Chapter 2
Biobank Design and Infrastructure: Biobank Engineering

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Abstract The availability of high-quality biological and environmental specimens for research purposes requires the development of standardized methods for collection, long-term storage, retrieval, and distribution of specimens. These practices require the implementation of a Certified Quality System specific for the Biobank (ISBER Biobank Proficiency Testing Program. https://www.isber.org/page/PTGI and BBMRI-ERIC Quality Management Services For Basic and Applied Research. https://www.bbmri-eric.eu/services/quality-management/).

In parallel, the biobank infrastructure needs to be designed and implemented (OECD Best Practice Guidelines for Biological Resource Centres. http://www.oecd-ilibrary.org/science-and-technology/oecd-best-practice-guidelines-for-biological-resource-centres_9789264128767-en; ISO/IEC 9001:2015 "Quality Management Systems requirements". https://www.iso.org/obp/ui/#iso:std:iso:9001:ed-5:v1:en; ISO 20387:2018, Biotechnology—Biobanking—General requirements for Biobanking. https://www.iso.org/standard/67888.html; and ISO/TC 212 "Clinical Laboratory Testing and in vitro diagnostic test systems". https://www.iso.org/committee/54916.html) with state-of-the-art technologies, and with the objective to be operative for periods up to 20–30 years. The commitment of the institution is critical to achieving this goal.

The technology which will be implemented (e.g., liquid nitrogen mechanical freezers, processing equipment, etc.) must be selected for present and future needs. Choices between manual and robotized equipment must be made, looking at future requirements, and considering the potential to improve the quality of the biobank. Backup systems (electrical and liquid nitrogen (LN_2)), remote back-up freezers, and sufficient space to expand are also mandatory for correct implementation and management of the biobank (OECD Best Practice Guidelines for Biological Resource Centres. http://www.oecd-ilibrary.org/science-and-technology/oecd-best-practice-guidelines-for-biological-resource-centres_9789264128767-en).

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In this chapter, we describe the most important aspects of biobank engineering, as complementary to, or integral to, the information included in the international guidelines for design and implementation of a state-of-the-art biobank.

Keywords Biobank engineering · ISO standard · Quality management system · Standard operating procedures · Biorepository accreditation program · Cryogenic room · LN_2 · Process laboratories

2.1 Introduction

The availability of high-quality biological and environmental specimens for research purposes requires the development of well-standardized methods of collection, processing, cryostorage, retrieval, and distribution of high-quality specimens. These practices require the implementation of a State-of-the-art infrastructure according to the International Guidelines [1–3], the definition of a Quality Management System (QMS) certified by ISO 9001:2015 [4] and were needed the accreditation of the Biobank QMS to CAP [5] (College of American Pathologists) and more recently by the new ISO 20387:2018 [6] specific for Biobanks.

The technologies and processes to be implemented (e.g., liquid nitrogen storage, mechanical freezers, processing equipment, etc.) should take into consideration present and future needs, looking at medium and long periods, according to the purpose/scope of the Biobank (e.g., Population, Disease, Animal, Environmental, Personalized Medicine, etc.).

Monitoring and Control Systems must be engineered to ensure the safety of the Biobank personnel and to guarantee the safety of the biospecimens stored by controlling the "cold chain." The infrastructure should have backup systems (electrical CO_2 and liquid nitrogen (LN_2)), remote storage and disaster recovery plan) in addition to sufficient space to expand and ensure medium-long time frame operability. Choices between manual and robotized equipment must be made, looking at future requirements, and considering the potential to improve the Biobank workflow and the quality of the biospecimens. The process laboratory should imply the Quality Control Procedures for all processes verified (if possible) by ISBER Assessment [7] and Proficiency [8] tools, and the SPIDIA self-assessment tool for molecular diagnostics to check pre-analytical workflows [9].

Management/Owners of the Biobank is fundamental for the success of the operation and its sustainability over time. Resources of the Biobank should be "structured" and trained in all aspects of Operation and Safety Procedure. The goal of the Biobank should be part of International Biobanking Networks (e.g., ISBER, ESBB, BBMRI, etc.) with the objective to distribute high-quality biospecimens and associated data to the Scientific Community.

2.2 Biobanking Engineering

Most of the information related to the construction and management of a Biobank are indicated in the guidelines prepared by major international biobanking societies (ISBER [3], NCI [2], BBMRI [14, 15], etc.) or international organizations (e.g., OECD [1], WHO [10, 11], etc.).

In addition, the International Standard Organization (ISO) has published the ISO 20387:2018 [6] "Biotechnology-Biobanking—General requirements for biobanking," to which all Biobanks should consider complying and be certified and/or accredited.

A Biobank should be engineered with state-of-the-art technologies taking into consideration the construction specificity for each of the following areas which are detailed in each specific chapter:

1. Cryogenic room (LN2 Distribution system; Cryogenic containers; etc.)
2. IT infrastructure (Monitoring and Control System; Laboratory Information Management System (LIMS))
3. Processing laboratories (Tissue, Cell and Molecular Biology, etc.)
4. Logistics and services (receiving and shipping services)

The Management of the Biobank should be formalized by a specific Quality Management System described in the following chapter.

2.3 Quality Management System (QMS)

A Quality Management System is a managerial tool that includes quality control and operational procedures like standard operating procedures (SOPs), to ensure consistent operations. The adoption of a QMS is a strategic decision for a Biobank since will improve its overall performance and provide a sound basis for sustainable developmental initiatives.

The potential benefits of implementing a "QMS" based on ISO 9001:2015 [4] are: (a) customer focus; (b) leadership; (c) engagement of people; (d) process approach; (e) continuous improvement; (f) evidence-based decision-making; and (g) relationship management.

This ISO 9001:2015 [4] International Standard promotes the adoption of a process approach when developing, implementing, and improving the effectiveness of a QMS, to enhance customer satisfaction by meeting customer requirements specifying general requirements for the competence, impartiality and consistent operation of biobanks including quality control requirements to ensure biological material and data collection of appropriate quality.

The new ISO 20387:2018 [6, 13, 17] standard specific for Biobanks is applicable to all organizations performing biobanking, including biobanking of biological

material from multicellular organisms (e.g., human, animal, fungus, and plant) and microorganisms for research and development.

Biobank users, regulatory authorities, organizations and schemes using peer-assessment, accreditation bodies, and others can also use this document in confirming or recognizing the "**Competence of Biobanks.**"

The ISO 20387:2018 [6, 13, 17] Standards do not apply to biological material intended for food/feed production, laboratories undertaking analysis for food/feed production, and/or therapeutic use.

2.4 Structural Requirements of a Cryogenic Room

A cryogenic room is an infrastructure designed and built for storage at low temperatures, generally through the use of cryogenic fluids, of biological material for research and/or clinical use. A cryogenic room must have suitable and dedicated rooms, with characteristics adapted for specific functions. The equipment used must be adequate for the activity that will be carried out and in compliance with current safety regulations. The staff must be structured, qualified and dedicated to the cryogenic activities and trained for each specific task and under the direction of a Manager with specific experience with cryogenic substances (e.g., Liquid Nitrogen, CO_2, etc.). This Management role may be covered by the Head of the Biobank. Standard Operating Procedures (SOP's) for all cryogenic activities must be in place according to the QMS of the Biobank.

The design of the cryogenic room must guarantee:

- the safety of the people working in the cryogenic room
- the safety of the biological material cryo-stored
- the safety of the data (clinical, biological, and identification/traceability).

Particular attention must be given to Environmental Conditions and to possible new conditions caused by "climate changes" differently affecting various areas of the world, where heavy rain, floods, and/or earthquakes were rare or unusual in the past geological era. Every year we observe devastating tornados, sometimes related to hurricanes (e.g., the Katrina tornado outbreak across the eastern United States from August 29 to August 31, 2005, etc.) destroy cities and can affect bioreposito-ries. This new reality must be taken into consideration when establishing a new biorepository infrastructure and defining a disaster plan. It is important therefore to look at the location of the biobank (examining the latest pattern of local disasters) and evaluate the risks of environmental conditions for the years ahead.

2.4.1 Definitions

- **Nitrogen (N_2)**: an inert, odorless, and colorless gas with a boiling point of 77.35 K (−195.8 °C).
- **Cryogenic fluid**: a fluid that boils at atmospheric pressure at temperatures below −73 °C.
- **Liquid nitrogen**: nitrogen is reduced to a liquid state by compression with a temperature of about −196 °C. It is part of the cryogenic fluids.
- **Liquid nitrogen storage tank**: cryogenic tank, complete with accessories required by the relevant regulations, consisting of two containers, one internal and one external, separated by an insulating cavity normally under vacuum. The cryogenic tank, normally placed in a suitable external environment, provides liquid nitrogen to the system and is the delivery point of the gas supplier.
- **Cryogenic container**: containers of variable dimensions containing nitrogen in liquid phase. Pressurized and non-pressurized containers can be distinguished.
- **Cryobiological container**: non-pressurized container of variable dimensions for short/medium/long-term nitrogen storage of biological samples. It is available in cryobiological containers with automatic and/or manual filling.
- **Programmable control rate freezer**: device used to gradually lower the freezing temperature of the biological samples.
- **Personal Protective Equipment (PPE)**: all the equipment worn and held by the worker in order to protect himself against any risk occurring during work activities. Risks related to personnel safety and/or health while at work, as well as any complement or accessory intended for this purpose.
- **Self-contained breathing apparatus**: device for breathing with air reserve in the case of low oxygen alarm.
- **Environmental oxygen detectors:** devices that continuously monitor the percentage of atmospheric oxygen inside the rooms, connected to an alarm system which alerts under-oxygenation in the room.
- **Aeraulic air treatment system**: set of all equipment, structures, accessories, and controls designed to ensure air quality maintaining specific microclimatic conditions. The definition includes air conditioning, thermo-ventilation, and ventilation.
- **Liquid nitrogen distribution system/cryogenic line**: pipelines that transfer liquid nitrogen from the external vessel to each cryogenic container. The line consists of a system of pipes that connect the main cryogenic vessel to the cryogenic container which does not need to be—insulated or vacuum insulated. The piping includes all necessary valves, fittings, and tools.
- **Safety valve**: automatic device whose function is to prevent that the pressure of a system containing liquids or gases can exceed a determined calibration and/or safety value.
- **Bursting discs**: safety device mounted on pressure vessels whose function is to prevent explosion or damage due to pressure build-up in a relatively short period of time.

2.4.2 Identification and Characteristics of the Cryogenic Area

The design and operation of the storage area (Cryogenic room) are very important, being the place where the biological material will be stored for long periods of time and where the safety of the biologicals and of operators must be guaranteed.

The cryogenic room must be of adequate size and have a location appropriate and designated for the specific purpose for which it will be used.

It is not recommended to handle and store liquid nitrogen in a local volume smaller than 20 m^3. Sufficient space must be provided for the handling of nitrogen containers, nitrogen samples, and personnel; it is advisable that the space of maneuvering is at least equal to the size of the largest cryogenic container. The distance between the nitrogen containers and the walls of the room should not be less than 30 cm and the distance between the nitrogen containers not less than 20 cm. It is also advisable to have a height of the rooms (net) not less than 2.70 m; in all cases, especially if the height is less than the recommended height, then it is recommended to furnish adequate ventilation systems able to maintain the percentage of oxygen at security levels.

The room must be physically isolated from other rooms or workplaces and must not be used as a passageway to access other locations. It should be dry, cool, well ventilated, and free of heat sources. It must be possible to view the interior of the cryobiology room through a window positioned on the door access or other viewing mode (e.g., glass walls). No other work must be carried out other than those processes provided for the management of liquid nitrogen and its use, nor should the room be used for the deposit of other material; however, it may be permitted to use the space for the positioning of freezers with CO_2 or nitrogen backup and for freezing biological samples with control rate freezers (Fig. 2.1a, b).

2.4.2.1 Access Door(s)

The access to the cryogenic room must be through an access door whose net size must be larger than the size of the largest containers contained in the location. Devices must be provided to prevent the spreading of gas in liquid or gaseous phase outside through the access door, which must also be provided with an opening toward the outside by means of a panic bar to allow rapid evacuation of personnel.

If the room has another access opening, it must also have the same access opening characteristics.

The access door must not be equipped with a spring closing device.

Usually, the access door is fitted with a visual device made of secure material which allows the room to be viewed from the outside (Fig. 2.2).

Fig. 2.1 (**a**) Cryo-room view 1 (**b**) Cryo-room view 2

2.4.2.2 Flooring and Walls

The room must be equipped with floors and walls (at least up to a height of 1.80), with waterproofing characteristics which can easily be sterilized. The floor and the cladding must be connected to each other in such a way as to avoid accumulation of dirt and dust and must be covered with a low-temperature resistant material easily maintained.

The cryogenic room floor must be covered with a special resin resistant to liquid nitrogen spills. The surface of the floor must also be very hard and strong in order to support the weight of the liquid nitrogen tanks and also very smooth in order to ease movements of the liquid nitrogen containers. The floor must not allow pouring liquid nitrogen into sewers or technical nets (Fig. 2.3).

Fig. 2.2 Access Door with windows and warning signs

Fig. 2.3 Cryoroom Floor made with material resistent to LN2 spill

2.4.3 Requirements for a Cryogenic Room

The cryogenic room is classified as a hazardous area. Any spill of liquid nitrogen and/or liquid nitrogen vapor can cause clouds of low oxygen atmosphere, both being very dangerous for the personnel. Liquid nitrogen vapor, being heavier than air, accumulates in the area near the floor level, creating a cloud with low oxygen concentration.

2.4.3.1 Safety Systems

Monitor and Control System

Each cryogenic room must have a monitor and control system. The system must control the critical parameters of the cryogenic room (e.g., low oxygen levels, low level of liquid nitrogen in each container, low temperature in each mechanical freezer, environmental conditions such as temperature, humidity, and ventilation of the cryogenic room). Any of these conditions must signal an alarm to the authorized personnel, who will intervene 24/7 to analyze and fix the problem. Each alarm condition must also be recorded and discussed during the internal audits where preventive actions will be planned to avoid their recurrence. The monitoring and control system must record "continuously" the temperature of the LN2 containers and mechanical freezers, in order to follow freezing conditions over time of the biological material stored in each LN_2 container or ultra-low freezer (Fig. 2.4a, b).

The authorized personnel must be on call 24 h per day, 7 days per week in order to guarantee rapid and prompt intervention. The personnel authorized to work in the cryogenic room must be also trained to work with liquid nitrogen and to intervene in case of a low oxygen alarm condition (Fig. 2.5).

Access Control

Access to the cryogenic room must be controlled and limited exclusively to the authorized personnel. The cryobiological room must be equipped with a system for the monitoring and recording (history) of the accesses. A Standard Operating Procedure must be available which describes the terms and conditions for access to the cryogenic room of authorized personnel and external visitors under the responsibility of the Biobank Manager.

The personnel authorized to work in the cryogenic room must be qualified and trained to use an oxygen mask. This equipment must be placed outside of the cryogenic room and used by skilled personnel in case an operator is trapped in a low oxygen atmosphere area. Access to the cryogenic room is permitted only for two people at the same time. Both of them must carry a portable oxygen sensor. It is advisable that a third person will remain outside the cryoroom to intervene in case of emergency. If this precaution is not applicable, it is necessary to put in place

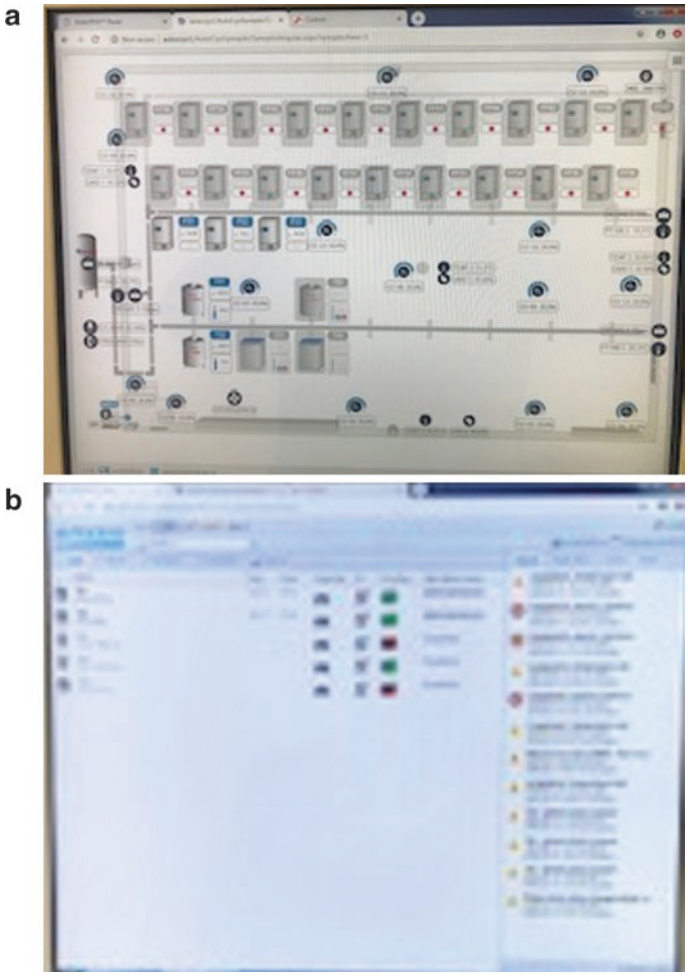

Fig. 2.4 (**a**) Monitoring and Alarm Systems Control Panel 1 (**b**) Monitoring and Alarm System Control Panel 2

alternative solutions that guarantee the safety of operators. Outside the cryogenic room must be an emergency kit consisting of self-contained breathing apparatus, preferably two-way (also to be assessed on the basis of risk assessment), gloves cryogenic, cryogenic apron, visor or goggles, and possibly cryogenic overshoes. These devices are located in a specially designed area identified. These devices must be periodically maintained and checked according to the specifications of the supplier (Fig. 2.6a, b).

Fig. 2.5 Alarm system workflow

Fig. 2.6 Oxhygen Mask position outside of the Cryoroom

Video Surveillance and Presence Detection System

The installation of video surveillance and presence detection system is recommended according to the Privacy laws. If the video surveillance system is considered excessive, it is necessary to set up a procedure that prevents the risk of health emergencies related to the sub-oxygenation of the cryogenic room.

Oxygen Detection

There must be environmental oxygen detectors (sensors) in the room that monitor the continuous concentration of oxygen inside. These detectors must be placed at a height not exceeding 1.2 m and in any case at a lower height to the respiratory tract of authorized personnel. These detectors, calibrated according to maintenance indicated by the manufacturer, must be located in less ventilated areas, close to the passage points, away from sources of steam and air intakes. The detection unit must allow the visualization of the values and of the oxygen concentration detected by the sensor(s) and must be positioned outside the hall, in the immediate vicinity of the entrance so that control takes place in a safe area. It is essential that an adequate number of detectors defined according to the configuration and volume of the room and according to the type and characteristics of the sensor. It is recommended to install at least one detector for every 50 m^3. The detectors must comply with the relevant standard in force and periodically be maintained according to the supplier's instructions.

The system must have at least two alarm thresholds, one at the concentration of oxygen at **19%,** the other at **18%**. If the percentage of oxygen detected falls below these thresholds the system must provide for the activation of an optical-acoustic alarm either inside the room and outside. In addition, the alarm must activate a forced ventilation system in the room and, at reaching the 18% oxygen threshold, should also involve closure of the vacuum line root valve, where present and the interruption of supply of nitrogen in case of an automatic filling system. The forced ventilation system must also be able to be started manually by an operator. An alarm repetition (remote control) must be foreseen, at least for the second alarm threshold, or in a location (Call Centre) operative 24/7 that allows to warn the staff in charge and possibly the emergency services and/or to health care or directly with the operators. The acoustic alarm systems and visual surveillance systems, the operation of the probes, and forced ventilation must be controlled and verified periodically.

A manual or computerized monitoring system must be set up for following the levels of nitrogen and temperature of each container, according to a procedure or instruction operational defined. The recording of these monitors must be available.

The oxygen sensors must be connected to a UPS (Uninterruptible Power Supply) line and to an electric line connected to an emergency generator, in order to function during a major electric power failure (Fig. 2.7a, b).

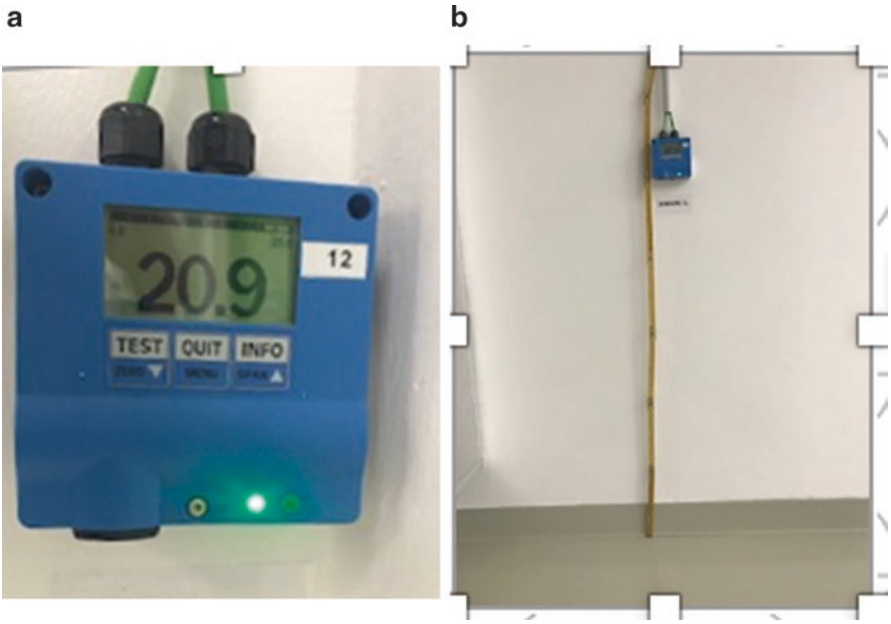

Fig. 2.7 (**a**) Oxygen sensor (**b**) Oxhygen sensor position

Ventilation and Environmental System

The cryogenic room must be equipped with an air treatment system able to control and maintain the temperature values between 18 and 25 °C to avoid condensation on the coldest parts of the cryogenic and ice deposition plant inside the storage tanks and humidity between 45–50% ± 5%, depending also on the seasonal period.

The ventilation system shall have an autonomous air intake and extraction system which need to ensure an adequate exchange of ambient air and avoid nitrogen accumulation. The ventilation system must be "full external air" type therefore without recirculation of the air taken from the environment and must ensure at least 6 air exchange/hour in "normal conditions" and 25 air exchange/hour (in any case not less than 20), in case of "alarm conditions."

It is of fundamental importance that the air intake takes place from above while the extraction takes place from below. The air extraction grille must be positioned preferably at a height of 10–15 cm from the floor. The mechanics of the system must be positioned in such a way as to prevent it from freezing in the event of abnormal leakage of nitrogen (Fig. 2.8a, b).

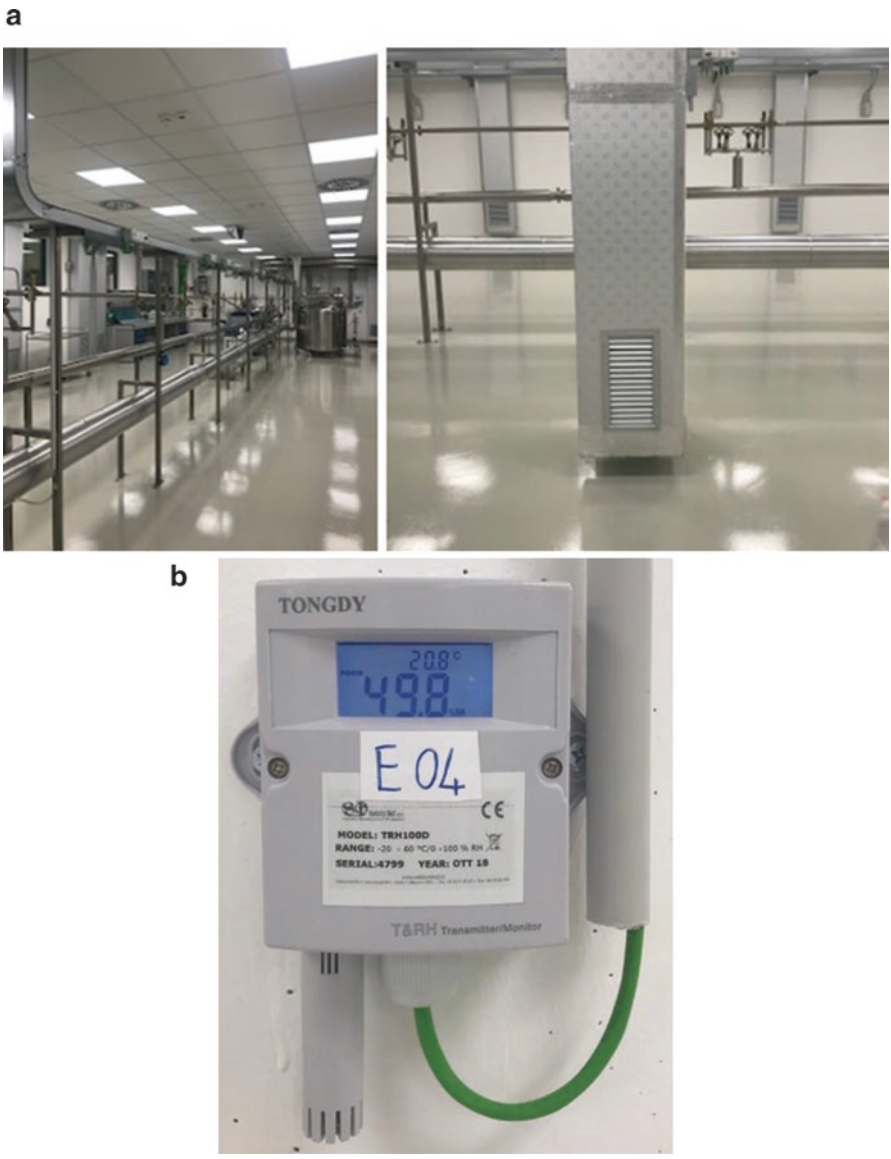

Fig. 2.8 (**a**) Cryo-room ventilation System Intake from top - Exhaust from Bottum (**b**) Temperature and Humidity sensor

Security Signs

At the entrance of the cryogenic room, signs must be displayed that indicate that the storage room is classified as dangerous: (1) sign of danger area: liquid nitrogen inside; possible low oxygen concentration; danger frostbite (2) sign requiring the wearing of personal protective equipment; (3) sign of warning: "In case of activation of the optical-acoustic alarm leave immediately the room and close the access door"; (4) prescription sign: "Inside of this room are permitted only operations of freezing and storage of biological material" (5) biohazard sign, etc. (Fig. 2.2).

Smoke Detection Systems

A fire detection system must be installed that can detect and report the presence of a fire inside the Biobank. A detection device smoke and fire are typically made up of electronic equipment that detects smoke and fire presence of smoke or variations in heat or the principle of fire. The anti-fire system must be remote-controlled and managed 24/7 (Fig. 2.9).

Fig. 2.9 Smoke sensorsr

Electrical and Lighting System

Natural and artificial lighting must comply with the National Electric Standard and regulations. An external switch must allow the internal artificial lighting to be switched on.

The power supply of the various types of equipment present in the cryogenic room must be insured, by adopting one or more general electrical panels, located outside the room, equipped with electrical power lines to guarantee separate lines for (a) Lights; (b) LN2 containers and/or mechanical freezers; (c) Other power appliances (video surveillance system and other accessories); (d) Uninterruptible Power Supply (UPS); (e) Emergency Generator; (f) Air treatment system; and (g) Oxygen monitoring system.

2.4.4 Technological Features of a Cryogenic Room

2.4.4.1 Storage Tanks and Liquid Nitrogen Supply

The liquid nitrogen distribution pipes must be vacuum pipes specifically designed for the purpose and must have safety valves that close automatically, in case of a low oxygen alarm in the cryogenic area, or in case of any malfunction or dangerous situation. Normally the liquid nitrogen reservoir is positioned outside the building as close as possible to the cryogenic room, and must be accessible by a trailer truck, and must have all safety features including the safety valve. The efficiency of the LN2 distribution system depends on the number of cryobiological containers, their size, their location, and distance from the nitrogen external tank. The LN_2 high-capacity tank must be placed outdoors, in an open-air fenced area with easy access to vehicles for refueling. It is strongly recommended that the tank is positioned in an area away from normal traffic routes and properly signed. The access to the tank must be limited exclusively to the authorized personnel. It is necessary to have an emergency stop button, located near the tank, in order to be able to stop the transfer of liquid nitrogen if needed. If the refilling of the cryogenic containers is done with pressurized containers, these must be placed in a dry and ventilated location, protected from atmospheric agents, away from heat sources, protected from fire risks. Even if the supplier owns the tanks, it is essential that the personnel has adequate knowledge of every aspect of its use system, and in particular the exact arrangement of the valves and switches in order to be able to close the tanks in case of emergency.

2.4.4.2 Liquid Nitrogen Distribution System

Cryogenic containers are usually connected to liquid nitrogen distribution system (vacuum stainless steel) with an automatic refueling system. The stainless steel pipes must be labeled to highlight the presence of liquid nitrogen and the direction

of the flow. Inside the cryogenic room, connections must be provided on the vacuum line, including cryogenic and safety valves, conveyed to the outside, for the connection of the cryogenic containers. The maximum pressure of the liquid nitrogen inside the pipes, must not exceed the maximum pressure indicated by the manufacturer of the cryogenic containers. The line must also be equipped with safety devices (safety valves or rupture disks) as described in the technical specifications to avoid any risk of explosion. In the case of insulated or vacuum distribution lines of considerable length, it should be equipped with an open-air vent valve (vent valve) position in the bottom of the line with external coating, for the removal of nitrogen vapors during the cooling of the line itself. All manual valves used on the line must be suitable for cryogenic applications. Distribution lines must not constitute a source of danger and must be prevented from being the source of formation of hazardous gas atmospheres as a result of leaks and ruptures, which can cause leakage and stagnation. They must be inspectable. At the beginning of the line must be installed a by-pass system with a solenoid valve. A planimetric representation of the piping system must be available with highlighting of the interception systems (Fig. 2.10a, b).

2.4.5 Equipment

2.4.5.1 Cryogenic Containers

The cryobiological container is a type of equipment capable of storing biological samples under controlled temperature. Various types of cryobiological containers are available: Liquid Nitrogen Tanks (−196 °C); Liquid Nitrogen Vapor Tanks (−80 °C, −155 °C); Mechanical Ultra-Low Freezers (−80 °C, −150 °C); Cold Rooms (from −20 to −80 °C); Automatic Storage Rooms (−80 °C); Liquid Nitrogen Vapor Freezers (−155 °C); etc.

The choice of the type of container must be made according to the characteristics of the biological material to be cryopreserved, the number of samples to be stored, and the characteristics of the cryogenic room and liquid nitrogen refueling system.

Liquid Nitrogen (LN_2) Containers

Biobanks should have a number of cryogenic containers, compatible with the structural characteristics of the room and connected to an automatic LN_2 filling system. The number of LN_2 containers must be compatible with the design specifications of the distribution system and the presence of containers in series. Cryogenic containers must be subject to control in accordance with the current standard and according to a specific maintenance plan. The containers must be equipped with racks according to the type and dimensions of the vessel (bags, cryo box, cryotubes, etc.) that hold the biosamples, allowing adequate protection and traceability during storage

Fig. 2.10 Liquid Nitrogen external vessel

and adequate protection of the samples during storage. Manual or automatic detection and recording systems must be provided, nitrogen levels and temperature of each cryobiological container. In both cases, such monitoring must be continuous and the storage/recording of data at the maximum every 4 h. The definition of container filling levels and values of the storage temperature must be subject to validation protocols, for the maintenance of the morphological, biological, and functional characteristics of the samples preserved. The alarm systems must be set up in case of deviation of the values measured with respect to the defined standard. Smaller tanks that are not connected to an automatic refueling system are subjected to manual control as specified by the relevant SOPs.

Manual Filling of Cryobiological Containers

In case of manual filling of liquid nitrogen, it is necessary that the container is empty and contains only nitrogen, not water or other cryogenic liquids. It is possible to use a funnel to transfer the liquid into a smaller container. It is recommended to use a transfer tube to extract the liquid or a pressure tapping system. Manual filling operations must be carried out in the cryogenic room or in any case in an adjacent room with the same security features. At least two operators must be present in the room, use PPE to avoid eyes and skin to get in contact with liquid nitrogen, cold tubes, or cold gas.

Handling of Cryogenic Containers

In the event that it is necessary to move cryogenic containers within the structure, attention must always be paid to unintentional releases of emissions of cold vapors from the containers, which may cause progressive gas accumulation in the environment by reducing the oxygen content of the air. If the move of the container requires elevator lifts, it is necessary that the containers, in particular for those of considerable capacity, are moved in the absence of personnel. Narrow and closed lift can quickly saturate creating serious danger to personnel. When moving the container use the appropriate handles or trolleys. Do not attempt to lift the container by yourself, but possibly get some help from a second operator. The transport container must be equipped with a safe gripping system and a suitable lid.

2.4.5.2 Mechanical Ultra-Low Freezers (−80 °C)

The Biobank shall have a number of Mechanical Ultra-Low freezers, compatible with the structural characteristics of the room itself and connected to an automatic LN_2 or CO_2 backup system. The number of Mechanical Ultra-Low freezers must be compatible with the design specifications of Electric Power; Ventilation Systems; and the LN_2 or CO_2 backup system. If the Ultra-Low Freezer does not have either a LN_2 or CO_2 backup system, they must be connected to the Emergency Generator. The Ultra-Low Freezers must be subject-specific maintenance plan. The characteristics of these Ultra-Low Freezers, how to use them, and their maintenance must be specified in the manual of use and maintenance of every single device. The Ultra-Low Freezer must be equipped with racks according to the type and dimension of the container (bags, cry box, cryotubes, etc.) in which the biosample is stored, allowing adequate protection and traceability of the samples during storage. Manual or automatic detection and recording of the temperature of each Ultra-Low Freezer must be provided and recorded at least every 4 h. The Ultra-Low Freezers and values of the storage temperature must be subject to validation protocols according to the morphological, biological, and functional characteristics of the samples

preserved. Alarm systems must be set up in case of deviation of the values measured with respect to the defined standard.

Check and cleaning procedures for air filters and ice formation inside of the doors of the freezers must be part of the maintenance plan.

2.4.5.3 Automatic Storage Systems (−80 °C, LN_2 Vapor −155 °C)

Biobanking storage technology evolved in the last 10–15 years with the development of several automatic storage systems which improve traceability, faster and precise storage/towing of biosample; steady temperature over time; space reduction, etc.

Installing Automatic Storage Systems requires an overall improvement of the Biobank design (structural characteristics, logistics, electric power, backup systems, monitoring and control systems, etc.) and needs to make significant advancement of the Biobank workflow, which requires significant effort in interfacing the Biobanking LIMS with Automatic Storing Systems software.

Automatic Storing Systems are suitable for Large Biobanks where management and distribution of a large number of biosample, or for Specialized Biobanks (e.g., Tissue Bank Stem Cell Banks, etc.) where traceability and steady temperature over time is fundamental. In these cases, smaller Automatic systems are suggested (Fig. 2.11a–c).

2.4.5.4 Cold Chain Monitoring and Control

The cold chain must be monitored and controlled 24/7 and recorded by the Monitoring and Control system. In particular, the temperature of all Liquid Nitrogen Containers and the Ultra-Low Freezers should be controlled with two independent temperature control sensors so that if one temperature sensor brakes, the other loop is monitoring the temperature (Fig. 2.12).

2.4.6 Personal Protection Equipments (PPE)

PPE must be used when risks cannot be avoided or sufficiently reduced by technical prevention measures. Personnel must use these devices, take care of them without making changes, reporting any defects or inconveniences encountered. The use of some PPE is required for training and education purposes. Each PPE must be accompanied by the required documents (declaration of conformity by the manufacturer, CE marking, information note issued by the manufacturer). The Liquid Nitrogen Safety Data Sheet provides an essential indication of PPE that must be used when handling liquid nitrogen. Likewise, the user and maintenance manual for the purchased equipment specifying which PPE is required. For the entire time, all operators are obliged to wear the PPE when handling liquid nitrogen.

Fig. 2.11 (**a**) 196°C Robotised Cryogenic Container (Brooks Biostore) (**b**) 80°C Robotised Cryogenic Cotainer (Brooks Biosotre) (**c**) Cryovilas loading system for Storing Room (**d**) Automatic -80°C Storing room (Brooks SampleStore) (**e**) 196°C Robotised Freezer (Angelantoni SmartFreezer)

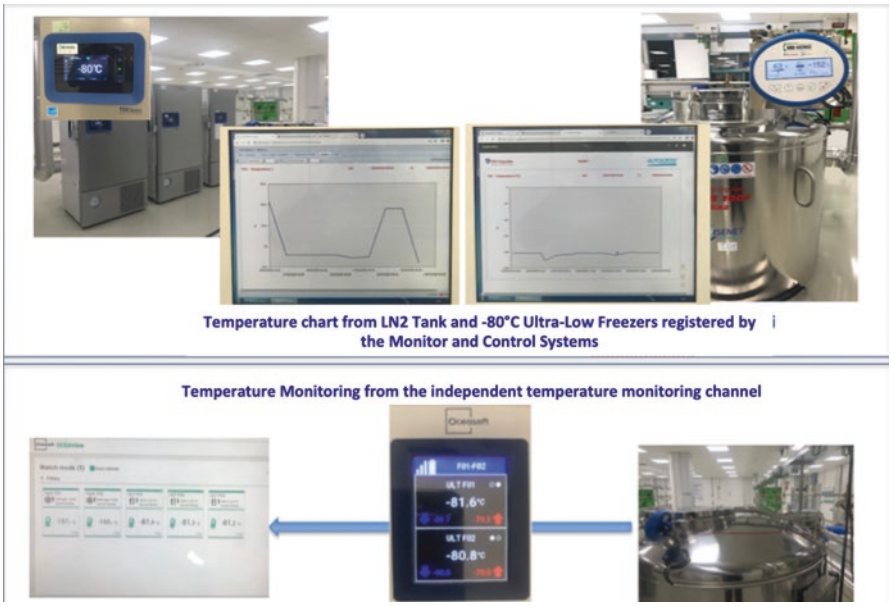

Fig. 2.12 Cold Chaim monitoring and control system

2.4.6.1 Hands and Arms Protection

Long gloves, made of specific and suitable fabric, must be worn in order to protect hands and arms. The gloves must fit broadly so that they can be quickly removed in case the liquid enters inside of the gloves. They must be checked before being used and inspected for damage or contamination (cuts, punctures, discolored spots, etc.). The gloves must be worn over the sleeves of the shirt, to avoid that drops of liquid fall on the shirt; moreover, they must be removed before resuming any other activity. The type of gloves and specifications for their use should in any case be detailed in a specific SOP.

2.4.6.2 Eyes and Face Protection

In case of particularly dangerous operations, situations which may give rise to splashes or, in any case, to penetration of substances through the eyes or the skin of the face, it is essential to use safety goggles with side shields (according to EN 166), better a visor or facial screen that protects the entire face.

2.4.6.3 Body Protection

For precaution, always wear trousers on the outside of boots or shoes. Generally, sandals or other **open-toed shoes are prohibited**. For special processing, including manual topping, which involves the exposure of the whole body at very low temperatures, protective aprons may be used or, in cases where more problematic, specific protection suits or gowns. It is strongly recommended to use cryogenic overshoes during manual filling operations, especially for small containers. Wear overalls or gowns, preferably without pockets.

2.4.7 Rules of Conduct

2.4.7.1 General Rules of Conduct which Must Be Adopted in a Cryogenic Room

Activities involving cryogenic fluids must be reserved only for those who have received adequate information and training on the correct procedures to be followed. All operations must be carried out according to SOP.

2.4.7.2 Specific Rules to Be Adopted in a Cryogenic Room

Below is a non-exhaustive list of specific behavioral norms of prevention:

- Always handle liquid nitrogen with utmost caution.
- Keep the container open for as short time as possible to avoid the danger of condensation and gas formation.
- Do not touch pipes and containers containing liquid nitrogen without PPI. There is a danger of skin burn.
- Do not pour unused liquid nitrogen into drains or on the floor; use only hot water to release frozen valves.
- Wear suitable PPE.
- Collect long hair behind the back of the neck.
- Always keep at a safe distance from boiling or splashing nitrogen and gas.
- It is advisable to use high or sufficiently closed shoes.
- When handling liquids in open containers take care not to spill them. Always wear trousers on the outside of the shoes.
- Always carry out the filling operations of a container or immersion of uncooled objects in the liquid in order to minimize boiling and splashes.
- Always use pliers with a secure grip to submerge or pull out objects immersed in cryogenic fluid, never use the hands.

- Avoid filling the containers beyond the safety level; excess liquid increases the evaporation rate and the danger of overflow during transport.
- To transfer full containers always use appropriate means (e.g., trolleys) and do not accompany them in the lift.
- Always remember that objects normally soft and foldable at room temperature environment become extremely hard and fragile at the temperature of these liquids.
- Avoid working alone during activities involving the use and/or the use of the liquid handling of liquid nitrogen.
- Warn colleagues before carrying out any operation particularly dangerous.
- Do not approach areas where hazardous operations are carried out if it is unnecessary.
- Respect all safety signs.
- Do not keep in the cryobiological room what is not strictly necessary for carrying out the activities (e.g., personal effects) and in particular bulky material or easily combustible.
- Do not use tubes to measure the level of liquid nitrogen (chimney effect).

2.4.7.3 Emergency Procedures

The availability of emergency operating procedures on possible expected accidental events is an indispensable protection system against associated risks on the use of cryogenic fluids; these procedures must be available and known by all workers.

To prevent emergency situations or allow problems to be resolved quickly it is essential to be able to recognize the signals that precede a failure in the system of containment. These can be:

- High pressures are indicated on the control pressure gauge.
- Unexpected frost formation on the containment system.
- Poor or abnormal venting in the containment system.
- Alarms indicating low oxygen levels in the work area.
- Unusual noise or absence of normal venting noise.

The typical signals of the release of a large amount of vapors due to evaporation of the cryogenic fluid are an increase in background noise and the formation of a plume of white fog. In this case, although the danger of under-oxygenation especially in poorly ventilated premises is never to be overlooked, generally the most harmful event probable is contact with gas or liquid at very low temperature with the consequences previously mentioned. In the event that the release is not large, for example, from a dewer of small size, it may be sufficient to transport the container outdoors and let the vapors escape into the atmosphere.

2.4.8 Information and Training

The Management of the Biobank, in collaboration with the Quality and Safety officers, has the obligation to provide adequate training for all operators working in the cryogenic room, including students, trainees, scholarship holders, guests, and other unstructured personnel. Training must be given in relation to the activities carried out, and the objective is to inform and train everyone on aspects such as risks related to the workplace and tasks; the possible damage resulting from the use of dangerous equipment or substances without due precautions; the prevention and protection measures to be implemented in each specific situation; fire-fighting measures and escape routes; emergency plan; and how to ensure the correct application of prevention and protection measures by all visitors to the cryogenic room itself.

2.5 Remote Storage

It is advisable that for renewable biospecimens (master and working cell lines, etc.) a biobank stores part of the stock (e.g., duplicates) in three different locations. (e.g., if the Biobanks generates 20 vials of one cell line, will store 12 vials in one cryogenic container; 4 vials in different containers in the Biobank; and the rest of the stock in a different accredited Biobank located 20–30 km away from the main location).

The Biobank can also be a reference to other Biobanks which will have the same needs.

2.6 Disaster Plan

A very important requirement for a Biobank is to establish a "disaster plan," which defines the actions to put in place in case of an unexpected "major disaster" (power failure, fire, flood, earthquake, etc.).

The disaster plan should consider the following aspects:

- ***Risk assessment of the Biobank Infrastructure*** for liquid nitrogen supply, electric power supply (also considering the emergency generators loads), environmental adverse events (historical statistics for floods, earthquakes, airplane disaster, etc.).
- ***Partner with a "Certified" or "Accredited" Biobank for support in case of a major disaster***. The choice of the partner biobank is very important and should follow a risk analysis looking at the following factors: (a) structured and certified biobanking infrastructure; (b) availability of free space to accommodate, in case

of major disaster, additional LN_2 containers and −80° Ultra-Low Freezers to be relocated from the original biobank; (c) sufficient liquid nitrogen and electric power supply; (d) low risk for environmental factors (flood, earthquake, tornados, etc.); (e) Biobanking LIMS for traceability; and (f) other factors.

- ***Agreements with specialized movers*** that have adequate equipment (e.g., trucks with electric supply), in order to have the possibility to refill the LN_2 containers and electric supply for the −80 °C ultra-low freezers during the transport of the cryogenic containers from one biobank to the other. It is also important to have the proper vehicle and transport authorization to transport tanks full of liquid nitrogen, etc.
- ***Understanding of local regulations to transport liquid nitrogen containers.*** Discuss and plan with local authorities with respect to the rules and regulations to follow during the move.
- ***For new Biobanking infrastructures***. Assess the local risks as indicated above and consider infrastructure solutions (e.g., building constructed to be earthquake-proof, cryogenic room located on the first floor, limit damage in case of a major adverse event such as basement flooding).

2.7 Process Laboratories

A Biobank is also characterized by the types and quality of the process/service able to perform. The process laboratories can be part of the Biobank as service unit, or part of the Hospital/Research Center where the Biobank is located.

The Process Laboratories are important to guarantee the highest quality of the biospecimen stored and distributed but must also be used to develop new procedures and standards to improve the quality of the biological material and shared with the Biobanking scientific community.

The types of Services and Laboratories can be identified according to their specialities:

– **Tissue process Laboratory:** dedicated to store frozen tissues (deep freezing technology) which will be stored in mechanical freezers at −80 °C.
– **Molecular Biology Laboratories**: dedicated to the quality control of the biomaterial, for example, nucleic acid purifications (DNA, RNA, microRNA) in addition to proteins that can be stored in mechanical freezers at −80 °C.
– **Cell Biology Laboratories**: dedicated to the establishment and immortalization of primary cell lines, eventually stored in LN_2 liquid at −196 °C or − 155 °C in LN_2 vapor tanks.
– Depending on the type and focus, the Biobank can have additional process and service laboratories such as:
– **Sequencing Facility**, usually for human biobanks or personalized medicine applications.

- **Tissue Microarray Core facility**, for tissue banks, which also store pathology archives, usually comprising paraffin-embedded tissues.
- **Other Core Facilities/Services complementing the "omics" platforms**.
- **Induced reprogramming adult stem cells and quality control Core facility**.

- The laboratories associated with biobanks are important for the processing of biological materials (such as whole blood) into derivatives such as buffy coats, plasma, cell lines, and nucleic acids. Laboratories are also involved in performing the quality control procedures in order to guarantee the integrity of the biological material stored and distributed and are also very important for offering services to the scientific community which may contribute to the recovery of costs of the Biobank operations.

In addition, considering the technological and scientific advancements of "Biobanking Science" the Biobanks shift their focus toward Personalized Medicine; Regenerative Medicine; Stem Cells and iPS; and most recently toward the generation and banking of 3D Organoids/Spheroids, which are used by the pharmaceutical industry for drug discovery research.

These shifts will require a change in the skills of the personnel of the Biobank and an expansion of the quality control procedures which will be used to characterize the biological material distributed.

The access to the laboratory must be controlled (with badge or other systems) and registered. Visits inside the laboratories should be discouraged. One solution, to avoid visitors entering inside the process areas, is to build the laboratory with large windows, and build corridors in the perimeter of the laboratories in order for visitors to have the possibility to view the activities in the process areas without entering them.

All the critical instruments should be connected to the electric power emergency line and/or to a UPS (Uninterruptible Power Supply) line.

2.8 Biobank IT Infrastructure

The IT infrastructure is one of the most important investments for a Biobank but is frequently overlooked and underestimated.

The choice of the Biobank Management Information System (LIMS) is not trivial (homemade or commercially available) and can be a very important part of the budget for the implementation of the Biobank and its efficient operation. It is important not to underestimate the effort of implementing the LIMS and the improvements that will be required during the years of the operation of the Biobank.

One other important aspect is the investment and effort required to store the data associated with the biospecimen, which are increasing exponentially considering the requirements of associates genetic data (e.g., sequencing data) and/or pathology images (which require large storage facilities). Backup and safety measures must also be planned and implemented.

It is also important to verify the risks and opportunities for the new technology (such as cloud computing) available today which will be improved and be used on a widespread basis in the near future.

The LIMS should have the capability to manage each step of the biospecimen life cycle including the administrative and financial aspects, which are important for the sustainability of the BRC.

The Biobanking LIMS must be able to manage the following aspects:

2.8.1 Clinical Data Management Information System

It is well known that biospecimens with associated high-quality clinical data are of great value and that biospecimens with no associated clinical data are generally less valuable. Therefore, the LIMS which will be implemented must be able to capture and manage clinical data, which needs to be associated with the biospecimen. This is not a trivial task, since the clinical data are usually stored in different sources (paper records, spreadsheets, clinical databases, etc.), often with different annotations/classification methods for the same disease.

The Biobank coordination center should define a minimum data set to be associated with each type of biospecimen and disease, in order to define a standardized LIMS module where the operators can upload the clinical data associated with the biospecimen in the correct format. Automated forms of data transfer are also possible and dependent on the organization of the collection site database and the relationship with the Biobank.

Biobank Management Information System (LIMS) should have the capability to track each phase of the biospecimen life cycle, from collection to distribution:

- **Biospecimen collection** (at donor collection site). The technician, at the collection site (usually a trained nurse), following specific SOPs, will obtain from the patient or donor minimum data set of clinical data and will place the biospecimens in bar-coded container (cryotubes, tissue cassette, etc.) which after being scanned will be up-loaded in a specific web page in the Biobank LIMS. After the biospecimen containers will be packaged and shipped to the Biobank site according to the specific SOP.
- The system should also have a specific section where to insert information relative to the shipping kit and the courier's tracking number. The LIMS will follow the shipment and send an email to the central biorepository with the information of the shipment.
- **Accessioning**. Upon arrival, the shipping kit will be accepted by a dedicated operator, who will upload the bar codes of the material received. The LIMS will check automatically if the biospecimens shipped are the same as the biospecimens received and generate an acceptance report or a rejection report in the event of a discrepancy. On the acceptance report, there is information such as shipping

date and time, high and low temperatures during the shipment, and delays at customs.
- According to requirements of the accessioning SOP for the specific project, which specify the intended use of each biospecimen collected, the tubes/containers will be transferred to the:
  - **Cryostorage room,** if the biomaterial received (e.g., frozen tissue, plasma, urine, PaxGene, etc.) does not need to be processed.
  - **Pathology Archive,** if the paraffin-embedded tissue blocks need to be archived.
  - **Molecular Biology Laboratory,** if the biological material needs to be processed (e.g., DNA purification from whole blood, saliva, etc.)
  - **Cell Biology Laboratory**, if the biological material needs to be processed for the establishment of primary or immortalized cell lines.
  - **Other destinations**, according to the relevant SOPS.
- **Processing of Biological material**. Each process for biological material must be performed according to a specific SOP. Each SOP will describe, for each biological material derived, the quality control or characterization data which must be uploaded into specific webpages available on the LIMS.
- It must be possible at each moment to track and verify a single process, progress, and any other problems. The LIMS will also periodically produce statistics (average time for each process, problems, etc.), which are to be discussed during the internal audits and generate corrective actions.
- **Inventory Management System.** The LIMS must incorporate an "Inventory Management System" to manage and track (via bar codes, radio frequency identification (RFID), or other identification methods) the biospecimen from the time of collection to the generation of derivatives (as a result of processing), to the final location storage container (LN_2 or Ultra-Low Freezer), minimizing the possibility of errors.
- **Storage facility**. The biological material can be stored at different temperatures (−196 °C in LN_2 Liquid Container; −155 °C in LN_2 Vapor Container; −80 °C Ultra-Low Freezer, −40 °C, −20 °C, +4 °C, and room temperature). The inventory system (embedded in the LIMS System) should guarantee the tracking of each biospecimen aliquot in its storage location. In some cases, for the same batch of samples different aliquots could be stored in different locations.
- The LIMS should also be interfaced with the monitor and control system in order to record alarm and storage conditions which must be associated with each specimen stored over time.
- **Quality Control**. Specific efforts must be dedicated to record the quality control data associated with each biospecimen stored and/or retrieved. Quality control data are not only the result of specific procedures (e.g., cell line viability, 260/280 nm ratio for DNA purity, etc.) but also the temperature of storage over time, and pre-analytical data if available. Quality Control reports should always

be available (via web) and accompany the biospecimen when distributed. In some cases, the QC reports are transmitted in the datasheet when the biospecimen is shared/distributed.

– **Distribution**. The possibility to distribute "high quality" biological material makes the difference between a Biobank and a Repository. The LIMS plays a very important role in tracking all phases of the distribution process, which starts with the request, authorization, retrieval of biomaterial, shipping, and invoicing. These administrative functions are very important for the sustainability of the Biobank.
– **The LIMS system should implement the following online functions**:
  - **Web-catalog**, with the list of the biomaterials stored and associated clinical data ready for distribution.
  - **Browse function of the web-catalog**, with the possibility to filter the biospecimen types and access the data (clinical and biological data) associated with the biospecimen.
  - **Requesting biospecimens**. This includes the possibility of accessing a web browser which will enable the researcher to browse for several parameters: demographic data (name, institution, etc.); informed consent (yes/no); clinical data (disease, follow-up, etc.); biological data (QC parameters); and number of biospecimens available. After the identification of the biospecimens needed, the researcher can fill a specific webpage (where it will be possible to upload the list of biospecimens needed) and fill in additional information such as name and institution information, abstract of the scientific project with a statement of the intended use of the biospecimens.
  - **Approval process:** This should also be managed online, where on a specific webpage the custodian of the biospecimens can follow the number of pending requests, can approve requests, or can ask for more information from the requester concerning the project and intended use, or can deny the authorization. At the same time, the requester and the biorepository manager can follow the approval process. After approval, the LIMS will send a work order to the biorepository with the authorization to retrieve and ship the material to the requester, according to conditions specified by the Material Transfer Agreement (MTA) (Fig. 2.13a, b).

2.9 Logistics and Services

The logistics and services units are as important as the other units since they keep the Biobank in functional order. In the following, there is a list of service units which may be part of the Biobank, according to its specific mission [16]:

1. **Collection Kit preparation**. Each project will have its specific collection needs, which requires the design of a specific collection kit. Usually, the collection kit includes (1) the appropriate collection vessel (e.g., Vacutainer for blood) with

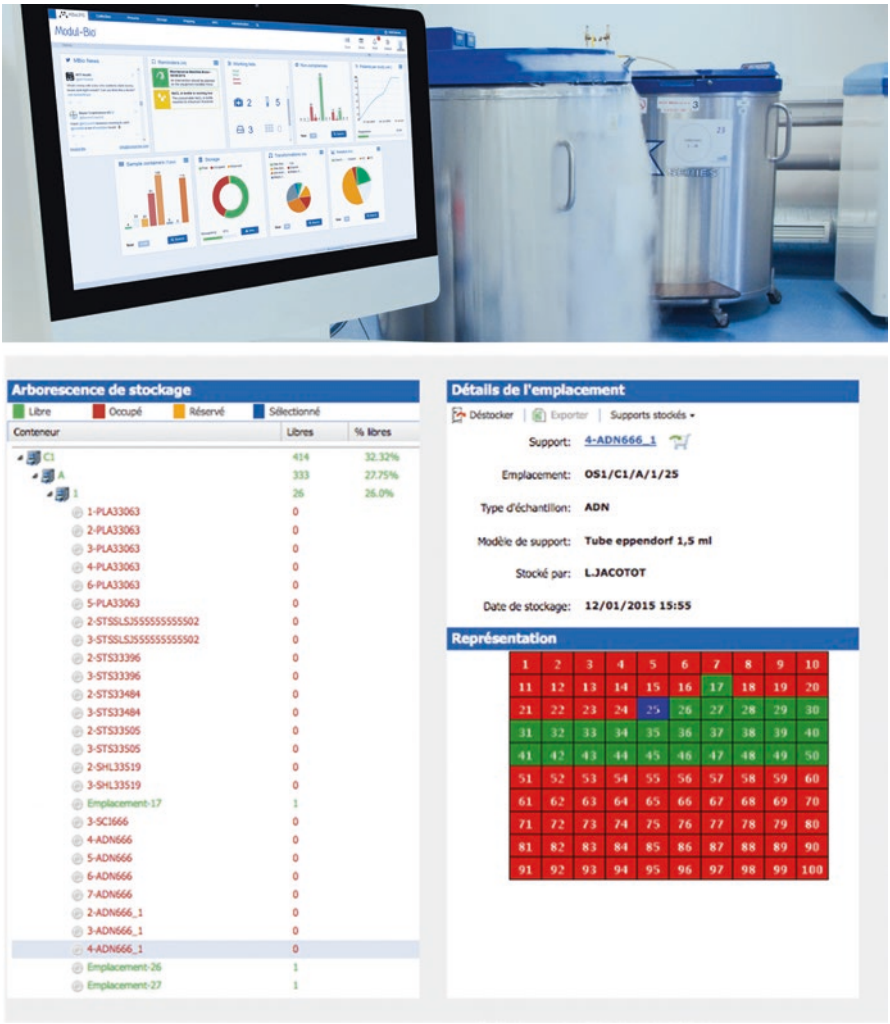

Fig. 2.13 Biobanking LIMS screen shot

specific reagents (e.g., EDTA, ACD, PaxGene, etc.) according to the type of the biological material and process (e.g., ACD for DNA extraction, PaxGene for RNA extraction, etc.); (2) a butterfly needle for standardization of blood collection; (3) Packing instruction; (4) shipping material (carton box, packing materials according to ADR or IATA regulations); and (5) preprinted shipping labels. The use of a preassembled collection kit will prevent errors during the collection of the biological material and will ensure use of the proper International Air Transport Association (IATA) shipping container, avoiding delays during the

custom authorization process. Shipping biological material across international borders can be very difficult. Therefore, in order to avoid problems, the biobank must provide the collection sites with a shipping container prepared according to the IATA regulations [11].

2. **Sterilization process.** In order to control contamination problems, several biobanks use glassware, which needs to be sterilized. It is well known that the sterilization process is very important but also very costly. If sterilization is necessary it needs to be well planned for, with sufficient room, equipment, and skilled personnel, with the possibility to expand.
3. **Media preparation Laboratory**. If the biorepository is specialized in the establishment of cell lines, the media preparation laboratory is a very important service unit. It must be built as a BSL2 laboratory [9, 12], with cold and warm rooms (to store the media) and managed by skilled personnel specialized in media preparation.
4. **Shipping/Distribution unit**. After receiving the approved work order and the biomaterial from the process laboratory (which will supply not only the biospecimen but also the QC report or datasheet) the shipping unit will prepare the material to be shipped in specific IATA approved containers for **room temperature, dry ice or liquid nitrogen vapor shipping.**
5. **Administrative/Financial Unit**. The LIMS, automatically, should also send to the requester, the invoice with the cost recovery price for the biomaterial shipped. This step is important for the sustainability of the Biobank and for the ability to recover some operative costs. However, the ability to recover costs is dependent on the local institutional rules and/or government regulations.

2.10 Conclusion

A Biobank is defined as an actual or virtual entity that is organized to receive, process, store, or distribute specimens and associated clinical data in support of a research or clinical study or multiple studies.

The mission of the Biobank should address the specific purpose for which the Biobank is constituted. The mission shall be reviewed over time to ensure that it is still appropriate for the needs of the Scientific Community considering that the surrounding conditions (e.g., technological advancement; social and political environment; public health, etc.) may require a change or adaptation of the Biobank to the new needs (e.g., Covid-19 pandemic [10]).

It is important that the equipment, facilities, staffing, and funding for the Biobank be established according to a structure that will support the mission and activities during the anticipated lifecycle of the Biobank. Policies must be created, enforced, and reviewed on a regular basis concerning specimen access, handling, destruction of samples, and the potential for the termination of the Biobank.

The availability of high-quality biological and environmental specimens for research purposes requires the development of standardized methods for collection,

long-term storage, retrieval, and distribution of specimens that will enable their future use. This approach requires the implementation of a Quality Management System (QMS), certified according to ISO 9001-2015 [4] standard and/or accreditation to ISO 20387:2018 [6] or College of American Pathologists (CAP) [5]).

The Biobank infrastructure needs to be designed and implemented with state-of-the-art technologies, to ensure the highest safety and operational standards and with the objective to be operative for periods up to 20–30 years and managed and operated by "structured" high skilled personnel. The commitment of the institution is critical to achieving this goal.

The technology which will be implemented (e.g., liquid nitrogen, mechanical freezers, processing equipment, etc.) must be selected to meet both present and future needs. Choices between manual and robotized equipments must be made, looking at future requirements and the possibility to improve the quality of the biospecimens. Backup systems (electrical and LN_2), remote backup, disaster plan, and sufficient space to expand are also mandatory for correct implementation and management of a Biobank.

The Process Laboratories are important to guarantee the highest quality of the biospecimen stored and distributed but must also be used to develop new procedures and standards to improve the quality of the biological material and shared with the Biobanking scientific community.

The Biobank must also be part of International Biobanking Societies and Networks (e.g., ISBER, ESBB, BBMRI, etc.) and have in the scope the goal to share the biological material collected, processed, and stored with the highest quality standard.

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