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ConcePTION

WP4 – Establishment of a non-commercial, Europe-wide breast milk biobank and analytical centre

D4.4 Description of basic quality management structure for biobanking and pre-analytical handling of human breast milk specimens

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Contents

1. Abbreviations

ADME: absorption, distribution, metabolism and excretion
ICH: International Council for Harmonisation of Technical Requirements for Pharmaceuticals for Human Use
ISO – International Organisation for Standardisation
Lactmed – Drugs and Lactation Database
Opt – Option
QC – Quality control
QM – Quality management
QMS – Quality management structure
SmPC – Summary of Product Characteristics
TR – Technical Report
UBB – Uppsala Biobank
UCR – Uppsala Clinical Research Centre
UDOPP - Uppsala Drug Optimization and Pharmaceutical Profiling platform

ISO 20387 Biotechnology – Biobanking – General requirements for biobanking
ICH-GCP: Guideline for of Good Clinical Practice E6 (R2)
ISO / TR 22758 Biotechnology – Biobanking – Implementation guide for ISO 20387
ISO 15189:2012 - Medical Laboratories – Requirements for quality and competence
ISO 20186 – Molecular in vitro diagnostic examinations – Specifications for pre-examination processes for venous whole blood
ISO 9001:2015 – Quality management systems – Requirements
Guideline FDA – Clinical Lactation Studies: Considerations for Study Design. Guidance for Industry

2. Summary

ConcePTION will establish a sustainable EU breast milk biobank and bioanalysis centre in Uppsala to enable research on medication levels in human milk. Uppsala, and other clinical centres around Europe, will collect and analyse breast milk and blood samples from nursing women who are under medical treatment. Those samples will be shipped for long term storage to Uppsala.
In order to guarantee the provision of high-quality samples and associated data, the breast milk biobank and analysis centre in Uppsala needs to run an appropriate Quality Management System (QMS) fulfilling state-of-the-art requirements as provided in (international) standards. Within WP 4 the basic structure of the QMS will be developed from a set of applicable European and International Standards for biobanking and pre-analytical sample handling (e.g. ISO 20387, ISO 9001, ISO 20186 etc.) and the guideline for Good Clinical Practice E6 (R2), ICH-GCP for the protection of donor rights and safety.

3. Description of basic quality management structure for bio banking and pre-analytical handling of human breast milk specimens

3.1 Organisation of the breast milk biobank and analytical centre Uppsala

Building a 'breast milk biobank and analytical centre" requires a comprehensive quality management approach, to secure and control all operations associated with conducting clinical trials, biobanking activities, and downstream analysis procedures at multiple process levels.

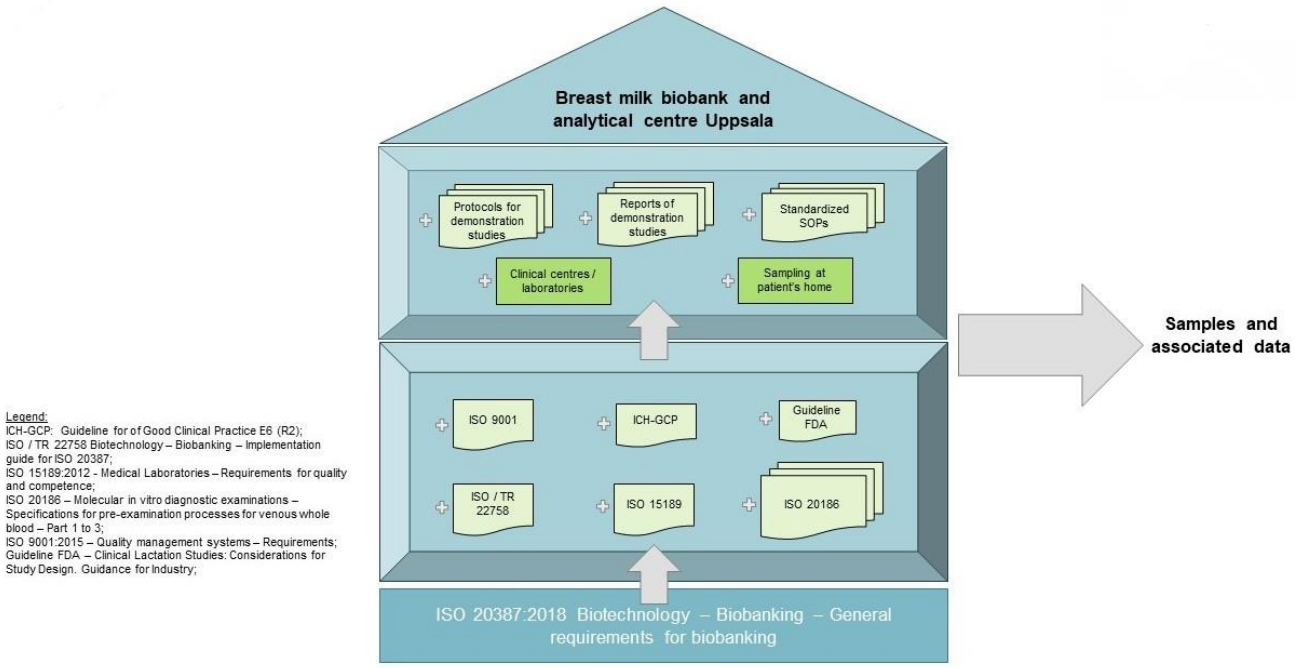

Fig. 01 Organisation of the breast milk biobank and analytical centre Uppsala

The basis of the QMS is the ISO 20387:2018 Biotechnology – Biobanking- General requirements for biobanking. This standard "specifies general requirements for the competence, impartiality and consistent operation of biobanks including quality control requirements to ensure biological material and data collections of appropriate quality. It is applicable to all organizations performing biobanking, including biobanking of biological material from multicellular organisms (e.g. human, animal, fungus and plant) and microorganisms for research and development"[1].

Based on this, the ISO / TR 22758 Biotechnology – Biobanking – Implementation guide for ISO 20387 is a technical report to consider. This document provides guidance on the implementation of the quality management, management, and technical requirements of the ISO 20387. "It expands on aspects of ISO 20387 and provides examples for illustration purposes. The aim of this document is to assist biobanks to address competency of personnel and appropriate quality of biological material and data collections. This technical report is equally applicable to newly established and existing biobanks"[2].

Other standards and guidelines that are important for the setup of the breast milk biobank and analytical centre are as following:

ISO 15189:2012:
The ISO 15189 specifies the requirements for the quality and competence in medical laboratories. This standard "can be used by medical laboratories in developing their quality management systems and assessing their own competence. It can also be used for confirming or recognizing the competence of medical laboratories by laboratory customers, regulating authorities and accreditation bodies"[3]. Since the laboratories of the Uppsala Biobank, which will be involved in the processing of the blood and human breast milk samples, are already ISO 15189-accreditated, this standard and its regulation must also be considered for the QMS of the breast milk biobank and analytical centre.

ISO 20186 – Part 1-3:
A standard, which adresses the standards and pre-analytical variables that are essentiel for working with samples is the ISO 20186 – Molecular in vitro diagnostic examinations – Specifications for pre-examination processes for venous whole blood. The standard gives guidance on handling, storage, processing and documentation of venous whole blood specimens during the pre-examination phase before a molecular examination is performed. "This document covers specimens collected in venous whole blood collection tubes. It is applicable to any molecular in vitro diagnostic examination performed by medical laboratories. It is also intended to be used by laboratory customers, in vitro diagnostics developers and manufacturers, biobanks, institutions and commercial organizations performing biomedical research, and regulatory authorities"[4].

ISO 9001:2015:
"The biobank shall establish, document, implement and maintain a QMS that is capable of supporting and demonstrating the consistent achievement of the requirements of this document and assuring the quality of biobanking"[5]. ISO 9001:2015 – Quality management systems – Requirements specifies the requirements to plan, establish, implement, operate, monitor, review, maintain and continually improve a documented management system used to manage quality. The requirements set in this standard are generic and intended to be applicable to any organization, regardless of its type or size, or the products and services it provides. The standard plays for the organisation and later implementation of the QMS an important role.

ICH GCP:
Another important document for the structuring of the QMS is the ICH-GCP: Guideline for of Good Clinical Practice E6 (R2). It is a harmonised guideline (published by the International Council for Harmonisation of Technical Requirements for Pharmaceuticals for Human Use / ICH) that "protects the rights, safety and welfare of human subjects, minimises human exposure to investigational products, improves quality of data, speeds up marketing of new drugs and decreases the cost to

sponsors and to the public. Three basic ethical principles of equal importance, namely respect for persons, beneficence, and justice, permeate all other GCP principles. Research involving humans should be scientifically justified and described in a clear, detailed protocol"[6].

Clinical Lactation Studies:
An additional guideline that has to be considered for setting up the QMS is the Clinical Lactation Studies: Considerations for Study Design . Guidance for Industry. This guidance provides recommendations for sponsors conducting clinical lactation studies. The document reflects FDA's current recommendations regarding pre- or post-marketing lactation studies by drug sponsors. It provides information to facilitate the conduct of lactation studies[7].

A further important element of the QMS are the SOPs, protocols, reports and standard documents for the pre-examination processes, which have already been developed within ConcePTION, respectively which will be developed in the course of setting up the structure. These documents will describe the sampling, handling and storing processes of the samples and will be drafted according to the intended use (i.e. clinical study and/or breast milk collection for biobanking purposes). All the documents and relevant literature are filed at the ConcePTION member area (https://members.imi-conception.eu/Member-Area/Work-Package-4?folderId=3339&view=gridview&pageSize=10) and are available for the ConcePTION consortium.

3.2 Structure of QMS* for breast milk biobank and analytical centre Uppsala

The breast milk biobank and analytical centre will be set up within the Uppsala Biobank (UBB) as an additional service to the existing structure. UBB as an organisation is not yet quality-certified or accredited, but the Uppsala Hospital laboratory and the laboratory at the Uppsala Clinical Research Centre (UCR) are both ISO 15189 accredited.
However, UBB is currently working on a QMS according to ISO 20387, independent of the ambitions of WP4, which are to set up the structure for the breast milk biobank and analytical centre. Since the analytical centre will function within UBB, it is all the more important that the structures are coordinated and synergies are used sensibly, taking into account the requirements of the standard(s). Therefore, the UBB QM team has been involved in the efforts from the very beginning, and regular coordination meetings are already in progress.

The Uppsala Biobank (UBB) started in September 2008 and had four aims: 1) to administrate UBB 2) to build a stable and long-term organization 3) to be a competence centre for biobank matters 4) to build an infrastructure for research[8]. Since then it became a research infrastructure and a centre of expertise for biobank issues at Uppsala University and Uppsala Region.
The UBB is organizationally linked to the UCR laboratory, where the head of the UBB is also the department head for the UCR laboratory. The UCR Laboratory is an accredited analytical laboratory that primarily performs biomarker analysis for researchers and businesses in a clinical setting. In addition to analysis, the laboratory can assist with laboratory-related advice, method development, verification, reformatting and sample handling, etc., among other things. (Find further information on UBB online at https://www.uppsalabiobank.uu.se/sv/).

* According to ISO 20387:2018

The QMS of the breast milk biobank and analytical centre Uppsala according to ISO 20387:2018 will be structured in the following chapters 01 - 06:

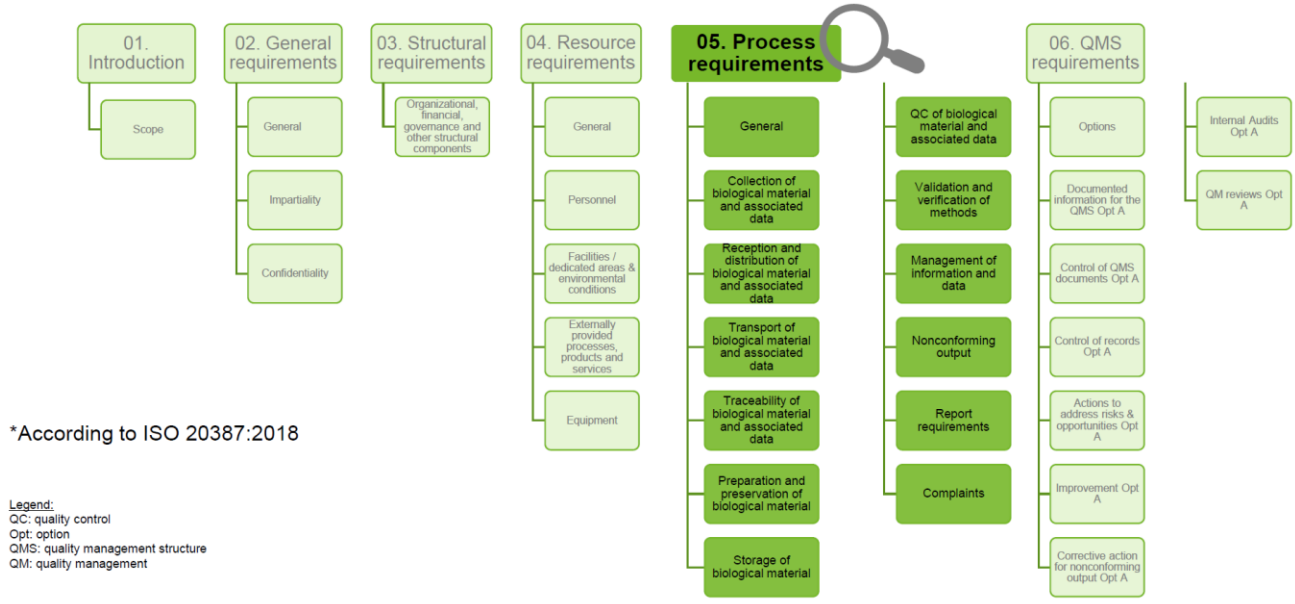

Fig. 02 Structure of QMS for breast milk biobank and analytical centre Uppsala

A short description of the requirements of the respective chapters is as following:

01. Introduction:
Will present the scope of the breast milk biobank and analytical centre Uppsala according to the ISO 20387:2018 and the general requirements for the competence, impartiality and consistent operation including quality control requirements to ensure that the biological material and data collections are of appropriate quality. It outlines the requirements to promote the confidence in biobanking and how fulfilling the requirements of the standard will enable to demonstrate competent biobank operation and the ability to provide biological material and associated data of appropriate quality for research and development.

02. General requirements:
Will give advice to define the purpose of the breast milk biobank (e.g. Mission and Vision of the biobank, etc.). Furthermore, it will describe the concept of impartiality and confidentiality and how it can be applicable to the biobanking area according to the requirements of the standard. A biobank, no matter what's the purpose of it is or what kind of samples it deals with, should respect these principles in a manner adapted to their specificity. Hence, the breast milk biobank QMS will be adapted accordingly.

03. Structural requirements:
The breast milk biobank will define the specifications of the organizational, financial, governance and other structural components and explains it in more detail by creating a documented QMS accordingly. The scope of conformity, a risk-based approach or the strategic direction of the biobank are just a few elements within the QMS which will be discussed and established in order to meet the requirements of the ISO 20387.

04. Resource requirements:
Chapter 04 and its sub chapters will deal with the general aspects of the necessary resources of the breast milk biobank, the personnel, facilities & dedicated areas & environmental conditions, externally provided processes, products and services and the equipment. The biobank will address its financial viability and safeguard it for their activities. The personnel has to act according to the confidentiality arrangements, it has to be competent and further personnel management activities have to be carried out. Considerations related to processes of safeguarding facilities and environmental conditions will be made, e.g. chemical safety, biosafety / biosecurity, physical safety, inventory protection, facility management, information / data security, fire safety and more, if applicable.
All the externally provided processes, products and services which are being supplied by a legal entity (or part thereof) that is not the biobank, will be checked for compliance with the UBB requirements. Regarding equipment, the biobank will use the equipment, needed for all the activities, in a controlled way and in time of need.

05. Process requirements:
These are important elements in the QMS of the breast milk biobank. All the processes that occur during the life cycle of a biological material and its associated data, including collection / acquisition, analysis, processing, storage, access and distribution, will be described.
Collection, reception and distribution, transport (internal / external), traceability, preparation and preservation, storage, retrieval and quality control of the sample and its data are key elements in the entire handling process. Since these steps will take place at different laboratories and clinical sites, a description of the standardized workflow will be absolutely necessary in order to guarantee the appropriate quality samples for further analysis and / or for the intended use.
The validation and verification of processing methods might also have an effect on the output (biological samples) and will be described accordingly.
The sub-chapter management of information and data will explain the requirements regarding the procedures for implementation, modification and use of computer systems, software, hardware and database(s) when applicable.
The sub chapters non-conforming output and complaints are connected with each other and will define the management, respective countermeasures and the required documented information in case the output that doesn't conform the predefined requirements and/or agreements with the recipient / user and/or agreement with the provider and resulting complaints.
The report requirements will describe the minimum information of the report the biobank has to provide for its stakeholder and users.

06. QMS requirements:
For the breast milk biobank, the QMS will meet the minimum requirements of the QMS according to the ISO 20387:2018 and will be in compliance with the ISO 9001:2015. In chapter 06 the requirements to plan, establish, implement, operate, monitor, review, maintain and continually improve a documented management system used to manage quality will be described in detail.

The details and content of the chapter 01 – 06 will be specially tailored for the breast milk biobank and analytical centre Uppsala, and will lead to a comprehensive documented QMS structure which will be developed in the coming months within ConcePTION.

Further details regarding the structure and required documented information of the QMS according to the ISO 20387:2018 is listed in the file *D4.4_QMS_Requirements_ISO20387_UBB_draft_current date* (Excel sheet) which is filed at the ConcePTION member area (https://members.imi-conception.eu/Member-Area/Work-Package-4?folderId=3339&view=gridview&pageSize=10) available for the ConcePTION consortium. Please note, that the excel sheet is a document in a constant draft status, since it will be worked on and content-wise developing further as the setup of the QMS progresses.

For the QMS of the breast milk biobank and analytical centre Uppsala within ConcePTION WP4 we will concentrate on the development and implementation of the 05. Process requirements, since the project partners and clinical sites are actively involved in these workflows. The elements of chapters 01 Introduction, 02 General requirements, 03 Structural requirements, 04 Resource requirements, 05. Process requirements and 06 QMS requirements are part of UBB which will be extended with the described requirements for the breast milk biobank together with the QM team of UBB. The key element of the successful implementation of the QMS will be the use of common synergies to develop the system further.

3.3 ConcePTION: From mother to mother - from patient to patient

In the clinical setting, the primary sample taken from the patient is processed following the routine for diagnosis and treatment purposes.
The processing in a biobank usually includes collection / acquisition, storage, processing analysis, access and distribution of various samples. At the beginning there is a patient or donor and samples are taken – during an examination, at a clinical site or at a sampling site. The sample collection has to be done according to the specimen type, the relevant routine procedure (depending on the intended end use) and in a sufficient volume for the further processing. The sample has to be appropriately tagged so that identification is maintained throughout the life cycle under the custody of the biobank.

The workflow for the sample processing within ConcePTION is in general comparable to the clinical routine (see figure 03):

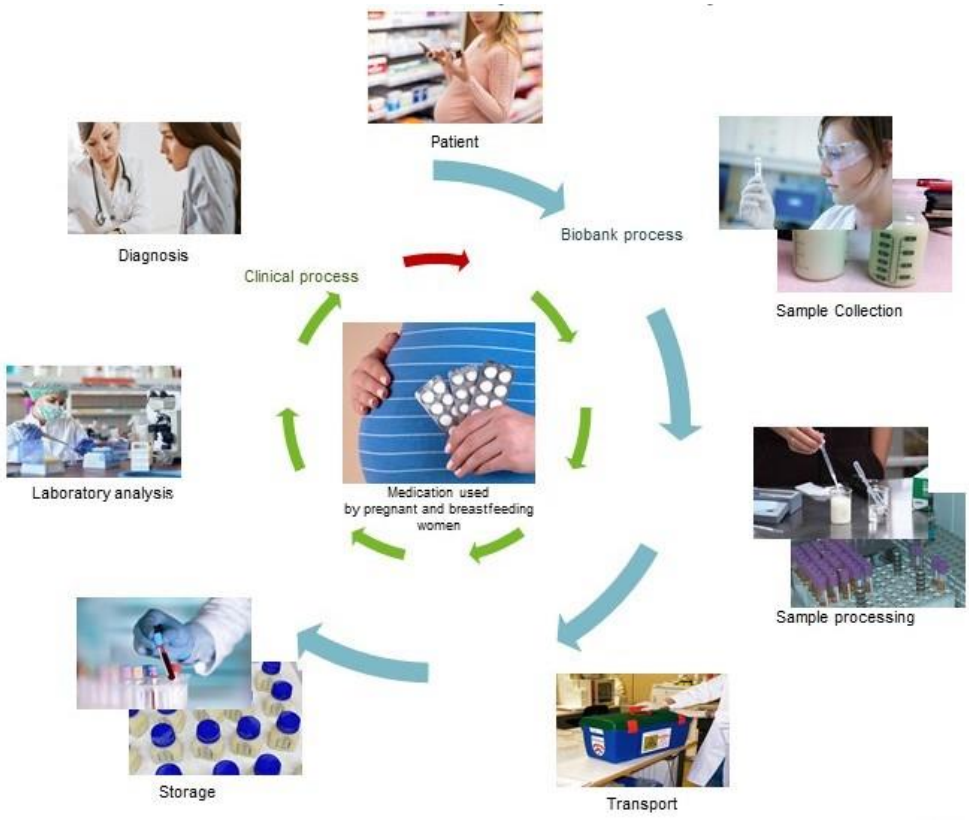

Fig. 03 ConcePTION: From mother to mother - from patient to patient

The samples will be taken from nursing women who are taking prescribed medication. The sampling will take place either at the clinical sites or at the women's home. Sample collection will be done

according to the defined routine procedure. Within ConcePTION we will mainly focus on women under medical treatment and analyse these samples accordingly. However, in the means of sustainability of the breast milk biobank and analytical centre Uppsala and to encourage research on breast milk in general within the EU, we will also collect samples from women who are not taking any medication at all. This fact will be taken into account when setting up the QMS and will be implemented in the corresponding standardised documentation as well.

Each sample will be appropriately tagged so that identification is maintained throughout the life cycle under the custody of the biobank. After interim storage, the samples will be transferred to the on-site laboratory. If the laboratory does not have the capacity to do the aliquoting, the samples will be sent to Uppsala Biobank, where the aliquoting, analysis and long-term storage is done.

The output of this standardised processes contributes to the quality of the samples. An adequate specimen collection and the further handling are essential prerequisites for the accurate test results of the laboratory analysis. To ensure a high degree of comparability of the sample quality, the requirements for the pre-analytical processes - from sampling to long-term storage - will be implemented in the QMS of the breast milk biobank and analytical centre Uppsala.

3.4 Pre-analytical steps: Part of the whole diagnostic workflow

The pre-analytical phase includes any actions from collection of a sample, transport, processing and stabilization, and (interim) storage until analysis.

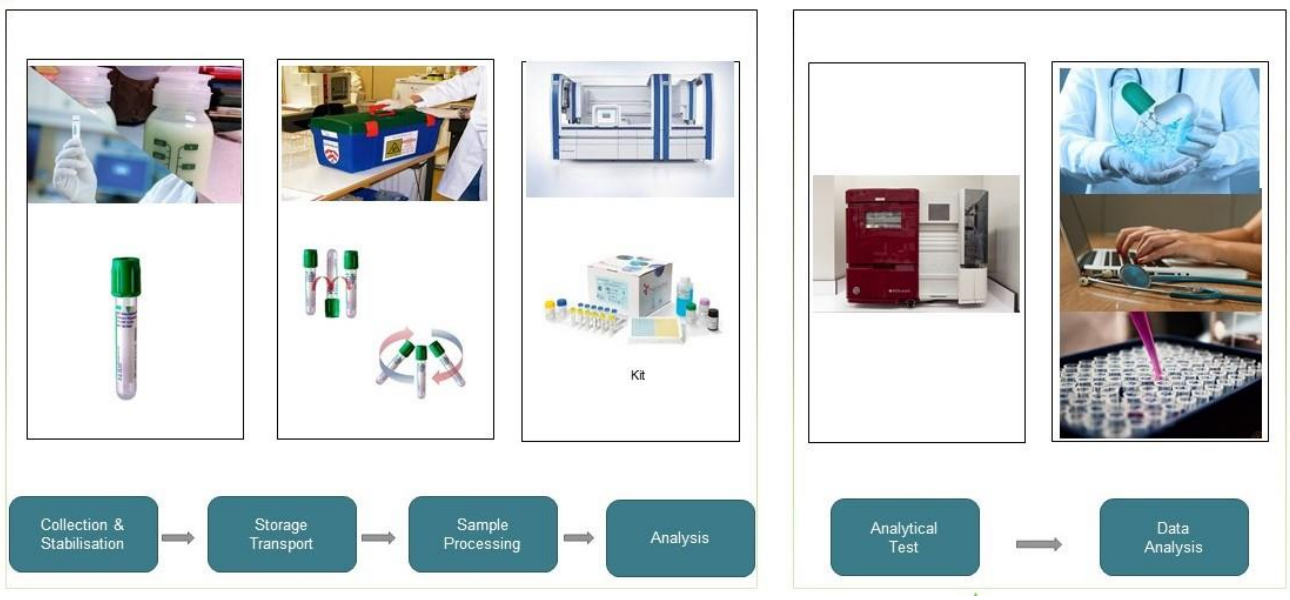

Fig. 04 Pre-analytical steps: Part of the whole diagnostic workflow

Regarding the pre-analytical phase of the milk and blood sample handling within ConcePTION the pre-analytical process steps will take place at four different clinical sites (Toulouse, Lausanne, Oslo and Uppsala) and partly at women's homes as well. Five demonstration studies within the following therapeutic areas and for the following drugs will be carried out:

- Diabetes – metformin
- Bacterial Infection – amoxicillin
- Allergy – cetirizine

- Depression – venlafaxine
- Rheumatologic and Inflammatory Bowel Diseases – infliximab

Drug selection was based on several scientific criteria and bearing clinical feasibility in mind (e.g. prevalence of use, current recommendations in clinical guidelines, databases like Lactmed and the SmPC).

The samples (milk and blood) are either taken at the clinical site or at the patients home. Regarding blood sampling, the tube in use depends on the specific study and if Plasma or Serum is being collected. After sampling the blood is transported to the laboratory.
After sampling the milk, it has to be stored in the freezer and then sent to the local laboratory. If the laboratory does not have the capacity to do the aliquoting, the samples are stored locally and will be sent on dry ice to UBB, where the aliquoting is performed. After the aliquoting and analysis the sample will be stored at UBB.
The detailed description for the steps of the sampling at the clinical sites or at home and the further processing can be found in documents (already developed within WP4): *Procedure for collecting and processing samples of breast milk at the clinical site* and *Procedure for collecting and processing samples of breast milk at the participants home* (part of D4.3*).* The documents will be filed at the ConcePTION member area (https://members.imi-conception.eu/Member-Area/Work-Package-4?folderId=3164&view=gridview&pageSize=10) and will be available for the ConcePTION consortium.

Within ConcePTION the drug analysis platform UDOPP at the SciLife Lab's Uppsala site will develop methods and technology to analyse drug residues in milk and blood. UDOPP is an in vitro ADME (absorption, distribution, metabolism and excretion) and pharmaceutical profiling platform, physically located at Uppsala University. UDOPP uses a state-of-the-art laboratory and cutting-edge research to help pre-clinical projects to optimize compound series and deliver candidate drugs of the highest possible quality.

The analytical phase includes all the factors related to the test platform and to the testing itself. Data analysis- or post-analytical phase is the final phase of the total testing process and involves the evaluation of laboratory test results, the release of test results in a timely manner to appropriate individuals, particularly critical results and the modification, annotation or revocation of results as necessary to support clinical data analysis.

4. Conclusion

Within WP4 a QMS will be established that meets the requirements of appropriate standards, technical specifications, guidelines and best practices (as described above) in accordance with ethical rules, regulations and laws based on a process approach. It also takes into account all settings relevant to the breast milk biobank and the analytical centre Uppsala and the associated risks, in order to improve scientific excellence by fulfilling the scientific requirements. For the further drafting and implementation, regular virtual meetings will be held with the QM of UBB to develop the system and use common synergies.

5. References

1 ISO 20387 Biotechnology – Biobanking – General requirements for biobanking. 2018.
2 ISO / TR 22758 Biotechnology – Biobanking – Implementation guide for ISO 20387. 2020
3 ISO 15189:2012 - Medical Laboratories – Requirements for quality and competence. 2014
4 ISO 20186:2019. Molecular in vitro diagnostic examinations – Specifications for pre-examination processes for venous whole blood – Part 1-3. 2019.
5 ISO 9001:2015 – Quality management systems – Requirements. 2015
6 ICH: E6 (R2): Guideline for good clinical practice. EMA/CHMP/ICH/135/1995. December 2016.
7 FDA, CDER, CBER. Clinical Lactation Studies: Considerations for Study Design". Guidance for Industry. May 2019.
8 Beskow A. Uppsala Biobank – the development for a biobank organization in a local, regional, and national setting. Upsala Journal of Medical Sciences. 2019, Vol 124, No 1, 6-8.