Rules of Good Practice Relating to the Collection, Preparation, Qualification, Treatment, Preservation, Distribution, and Delivery of Milk on Medical Prescription by Milk Banks (lactariums)

Preamble

· This text aims to define the rules of good practice regarding the collection, preparation, qualification, treatment, conservation, distribution, and dispensing of breast milk to ensure the quality and safety of the products distributed and delivered by milk banks.

· These provisions complement the obligations outlined in the decree concerning the operational conditions and organisation of milk banks, as implemented under Article L. 2323-3 of the Public Health Code. The public health mission undertaken by milk banks is particularly based on promotional activities for donations that are essential to ensure the provision of care.

· The rules described in these good practices contribute to the improvement of services related to the activities of milk banks by integrating a quality approach at all stages. These rules apply to milk from both anonymous and personalised donations.

· This decision consists of:

- Common provisions relating to operational activities and "support" activities carried out in milk banks;
- "Annexes": specific chapters that detail technical requirements aimed at regulating particular areas associated with identified health risks. These annexes address the following areas:
  - Information system;
  - Microbiological analyses;
  - Biochemical performance markers of processes;
  - Metrological parameters of processes;
  - Hygiene requirements for donors;
  - Medical contraindications for donation candidates;
  - Algorithms for processing the results of serological tests of donation candidates;
  - Characteristics related to freeze-drying.

Glossary

Active Ingredient
An essential component that gives milk its active properties on infant health **Anonymous Donation**
Donation of milk from a donor to an infant other than her own. The term "donor" used in these good practices is equivalent to the term "woman" used in Articles D. 2323-1 and following of the Public Health Code, and the term "infant" used in these good practices is equivalent to the term "child" mentioned in the aforementioned articles.

Audit
A systematic, independent, and documented examination aimed at determining whether the procedures and results related to quality are capable of achieving the set objectives. This examination should be conducted on internal processes as well as those performed by service providers.

Authorisation
A documented decision that permits a person to perform a specific activity.

Authorised Person
A person authorised by their functional manager to perform assigned tasks.

Batch
A defined quantity of prepared milk (produced in one operation or several operations) that can be considered homogeneous.

Batch File
A file containing all information related to the preparation, processing, packaging, and controls of the prepared batch, identified upstream by a batch number, serving as a key to collect all necessary

elements for traceability. This file gathers all documentary evidence that allows for the determination of the conformity of all products and links them through the batch number.

Biovigilance

Biovigilance aims to:

- systematically monitor all incidents and adverse effects;
- promptly report serious incidents and unexpected adverse effects to the local biovigilance contact;
- report serious incidents and unexpected adverse effects to the Biomedicine Agency without delay from the moment they are identified;
- analyse, evaluate, and utilise this information to limit the likelihood of any new serious incident or unexpected adverse effect or to reduce their severity;
- conduct any investigation or study related to serious incidents and unexpected adverse effects.

Complaint

An observation, dispute, or expression of dissatisfaction from an external organisation or individual regarding a service or product that does not meet their needs and expectations, or is not compliant with current regulations.

Computerisation

The implementation of a computer system including, in particular, data entry, electronic processing, and the output of information intended for automatic control, reports, or traceability purposes.

Control

A set of operations aimed at determining the conformity of the product to specific requirements.

Critical

Describes a device, material, operation, or process whose failure may ultimately affect the health of individuals, the quality, or the availability of milk.**Self-Assessment**

Evaluation of the quality management system and risk by the milk bank staff according to an established methodology.

Design Qualification (DQ):

Design qualification aims to:

- verify that the process data are well defined so that the designer can respond to the project in accordance with requirements;
- ensure that all process needs are considered in the design proposed by the designer and suppliers;
- formalise the assessment against pre-established acceptance criteria regarding conceptual and functional aspects. It is performed if the subject of qualification has been specifically designed under an order from the acquiring establishment.

Deviation

A formal decision to depart from internal requirements for a defined area and duration within a specified framework. This decision is made by an authorised person.

Disinfection

An operation that removes or reduces undesirable microorganisms to an acceptable level. It is the first treatment to be performed on soiled objects and materials to eliminate microorganisms and facilitate subsequent cleaning and sterilisation.

Dispensing

Provision of pasteurised milk on medical prescription for administration to a newborn.

Distribution

Provision of pasteurised milk to a care service in a healthcare facility or to another milk bank.

Donor

Any candidate for donation from whom a donation has been collected, even if the donation has been rejected following serological tests, post-donation information, or biological analyses of the milk.

Donor File
A file containing the identification details of the donor and all the results of biological analyses and screening tests.
Donation
In these good practices, breast milk characterised by a specific collection time and date that has only undergone preservation operations at the donor's location and transport operations.
Exclusive Personalised Donation
Donation of milk that cannot, under any circumstances, be administered to an infant other than that of the donor.
Hazard
An intrinsic property of any element that may lead to a serious incident or adverse effect.
Installation Qualification (IQ):
Installation qualification aims to:

- verify that the system is correctly installed. It is conducted according to a protocol that describes responsibilities, objectives, and acceptance criteria related to the IQ phase. Documents include installation scripts, the IQ report, and incident reports;
- verify through documentation that a piece of equipment, location, or system has been constructed, assembled, installed, and connected in accordance with regulatory specifications and those of the specifications document, and that the supplier's recommendations have been taken into account.

Lactarium: human milk bank
Maintenance
A set of actions to maintain or restore an entity to a state that allows it to perform an expected function.
Management Review
A planned and periodic meeting held within an organisation to assess its management system and demonstrate effective oversight by management.
Milk
In these good practices, refers to breast milk, including donations and milk that has undergone processing.
Non-Conformity
Any situation (deviation, etc.) in which a specified requirement (specifications, procedures, protocols, etc.) is not met or does not meet an expectation.
Operational Qualification (OQ):
Operational qualification aims to:

- verify the adequacy between the service provider's response and the functionalities of the system. It is conducted according to a protocol that describes responsibilities, objectives, and acceptance criteria related to the OQ phase. Documents include test scenarios, the OQ report, and incident reports;
- provide demonstration, supported by the documents defined during the installation qualification, that the components of the system or equipment to be tested or measured (automation, data acquisition systems, recording, regulation, alarms, and safety mechanisms) operate reproducibly within the performance ranges specified by the user in the specifications document, in accordance with the supplier's documentation and limits established by the specifications. This qualification follows the installation qualification.

Pasteurisation
A process aimed at reducing the microbial load of milk through heat (defined temperature and duration), while preserving its active principles as much as possible. Microbiological criteria for the milk before and after pasteurisation are set out in ***Appendix 2.***
Performance Qualification (PQ):
Performance qualification aims to:

- verify and prove that the equipment or system as a whole operates correctly and reproducibly under real usage conditions and meets the needs expressed in the user's specifications;
- verify and prove, using appropriate tests, that the system as a whole operates correctly and reproducibly under real usage conditions and that the product obtained is compliant.

Performance qualification follows operational qualification or is conducted concurrently with operational qualification.

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Performance qualification aims to:

- verify and prove that the equipment or system as a whole operates correctly and reproducibly under real usage conditions and meets the needs expressed in the user's specifications;
- verify and prove, using appropriate tests, that the system as a whole operates correctly and reproducibly under real usage conditions and that the product obtained is compliant.

Performance qualification follows operational qualification or is conducted concurrently with operational qualification.

Personalised Donation

Donation of milk from a donor to her own infant. The term "donor" used in these good practices is equivalent to the term "mother" used in Articles D. 2323-1 and following of the Public Health Code, and the term "infant" used in these good practices is equivalent to the term "child" mentioned in the aforementioned articles.

Procedure

A specified and formalised manner of performing an activity or process.

Product

In these good practices, it refers to the result of a milk treatment.

Quarantine

The status of a product, equipment, or medical devices that are physically isolated or otherwise effectively secured to prevent their use, for a variable period of time, pending a decision regarding their conformity or status

Quality Management

Coordinated activities aimed at directing and managing an organisation regarding quality.

Qualification

An operation aimed at demonstrating the suitability of a piece of equipment, system, device, or installation to meet specified quality and safety requirements.

Quality Assurance

A part of quality management aimed at providing confidence through compliance with quality requirements. This is specifically the component of the quality management system that ensures that milk, from collection to distribution or dispensing, meets the necessary requirements for its intended use.

Quality Indicator

A variable intended to measure and assess a state or progression.

Raw Milk

For the activities of the milk bank, milk considered as raw material intended for pasteurisation. It is stored refrigerated or frozen

Record

A document presenting results obtained or proof of the completion of an activity.

Release

Authorisation to proceed to the next step of a process or to the following process. This operation allows for the lifting of quarantine either for donations collected for processing or for processed batches intended for distribution or dispensing, after a decision regarding their conformity.

Risk Management

Coordinated activities aimed at directing and managing an organisation concerning risks.

Risk
The probability of an incident or adverse effect occurring, or the effect of uncertainty on achieving objectives.
Specifications
Formal requirements expressed numerically with appropriate units, specifying the limits beyond which the value of the concerned parameter must not fall.
Standard Operating Procedure
A formal and detailed description of how to perform an activity
Sterilisation
An operation aimed at eliminating all living microorganisms contaminating an object or product.
Sub-Batch
A mixture of donations from the same donor intended to be part of a batch of milk. Sub-batches are an intermediate phase before forming batches.
Traceability
The ability, based on recorded identification, to trace the history, use, or location of milk at all stages, from collection to distribution or dispensing. The traceability of a batch of milk refers to establishing the link between the donor, the donation, the distributed or dispensed batch, including if it has been destroyed, the recipients, and the various elements that may influence the quality and safety of the product (consumables, containers, etc.).
Validation
An operation that provides proof that the expected results have been obtained under satisfactory technical conditions. Validation of a method or process must at a minimum assess its repeatability, reproducibility, and robustness.

1. Quality and Risk Management System

· The quality and risk management system includes: quality assurance, quality control, the collection, analysis, and management of non-conformities, risk management, and system oversight through an audit or self-assessment process

· This system encompasses everything that can individually or collectively influence the quality and safety of processes, donations, and products. The fundamental requirements for quality and risk management are based on suitable facilities, trained personnel, identified, assessed, and controlled risks, and procedures for the collection, preparation and qualification, processing, storage, distribution, or dispensing of the product, as well as for managing interfaces with other hospital departments or service providers.

· Achieving the objective of quality improvement and risk management is the responsibility of management and the medical officer responsible for the milk bank. It requires participation and commitment from staff at all levels.

· Computerisation is an important tool in the quality and risk management system that facilitates the automation and security of information transfer, thereby reducing errors and the burden of manual data entry.

· ***Appendix 1*** details the risk management procedures inherent to the information system. When computerisation is not possible, specific procedures outline the technical methods for controlling manual data record keeping.

· Every milk bank must have a system in place to ensure quality and risk management. This system is the responsibility of the medical officer in charge of the milk bank or a competent person they have formally designated. The establishment and maintenance of a satisfactory quality and risk management system relies on all staff. The medical officer oversees the activities of the milk bank, particularly using relevant quality indicators.

· The established quality and risk management system must be evaluated periodically with the management teams involved in the operation of the milk bank. A management review allows for the

periodic evaluation of quality indicators, monitoring of non-conformities, the implementation of action plans related to quality and risks, oversight of audits and self-assessments, training assessments, and equipment investment plans.

· In line with the establishment's policy, objectives are reviewed during the management review, and, if necessary, new objectives are set.

1.1. Documentation

1.1.1. Document Management

· Documentation is an essential element of quality assurance. It consists of internal documents, primarily: procedures, operating modes, forms, and records, as well as external documents (such as regulatory texts and equipment manuals).

· Its organisation is described in a document management procedure. Any document that influences the quality and safety of the product must be checked by competent individuals and then validated by the medical officer responsible for the milk bank before it is implemented. All critical processes (selection of donors, transport of milk, pasteurisation, etc.) must have an adequate level of documentation (process sheets, procedures, and operating modes). A list of applicable documentation is accessible to personnel involved in the activities of the milk bank.

· Documents may be handwritten or computerised.

· Clear records prevent errors inherent in verbal communication and allow for tracing the history of operations. Milk banks must establish a process to collect and retain information that ensures the traceability of operations and critical elements (notably critical premises, materials, and consumables).

· Documentation must be current and accessible to staff who require it. It must be known and applied by the relevant personnel. Provisions are in place to ensure that instructions (procedures, operating modes, memos, etc.) are acknowledged and that information deemed critical is well understood. Acknowledgement of documents that impact the quality and safety of the product is evidenced by the handwritten or electronic signature of the relevant individuals.

· Any modification of documents must be controlled, dated, and approved by the person authorised to carry out this task.

1.1.2. Archiving

· All documents must allow for tracing the history of each batch of milk distributed, dispensed, or destroyed. All documents are retained by the milk bank in accordance with current regulations.

· The archiving methods comply with confidentiality and data security requirements regarding personal information. The rapid availability of data is periodically verified.

· Information from the infant's and donor's medical files is retained in accordance with regulatory requirements, notably as specified in Article R.1112-7 of the Public Health Code.

· Documents not included in the medical file of the donor or infant, which relate to the product (batch file or equipment qualification file, etc.), are retained for at least 10 years.

· For other documents (quality instructions, records, etc.) that do not relate to the products, if no specific regulation applies, the retention period is determined based on the document's relevance, within an administrative usage period of no less than 2 years after the end of the milk's expiry.

1.1.2.1. Documents Relating to the Donor

· These documents consist of the donor's file (see glossary).

1.1.2.2. Documents Relating to the Distributed or Dispensed Product

· Documents relating to the distributed or dispensed product consist of the donor's file, the infant's file, and the batch file. The management and electronic archiving of documents allow for the quick availability of all required information during a health alert. If this is not possible, the milk bank has a system in place to achieve the same objective. The methods for establishing traceability in a degraded mode are defined.

· The milk bank conducts and documents alert exercises (batch withdrawal, urgent information search, etc.) to evaluate the effectiveness of documentation organisation. This evaluation focuses at a minimum on the time required to obtain all relevant

information, the stakeholders' knowledge of the procedure to be followed, and, if applicable, the follow-up on crisis management procedures.

- A batch file, in either paper or electronic format, must allow for the retrieval of the following documents:
  - Documents describing the composition and controls of the milk batch;
  - The number and identification of the sub-batches constituting the batch (identities of donors, dates of donations, results of sub-batch analyses);
  - Results of bacteriological analyses before pasteurisation;
  - Results of bacteriological analyses after pasteurisation;
  - Recording of pasteurisation parameters and, if applicable, the lyophilisation diagram;
  - All documents showing the fate of the milk, notably medical prescriptions or order forms or records of destruction.

1.2. Quality Control

- Quality control aims to verify and ensure the conformity of products and methods to pre-established specifications or a specification document.
- Quality control applies to all products, methods, consumables, reagents, premises, and materials involved in the processes of collection, preparation, qualification, processing, storage, distribution, or dispensing of the product.
- Quality control includes the implementation of checks, analysis of results, and acceptance or rejection conclusions of donations.
- It also encompasses control methods and their validation, as well as the implementation of provisions that ensure the necessary checks have been carried out.
- Checks performed in the preparation or treatment area must be conducted according to procedures that guarantee product quality and safety.

Incoming checks of consumables and reagents must be documented. Data regarding the controlled product, the execution of checks, the results obtained, and the decisions of acceptance or rejection must be recorded.

- Results of checks must be made available promptly to allow for the implementation of appropriate corrective measures or the quarantining and withdrawal of the product, if necessary.
- To leverage scientific and technical advancements and knowledge, other processes than those described in these good practices (pasteurisation, bacteriological tests, etc.) may be applied. However, any modification of a critical process cannot occur without prior validation of the new procedure. Validation involves formally gathering evidence that the new procedure maintains or improves the quality and safety of the product in a repeatable, reproducible, and robust manner in accordance with the established characteristics in ***Appendix 2 and 3***.

1.3. Management of Non-Conformities

- To ensure the improvement of the quality and risk management system, the milk bank must collect non-conformities (including customer complaints), assess them, and implement appropriate actions (immediate corrective actions and/or corrective or preventive actions after analysing the observed defect) and ensure follow-up.
- Non-conformities that may fall under vigilance requirements must be reported to the relevant correspondents of these vigils, adhering to regulatory requirements. When a non-conformity affects a critical parameter, the implementation of corrective actions must be preceded by a root cause analysis and followed by an effectiveness measure of the actions taken. In these cases, the necessity for a biovigilance report must be systematically considered with the local biovigilance correspondent. Management of these non-conformities must be followed up, if necessary, with the local biovigilance correspondent and systematically during meetings with the management of the establishment, along with feedback that may be shared with other milk banks.

· A document allows for deviations from the requirements of the quality management system for techniques, products, or services considered non-conforming to the specified provisions, in cases where it is necessary to respond to an unforeseen situation, provided this deviation yields a benefit greater than the potential risk. This document defines the conditions governing these deviations. Deviations must be recorded and validated by those authorised to perform this function.

1.4. Self-Assessment / Audit

· Self-assessment and audit are control methods that provide quality assurance and must be conducted at defined intervals to monitor the implementation and compliance with good practice rules and propose necessary corrective measures. These practices must be documented.

· These processes are designed to measure the effectiveness of the quality system. They include evaluations conducted on the quality and risk management system, specific systems (hygiene audit, IT system audit, etc.), and critical service providers.

· All this data must be reviewed during the annual management review, and based on this data, quality action plans must be implemented and monitored.

1.5. Risk Management

· An organisation is established to ensure that:
  - Risk assessment is based on scientific knowledge and experience of processes;
  - It is closely linked to the protection of infants and donors;
  - The level of detail in formalising the description of the risk management process is proportionate to the level of risk involved.

· The approach to be followed, regardless of the starting point (activities, processes, product, etc.), must include at least the following steps:
  - Establishing the context;
  - Identifying hazards;
  - Analysing risks using a method controlled by the operator;
  - Evaluating existing means to eliminate, reduce, or manage risks;
  - Treating the risk;
  - Evaluating residual risks after implementing preventive actions;
  - Monitoring and reviewing the actions taken in a process of continuous improvement.

· A risk analysis and evaluation of all processes in the human milk bank (including, where applicable, the establishment and maintenance of the information system) are conducted. This process must also consider the existing interfaces between the human milk bank and the partners involved in its activities.

· Critical processes are formally identified. An action plan is established that prioritises actions to be taken, relating both to the level of risk and to the control of critical processes. This plan is formally reviewed each year during the management review.

· Any modification of a process or organisation must undergo a prior risk analysis before implementation. The application modalities of this requirement are defined in a procedure, which specifies that, for critical processes, a risk assessment of the process and its interfaces must be formalised, along with, if necessary, the monitoring of an action plan.

2. Staff

· It is necessary to have a qualified and sufficiently staffed personnel to carry out all the tasks assigned to them.

· All staff in the human milk bank are under the responsibility of the designated medical officer mentioned in Article D.2323-7 of the Public Health Code.

· A named organisational chart of the human milk bank detailing the various activities must be established. This chart or an accompanying document should also specify the management procedures for the interfaces existing with service partners or external organisations.
· The missions, roles, tasks, and individual responsibilities must be clearly defined in writing. The document produced for this purpose should be updated and endorsed by the position holder and the medical officer. Critical operations carried out are identified in this document and are subject to evaluation as part of the establishment or renewal of an authorisation. The scope of functions and missions conferred on a single individual must not pose a risk to their proper execution. Deputies for management positions are designated and authorised for a precisely specified area of responsibility. This also applies to positions involving critical steps that are only managed by a limited number of individuals.
· Supervisory personnel ensure the required qualifications and initial training of staff.
· Staff receive theoretical and practical training tailored to their roles, enabling them to be authorised for the tasks and responsibilities entrusted to them. This training, whether conducted internally or externally, should particularly cover milk, breastfeeding, good practice guidelines, and hygiene and safety measures concerning personnel.
· Continuous training must be provided to maintain and develop staff skills and effectiveness. Mandatory training covers areas such as quality and risk management, biovigilance, and hygiene.
· Documents certifying the training undertaken must be established. A system is put in place to evaluate, at least annually, the contribution of the training completed by the staff.
· Authorisation is time-limited and must be periodically renewed based on the assessment of the skills relevant to the roles performed and the ability to carry out critical operations.

3. Premises and Equipment

The premises and equipment must be subject to qualification, organised according to a master qualification plan. The initial qualification should be as comprehensive as possible, while subsequent qualifications may be simplified as indicated in the master plan. These qualifications must follow a complete process of installation qualification, operational qualification, and performance qualification, and, where applicable, design qualification as defined in the glossary.

3.1. Premises

· The premises must be located, designed, constructed, adapted, maintained, and cleaned in a manner suitable for the operations to be performed. Their cleaning is governed by operating procedures tailored to their use.
· They are qualified periodically and each time a critical element is modified. For this qualification, it must be specifically verified that the premises are arranged according to the logical sequence of milk processing operations and according to appropriate cleanliness levels. The maintenance of these cleanliness levels is subject to formalised controls.
· Lighting, temperature, humidity, and ventilation must be appropriate so as not to affect the product, directly or indirectly, during its packaging and processing.
· Anyone entering the human milk bank must wear protective clothing appropriate to the operations taking place. Any unhygienic practices are prohibited. Changing areas are designated according to a displayed procedure.

3.2. Equipment

· The equipment must be designed, installed, maintained, and cleaned according to its use and to minimise risks. It must comply with safety standards and protect personnel. Its cleaning is governed by operating procedures.
· A list of critical equipment is established. Critical devices must undergo qualification, reviewed periodically. By default, the qualification frequency is annual. Qualification reports are signed by the medical officer responsible for the human milk bank or a person authorised to perform this task.

· The qualification of the equipment involves demonstrating that it functions correctly and produces the expected results. It is mandatory for new equipment, after repairs, or after relocation that may impact the device's operation.
· The maximum tolerable deviations of the parameters considered in the qualifications (temperatures, durations, etc.) are defined, by process, in ***Appendix 4***.
· Regular maintenance and cleaning of the equipment are essential conditions for the quality of the distributed or delivered product.
· A life record for the equipment (either digital or paper) is established, including elements related to identification, maintenance, initial qualification, and maintenance and requalification operations. This record, which is an important element of traceability, is accessible to technical services and human milk bank personnel. In the event of a breakdown of critical equipment, the degraded operation mode is defined in a procedure.
· The temperature and duration of pasteurisation are set in accordance with the conditions mentioned in ***Appendix 4***. They are monitored throughout the entire duration of pasteurisation, and the recording of these checks is endorsed by the operator performing the pasteurisation and verifying its compliance. The record is retained with the reference and batch numbers of the corresponding milk.
· In the human milk bank, milk conservation equipment may not be used to store other health or food products.
· The temperature-controlled storage units, whether negative or positive, must be of sufficient size and designed to ensure proper storage conditions, as well as orderly storage to avoid errors in milk orientation. They must be clean and cleaned according to procedures. A continuous temperature monitoring system with alarms must be implemented and regularly checked to ensure the preservation of the milk.
· Quarantined milk bottles are stored in clearly identified separate areas. At each stage of the milk flow within the human milk bank, it must be possible to determine in real time the status of the product (raw milk, milk in quarantine, or deliverable).

3.3. Environmental Monitoring

· Microbiological monitoring of the environment is implemented when the processes used require the opening of bottles after pasteurisation or when repeated contaminations of pasteurised milk by environmental germs exceed a threshold defined in relation to routine observed results.
· Monitoring of the microbiological quality of water is established when it participates in a critical process. An evaluation of the risk of milk contamination by the pasteuriser water is conducted, and measures are taken accordingly.

4. Collection

4.1. Promotion of Donation

Actions to promote breastfeeding and donation are organised and documented. They are reviewed during management meetings. When national information documents are available, they are used to promote public health improvement initiatives.

4.2. Selection of Donors

The initial contact between the donor candidate and the team responsible for collecting donations establishes a climate of mutual trust.

The preliminary interview mentioned in Article D.2323-11 of the Public Health Code occurs in two stages.

Firstly, an informational interview is conducted with the donor candidate by a trained individual under the supervision of a doctor, midwife, or nurse designated by the medical officer responsible for the human milk bank. This interview aims to inform the donor candidate about the requirements for donating milk and the hygiene and aseptic conditions for collection and storage of the donation.

Secondly, for anonymous donations, a medical interview conducted by a doctor or midwife seeks to identify any medical contraindications to the donation, with a view to protecting both the donor and the receiving infant.

4.2.1. Informational Interview

· This informational interview aims to raise awareness and responsibility among the donor candidate regarding the potential risks of transmissible diseases via milk, the importance of the risks associated with medication use, and the hygiene measures to be followed during the collection of the donation (***Appendix 5***). The individuals conducting this interview have a support document outlining essential messages to communicate, methods to ensure understanding of critical information, and identification of individuals who can answer specific questions. This document is reviewed periodically.

· The donor candidate is informed about the regulatory provisions concerning mandatory screening tests before selection.

· This information is supplemented by the provision of clear explanatory documents. During the initial interview, the benefits of anonymous donation in cases of surplus personalised donations are highlighted. To this end, a medical questionnaire for anonymous donation is provided to the donor candidate.

· At the end of this informational interview, the donor's identification is completed.

· The human milk bank must be able to evaluate the effectiveness of the interviews conducted.

4.2.2. Identification of Donors

4.2.2.1. Traceability Necessary information

At the time of the first donation, the donor's identification is recorded.

The mandatory information for identifying the donor includes:

- The qualified national health identifier (INS) in accordance with the national identity vigilance framework when available, or if not, the birth name, first name, and date of birth;
- The date and place of delivery;
- The complete personal address, phone number, and, if applicable, email address.

This information is confirmed at each donation collection.

For anonymous donations, a unique number is assigned to each donation collection. A procedure is established to ensure the uniqueness of this number.

4.2.2.2. Traceability of Identification

· Measures are implemented to minimise the loss of milk from personalised donations (for example, systematically obtaining consent for the use of surpluses in anonymous donations, limiting stocks of pasteurised milk for a donor, etc.).

- The personalised donation file includes administrative elements, the results of the donor's serological tests, and the results of the bacteriological analyses of their donations.
- The anonymous donation file includes administrative elements, the completed medical questionnaire, the results of the donor's serological tests, renewed every three months if necessary, and the results of the bacteriological analyses of their donations.
- Personal data complies with current regulations.
- For each donation, the donor's file is consulted and verified under the responsibility of the human milk bank 's medical officer. The files are completed and validated before administering the product to infants, to ensure traceability of the donation and to release only compliant batches.
- The authorisation of human milk bank staff must determine whether consultation and modification of the donors' files are permitted.
- A procedure is established to specify the rules for managing this data.

4.3. Qualification of Donors

- The selection of donors aims to identify any medical contraindications to donation, with a focus on protecting the donor and the infant. This process includes mandatory serological screenings.
- The biological analyses to be conducted on blood samples taken during donation are stipulated by current regulatory texts.
- These acts are carried out under medical prescription.

4.3.1. Qualification Data for Donors in <u>Internal Use human milk banks</u>

- The medical interview with the donor, described in paragraph 3.2.2 regarding the qualification of anonymous donations, is not mandatory for personalised donations.
- Exclusive personalised donations can only be implemented if there are effective provisions in place to control the entire process leading to the delivery of the product to the intended infant.
- Serological tests must be conducted to qualify the donor during pregnancy or at the time of donation. The results of these tests are interpreted according to the algorithms in ***Appendix 7*** to qualify the donor.
- Serological data is essential for the use of donations and for the release of products.
- The conversion of a personalised donation into an anonymous donation is contingent upon the completion of a medical interview with the donor and the interpretation of serological test results that are less than three months old.

4.3.2. Qualification Data for Donors in <u>Internal and External Use human milk banks</u>

- If the donor is at home, they provide individuals in charge of collection at the human milk bank with a blood sample labelled with their identity. Arrangements are made to collect the collector's signature, the date, and the time of the sample.
- In the absence of this data, the donor cannot be qualified.
- When the transport of the blood sample is carried out by the human milk bank, this operation is conducted according to a procedure that complies with current regulations.

4.3.2.1. Personalised Donation

- The requirements for serological tests, as described in ***paragraph 3.1***, apply: serological data obtained during pregnancy or prior to donation are essential for the use of donations and for the release of products.

4.3.2.2. Anonymous Donation

- Donors are selected following a medical interview conducted by a doctor or midwife. This interview assesses the presence of risk factors.
- A medical questionnaire that detects potential medical contraindications defined in ***Appendix 6*** is completed by the donor candidate to obtain the essential information for their selection. It is submitted by the donor candidate to the doctor or midwife, who evaluates the donor's suitability during the medical interview and ensures that the donation will not harm the donor's health or that of the infant. Risk factors must be

assessed by the individual conducting the medical interview, taking into account identified hazards, frequency, and the date of the last exposure to hazards.

- The medical interview may identify risk factors not listed in Appendix 6.
- Screening tests for transmissible diseases are offered to donors during this interview.
- A prescription for screening tests for transmissible diseases may be provided to the donor during this interview, if applicable. Informed consent for the donation from the donor candidate is obtained.

4.3.3. Qualification of the Donor and Management of Donations

- Milk can only be used by the human milk bank if the conclusions of the algorithms for processing the serological test results of donor candidates (***Appendix 7***) permit it, and for anonymous donations, only in the absence of risks identified during the medical interview with the donor.
- The medical officer responsible for the human milk bank, or a doctor designated by them, ensures before any use of the donation that the results of the aforementioned analyses comply with the algorithms established by ***Appendix 7*** and endorses the analysis sheet or electronically validates the file.
- In the event of a serological screening test result that does not comply with the algorithms set out in ***Appendix 7***, the medical officer responsible for the human milk bank, in consultation with the doctor from the establishment where the donor candidate delivered, compares the results with those from the beginning of the pregnancy. Depending on the algorithms in ***Appendix 7*** that establish the processing of serological test results, they inform the donor candidate, request a new blood sample for retesting, and encourage the candidate to consult their primary care physician.
- These actions are recorded. The medical officer ensures the destruction of milk upon formal notification of non-compliant results, in accordance with the algorithms in ***Appendix 7***. The destruction of non-compliant products is carried out according to the procedures established by the institution.

4.4.4. Collection of Donated Human Milk

- The human milk bank provides written instructions to donors and ensures their understanding regarding the hygiene rules to be followed during the collection of donations, the equipment to be used, and the storage rules for the donation, including cleanliness requirements (cleaning and disinfection) for storage containers and transport containers. These instructions are detailed in ***Appendix 5***.
- The collected donation is typically stored with the donor or in healthcare facilities before being transported to the human milk bank.
- The donor commits in writing to adhere to these rules before the collection of their donation.

4.4.1. Collection of Donated Human Milk

- The collection is a crucial step in ensuring the subsequent quality and safety of the milk.
- The donation is collected according to the aforementioned hygiene rules detailed in ***Appendix 5.***
- Bacteriologically clean bottles are provided by the human milk bank along with the equipment for collecting the donation (breast pump). The bottles are pre-labelled or accompanied by labels to attach. Single-use equipment should be prioritised.
- All equipment in contact with the skin or the donation, especially the consumables for breast pumps, is systematically washed and disinfected according to the conditions set by the human milk bank.
- As soon as the donation is collected, the bottle is sealed and placed as quickly as possible in a freezer at a temperature of -18°C or lower, or in a refrigerator at a temperature between 0°C and 4°C, without exceeding 48 hours. A bottle is used for only one collection. Milk that has just been collected must never be mixed with previously cooled milk. However, after cooling,

several collections from the same day may be mixed in a bottle used solely for freezer storage. Milk that has been cooled to +4°C must not be placed on top of already frozen milk.

· Each bottle carries all the information needed to identify the donor, the date of collection, and any medications taken by the donor during their breastfeeding period.

4.2. Conservation of Donated Human Milk

· As soon as the donation is collected, the bottle should be sealed and placed in the freezer as quickly as possible.

· If freezing is delayed, the storage time in the refrigerator at a temperature between 0°C and 4°C must not exceed 48 hours. The duration for which frozen donations can be stored at the donor's home or in healthcare facilities is set by the milk bank and does not exceed 4 months.

4.3. Transport of Donated Human Milk

· The transport of the donation must adhere to the conditions outlined in ***Appendix 4***, which are specifically established to maintain the cold chain, as well as the requirements described in ***Chapter X***.

· Upon receipt at the milk bank, before being placed in storage containers, a check is carried out on the milk bottles according to predefined criteria, including verification of transport conditions, the state of the donation and bottles, and their identification. This check is recorded.

4.4. Monitoring the Collection Process

· The personnel assigned to collection must regularly ensure that donors are well-informed of the instructions and, if possible, that they are being followed. These reminders and checks must be documented.

· Donors should report any anomalies that could compromise the quality and safety of the donation as soon as possible. This requirement is reiterated in the written instructions provided to the donor. Non-conformities must be analysed and addressed by the milk bank, particularly to prevent their recurrence and any direct or indirect effects on unused donations.

5. Conservation of Donated Human Milk

· The first process applied to donations in a milk bank is the conservation process. This occurs between each step of the milk treatment circuit. Its reliability depends on proper management of equipment, effective monitoring of temperatures, and the establishment of a proven operational procedure for degraded mode (see ***Appendix 4***).

· To avoid any errors, measures must be implemented to distinguish the status of the milk: raw milk in quarantine, raw milk eligible for pasteurisation, pasteurised milk awaiting the results of biological qualification of batches, non-compliant milk, or milk that can be distributed or delivered. Bottles of milk from personalised donations are stored in designated areas.

· The durations of conservation for donations are defined in ***Appendix 4.***

6. Preparation

· Preparation includes selecting the milk to be treated, a defrosting stage, and grouping bottles into sub-batches or a batch. Labelling is a critical step that maintains the link between the donor, the donations, and the sub-batch or batch being handled.

· Preparation operations must follow instructions and procedures. Risk management is implemented to determine the measures to be taken to protect the product from environmental contamination at each stage of preparation. The effectiveness of these measures must be evaluated.

6.1. Selection of Milk to be Treated

The milk to be treated is chosen based on the following criteria:

- The demand from prescribers;
- The expiration date of the milk as defined in ***Appendix 4***, starting from the date of pasteurisation;

- The capabilities and modalities of pasteurisation;
- The management of available conservation volumes.

6.2. Thawing of Milk

· The defrosting of raw milk is carried out according to a defined protocol aimed at preserving the quality of the milk while respecting conservation conditions.

· Risks of contamination, microbial proliferation, and degradation of milk components must therefore be carefully considered.

· The actual defrosting conditions are recorded.

6.3. Creation of Sub-batches and Batches

· Before starting the preparation of batches and, if applicable, sub-batches, it is essential to verify that the working areas and equipment used are disinfected.

· During the formation of sub-batches and batches, the major risks to be considered are the risks of contamination and microbial proliferation, as well as the loss of traceability between the donor, the donation, and the milk to be pasteurised.

· Grouping the bottles from a donor who has donated milk for their own infant constitutes a batch. For the preparation of exclusive personalised donation batches, the milk bank must take measures to prevent any risk of misattribution.

· For anonymous donations, sub-batches may be formed. These group the milk donations from the same donor and are clearly identified. The formation of a batch is accomplished by combining sub-batches that may come from several donors. The maximum volume of the batch must be established by the milk bank to allow for effective homogenisation and to avoid increasing the risk of biological contamination of the infant. The maximum number of sub-batches that can be combined into a single batch must be limited and documented by the milk bank.

· A microbiological sample is taken before pasteurisation. The operational conditions and materials used for this purpose are chosen to ensure that the sample is representative of the sub-batch or batch from which it is taken.

6.4. Labelling

· All bottles that are prepared and treated must be labelled.

· The labelling of the bottles from sub-batches and batches of milk is performed at the time of their formation.

· In all cases, a procedure specifies the labelling methods and appropriate controls identified following a risk analysis, which are implemented to avoid the risk of errors.

· The labelling of the finished product can be done at the time of batch formation or as quickly as possible after pasteurisation or freeze-drying.

· The label on the finished product includes:

- The identification of the milk bank;
- The date of pasteurisation or freeze-drying;
- The batch number;
- The use-by date.

· The status of the product, whether compliant or non-compliant, must be determinable via the computer system or instantly by any other means. The labels for personalised donations also indicate the identification of the donor (name and surname) as well as the names of the infants who are the intended recipients.

7. Milk Treatment

The treatment of milk involves technical processes applied to enhance certain properties of the milk. Freeze-drying is one such process that can only be applied after pasteurisation or an equivalent microbiological inactivation process in terms of product quality and safety. This process is detailed in ***Appendix 8.***

7.1. Pasteurisation

- The purpose of pasteurisation is to limit the microbial load of the milk.
- Where possible, pasteurised volumes are homogeneous. If this is not the case, a validation is carried out to ensure there is no impact on the quality and safety of the product.
- Milk batches are treated by pasteurisation according to the conditions specified in ***Appendix 4***.
- A sample is taken to control the effectiveness of the pasteurisation. The operational conditions and materials used for this purpose are chosen to ensure that the sample accurately represents the treatment applied to the batch from which it is taken.

7.2. Cooling of Pasteurised Milk

- The milk is cooled and placed in storage containers under the conditions defined in ***Appendix 4.***
- Pending the results of bacteriological analyses, the milk is stored in quarantine until its conformity is confirmed.

8. Biological Qualification of Batches

- Each batch of milk is subject to systematic biological analyses.
- All collected milk is qualified before being released. The release process (which minimally involves the transmission of information from laboratories, verification of compliance with release criteria, validation of results, etc.) is critical and thus receives special attention, including risk management.
- The biological qualification of batches includes bacteriological analyses. These analyses are systematically performed to highlight any deterioration in the quality and safety of the milk.
- ***Appendix 2*** sets out the minimum conditions to be respected. More effective methods may be implemented following validation that demonstrates improvements or, at a minimum, maintains the level of quality and safety of the milk.
- The biological analyses of the milk are conducted under the responsibility of a biologist who ensures the validation of the techniques and results. Formal validation of the techniques includes those for pre-analytical steps, particularly the sampling process.
- The biologist must also consider, as pre-analytical steps, the transport conditions (notably temperature and time limits) in the case of transporting samples to the laboratory.

8.1. Analyses Before Pasteurisation

8.1.1. Analyses to be Performed on Sub-batches

- When sub-batches are produced, while awaiting the results of bacteriological analyses, the milk is stored between 0°C and 4°C for a maximum of 24 hours or pasteurised immediately, then frozen and placed in quarantine until its conformity is confirmed.
- The requirements for microbiological analyses are described in ***Appendix 2.***

8.1.2. Analyses to be Performed on Batches

Batches of milk to be pasteurised undergo systematic bacteriological analyses. These analyses and their specifications are defined in ***Appendix 2***

8.2. Post-Pasteurisation Analysis

- A final bacteriological analysis is conducted after pasteurisation according to the conditions defined in ***Appendix 2.***
- After pasteurisation and cooling, and pending the results of the analysis, the bottles of milk are placed in quarantine. They must be stored under the conditions defined in ***Appendix 4.***

· Any batch for which the post-pasteurisation analysis is non-compliant is destroyed. The destruction of non-compliant products is carried out according to the procedures established by the facility.

· A documented analysis is conducted to identify and address potential causes of repeated non-conformities.

8.3. Biochemical Analyses

· To meet the demands of prescribers, milk may be characterised by biochemical analyses.

· The consideration of characterisation data for milk batches in subsequent processes can only be effective if the materials used are qualified and the prescriber is informed of the limitations of the techniques employed.

· Before introducing a new milk treatment process, validation must be undertaken, including biochemical analyses of the pasteurised milk. ***Appendix 3*** presents the characteristics to be studied to ensure the maintenance of active ingredient levels in the milk.

9. Release of Batches, Distribution, and Delivery

9.1. Release of Batches

· Only compliant products can be released for distribution or delivery and are accepted for freeze-drying.

· A batch release procedure is established based on risk management of the process routinely followed and in degraded mode. This takes into account all relevant data regarding:

- The qualification of the donor, which may be challenged by information available post-donation;
- The biological qualification of the batches;
- Any non-conformities that may have affected the processes of the milk bank or its partners (e.g., hygiene service, technical services, or laboratories).

9.2. Distribution and Delivery

· Pasteurised or freeze-dried milk must be delivered to neonatal services, paediatric services, or to infants whose health condition justifies it.

· Pasteurised or freeze-dried milk must be distributed at the request of the aforementioned services or another milk bank.

· An agreement between the milk bank and the transport service providers must be established to determine their roles and responsibilities.

· For each user service and at least annually, the milk bank reminds that milk from a personalised or anonymous donation is a health product and as such:

- It is a product for which an interruption in administration represents a significant loss of opportunity for the patient in terms of their development or protection against pathogens;
- It is a fragile and sensitive product;
- It is the responsibility of the user service to ensure complete traceability of its storage, use, or destruction;
- Any serious incident and any unexpected adverse effect must be reported for biovigilance.

· All regular supplies are subject to a contract between the facility hosting the milk bank and the facility receiving the milk. This document includes the elements mentioned above. It outlines the rights and obligations of each party, particularly in terms of biovigilance, and specifically the role of the local biovigilance correspondent, whose name must be mentioned along with that of their deputy. It designates the individuals to contact in case of problems or emergencies.

· The milk bank must ensure that the purchase order is properly validated and must record the distribution date, the numbers of the distributed batches, and the identification of the receiving service. Additionally, it must ensure proper transport conditions to the recipients

when it holds this responsibility. In this latter case, it must retain traceability elements attesting to the respect of the cold chain and validation upon receipt by the recipient, under the conditions set out in ***paragraph 1.2.*** on archiving.

· The appearance of the product and the integrity of the container and labelling must be checked during distribution or delivery.

· No frozen milk bottle can be returned to the milk bank after its distribution or delivery.

· Freeze-dried milk bottles can be restocked after checking and verifying the integrity of the bottle.

· The management of delivery must be conducted in a way that allows traceability to the recipient.

· Several types of milk (raw milk or milk treated by the milk bank) may be sent out for further administration (inter-service transfer, inter-establishment transfer, or transfer to the donor). To avoid confusion, a document specifies the number and type of products delivered and their use-by dates. This document, which accompanies the products, reminds of the conservation and hygiene instructions. A copy of this document signed by the donor is retained by the milk bank.

· The duration and conditions of milk conservation must comply with ***Appendix 4*** to allow for its distribution or delivery.

· When milk is distributed, traceability must be established to the recipient service that placed the order.

· The information required for distribution is minimally:

- The identification of the requesting service;
- The date of the order;
- The quantity and type of products requested.

10. Transport

· This chapter aims to define the requirements to be met for the transport of:

- Raw milk intended for treatment by the milk bank;
- Frozen pasteurised milk;
- Freeze-dried milk.

· Transport must strictly adhere to the conservation conditions of the products in compliance with the requirements set out in ***Appendix 4***. It may be handled by a hospital service or subcontracted to a service provider or a third party (e.g., the donor's spouse). In all cases, it is subject to a document approved by both parties (agreement, contract, or protocol) that specifically defines each party's roles and responsibilities, contact details for individuals to reach in case of problems, and procedures to follow in case of issues. Periodic audits are conducted by the order giver to ensure compliance with the provisions established with the transporter.

10.1. Transport of Donations Intended for Pasteurisation

· When the transport of raw milk is undertaken by a third party, the milk bank communicates guidelines to ensure the hygiene of the containers used for transporting the bottles, stabilising the bottles to avoid damage, and maintaining the cold chain.

· Regardless of the type of transport, a verification of compliance with transport instructions, appropriate labelling of bottles, absence of leaks, and compliance of containers is performed upon receipt. These checks are recorded.

· For subcontracted transport, any non-compliance regarding the condition of parcels, maintenance of temperatures, or adherence to schedules and transport durations must be reported immediately and will be subject to a written complaint followed in the non-conformity management system.

10.2. Transport of Finished Products

· Packaging is carried out under the responsibility of the milk bank following the procedure established for this purpose. This specifies the containers used for transporting the bottles,

temperature maintenance devices, the maximum and minimum number of bottles determined based on their volume, as well as the documents that must accompany the shipment (product list and related information).

· Provisions to guarantee the maintenance of the cold chain are put in place, such as validations of transport conditions or continuous monitoring of the temperatures of qualified containers. Records attest to compliance with these requirements.

· Containers are labelled to indicate the nature of the products and their storage temperature.

· The contact details of the milk bank as well as those of the recipient to contact in case of an accident are also indicated.

· When the milk bank handles transport, its responsibility extends until the product is received by the recipient. The milk bank issues a transport document. It ensures that transport conditions comply with regulatory requirements aimed at ensuring the safety of the transport of products and individuals. To this end, the verification and acceptance of the products upon receipt by the client are formally recorded and retained by the milk bank.

· When transport is undertaken by the recipient or their service provider, they are responsible for it. Before handing over the container to the transporter or the client, the milk bank ensures that the expected products are correctly delivered and that the parcels are in good condition. It asks the person to whom it delivers the products to verify these elements and to confirm this check and their acceptance of the products on a delivery receipt document.

· In the case of transferring milk to another facility, each type of product (raw milk and pasteurised milk) is placed in different containers that are clearly identified. The transfer of products in quarantine, due to awaiting microbiological results, can only be carried out if a proven system is in place to prevent any consumption of non-compliant products.

Appendix 1: Information System

Principle

· The information system encompasses all elements necessary for the collection, management, and electronic dissemination of information within an organisation. It provides the data required for the operation of management systems and operational systems to carry out the organisation's missions. Manual data entries and the configuration of the information system are among the critical sources of error for the functioning of this system.

· To define the system in collaboration with the supplier, developer, or services providing support on behalf of the milk bank, the user must establish a description of the system, the functions it must perform, and the interactions with operators. This specification document takes into account the security measures of the system, as well as the main characteristics of the system's operation and its interaction with other systems and procedures. This document includes a list of risks that must be managed (risks related to medical technical processes and the identification of the donor or infant, as well as IT risks).

· The risks considered include those inherent to information systems that concern security in terms of access and data availability.

1. Organisation of the Information System

The establishment of an information system is essential for ensuring adequate and secure management of milk from anonymous donations and its traceability.

1.1. Personnel in Charge of the Information System

· The information system is under the responsibility of specifically designated individuals, at least one of whom belongs to the milk bank (the responsible physician or a person to whom this function is delegated) and to the facility to which it is linked. These individuals ensure that the information system is designed and maintained to guarantee:

- the availability and backup of data;
- the compatibility of the software and its interfaces;
- initial validation and validation of changes;
- the organisation of physical and logical means to ensure the security of the information system;
- documentation and user support.

· A document managed within the quality system of the milk bank (charter, procedure, agreement) complements the role description of the above-defined responsible person and outlines the tasks and responsibilities of the partners. It is reviewed at least annually during a steering meeting of the information system process.

1.2. Suppliers

· When an external company is engaged for a service in the IT field, a written agreement specifies, in particular, that:

- the staff from this organisation is subject to professional secrecy rules;
- the necessary measures are implemented to ensure the protection and confidentiality of data;
- every intervention carried out on-site or remotely via telemaintenance is performed, at the request of the information system manager, by authorised and identified personnel. It is documented, includes the identification of the intervener, and is addressed to the system manager. Measures are implemented to prevent any connection prior to the authorisation of the milk bank manager or the delegated person. The competence and reliability of the supplier are key factors in the selection of equipment, software, or services. The user of the information system must take all necessary measures to ensure that the elements of the information system or

purchased services have been produced in accordance with a quality assurance system. The decision to conduct an audit at the supplier must be based on a risk assessment of the outsourced process.

1.3. Maintenance Service

· The methods and frequency of interventions on the elements of the information system, including equipment, software, applications, and operating systems, are defined.

· Every intervention (preventive or corrective) and its outcome are recorded in the form of a report. When carried out by an external intervener, it is essential to ensure that a formal agreement specifies the objective, the framework of the intervention, and the name of the internal responsible person in charge of monitoring the service.

1.4. Milk Bank Staff

· All personnel must have appropriate qualifications and access levels, with their assigned responsibilities formalised.

· Any major implementation or modification of the information system must be monitored and led by a structured organisation, such as a project management group, involving the various stakeholders (milk bank staff and the IT service of the facility, service providers, etc.).

2. Equipment and Premises

· The equipment is installed in premises that ensure physical security (including physical access and protection against destruction risks, particularly from fire) for the equipment and data.

· The premises housing the information system are subject to qualification against specific criteria.

· Backed-up data must be archived according to established deadlines for documentation archiving (Chapter 1.2), in separate and secure locations.

· A mapping of the information system is established in relation to the system's input and output data.

3. Data Security

· As part of risk management inherent to the information system, the following requirements must be met:

- Data is only entered, transferred, modified, or destroyed by authorised personnel. When significant data is entered manually, additional control must be provided to verify the consistency of what is recorded. This control can be performed by a second operator or through validated electronic means. A list specifying the rights concerning data for each authorised person (reading, writing, modification, etc.) is established;
- A procedure is established for granting, withdrawing, and determining the level of authorisation for entering, transferring, modifying, or destroying data, including modifications to personal passwords;
- The system allows for data entry control. It records the identity of the operators who enter, transfer, modify, or destroy any data. Any data modification is tracked;
- Data is protected against accidental or intentional damage. Each time data is acquired, transferred, or transformed, the system applies consistency controls between the initial data and the acquired, transferred, or transformed data. Any modification of significant data must be authorised and recorded, along with the reason for the change. Effective means are in place to limit unwanted intrusions and the installation of malicious software (firewalls, antivirus, etc.);
- The system must be capable of clearly restoring all data transfers, entries, modifications, and destructions;
- Backup and restoration procedures are regularly subject to reliability checks.

· Data availability is compatible with the exercise of activities. It is particularly important, throughout the entire archiving period, to be able to restore data in a timely and readable manner.

· If modifications to the IT equipment or its programmes are proposed, the aforementioned controls are performed at a frequency appropriate to the information storage medium. The data migration process must be defined, documented, and tested appropriately. This should ensure complete traceability, including necessary data archiving.
· A procedure is in place for degraded mode operation or waiting in case of unavailability of the information system. In the event of failure or breakdown, including any potential impact on data, corrective measures that have been tested and validated are established to address the encountered issue based on the defined degree of urgency. This procedure specifies the management of data during the return to normal operation.

4. Control of the Information System

· When implementing an information system or part of it, consideration must be given to the risk of losing certain functions of the previous system.
· Before being put into service and throughout its operation, any computerised system is checked to validate its capacity to meet specified objectives. If it is to replace a manual system, the quality of the product or quality assurance must not be affected, and both manual and computerised systems must operate in parallel for a specified duration within the testing and validation procedure.
· All tests and validation stages must be carried out, documented, and approved before routine use of the system.
· Any modifications to hardware, interfaces, software, configurations, or data structures are carried out according to defined procedures that include provisions regarding validation, control, authorisation, and implementation of the modification. Any modification is validated and can only be executed with the authorisation of the information system manager and must be recorded. Depending on the significance of the modification, the implementation of resources and the conduct of validation are entrusted to specifically identified individuals. Validation begins when the decision to acquire a new system or to implement a new process is made.
· It includes the steps described below.

4.1. Specification Document

· This is a precise description of the specifications expressed by the users. The representation of processes using algorithms should be encouraged, particularly to highlight control, blocking, or alert steps and their consequences.
· The first step to follow when computerising a milk bank is the establishment of a specification document.

4.2. System Selection

· This choice is made after sending the specification document to suppliers, analysing their responses, and, if applicable, their audit reports. Assurance that the materials and software (applications and operating systems) have been designed and produced in accordance with a quality assurance system is sought.
· A Design Qualification (DQ) protocol is established during the development of a new device or its adaptation, requiring a development phase. This protocol is part of the validation plan.

4.3. Risk Management

· This refers to the documented and reasoned assessment of the risks associated with the system. Risk management particularly includes and distinguishes:
    - IT risks;
    - process risks.
· Risk management defines severity levels, impacts on confidentiality, integrity, and data availability. This analysis allows for determining the required level of validation for managing a modification to the existing system.

4.4. Qualification Master Plan

· It describes the qualification steps and mobilises, as needed, the following protocols and their execution reports:
    - Design Qualification;

- Installation Qualification;
- Operational Qualification;
- Performance Qualification.

· Initial qualification must be as comprehensive as possible; subsequent qualifications can be streamlined as indicated in the master plan.

· The conclusion of these reports formally states the decision to proceed with validation by moving to the next stage.

· Whenever possible, the author of a qualification protocol should not be the person reviewing the results of the tests, approving, or rejecting them.

· System acceptance tests should verify the installation (installation tests, configuration tests), all functions, and performance of the system (functional tests, requirement tests) and also identify failures and the limits of the system's acceptable operation. If applicable, the transfer of data from one information system to another is also tested and validated. Each test case is documented.

· Any evolution or modification of the system is subject to an analysis identifying the functions potentially impacted by the change. Non

· Any evolution or modification of the system is subject to an analysis that identifies the functions potentially impacted by the change. Regression tests provide evidence that all previous functions are fully preserved.

· The qualification master plan also includes the main documents, which particularly cover:

- software or hardware changes;
- management of anomalies during validation;
- access management;
- data backup and restoration;
- contingency planning;
- training and authorisation of personnel.

4.5. Final Report

This report confirms that all acceptance criteria have been met. It indicates that any non-conformities or anomalies identified have been addressed. It concludes with the approval for production deployment.

Appendix 2: Microbiological Analyses

Principle

· The contamination of milk is due to the external introduction of microbial agents, which can begin with contamination from the donor or may arise from environmental germs. Furthermore, environmental conditions, particularly the storage temperatures of the milk, can promote the amplification of contaminants.

· The presence of microorganisms in milk is not a risk in itself, as scientific literature has shown that, on the contrary, the presence of certain germs can be beneficial, particularly for establishing the microbiota of infants, which is necessary for their current and future quality of life. However, milk is a medium that allows the proliferation of pathogenic germs, which, depending on the physiological state of the infant, can have serious adverse effects.

· The risk taken into account is the contamination of the infant by a pathogen harmful to their health.

1. Pre-pasteurisation Analyses

1.1. Standards for Sub-Batches

· When sub-lots are created, a sample is taken from each sub-lot to perform a count of the total aerobic flora. This analysis is conducted on blood agar or by a validated equivalent technique, with improved sensitivity and/or specificity compared to the reference method, after 24 hours of incubation at 37°C. The dilution of the milk to be performed depends on the inoculation method chosen by the biologist. While awaiting analytical results, the sub-lot is placed in quarantine at temperatures between 0°C and 4°C.

· Sub-lots are declared non-compliant if the total aerobic flora is equal to or greater than 10^6 bacteria per millilitre, after 48 hours of incubation at 37°C on blood agar, or 24 hours depending on the analytical method.

· Any non-compliant sub-lot is destroyed by the human milk bank, which will contact the donor to investigate the source of contamination.

· Compliant sub-lots are grouped into batches, and each batch undergoes bacteriological analyses before being bottled and pasteurised.

1.2. Standards for Batches

· The analyses performed are:
  - A count of the total aerobic flora on blood agar after 48 hours of incubation at 37°C;
  - A search and count of coagulase-positive Staphylococcus germs using a validated technique with improved sensitivity or specificity compared to the one using Chapman medium, after 48 hours of incubation at 37°C.

· The dilution of the milk to be performed depends on the inoculation method chosen by the biologist to detect the thresholds defined below.

· Batches are declared non-compliant if:
  - The aerobic flora is equal to or greater than 10^6 bacteria per millilitre;
  - Or if the count of coagulase-positive Staphylococcus germs is equal to or greater than 10^4 bacteria per millilitre.

2. Post-pasteurisation Analysis

· A final bacteriological analysis is conducted after pasteurisation by inoculating 0.5 ml of undiluted milk on blood agar, incubated for 48 hours at 37°C.

· Any culture result showing one or more colonies is deemed non-compliant. The corresponding batch is then destroyed.

· The destruction of non-compliant batches is carried out in accordance with the applicable regulations for waste disposal.

· A documented analysis is conducted to identify the causes of repeated non-compliances.

· After pasteurisation and cooling, and while awaiting analysis results, the bottles of milk are placed in quarantine. They can either be stored between 0°C and 4°C for a maximum of 48 hours before being frozen at a temperature below -18°C, or they can be frozen immediately at a temperature below -18°C.

· Only bottles of milk from batches declared compliant may be released for distribution or dispensation, or accepted for freeze-drying.

Appendix 3: Biochemical Performance Markers for Processes

Principle

· The milk processing procedures used at the human milk bank include conservation, thawing, freezing, blast freezing, pasteurisation, and freeze-drying of milk.

· Developments will impact existing processes in the medium to long term, and new processes may be introduced.

· To evaluate the impact of these modifications and new processes on the quality and safety of the milk, it is necessary, in addition to the microbiological quality of the product, to define markers that ensure the maintenance or improvement of the levels of active principles present in the milk. Thus, the process or technique to be evaluated should not create new risks. It must provide an improvement, at the very least maintaining the level of active principles achieved compared to the previous technique or process.

· The risks considered are the reduction of active principle levels and the risk of microbiological or chemical contamination due to the introduction of new processes that present improvements in one or more characteristics of the product or processes.

1. Selection of Markers

The criteria for selecting markers are as follows:

- Elements that are sensitive to environmental conditions (mainly temperatures);
- Elements unequivocally recognised (state of the art) as active principles of milk;
- The existence of a standardised reference analysis method for the selected element.

2. Markers and Analysis Standards

· The markers and analysis standards are:

- Secretory immunoglobulins (IgA) (proteins with immune properties): comparison of immunoglobulin levels before and after treatment;
- Lactoferrin (a protein with metabolic and immune activity): comparison of lactoferrin levels before and after treatment;
- Lipase (a protein with metabolic activity): comparison of lipase levels before and after treatment.

· These markers are used for process validation studies.

Appendix 4: Metrological Parameters of Processes

Principle

· The facilities and equipment intended for essential operations for the quality and safety of the product undergo qualification prior to their first use, which is maintained in a valid state with regular maintenance throughout their use. In this context, the critical parameters of the equipment that affect storage in human milk banks or during transport, thawing, pasteurisation, or freezing of milk must be standardised across all human milk banks.

· The risks considered are the microbiological contamination of milk, bacterial or fungal proliferation, and the loss of active principles.

1. Storage of milk

· The milk storage areas are designed to ensure storage conditions for the products in accordance with current regulations. To this end, they are maintained within temperature limits that guarantee the preservation of the various products. The specific conservation conditions are adhered to, measured, and continuously controlled. The relevant areas are placed under effective alarm.

· The refrigeration period at a temperature between 0°C and 4°C must not exceed 48 hours.

· Refrigerated donations from donors are frozen upon receipt and maintained at a temperature between -40°C and -18°C. The same storage conditions apply to pasteurised milk. The shelf life of frozen pasteurised milk is 8 months from the date of pasteurisation, and 18 months for freeze-dried products stored away from light at temperatures not exceeding 28°C.

2. Transport of milk

The transport of milk, from collection to distribution or dispensation, is conducted strictly following the cold chain.

2.1. Donations Intended for Pasteurisation

· For transport durations not exceeding 30 minutes, no threshold temperature is set. The donation must remain refrigerated or frozen according to its initial state of preservation, and transport should be carried out in insulated containers with eutectics to maintain a temperature close to the storage temperature.

· For transport durations of 30 minutes to 2 hours, donations must be transported:

- Either in validated containers to maintain temperature conditions between 0°C and 8°C or below -10°C, depending on whether they are refrigerated or frozen donations;
- Or in containers where the temperature of the donations is monitored upon receipt and is between 0°C and 8°C or below -10°C, depending on whether they are refrigerated or frozen donations.

· For transport durations exceeding 2 hours, the donation must be transported frozen and maintained at a temperature between -30°C and -10°C.

2.2. Pasteurised Milk

· For transport of frozen products not exceeding 30 minutes, transport must occur in insulated containers that maintain the product in a frozen state. Products thawed before or after transport must be stored at temperatures between 0°C and 8°C for use within 24 hours of thawing. Milk placed at room temperature must be consumed within one hour.

· For transport durations of 30 minutes to one hour, transport must be carried out in containers where the temperature is continuously monitored or in validated containers regularly tested for their ability to maintain the required temperature conditions between 0°C and +8°C or below -10°C, depending on whether they are refrigerated or frozen donations.

· For transport durations exceeding one hour, the transport chambers or containers are qualified to maintain the product at temperatures between 0°C and 8°C for refrigerated products, or between -40°C and -18°C for frozen products. The transport temperature of the

products is recorded upon receipt, and this information must be included on the delivery note and condition the acceptance of the product by the recipient.

2.3. Pasteurised and Freeze-Dried Milk

· Freeze-dried pasteurised milk is transported away from light and at an ambient temperature below 28°C.

3. Thawing Of Milk Before Pasteurisation

· Milk must be thawed under conditions that limit the effect of temperature on active principles and the proliferation of microorganisms. In this context, the thawing method must be validated to ensure that the product temperature does not exceed 8°C within a period of less than one hour.

· If a storage phase follows, the thawing phase must not exceed 24 hours, and the product temperature must not exceed 4°C.

4. Pasteurisation

· Pasteurisation is characterised by the parameters of duration and temperature. The requirements described below regarding these two parameters must be met to ensure the quality of the milk and reduce the risk of biological contamination. The pasteurisation plateau is characterised by maintaining the temperature between 62.5°C and 64.5°C for a duration of between 30 and 35 minutes, and exposure to temperatures above 58°C for less than 50 minutes.

· The qualification of the pasteuriser takes into account these data as well as internal references for temperature rise and fall during the pasteurisation processes.

· The use of methods equivalent to pasteurisation is subject to a bibliographic analysis of the benefits and risks and to a validation of the process conducted according to ***Appendix 2 and 3.***

5. Freezing Milk After Pasteurisation

· The cooling kinetics of the products are optimised to reduce bacterial proliferation and lipid and protein degradation. The temperature of the products must be reduced to between 0°C and 8°C within a maximum period of 2 hours.

· Whenever possible, milk is frozen directly after the pasteurisation phase. If operations such as sorting batches before freeze-drying need to be carried out, the product is kept refrigerated for a duration that should be optimised.

Appendix 5: Hygiene Requirements for Donors

Principle

· Hygiene requirements for donors are necessary to minimise contamination of the donation during collection and to prevent the proliferation of residual flora in the donation.

· The milk bank provides written instructions to donors regarding the hygiene rules to follow during the collection of donations, the equipment to use, and the storage rules for the donation, including appropriate cleanliness measures (cleaning and disinfection) to be carried out at least once a month for the storage area (refrigerator and/or freezer).

· The donation is collected in accordance with the aforementioned hygiene rules and is stored at the donor's home under temperature and storage duration conditions established by the milk bank. The donor commits in writing to adhere to these hygiene rules prior to the collection of their donation.

· The risk considered is the contamination of the donation, which could lead either to the loss of a product deemed non-compliant or to the contamination of the infant by an undetectable pathogen.

1. Equipment for Collecting Donated Milk

· Donations are collected in single-use bottles provided by the milk bank, which manages their distribution.

· Breast pumps and their accessories are either supplied by the milk bank or obtained through a prescription issued by a physician associated with the milk bank. In all cases, an instruction manual for these devices is provided, and the milk bank conducts follow-ups to ensure proper adaptation, use, and maintenance. Specifically, the cleaning, disinfection, and storage of reusable items are defined by the milk bank.

2. Rules for Collecting Donated Milk

The cleaning procedures for the breasts and items that come into contact with them (clothing, gloves, towels, etc.) are part of the written information provided to donors by the milk bank.

· These documents emphasise the importance of handwashing before collection and daily washing of the breasts.

3. Rules for Storing Donated Milk

· The collected donation must be placed in the refrigerator or frozen as soon as possible, and no later than 30 minutes after collection. It can be stored in the refrigerator for a maximum of 48 hours after collection.

· The mixing of refrigerated donations with newly collected donations can only occur after the latter has been refrigerated.

· The cleaning procedures for storage areas and temperature monitoring requirements are defined.

· Storage conditions are specified to prohibit the use of areas exposed to significant temperature fluctuations (such as the door of refrigerators) or in contact with potentially contaminating foods.

Appendix 6: Medical Contraindications for Donor Candidates

Revised version dated 4 September 2025

Principle
Donors are selected following a medical interview—mandatory for anonymous donations—designed to identify risks. Some contraindications may be temporary. Donors must be informed that they are required to report any change in their circumstances to the milk bank.
The risk factors listed below lead to:
• contraindication for the current donation, or permanent exclusion;
• or temporary contraindication, depending on the conditions described.

1) USE OF TOXIC SUBSTANCES
1-a) Current use of tobacco or nicotine-containing products, in any form (cigarettes, patches, e-cigarettes, gum, inhalation, etc.).
1-b) Current or past intravenous drug use by the donor or her current partner.
1-c) Current use of other illicit drugs by non-intravenous routes (e.g. cocaine).
1-d) Use of cannabis or CBD within the past 12 months, in any form: temporary contraindication for 12 months after the last use.
1-e) Regular alcohol consumption.
1-f) Occasional alcohol consumption: temporary contraindication, subject to medical assessment.

2) EXPOSURE TO INFECTIOUS AGENTS
2-a) Bacterial, fungal, parasitic or viral infection transmitted through sexual relations (particularly due to risky sexual behaviour by the donor or her partner), or acquired during a stay in areas at risk of vector-borne or otherwise transmissible infections as defined by Santé Publique France.
2-b) Active hepatitis B infection in the donor or her current partner.
2-c) Active hepatitis C infection in the donor or her current partner.
2-d) Donor or current partner has had high-risk sexual relations or multiple sexual partners: temporary contraindication of 4 months after the last exposure and cessation of such practices.
2-e) Donor or partner has had a sexually transmitted infection: temporary contraindication of 4 months after symptoms have resolved.
2-f) Sexual intercourse with a former partner (with whom sexual relations have ceased) who has a positive serology for HIV, HTLV, or hepatitis B or C: temporary contraindication of 4 months after the last intercourse.
2-g) Needlestick or blood exposure injury: temporary contraindication of 4 months after exposure.
2-h) Tattoo, piercing (including ear piercing), acupuncture, varicose vein sclerotherapy, mesotherapy using multi-use needles: temporary contraindication of 4 months after the procedure and provided no new procedure occurs during the donation period.
2-i) Stay in countries with infectious risk, or contact with certain infectious diseases (list published by Santé Publique France): temporary contraindication of 4 months after returning from the stay.
2-j) Positive serology for HIV or HTLV in the donor or her current partner.

3) EXPOSURE TO UNCONVENTIONAL TRANSMISSIBLE AGENTS
3-a) Treatment with growth hormone prior to 1989.
3-b) Surgical procedures where the risk of transmission of unconventional agents is not controlled: tissue or organ transplant, history of neurosurgery (brain or spinal surgery), surgery of the eyeball (other than for myopia) before 1 April 2001.
3-c) Transfusion of labile blood products (blood, platelets, fresh frozen plasma, freeze-dried plasma) and exchange transfusion, regardless of date.
3-d) Personal and/or family history of neurodegenerative disease (e.g. Creutzfeldt–Jakob disease).

3-e) Travel or stay in the United Kingdom for more than one cumulative year between 1 January 1980 and 31 December 1996.

4) MEDICATIONS OR FOOD SUPPLEMENTS

Consumption of medicines contraindicated for infants, herbal products or food supplements may constitute a contraindication to anonymous milk donation.
The milk bank must carry out a detailed analysis of the products consumed by the candidate, as donor milk is primarily intended for premature newborns.
The milk bank has access to an updated and standardised list of medications contraindicated for infants, regularly updated by the French Milk Banks Association (ADLF). For herbal or dietary supplements, the composition and origin must be verified to determine compatibility with donations. In the absence of data, donation must be contraindicated.
The milk bank's responsible physician ensures that medical questionnaires have been completed by each donor and reviewed by a doctor or midwife.

Explanatory notes on Appendix 6 about Medical contraindications for donor candidates

Revised version 4 September 2025

These notes provide additional information prepared by the French Human Milk Bank Association (FHMBA) to assist milk bank professionals in determining whether a potential donor may donate her milk.
2-a) Discussions regarding risks linked to a stay in an at-risk area should be carried out on a case-by-case basis with the milk bank team, referring to the Ministry of Health websites (list of diseases on Santé Publique France: www.santepubliquefrance.fr/maladies-et-traumatismes/maladies-a-transmission-vectorielle
2-b) If the partner's hepatitis B infection is active, but the mother is vaccinated against hepatitis B and the presence of anti-HBs antibodies has been confirmed, donation is possible.
2-c) A resolved hepatitis C infection (see flowchart in the 2022 Good Practice Guide) is not a contraindication if the PCR test is negative.
2-e) Sexually transmitted papillomavirus infections and fungal infections are not contraindications, as they are not transmitted through breast milk.
2-e) Syphilis is not transmitted through breast milk, but it is a sexually transmitted infection and is therefore a temporary contraindication for 4 months (see point 2-d).
2-g and 2-h) Blood exposure accidents, tattoos, piercings, acupuncture, varicose vein sclerotherapy, and mesotherapy using reusable needles are temporary contraindications for 4 months. This differs from blood donation, where the use of viral genomic diagnostics reduces this period to 2 months. Note that there is no contraindication if single-use equipment is used. Endoscopy is not considered a contraindication for milk donation.
3-a) Treatment with human-derived gonadotrophins (fertility treatment) is not a contraindication. Unlike human growth hormone, which used to be extracted from the brain, human gonadotrophins are extracted from urine or placenta, which greatly reduces the risk.
3-b) Artificial insemination, with or without prior donor screening, is not a contraindication, as it inevitably took place more than 4 months earlier.
3-c) Autotransfusions, injections of iron, and immunoglobulins (e.g. Rophylac®) carried out in healthcare facilities (not for sports doping or bodybuilding, for example) are not contraindications.
3-d) Personal and/or family history of Alzheimer's disease or Parkinson's disease is not a contraindication.

Appendix 7: Algorithms for Processing Serological Test Results of Donor Candidates

Principle

· The results of serological tests are analysed with the aim of protecting the infant, as well as serving as tools to guide the treatment of the donor when a pathology is suspected.

· The risks considered are the wrongful exclusion of donor candidates and the loss of opportunity for individuals who may be seropositive for one of the markers being tested.

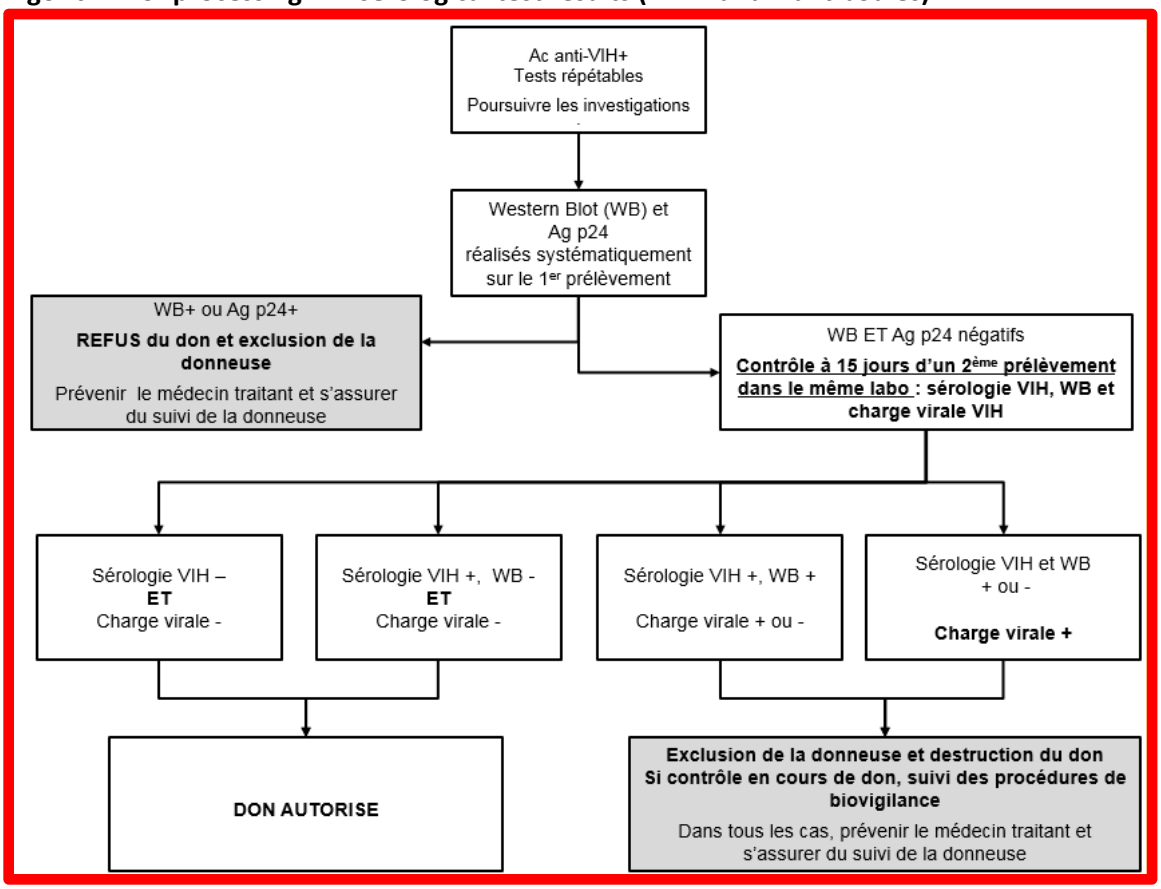
· The role of the human milk bank physicians is to establish prescriptions for screening tests if they have not already been conducted, in compliance with current regulatory requirements. In cases of initial tests that are non-compliant with the conclusions of these algorithms, they must refer the donor candidate to a specialised service or ensure that this has been done.

· The algorithms allow for a determination on the ability to accept a donor candidate presenting an initial non-compliant test.

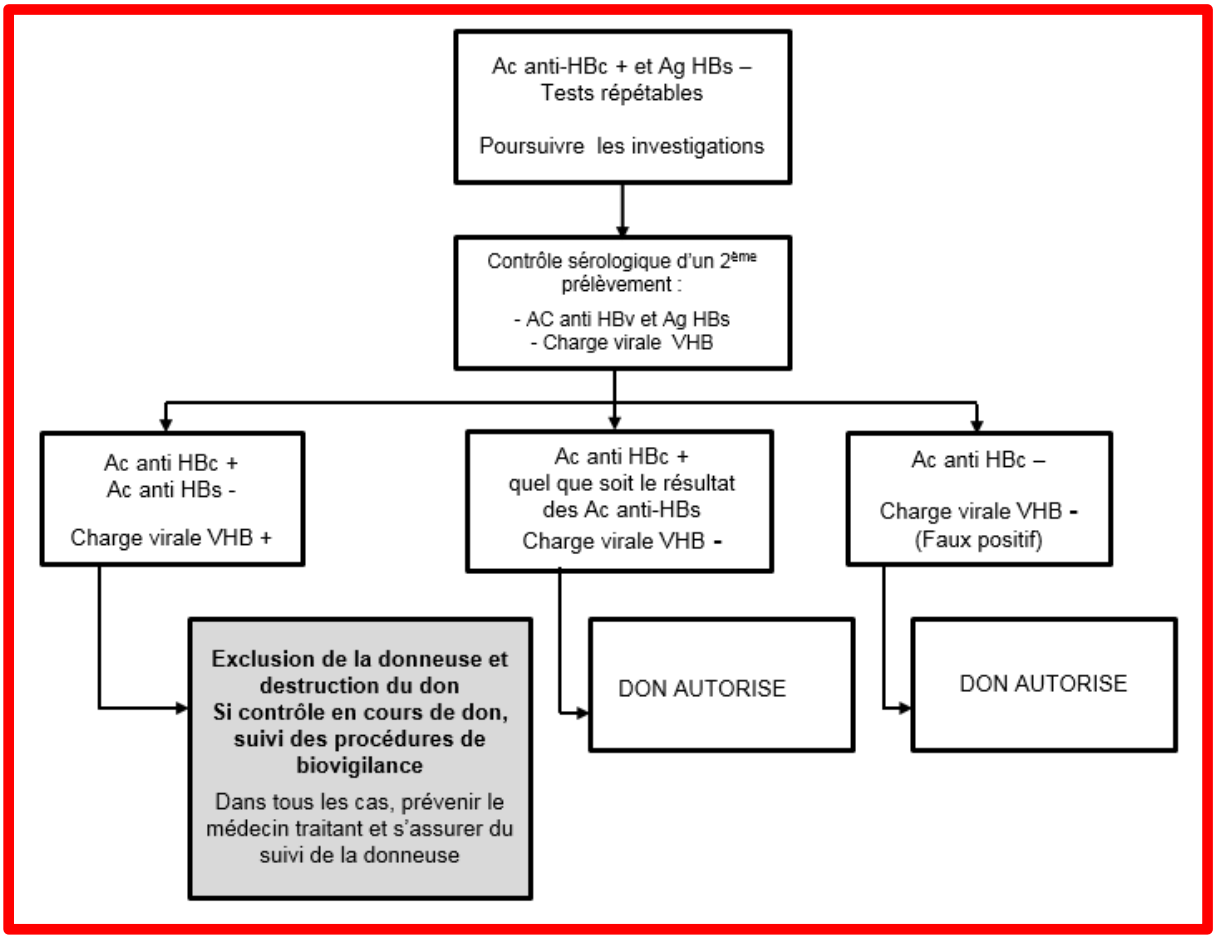
Figure Legend (Algorithm)

+ : Positive test reaction
- : No detection in the test performed
Viral load detected through RNA or DNA detection using a validated viral genome screening method.
Ac : Antibodies
Ag : Antigen
HTLV : Human T Lymphotropic Virus
HIV : Human Immunodeficiency Virus
HBV (or C) : Hepatitis Virus (B or C)
WB : Western Blot

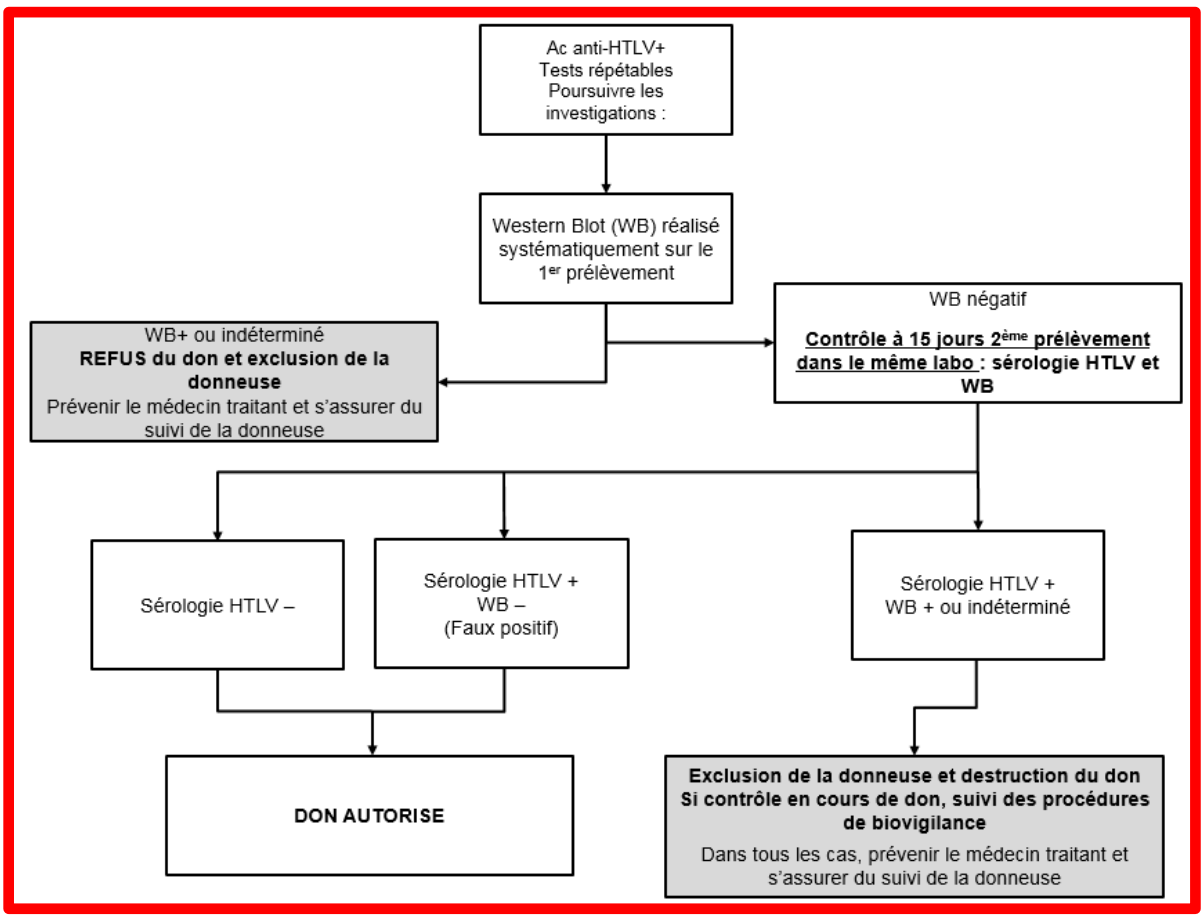
Algorithm for processing HIV serological test results (HIV 1 and 2 antibodies)



Algorithm for processing HBV serological test results (HBcAb and HBsAg)


Ac anti-HBc + et Ag HBs –
Tests répétables
Poursuivre les investigations
Contrôle sérologique d'un 2ème prélèvement :
- AC anti HBv et Ag HBs
- Charge virale VHB
Ac anti HBc +
Ac anti HBs -
Charge virale VHB +
Ac anti HBc +
quel que soit le résultat des Ac anti-HBs
Charge virale VHB -
Ac anti HBc –
Charge virale VHB -
(Faux positif)
Exclusion de la donneuse et destruction du don
Si contrôle en cours de don, suivi des procédures de biovigilance
Dans tous les cas, prévenir le médecin traitant et s'assurer du suivi de la donneuse
DON AUTORISE
DON AUTORISE

Algorithm for processing HCV serological test results (anti-HBc)



Appendix 8: Characteristics Related to Freeze-Drying

Principle

· The design, use, and maintenance of the facilities and equipment (materials, medical-technical computer systems or device control systems, monitoring systems, air treatment units, etc.) used in the freeze-drying of milk are essential elements in controlling the risk of contamination. This risk particularly exists during the freeze-drying phase, especially when opening vials.

· A satisfactory level of control is achieved by adhering to the following instructions concerning:

- the qualification of the premises and equipment intended for the freeze-drying of milk or for controlling the environment of this operation, and the validation of methods (freeze-drying, cleaning, sterilisation);
- the use and maintenance of the premises and equipment intended for the freeze-drying of milk or for controlling the environment of this operation;
- the performance of microbiological analyses post-freeze-drying.

· The risks considered include microbiological contamination during or after freeze-drying, or a significant loss of active ingredients.

1. Qualification of Premises and Equipment for Milk Freeze-Drying and Method Validation

The premises and equipment intended for the freeze-drying of milk are qualified according to a master plan that follows these steps:

1.1. Needs Analysis and Risk Management

· A precise description of the freeze-drying process and the preceding steps that may influence this operation is an essential part of these processes.

· The needs analysis and risk management are documented. They lead to the definition of functional specifications for the premises and materials in terms of required functions and performance. This not only defines the characteristics of the equipment but also the handling procedures for products (transport of products, loading and unloading methods for freeze-dryers), as well as microbiological and particulate monitoring of the environment or cleaning and sterilisation procedures.

· These specifications must be reviewed and approved by the human milk bank.

1.2. Design Qualification

· The products (raw materials and finished products) and containers must be characterised to track the freeze-drying process.

· The parameters of the freeze-drying process and their tolerances must be established and documented (temperature and pressure ranges, freezing rate, duration at a given temperature and pressure, capacity, etc.).

· The design phase must also consider the means of monitoring the process, maintenance procedures (especially cleaning and on-site sterilisation specifications), calibration of measurement systems, and alarm systems as well as degraded operation modes. The design qualification dossier must be formally conclusive and determine the progression to the next stage.

1.3. Installation Qualification

· The acceptance of the premises and equipment is subject to verification.

1.4. Operational Qualification

· Operational qualification must consider, within the specified operational limits, at a minimum, leak tests, thermal control system tests, vacuum installation tests, condenser refrigeration tests, thawing tests, cleaning and sterilisation tests, vial sealing tests, and temperature distribution tests on vial supports.

· Upon validation of this stage, production may commence.

1.5. Performance Qualification

· The performance qualification dossier must be formally conclusive.

1.6. Validation of the Freeze-Drying Process

· A study conducted on products from at least three production lots allows for characterisation of the freeze-drying process.

· Validation of this process is established when the results of this study correspond to the expected characteristics of the products.

· Data must be obtained periodically to demonstrate that the process validation is maintained.

2. Use and Maintenance of Premises and Equipment for Milk Freeze-Drying

Detailed instructions concerning personnel, premises, and equipment are established and followed in the context of the freeze-dried milk production process and environmental monitoring.

2.1. Staff

· Special training should be provided to individuals working in areas where contamination may pose a particular risk, such as controlled atmosphere zones.

· Personnel clothing and quality must be appropriate for milk processing and the classes of work areas. They must be worn in a manner that protects the product from contamination.

2.2. Premises and Equipment

· The premises must be located in an environment that, taking into account measures taken to protect the milk processing, does not present a risk of contamination for the products.

· Cleaning and disinfection operations must follow written and validated protocols.

· Milk must be protected from any risk of contamination, particularly during phases when vials are uncapped. This protection is achieved by controlling the particulate concentration in these controlled atmosphere zones, for which a maximum number of particles is defined, both at rest and during activity, to ensure a required cleanliness level.

· These zones must be monitored with appropriate frequency and sampling so that any changes in contamination levels and any system failures are detected. Alert thresholds and action thresholds must be defined, and a procedure must outline the actions to be taken in case of exceeding the action threshold.

· Microbiological and particulate controls of the air and surfaces are carried out in accordance with methodological recommendations from ISO standards related to clean rooms and related controlled environments, according to a periodicity, a monitoring plan, and validated sampling methods described in a procedure. These controls address contaminations related to bacterial and fungal flora.

· A degraded operation procedure must be established.

3. Post-Freeze-Drying Analyses

· The freeze-drying operation should not increase the microbiological load of pasteurised milk, and the analyses to be performed are those defined for pasteurised products in ***Appendix 2, paragraph 2***.

· The water content must be determined to ensure the preservation of the finished product for 18 months at ambient temperature. This characteristic is a validation element of the process that must be taken into account for the release of each lot.

· After freeze-drying and pending analytical results, the milk vials are placed in quarantine.

· Any lot with non-compliant analysis after freeze-drying is destroyed.

· A documented analysis is conducted to identify the causes of repeated contaminations.