which in turn are composed of one or more procedures.

The specifications for a sub-process may be adapted for each project, collection or fee-for-service contract, based upon the client needs. These needs are documented in contracts and communicated to the organization by the documented quality system. Consequently, a customer service can include all process steps or only a part of them.

Sub-process	Input	Actions	Output
Contract Management	Customer requirements Legal requirements IBBL standard procedures	Definition and documentation of the project scope (e.g. specifications, responsibilities, timelines, budget)	Project-related Contract(s) and related operational documents (e.g. WIs/APs, SOPs)

Sub-process	Input	Actions	Output
Collection & Transport	Project-specific requirements (e.g. consenting, type of biospecimens, conditions of collection, transport...)	Collection & Transport of Biospecimens and Samples according to project specifications	Biospecimens & Samples collected and transported to IBBL
Biospecimen/Sample Receipt & Registration	Biospecimens/Samples collected and transported to IBBL	Verification of received biospecimens/samples and associated data against the project specifications; registration in the LIMS; verification of consent.	Received biospecimens/samples are registered and identified with unique identifier at IBBL; any discrepancies from specifications are documented
Processing	Received & Registered Biospecimens/Samples	Processing of samples according to project specifications	Samples as specified in the project scope are produced; related records are available; nonconformities are documented and followed-up
Testing	Received & Registered Biospecimens/Samples or Samples produced at IBBL (see "Processing")	Testing of samples according to project specifications	Quality of biospecimens/samples has been established according to project specifications; nonconformities are documented and followed-up
Storage	Received & Registered Biospecimens/Samples or Samples produced at IBBL (see "Processing") or Samples tested at IBBL (see "Testing")	Storage and registration of biospecimens/samples in defined storage locations following the project-specific requirements Management of sample movements maintaining integrity and traceability. Continuous control of environmental conditions related to storage.	Samples are physically stored in defined storage locations under controlled environmental conditions; sample information and sample location are recorded in the LIMS; sample movements are performed maintaining integrity and traceability of the samples; nonconformities are documented and followed-up
Retrieval	Internal or External Distribution Request for Samples and/or Data Stored Biospecimens/Samples	Preparation of sample picklist and picking of samples; Preparation of related data – both according to the provisions of the project scope and in accordance with the Distribution Request	Samples ready for shipment; Data ready for transfer
In-house R&D (outside the certification scope)	Samples retrieved from stock	Execution of Biospecimen Research projects	Evidence-based information about the impact of pre-analytical conditions on the "fitness-for-purpose" of samples
Outgoing Shipment	Samples ready for Shipment; Data ready for transfer	Packing and organization of shipment of samples according to project-specifications, the Distribution Request and legal requirements; Transfer of Data to the Recipient ensuring data security and data integrity.	Samples are shipped to the Customer or a Third Party (according to project scope); receipt of samples has been confirmed; Data are transferred to the Customer or a Third Party (according to the project scope); data are received in integrity and securely by the recipient; nonconformities are documented and followed-up.
Destruction	Client Request Withdrawal of consent Quality issue	Samples and data (when applicable) are safely destroyed	Destruction records

Sub-process	Input	Actions	Output
Distribution: External R&D	Samples are shipped to the Customer or a Third Party (according to project scope); receipt of samples has been confirmed	Customer or Third Party perform research using the provided biospecimens & samples	Research output such as publications, diagnostic or prognostics markers/tools, personalized medicine...

Exhibit C provides an overview of the main actors for each of these sub-processes.

Exhibit D shows the schematic workflow of a typical testing process.

Only the web version is valid

Commitment of Management

Mission & Vision

Mission

Our mission is to provide accredited biospecimen-related services and a biobanking infrastructure for applied medical research.

Vision

Our vision is to be an international center of excellence in biobanking and a valued partner in developing better healthcare solutions.

To accomplish our aims, we have identified two strategic goals:

- Support Luxembourg biomedical research
- Be a preferred European partner for accredited biospecimen-related services and biobanking infrastructure

Quality Policy

The quality policy aims to build the framework for achieving IBBL's mission and vision, the strategic goals and related quality objectives.

- The Board of Directors, the IBBL Management Committee and the Staff commit to implement and maintain a working environment to constantly provide service quality that meets the expectations of our customers, partners and other interested parties.
- The IBBL Management lives this commitment by the implementation and maintenance of a Quality Management System and its certification/accreditation by external bodies. Ensuring compliance with the requirements of the certification and accreditation standards in the certification/accreditation scope and the applicable legal and statutory requirements is our aim. Changes in the organization are managed to preserve the consistency and integrity of the QMS.
- IBBL strives for continuous improvement of the organization and the optimization of its services by careful planning of its activities with a focus on customer satisfaction, legal compliance and effectiveness & efficiency of its operations. Through regular monitoring and measuring of the performance level and the follow-up of scientific advances in the area of biospecimen science and biobanking practices IBBL is able to identify and implement adequate measures in case of quality problems or opportunities identified for improvement.
- All IBBL staff members are committed to familiarize themselves with the provisions of the QMS and to apply the defined procedures at their level of responsibility.
- IBBL fosters communication of its mission, vision and objectives internally and externally.

Quality Objectives

IBBL utilizes different means to continuously determine the performance levels of its processes. Wherever possible, this takes place by the definition and monitoring of Key Performance Indicators (KPI) and Quality Indicators (QI) as measurable quality objectives. *WI CI-001 Continuous Improvement* summarizes all applicable tools.

Interested Parties

As an infrastructure dedicated to support biomedical research, IBBL seeks to satisfy the requirements of its interested parties. A specific organization can fall into one or more of the categories listed below.

Interested Party Category	Interested Parties (Explanations and Examples)	Requirements relevant to the quality of IBBL's service provision
IBBL	--	Fulfillment of vision and mission (see page 19)
Funding Bodies	Ministry of Higher Education and Research (MESR)	A multi-year performance contract 2018-2021 contains the obligations of LIH and IBBL; this includes the definition of key performance indicators as well as the mechanisms for measuring performance.
	National and International Competitive Funding Bodies, e.g. those funding H2020, IMI, FNR, JNPD...	Project-specific contracts define the obligations of IBBL. They include deliverables and performance indicators as applicable as well as the mechanisms for measuring project performance.
	Humanitarian funders of research, e.g. Patient organizations, Rotary Club...	Infrastructure and operations that demonstrate an innovative and/or effective contribution to biomedical research
Clients	Public or private organizations to whom IBBL provides services, without sharing a common (research) goal, e.g. Precision for Medicine, EORTC...	Flexibility, scientific and operational excellence paired with customer focus and embedded in a well-established QMS. This encompasses for example: <ul style="list-style-type: none"> ✓ Responding to customers' needs and expectations and the ability to understand and forecast such needs ✓ Providing samples and services in compliance with customers' needs and expectations ✓ Assuring the quality of our services and support ✓ Having competent and available staff, able to provide information and advice on samples and services
Sample Collection Partners	National and international partners for the establishment or management of sample collections with a shared (research) goal, e.g. Luxembourg Clinical Researchers (from Hospitals and/or Public Institutions), Consortium partners...	Availability of reliable, standardized, state-of-the-art biobanking infrastructure and operations for: <ul style="list-style-type: none"> ✓ Reception, storage and re-distribution of biological resources under controlled, optimal conditions ✓ Provision of "fit-for-purpose" biological resources ✓ Provision of (accredited) test and characterization data of biological material Contribution of IBBL to innovation by performing biospecimen research activities
Healthy Donors & Patients	IBBL does not have direct contact with donors, but keeps indirect contact via relevant patient organizations.	Strict application of ethical, regulatory and quality standards in the scope of sample collection, transport, processing, storage and re-distribution as sign of respect and valorization of the donor's contribution to research.
Biospecimen Research Collaborators	Biospecimen research activities in collaboration with national and international academic, public and private research collaborators, e.g. Suppliers of consumables, suppliers of equipment, other biobanks, universities...	Set-up and execution of research studies to establish evidence-based procedures for the collection, processing, testing and handling of biological resources. Communication of research outcome for the benefit of the scientific community. Integration of research outcome into the operational activities of IBBL, so that interested parties benefit from IBBL's research.
Governmental Bodies	CNPD – Commission Nationale pour la Protection des Données	Internal processes and provision of services to customers in line with national and international data protection and privacy rules
	CNER – Comité National d'Ethique de Recherche	Services in line with national and international ethical rules with respect to human biological resources

Interested Party Category	Interested Parties (Explanations and Examples)	Requirements relevant to the quality of IBBL's service provision
	ITM – Inspection du Travail et des Mines	Infrastructure and operational processes in line with rules with respect to health and safety at the workplace
Proficiency Testing (PT) Partners & Participants	Biobanks and other laboratories processing and testing biological samples Consortia ISBER	Contribution to the overall improvement of comparability of biological resources by: ✓ Providing a general, open proficiency testing program that serves the biobanking community to benchmark the performance of their processing and testing methods ✓ Providing case-by-case, customized PT programs
Suppliers	Supplier of equipment and consumables; Subcontractors	Establishment of contractually based (long-term) relationships for supplying goods and services to IBBL Acknowledgement of suppliers as collaboration partners in the provision of IBBL's services
General Public of Luxembourg and the "Grand Region"	Citizens of Luxembourg and the "Grand Region" are tax payers and thus indirectly contributing to the funding of IBBL They are also potential donors of biological resources	Information in formats and words understandable by laymen about: ✓ Personalized medicine and the role of biobanks in medical research at Luxembourg and abroad ✓ IBBL's contribution to achievements for the benefit of Luxembourg's population ✓ Information about possibilities how to support medical research Communication channels to IBBL (e.g. via Twitter, Facebook, Website, meetings)
Personnel	Staff of IBBL Staff of LIH	A working environment which ✓ has defined roles and responsibilities ✓ promotes the valorization of individual contributions to the objectives of the organization ✓ provides a motivating elements in compliance with labor laws and other related agreements
Students	National and international students registered in the University Certificate for biobanking course (provided by IBBL in collaboration with the University of Luxembourg)	Training by competent staff covering all themes relevant for biobanking operations with actionable information
Neighbors	Co-tenants in IBBL's premises: LNS – Laboratoire National de Santé LMVE – Laboratoire de Médecine Vétérinaire de l'Etat	Collaborative relationships linked to the use of the same building and infrastructures

Exhibit A: Example Workflow for a Collaborative Collection Project

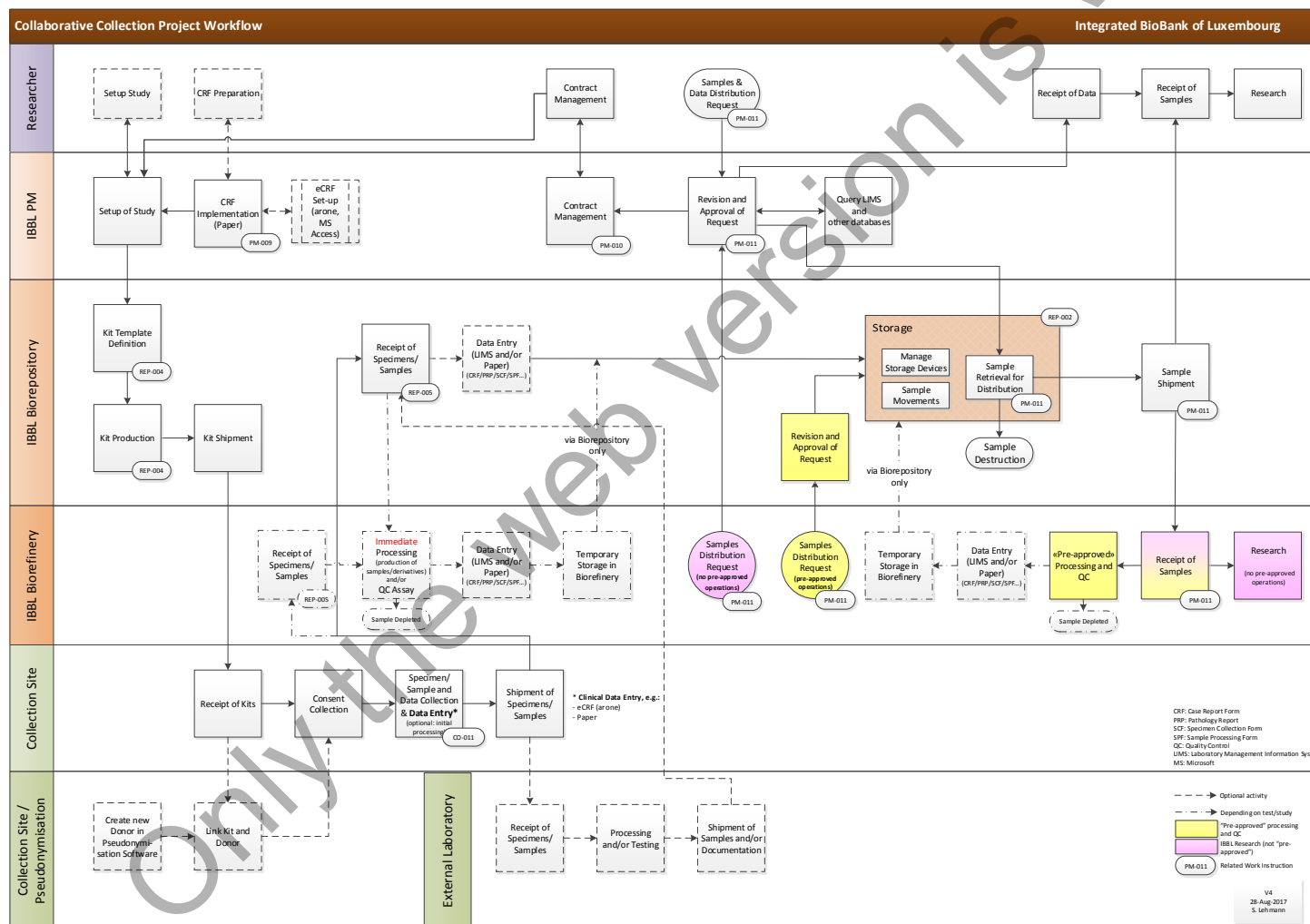


Exhibit B: Example Workflow for a Client Collection Project

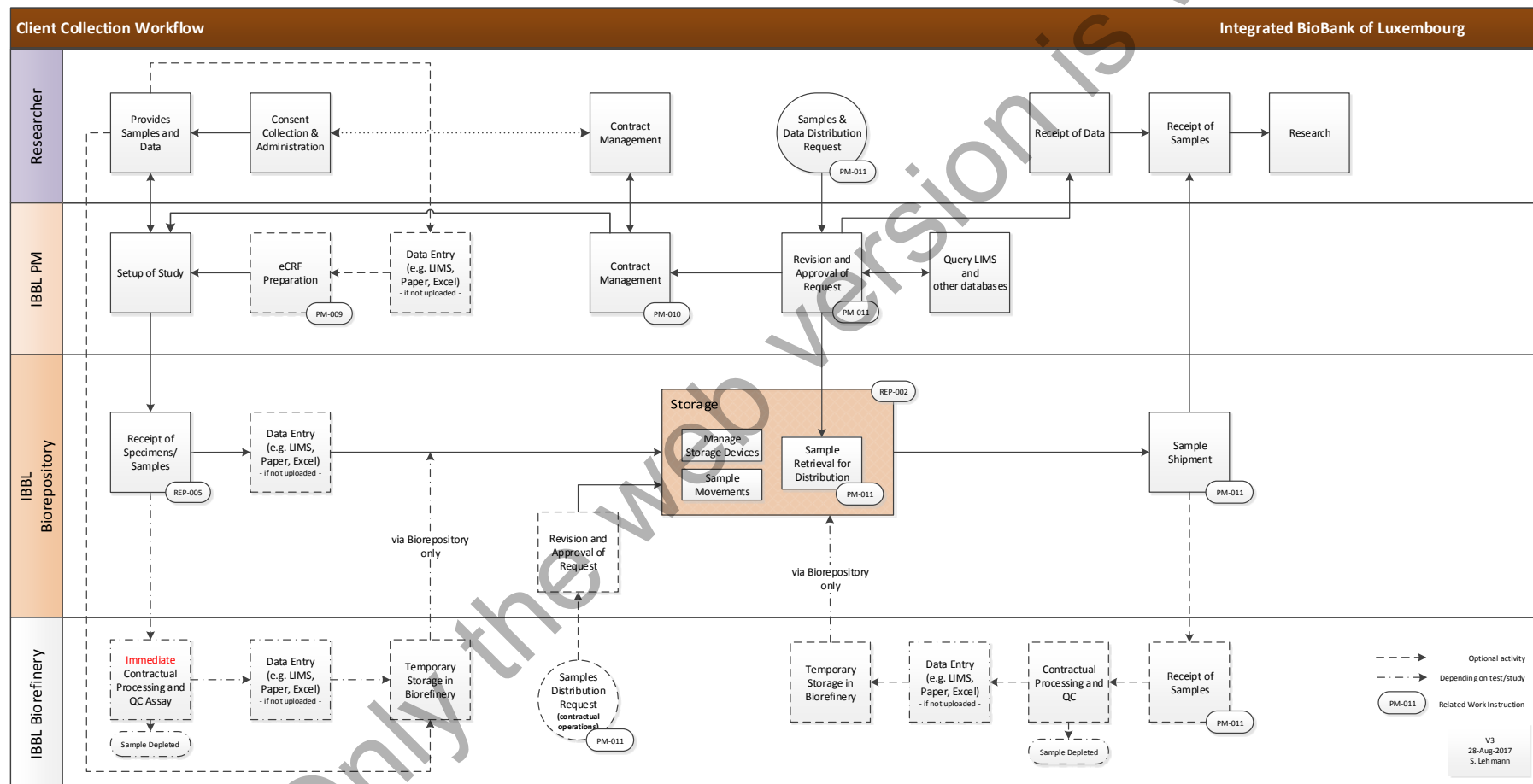


Exhibit C: Actors in standard sub-processes

The table below provides an overview of the involvement of IBBL's operational departments in the different operational sub-processes.

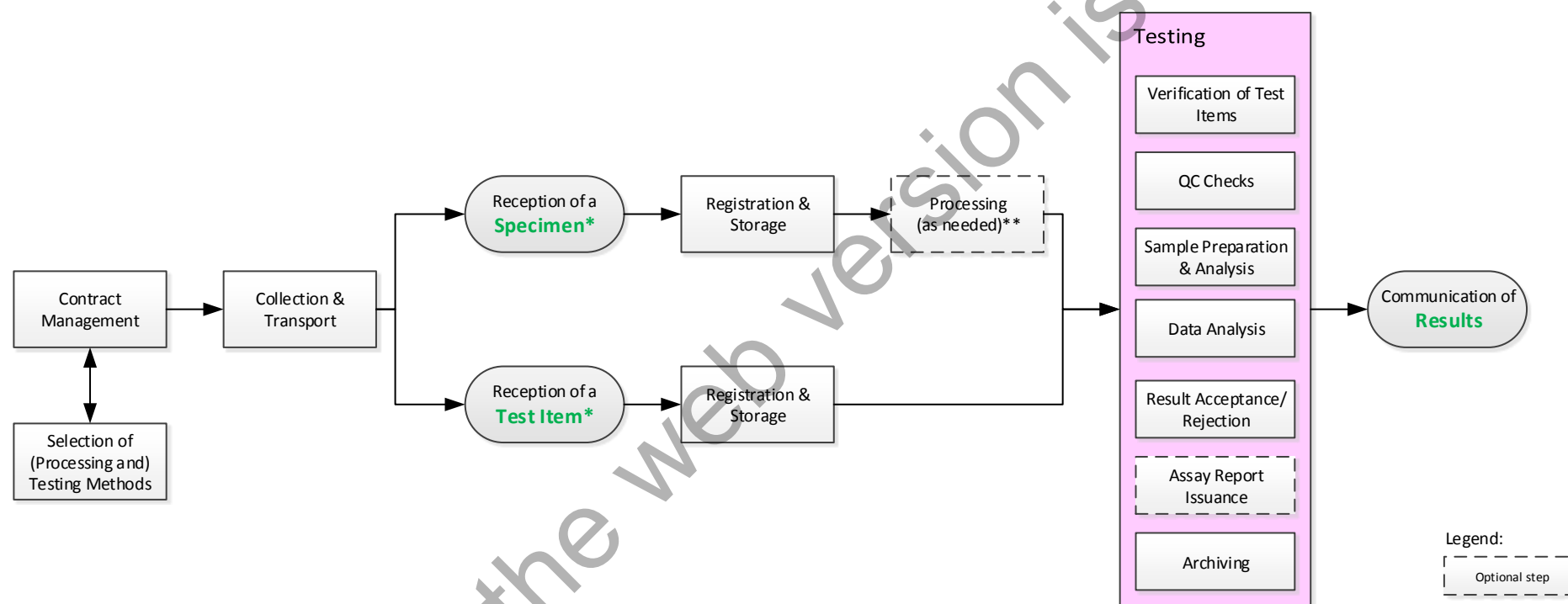
	Contract Management	Collection & Transport	Specimen/ Sample Receipt & Registration	Processing	Testing	Storage	Retrieval	In-house R&D*	Outgoing Shipment S = Samples D = Data	Destruction	Distribution: External R&D
PM	X	●		●	●		X		● (S,D)	X	X
Admin	X										
Pathology	●	X	●	X	X	●	●	X		●	
Biorefinery	●		●	X	X	●	●	X		●	
Biorepository	●	X	X			X	X		X (S)	X	X
BIS	●								X (D)		●
QMS Sub-chapter	PM	CO/REP	REP	REF	QC	REF/REP	REP/PM	--	REP/PM/IT	PM/REP	PM/REP

* outside the certification/accreditation scope

X Main actor

● Contributor

Exhibit D: Schematic Workflow for a Testing Process



* **Specimen** = primary biological material received in the scope of a research/collaboration/fee-for-service project, typically requiring “processing” before being submitted to a test
Test Item = biological material received from a customer; in most cases “ready for testing”, i.e. not requiring “processing” before being submitted to a test.

** **Processing** = production of the item to be submitted for testing, when the provided specimen cannot be directly submitted to the test method
 (e.g. The specimen “PAXgene stabilized blood” is provided to IBBL for the determination of quantity and integrity of RNA [extracted (i.e. “processed”) by IBBL from the delivered specimen]);
 this processing shall not be confused with any “sample preparation”, specifically required for the execution of the test method.

Exhibit E: List of Referenced Documents

Document Code	Title
None	Organizational Chart
SOP GM-HR	Human Resources
SOP GM-FP	Finance & Procurement
SOP GM-PM	Project Management
SOP QM-DC	Document Control
SOP QM-QM	Quality Management
SOP QM-QA	Quality Assurance / Quality Control
SOP IN-FA	Facilities
SOP IN-EQ	Management of Equipment
SOP IN-IT	Information Technology
SOP OP-CO	Collection
SOP OP-REP	Biorepository
SOP OP-REF	Biorefinery
SOP OP-QC	Quality Control Assays
WI QM-004	Continuous Improvement
WI DC-901	Corporate Quality Document Administration

Exhibit F: Abbreviations, Acronyms, Definitions

A	Annex	IT	Information Technology
AP	Assay Protocol	KPI	Key Performance Indicators
AS	Assay Sheet	L.I.H.	Luxembourg Institute of Health
BIS	Business Information Solutions	MESR	Ministère de l'enseignement supérieur et de la recherche (Ministry of higher education and research) (Luxembourg)
BRC	Biological Resource Centre	NCI	National Cancer Institute (USA)
CSO	Chief Science Officer	NF	Norme française (French norm)
CEO	Chief Executive Officer	OECD	Organization for Economic Co-operation and Development
CFAO	Chief Financial and Administrative Officer	OP	Operations
CIO	Chief Information Officer	PM	Project Management
CO	Collection	PRO	(Corporate) Procedure
COO	Chief Operating Officer	PSOP	Project-specific Standard Operating Procedure
DC	Document Control	PT	Proficiency Testing
DNA	Deoxyribonucleic acid	QA	Quality Assurance
EQ	Equipment	QC	Quality Control; Quality Control Assays
F	Form	QM	Quality Management, Quality Manual
FA	Facilities	QMS	Quality Management System
FP	Finance & Procurement	R&D	Research & Development
GCLP	Good Clinical Laboratory Practice	REF	Biorefinery
GM	General Management	REP	Biorepository
HR	Human Resources	RNA	Ribonucleic acid
IBBL	Integrated BioBank of Luxembourg	S	Spreadsheet
ICT	Information & Communication Technology	SOP	Standard Operating Procedure
IEC	International Electrotechnical Commission	SS	Study Summary
IHC	Immunohistochemistry	T	Template
IN	Infrastructure	WHO	World Health Organization
ISBER	International Society for Biological and Environmental Repositories	WI	Work Instruction
ISO	International Organization for Standardization		

Simple Derivatives (SD):	Any derivative prepared by simple laboratory manipulations from a Specimen, without addition of chemical substances (e.g. plasma, serum, homogenized tissue or urine pellet)
Complex Derivatives (CD):	Any derivative prepared through complex multi-step laboratory manipulations from a Specimen or SD, with or without addition of chemical substances (e.g. isolated viruses, isolated bacteria, metabolites, DNA, RNA, formalin fixed paraffin-embedded tissue (FFPE))
Substantially Modified Derivatives (SMD):	Derivative of an SD or CD whose molecular structure and/or its associated molecular path-ways are not found in the source Specimen, SD or CD (e.g. immortalized cell lines, induced pluripotent stem cells (iPSCs), genetically modified micro-organisms and hybridomas)

DOCUMENT METADATA

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Author(s):	Sabine LEHMANN	Quality Manager	19/06/2018
Approver(s):	Dominic ALLEN, Fay BETSOU, Arnaud D'AGOSTINI, Karl-Heinz DICK, Catherine LARUE, Marc VANDELAER	Chief Operating Officer, Chief Scientific Officer, Head of Marketing & Communication, Chief Financial and Administrative Officer, Chief Executive Officer, Chief Information Officer	19/06/2018, 19/06/2018, 19/06/2018, 19/06/2018, 22/06/2018, 19/06/2018
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Updates to cover ISO 9001:2015 requirements; removing certification for NF S96-900 and removing suspension of accreditation; update of some charts; editorial updates.		(see separate section for history of changes for documents updated before the implementation of eQMS)	
		01 - 15/09/2014 - Legacy Document import., 02 - 09/06/2015 - Legacy Document import., 03 - 19/07/2016 - Legacy Document import., 04 - 17/10/2016 - Legacy Document import., 05 - 25/09/2017 - Regular update; update of members of Board of Directors; clarification of "Core Administrative Services" and their role in IBBL QMs; clarification of "Corporate Quality Documents" in the role of IBBL QMS., 06 - 19/01/2018 - Change of address after move; indication of voluntary interruption of accreditation due to move; addition of "neighbors" as interested parties after move.	

REVISION HISTORY

Version	Effective Date	Author	Summary of changes
.01	15/SEP/2014	Sabine LEHMANN	New document
.02	09/JUN/2015	Sabine LEHMANN	Changes related to the merger with CRP-Santé (e.g. "The organization", "Management Structure"); update of section "Service offers"; update of section "Quality Manual" to integrate requirements for ISO 17025 accreditation; update of "Process Overview" flowchart; update of "Interested Parties" section to include the 'General Public of Luxembourg' and the 'Grand Region'; two Exhibits added (C, D); renumbering of all Exhibits; minor editorial changes throughout the whole document.
.03	19/JUL/2016	Sabine LEHMANN	Revision of section "Service Offers" to align it with the updated marketing strategy of IBBL; section "Management Structure": update of board members; section "Quality Manual": inclusion of methods for extension of the accreditation scope; section "Document Hierarchy": inclusion of "Corporate Documents"; update of the "Mission & Vision" section; minor editorial changes throughout the whole document.
.04	17/OCT/2016	Sabine LEHMANN	Clarification of certification & accreditation scope; addition of the law of 3 rd December 2014 as reference; elucidation on the roles & responsibilities of technical management and quality manager; clarification of terminology used in Annex D.

*** End of document ***