Quality Manual

CRBIP,

Biological Resource Center of Institut Pasteur

The following documents are referred to in such a way that some or all of their content is applicable:

ISO 9001:2015
Quality management systems — Requirements

ISO 20387:2018
Biotechnology — Biobanking — General requirements for biobanking

ISO 21710:2020
Specifications on data management and publication in microbial resource centers

SUMMARY

1. PRESENTATION OF THE BIOLOGICAL RESOURCE CENTER OF INSTITUT PASTEUR

The Biological Resource Center of Institut Pasteur (CRBIP) is a biobank created in 2001 with the mission of harmonizing the management of Institut Pasteur's collections under a common Quality Management System (initially, NF S96-900). It brings together three collection units:

- The "Collection de l'Institut Pasteur" (CIP),
- The Pasteur Cultures of Cyanobacteria (PCC),
- The Collections for Human health of Institut Pasteur (CHIP).

In 2018, a fourth unit joined the CRBIP: the National Collection of Cultures of Microorganisms (CNCM).
Since 2022, a process of Fungal (CFIP) collections into the CIP has been in place.
A CRBIP Project Management Office (PMO) has been formalized in 2022 with a transversal role in the management of projects - other than internal research projects. Collection managing units are responsible for the biobanking activities related to their specific bio-resources and for their internal research projects.

The CRBIP is located on the campus of the Institut Pasteur in the 15th district of Paris.

The fact of integrating within its scope one of the first collections of microorganisms in the world, the CIP; the Global Reference Collection for Cyanobacteria, PCC; the only IDA (International Depository Authority) collection in France, the CNCM; together with a collection of bio-resources of human origin, CHIP ; as well as the fact of being part of Institut Pasteur, give to this center a unique positioning at the national and international level. It also encourages CRBIP to develop a range of professional products and services, and to further develop certain units towards accreditation to the ISO 20387 standard by 2027.

1.1. Structure of the CRBIP

The CRBIP brings together four collection units, under a single hierarchical link (Appendix 01 to 06):

- **The CIP (Collection de l'Institut Pasteur) unit** was created by Dr. Binot, who began to preserve bacterial strains as early as 1891. For more than a century now, the CIP's premises have been located on the campus of the Institut Pasteur. The CIP hosts a high biodiversity with more than 26,000 bacterial strains belonging to more than 5,000 different species. Freeze-drying has started at CIP in the 1950s.
    - **The CFIP (Fungal Collection of Institut Pasteur)** aims to reintegrate the strains of yeasts and filamentous fungi (about 2,000 strains) from the former Institut Pasteur's fungal collection "UMIP", which closed in 2013. This historical collection includes specimens of different origins, mainly preserved in mineral oil and in a freeze-dried state. A CFIP Group Leader (Scientific Liaison) from the NRC "Invasive mycosis" (CNR Mycoses invasives) of the Institut Pasteur is assigned to the CFIP.

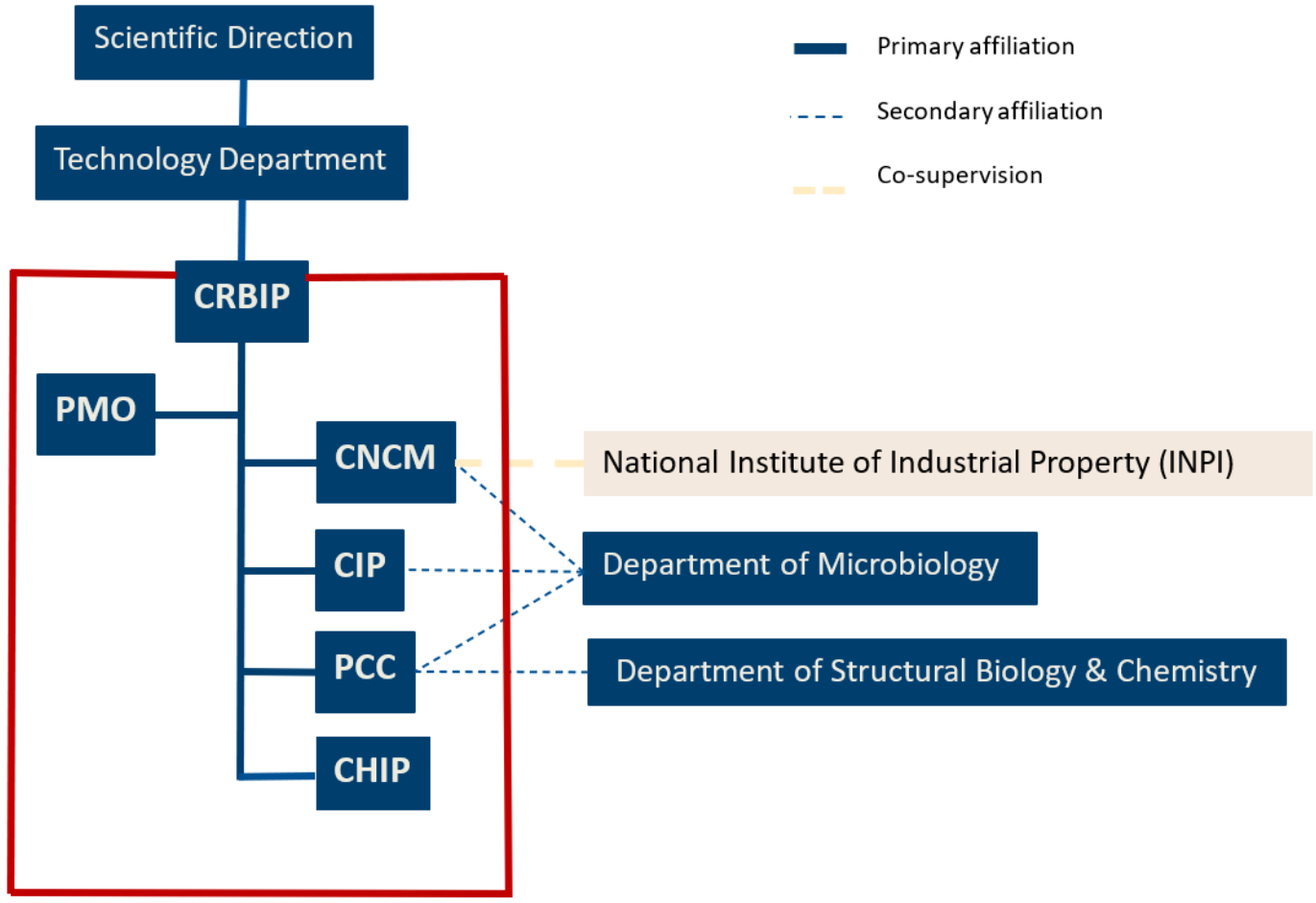
- **The PCC (Pasteur Cultures of Cyanobacteria) unit** contains a collection of 750 isolated pure strains of cyanobacteria, which represents a large part of the morphological, physiological, and ecological diversity of this phylum.

- **The CHIP (Collections for Human health of Insitut Pasteur) unit** collects and offers various human biological resources from healthy volunteers and patients to the scientific community, such as: blood and derivatives, saliva, stool, nasopharyngeal swabs, etc., for a total of more than 150,000 samples in stock.
  CHIP supports clinical trials in close collaboration with the Institut Pasteur's Medical Department, in particular the Clinical Research Coordination Center (PC-RC) and the Institut Pasteur Medical Center (CMIP).

In addition, this unit hosts collections from research projects that have been completed with the aim to reuse them.

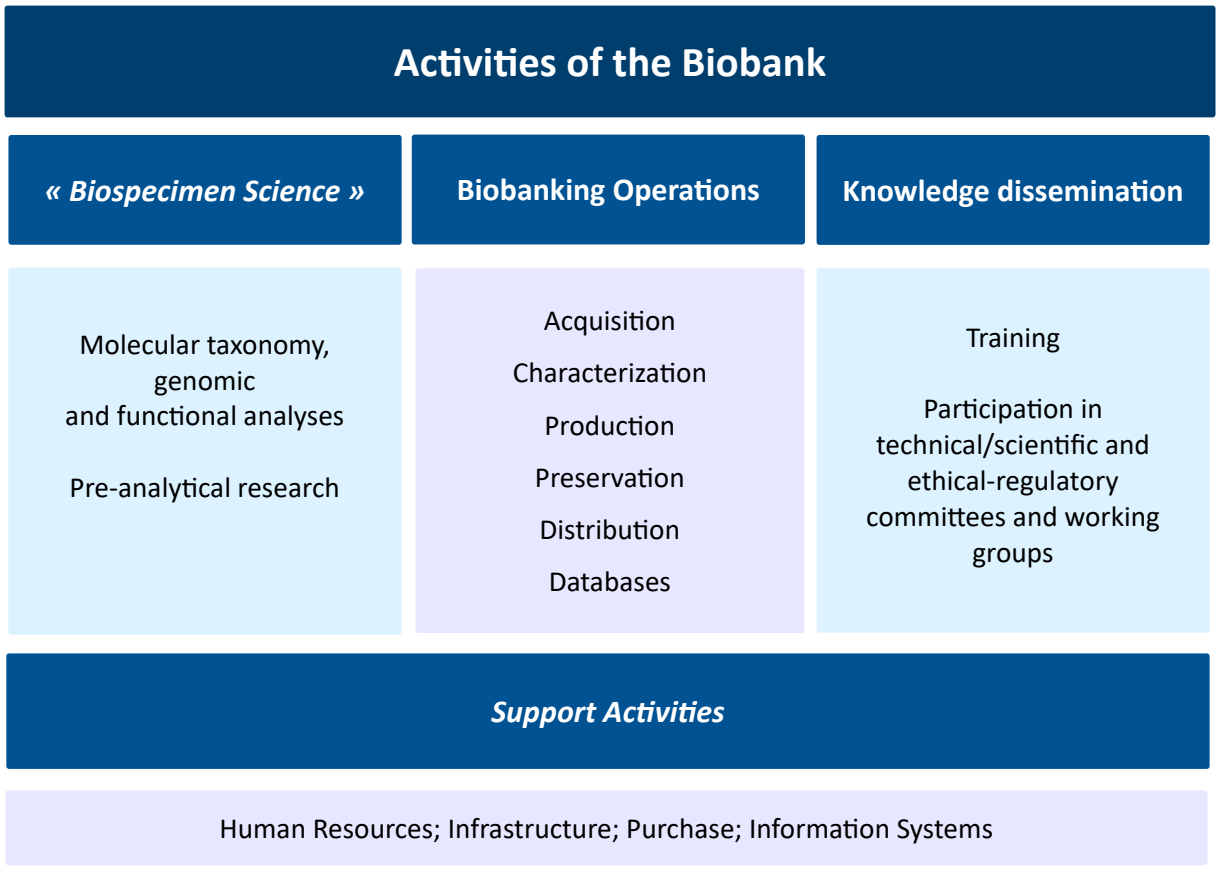
- **The CNCM (National Collection of Cultures of Microorganisms)** is an international depositary authority (IDA) under the Budapest Treaty for the purposes of national and international patent proceedings. It is the only such unit allowed to collect bacteria, filamentous fungi, yeasts, viruses and animal and human cell lines with this purpose in France. Microorganisms are accepted regardless of whether they are genetically modified or not. The provision of biological material held at the CNCM is governed by the Regulations under the Budapest Treaty.

Finally, a Project Management Office (PMO) is responsible for managing the CRBIP's transversal activities: quality, project development and management, communications, regulatory and normative monitoring, data management, business development.



1.2. Activities of the CRBIP

The CRBIP is a solid infrastructure - scientifically and operationally - for microbial and clinical biobanking. It promotes harmonization between CRBIP units, technologically advanced solutions, taxonomic and biospecimen research, leveraging collaboration with internal analytical and data platforms and implementing a strong and harmonized Quality Management System (QMS).



Legend:

QMS Scope

1.3. List of CRBIP services

- **Deposit and Storage**
  - **Microbial materials**
    - Patent deposit / storage, -80°C and LN2
    - Open deposit / storage controlled at room temperature, -80°C and LN2
    - Institutional deposit of bacterial, fungal strains /storage controlled at room temperature, -80°C and LN2
  - **Human biological materials**
    - Patent deposit of cell lines / storage LN2
    - Institutional deposit/storage -80°C and LN2

- **Preparation of biological materials**
  - **Microbial materials**
    - Culture of fungal strains on solid media
    - Culture and maintenance of live pure strains of cyanobacteria
    - Freeze drying
    - DNA extraction from bacterial pellet
  - **Human biological materials**
    - Serum, plasma, urine, saliva, swab medium aliquoting (option in P2+, option automated)
    - PBMC isolation and cryopreservation
    - DNA extraction from whole blood

- **Characterization of biological materials**
  - **Microbial materials**
    - DNA quantification by spectrofluorometry
    - Taxonomic confirmation
      - By MALDI-TOF and/or Illumina WGS
    - Single genome analysis (genome <10Mb)
      - QC Bioinformatics Analysis of Genome Sequence
      - Identification and contextualization of sequences of concern
      - Curation of data in the existing cgMLST (core genome Multilocus Sequence Typing) database
    - Multiple genomic analysis (genome <10 MB)
      - Comparative genome analysis (phylogeny, ANI (Average Nucleotide Identity))
    - Support for strain collection
      - Private genomic database and analytical web tools
  - **Human biological materials**
    - DNA/RNA quantification and purity analysis by spectrophotometry
    - DNA quantification by spectrofluorometry
    - PBMC enumeration and viability measurement

List of services in development:

- ***Preparation of biological materials***
  - ***Microbial materials***
    - *Culturomics*
  - ***Human biological materials***
    - *Stool aliquoting under anaerobic conditions*
    - *Stool culture in anaerobic conditions*
    - *RNA extraction from whole blood*

- ***Characterization of biological materials***
  - ***Microbial materials***
    - *Enumeration of cultivable bacteria (CFU/ml)*
    - *BioLog analyses*
    - *Quantification of bacterial genome copy numbers (dPCR)*
  - ***Human biological materials***
    - *Hemolysis automated evaluation*
    - *Complete Blood Count and CRP measurement*
    - *Urinalysis*
    - *DNA/RNA size analysis by microfluidic electrophoresis*

2. COMMITMENT OF THE MANAGEMENT

The vision of the CRBIP is to be a reference biological resource center in the field of microbiology and human diseases.

The CRBIP values:

- Bioethics: The CRBIP is committed to respect the ethical principles and corresponding national and international regulations applicable within its units. So, the CRBIP units rely on reference texts formalized through the lists of external documents, the modalities and tools put in place at institutional level, such as the ethical charter or the scientific integrity committee.
- Impartiality: To guarantee the impartiality of its activities and more specifically independent access to its biological resources, the CRBIP wished to set up an organization dedicated to this issue. A Sample Access Committee (with a majority of external members) is set up to ensure the impartiality of decisions taken on access requests, particularly for non-renewable resources.
- Confidentiality: Staff are required to respect confidentiality during their activities, especially in situations concerning:
    - The General Data Protection Regulation (teams, researchers, users, donors participating in research, etc.) due to personal data potentially held by certain CRBIP units.
    - Intellectual property related to biological resources or their uses.

The mission of the CRBIP is to preserve and enable access to microbial and human-derived biological samples and associated data and services, to support high-quality and reproducible research by the Institut Pasteur teams and the scientific community at large, and to contribute to the development of research applications.

2.1. The Institut Pasteur's Quality, Safety and Sustainable Development policy

The Institut Pasteur must conduct its research, teaching and public health missions with the best Quality of operations while ensuring the health of its staff and respect for the environment. This approach is part of its sustainable development approach, called the Institut Pasteur's Corporate Social Responsibility.

This commitment translates into:

- Control of quality, safety, and sustainable development risks in the conduct of the Institut Pasteur's activities and projects.
- Maintenance and provision of a high level of expertise in quality, safety, and sustainable development for all Institut Pasteur units.
- Compliance with legislation and regulations related to Quality, Safety, and the Environment.
- Provision of all the necessary resources (Appendix 07) for the deployment of projects and a carefully thought through management of Quality, Safety and Sustainable Development resources.

2.2. CRBIP's Quality Policy

The CRBIP's Quality Policy echoes and supports the development of the CRBIP's various strategic objectives, which are the improvement of its infrastructure, the increase in the distribution of biological resources and the strengthening of the services provided to the scientists of the Institut Pasteur and their scientific partners.

To achieve these quality improvement objectives, the CRBIP CODIR (Comité de Direction) is committed to:

- Maintain the monitoring and evolution of the Quality Management System within all CRBIP units committed to the ISO 9001 standard, including the quality and conformity of biological materials and associated data.
- Ensure the satisfaction of stakeholders.
- Maintain and improve communication (catalogue, website, satisfaction surveys).

2.3. CRBIP Stakeholders

As a biobank in the field of microbiology and human diseases, the CRBIP seeks to meet the requirements of its stakeholders.

Stakeholder Category	Stakeholders	Stakeholder Needs and Expectations
CRBIP	CRBIP Staff	- Alignment of the units' activity with the strategy and objectives set by the CRBIP - Respect for working conditions - Assignment of roles, responsibilities, and objectives according to each person's competencies - Training and development of skills - Transparency, trust, benevolence, impartiality
Institut Pasteur	The Institut Pasteur Departments: Scientific Department, Medical Department, Technology Department, Research Applications and Industrial Relations Department	- Alignment of the CRBIP's activity with the Institut Pasteur's strategic plan - Being an essential and growing component of the research projects developed by the research units - Meeting biobanking needs, participating in the development of research protocols - Meeting the needs of research teams by providing them with quality biological resources - Facilitating the grant applications and the development of contracts
	Internal support department	- Precise formulation of the need - Compliance with institutional procedures
Users/Clients	Academics, private industrial companies...) IP or CNR Research Units Co-Investigators and Investigators, Investigator Centers: CMIP, hospitals, CRO, learned societies Networks and consortia	- Flexibility, scientific and operational processes associated with Customer orientation and integrated with the Quality Management System (QMS). - Availability of reliable, standardized biobanking infrastructure and operations for the reception, storage, and redistribution of biological resources under optimal and controlled conditions. - “Fit for purpose” biological resources - Support in the management of complex research projects.

Stakeholder Category	Stakeholders	Stakeholder Needs and Expectations
Competent Authorities	Ministry of Higher Education, Research and Innovation SGDSN (General Service for Defence and National Security) CPP, CNIL Ministry of Solidarity and Health, ANSM, HAS Ministry of Economy Ministry of Agriculture	- Compliance with regulatory requirements
Sample Access Committee	External Members, Internal Members	- Annual reporting on CHIP's activities
Civil society	Research Participants	- Compliance with good clinical practices (deontology, ethics, confidentiality) and informed consent - Involvement in the design and evolution of projects impacting them - Right to change or revoke informed consent
Networks and other external partners	3-CR, BBMRI, MIRRI, WFCC, ECCO, GBIF, Nagoya Expert Group, ISBER, WHO (Appendix 08)	- Participation in the evolution of the activity within the network - Sharing knowledge and experience - Reflection on specific themes via working groups
Suppliers / External service providers of the Institut Pasteur	Suppliers of hardware, consumables, solutions and services related to the biobanking business P2M platform	- Precise formulation of the need - Compliance with established procedures and commitments - Customer loyalty / Relationship of trust

3. QUALITY MANAGEMENT SYSTEM

The use of standardized procedures for the collection, preparation, storage, and distribution of biological materials is necessary to ensure that samples can be used in a compliant, "fit" and reproducible manner. The use of standardized procedures is a key requirement to ensure the quality of results, eliminating pre-analytical variations and bias. Therefore, the CRBIP is committed to managing its operations under the control of a Quality Management System (QMS).

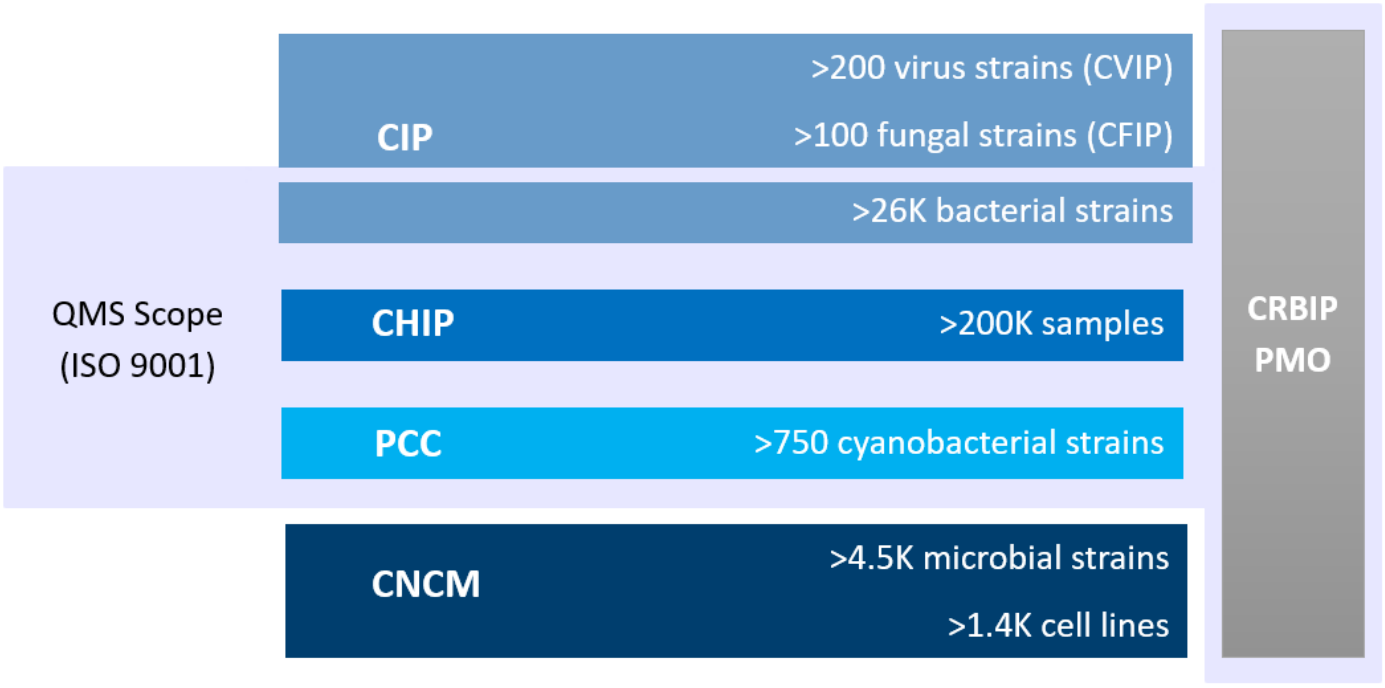
The CRBIP Management delegates to the CRBIP Quality Manager the organization and the continuous improvement of the CRBIP Quality Management System, in collaboration with the Quality Engineer of the Institut Pasteur Quality Department (affiliated to the Technical Resources and Environment Department of the Institut Pasteur). The Quality Manager also coordinates actions with the various Quality Liaisons of the units that constitute the CRBIP.

3.1. Scope of the QMS

The QMS of the CRBIP covers the activities of acquisition, production or preparation, quality control or characterization, preservation/storage and distribution of biological resources, microorganisms, and human biological samples. It applies to all four units: CRBIP-PMO, CIP, PCC, and CHIP.

Following the end of the certification cycle according to NF S 96-900, the CRBIP follows the ISO 9001:2015 standard while preparing for ISO 20387:2018 accreditation.

Chapter 8.3 "Design and development of products and services" of ISO 9001 is excluded from the scope.

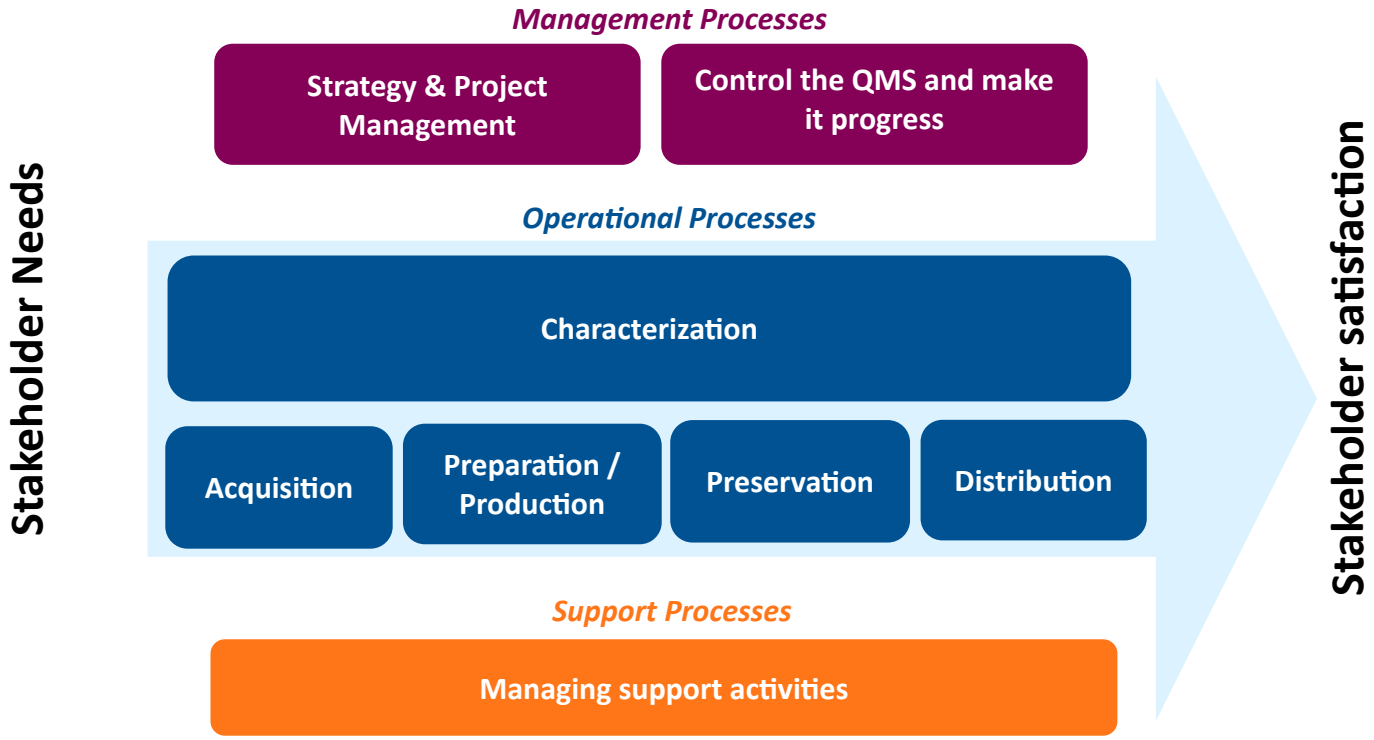


3.2. CRBIP Process Mapping

The management processes (Appendix 09) are focused on listening to and respecting the needs and requirements of stakeholders in accordance with applicable laws and regulations. The quality policy and quality objectives are in line with the CRBIP's strategy and form the basis for the quality and continuous improvement of the CRBIP.
This strategy is also risk-based and continuous monitoring of performance, effectiveness, compliance, and client satisfaction ensures evidence-based decision-making and continuous improvement of the organization.

The operational processes are composed of the following stages: acquisition, preparation/production, preservation, distribution, and a transversal process of characterization/quality control of the biological resources deployed across all operational stages.

Services related to process “Managing support activities” are outsourced to the corresponding Institut Pasteur services.



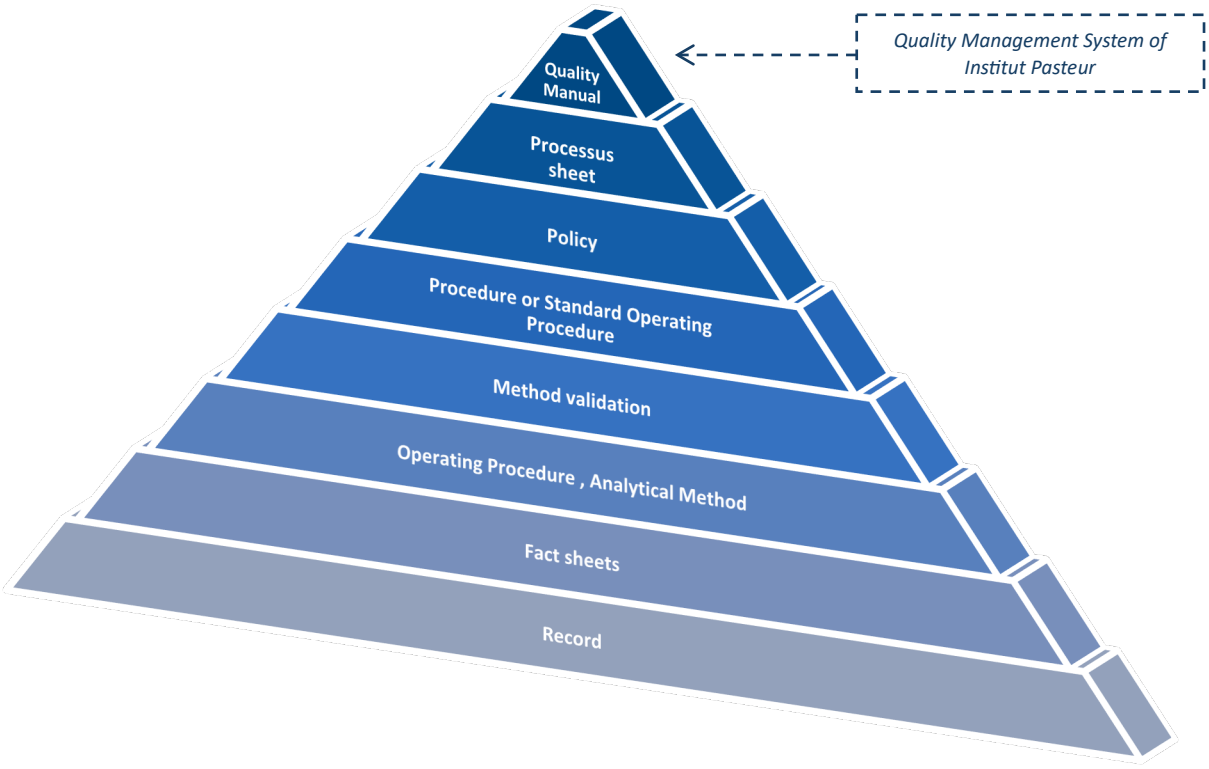
3.3. Document management

The CRBIP uses a document management system that corresponds to the various processes of the CRBIP and is built to comply with the normative requirements: ISO 9001:2015 and ISO 20387:2018.

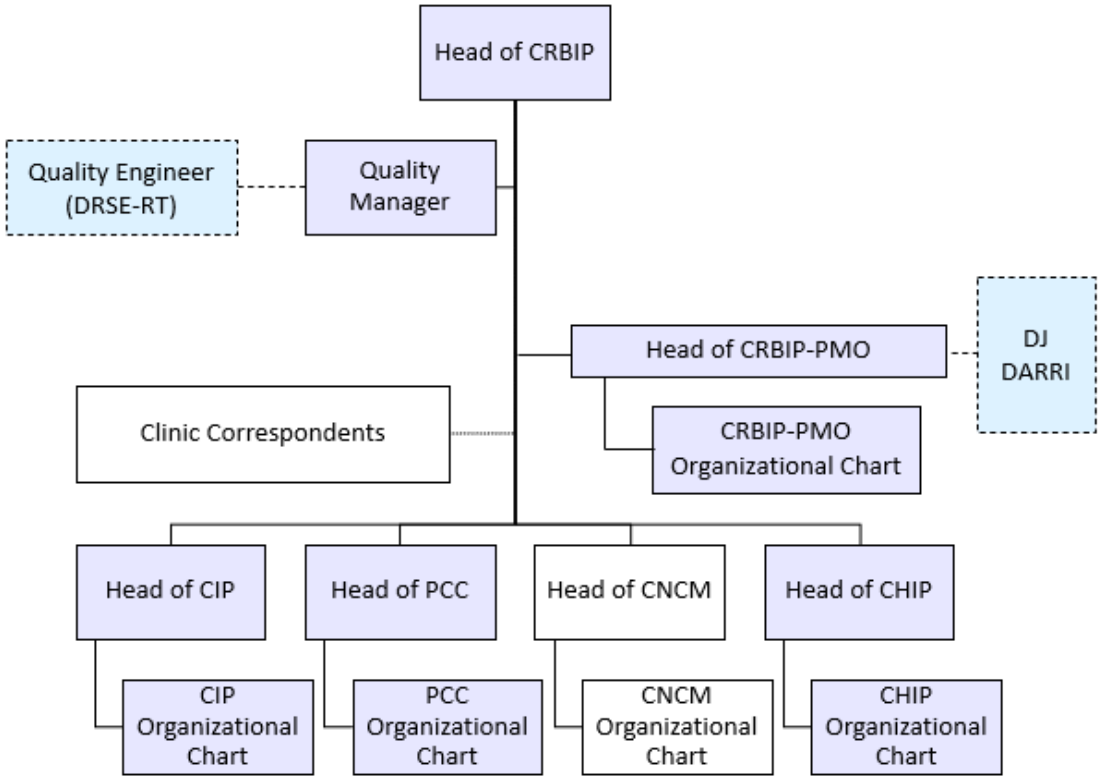
Process	Abbreviation	Wording
Strategy & Project Management	PM	*Project Management*
Control the QMS and make it progress	MANQ	*Quality Management*
Characterization	CAR	*Characterization*
Acquisition	ACQ	*Acquisition*
Preparation / Production	PRE	*Preparation*
Preservation	CON	*Conservation*
Distribution	DIS	*Distribution*
Managing support activities	HSE	*Health & Safety*
	EQP	*Equipment*
	ACH	*Purchase*
	INF	*Computer science*
	RH	*Human Resources (Skills Maintenance)*

Document management related to the Institut Pasteur's cross-functional institutional processes is described in the institutional procedure "Document management". Regarding the document management of the CRBIP, additional specifications are applied and described in the CRBIP document: CRBIP_MANQ_PO_001. The general documentation of the CRBIP is available on the SMQ software “Kalilab”, document management tool.

Documentary Pyramid:



APPENDIX 01: CRBIP ORGANIZATIONAL CHART

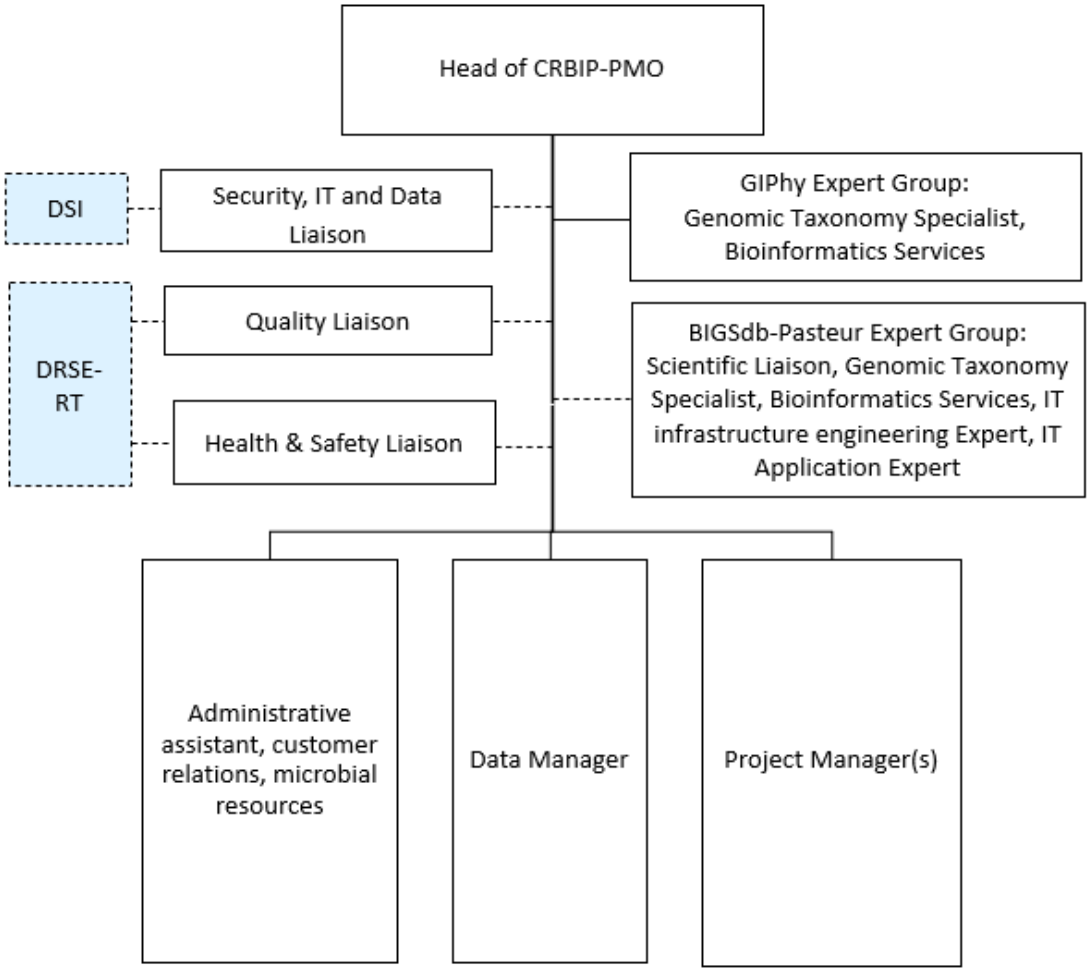


Legend:

———	Reporting relationship	DARRI	Technology Transfer and Industrial Partnership Department
- - - - - -	Functional link	DJ	Legal Department
	Support Service		QMS Scope

DRSE-RT: Department of Corporate Social Responsibility and Technical Resources

APPENDIX 02: CRBIP-PMO ORGANIZATIONAL CHART



Legend:

Reporting relationship

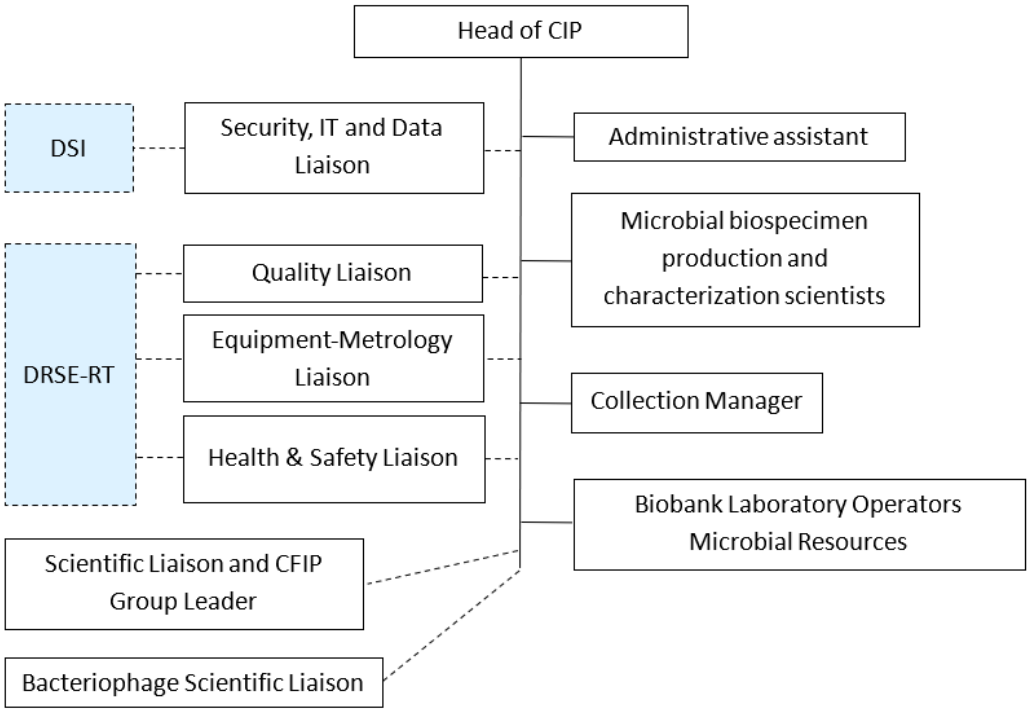
Functional link

Support Service

DSI: IT Department / Information Systems Department

DRSE-RT: Department of Corporate Social Responsibility and Technical Resources

APPENDIX 03: CIP ORGANIZATIONAL CHART



Legend:

Reporting relationship

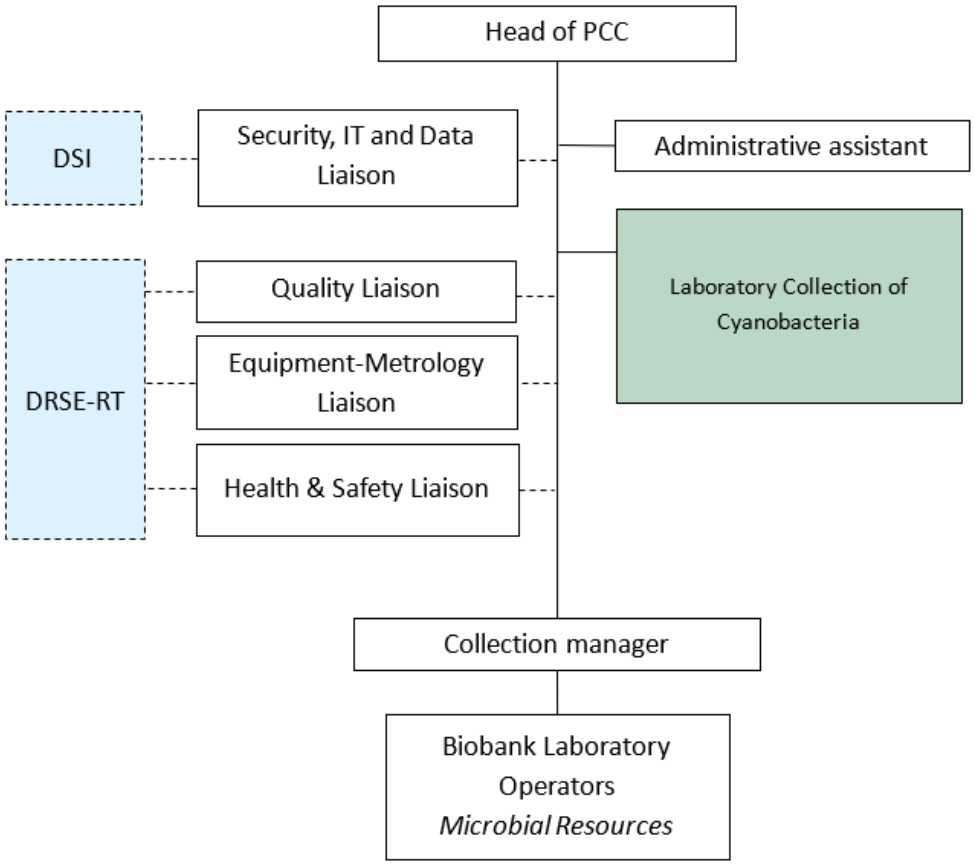
Functional link

Support Service

DRSE-RT: Department of Corporate Social Responsibility and Technical Resources

DSI: IT Department / Information Systems Department

APPENDIX 04: PCC ORGANIZATIONAL CHART



Legend:

Reporting relationship

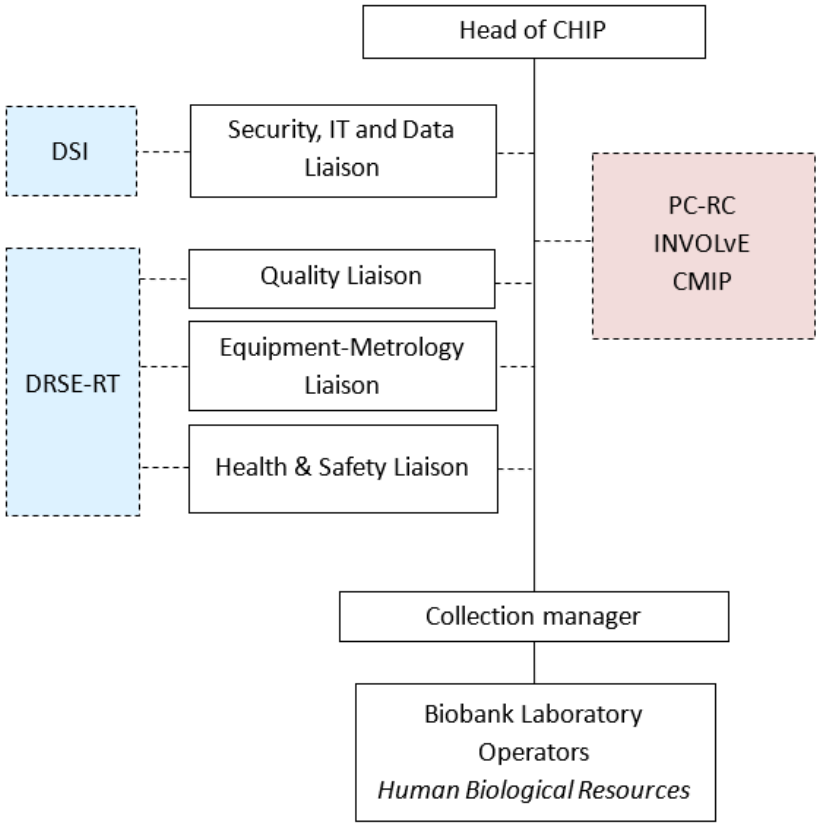
Functional link

Support Service

DRSE-RT: Department of Corporate Social Responsibility and Technical Resources

DSI: IT Department / Information Systems Department

APPENDIX 05: CHIP ORGANIZATIONAL CHART



Legend:

——— Reporting relationship

------ Functional link

Support Service

Medical Department

DRSE-RT: Department of Corporate Social Responsibility and Technical Resources

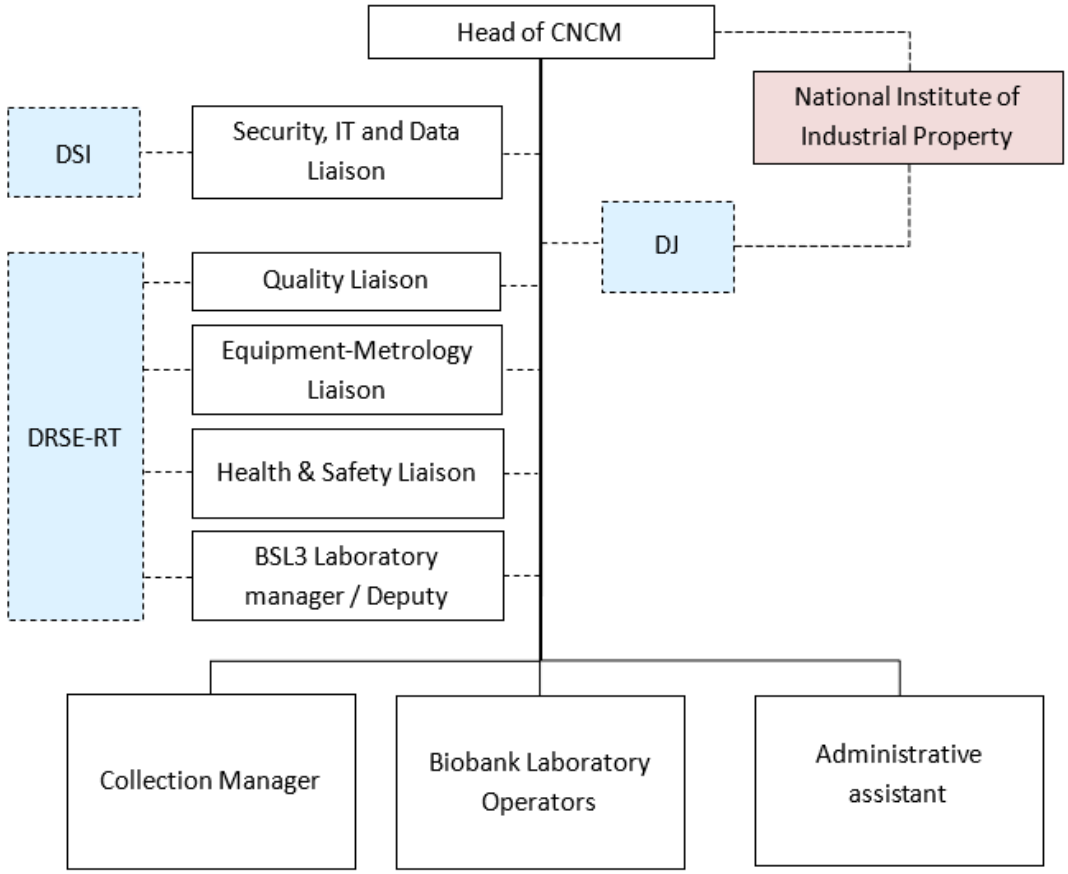
DSI: IT Department / Information Systems Department

PC-RC: Clinical Research Coordination Center

INVOLvE: Clinical Investigation Center

CMIP: Medical Center of the Institut Pasteur

APPENDIX 06: CNCM ORGANIZATIONAL CHART



Legend:

Reporting relationship

Functional link

Support Service

Co-tutorship

DRSE-RT: Department of Corporate Social Responsibility and Technical Resources

DSI: IT Department / Information Systems Department

DJ: Legal Department

APPENDIX 07: INSTITUT PASTEUR'S INTERNAL PARTNERS

Management of the Institut Pasteur	Mission
General Direction	Institut Pasteur's Quality Policy and Strategic Orientation
Medical Department	Development of medical research, strengthening of public health activities, organization of partnerships with hospitals and medical research structures, advice and evaluation of international medical and scientific affairs
Human Resources Department	Administration of personnel files, recruitment and mobility, implementation of training plans
Legal Department	Design and validation of MTA (Material Transfer Agreement), validation of General Sales Conditions, legal formatting and finalization of contracts negotiated by DARRI, legal monitoring and application of legislative and regulatory texts on microbial collections (e.g., Nagoya, Budapest Treaty) and human collections (e.g., Jardé Law), other legal missions
Finance Department	Budget management, cost analysis, purchase orders, new customer creation, sales invoicing
Training Center	Management of teaching activities on biodiversity of microorganisms and biobanking
Technology Transfer and Industrial Partnership Department (DARRI)	Negotiation of the contractual conditions with the industry partners, of the IP patent deposits
Scientific Evaluation Department (DES)	Evaluation of Scientific Units
International Department - International Network of Institut Pasteur (RIIP)	Collaboration in the scope of the RIIP organizations holding collections
Information Systems Department	Design and management of software and other database management tools Data backups Management of interfaces between information systems
Scientific Careers Department (DCS)	Evaluation of Scientist careers
General and Scientific Secretariat (SGS)	Management of the "Research" website Implementation of decisions after evaluation of research units
Communication and Sponsorship Department	Management of the "Public Health" website
Department of Corporate Social Responsibility and Technical Resources (DRSE-RT)	Preparation of culture media Service: Preparation of culture media, preparation and distribution of laboratory glassware and consumables Technical Services: Maintenance, intervention and upkeep of equipment, "OCEASOFT" management, printing of informative material (brochures, posters, etc.) for communication Risk Prevention Department: Training in the prevention of biological, chemical and other risks, assistance in the application of regulatory requirements and controls (GMOs (Genetically Modified Organisms), MOTs (Toxins and Microorganisms), etc.) Quality, Environment and Sustainable Development Department: Support, advice and facilitation for the QMS, organization of audits,

Management of the Institut Pasteur	Mission
	Kalilab tool administrator, management of general procedures, metrological services, cleaning services, training/awareness-raising Logistics Department: reception of shipments, collection and dispatch of products, mail management, shipments-out
Archives service	Archiving of paper records, study documents, medical records
Technology Department	Main affiliation of CRBIP, strategic collaboration in projects for the development of new technologies, support for projects requiring bioinformatics expertise (Hub C3BI - Bioinformatics and Biostatistics)
Grant Office Department	Monitoring and support for responding to calls for proposals (national, European and international)
Security Department	Management of national safety and protection rules: Protection of strategic knowledge and know-how, as well as sensitive technologies.

APPENDIX 08: CRBIP PARTICIPATION IN NETWORKS AND INFRASTRUCTURE

France

Club 3C-R (The Biological Resources Network)

IBISA (Infrastructures in Biology, Health and Agronomy)

GIS CYANOBACTERIES

RARe (Réseau français de Centres de Ressources Biologiques pour la recherche en biologie, agronomie et environnement)

Europe

ECCO (European Culture Collections' Organisation)

MIRRI-ERIC (Microbial Resource Research Infrastructure)

International

ISBER (International Society for Biological and Environmental Biorepositories)

WFCC (World Federation for Culture Collections)

APPENDIX 09: DESCRIPTION OF THE CRBIP PROCESSES

Process	Input data	Actions / Purpose of the process	Output data
Strategy & Project Management	Institut Pasteur Strategic Plan CRBIP Strategic Plan Institut Pasteur Quality Policy CRBIP Quality Policy Financial Plan European projects Listening to PIs (Principal Investigators) (needs and expectations) Biological Resources Application Form Regulatory, scientific and technical monitoring Management Review n-1 Quality Reviews n-1	- Define the strategic directions of the CRBIP and enforce them. - Define and monitor the strategic projects of the CRBIP.	Quality Manual Management Review Quality Reviews Communication documents Project Briefs List of projects 3-5-year strategic plans of Units
QMS monitoring and progress	Incidents Complaints Internal Audits / External Audits Risk Analysis Listening to Interested Parties (feedback, emails, proposals, opportunities) Satisfaction surveys Objectives and Indicators Supplier/Provider Evaluations	- Coordinate the entire CRBIP to advance the QMS. - Measure indicators and incidents and draw up corrective and preventive actions.	Table for follow-up of improvement actions Annual Internal Audit Program Indicator Tracking Table
Acquisition	Cyanobacteria deposit (PCC) Deposit Forms (CIP/CNCM) Biological Resources Request Forms / Sample processing Forms / Documents Associated with Closed Collections (CHIP)	- Enrich collections with new strains/samples of human origin. - Establish a computer database and/or catalogue covering each of the collections.	Passaging Culture Production Distribution Updated BIMS
Preparation / Production	Documents related to the protocol of the collection concerned or of the application Acquired bioresources Passaging schedule and Passage Sheet (PCC) Production Planning and Production Sheet (CIP) BIMS	- Prepare/Produce samples or derivatives from primary biological resources and their associated data according to the work instructions pre-established in the protocol documents of the relevant collection. - Obtain enough biological material.	Biological material and associated data (Secondary samples stored, Strains produced, Strains passaged) Updated BIMS
Preservation	Biological material and associated data Preparation Sheets (CHIP)	- Guarantee the quality of biological material (controls).	Biological material and associated data Specification Sheet (PCC)

Process	Input data	Actions / Purpose of the process	Output data
	Production Sheets / Control Sheet (CIP) Passage Sheet (PCC) BIMS	- Control traceability from acquisition to distribution.	Production Sheet / Control Sheet (CIP) Census of Biological Collections File (CHIP) Updated BIMS
Distribution	Catalogue Purchase orders Request for Access to Biological Materials Biological material Related data	Ensure the distribution of biological materials in accordance with applicable procedures.	Creation of a new customer account if not existing Creation of an order and invoicing number via the accounting management tool Assigning a budget line Parcels and related data Shipping Requests via the Shipment Management Tool Customs documents, delivery notes (CIP / CHIP) Contacts of users
Characterization	Biological material and associated data Reference material Non-Compliance / Complaint Periodic QC Plan	Guarantee the quality of biological material through controls.	QC Worksheet or Report Production Sheet / Control Sheet (CIP) Technical Form (CHIP) Passage Sheet (PCC) LIMS
Managing support activities	Institut Pasteur Strategic Plan CRBIP Strategic Plan Management Review Quality Reviews Needs of the CRBIP	Ensure the availability of the necessary resources for the implementation of the activities of the CRBIP: - Manage Human Resources - Manage equipment, consumables, import/export, cleaning, waste, media and material - Manage Financial Resources - Manage Information Systems - Manage the regulatory and legislative framework - Provide support for scientific projects using human biological samples and procedures requiring ethical-regulatory compliance.	<u>Human resource:</u> Job description / Job description Flowcharts Task Breakdown Charts Professional Annual Maintenance Carried Out Trainings carried out and evaluated <u>DRSE-RT</u>: Completed equipment files (equipment folder, maintenance, mapping, etc.) Completed Materiel Management Tables Batch Tracking Supplier / Provider Reviews Collaborative Agreements <u>Finance</u>: Annual Budgets Allocated to Projects / Invoices <u>Information systems</u>: Collection Management Software Catalogues

Process	Input data	Actions / Purpose of the process	Output data
			Computer equipment Data protection Collaboration Agreement Legal: GDPR MTA (Material Transfer Agreement) IP-INPI Contract, Form and Contract for the Deposit of Biological Materials (CNCM) PC-RC: Research protocols (CHIP)