Validation Master Plan

Ex vivo Facility

Ex Vivo Facility (EVF) for Stem Cell Treatment, Cellular Therapy and Regenerative Medicine, at Haukeland University Hospital

APPROVAL OF DOCUMENT				
Role	**Name**	**Signature**	**Initials**	**Date (d/m/y)**
Author (AIT)	Kimberley J. Hatfield		KJH	
Approved by				
Project consultant (MC)	Jan Aksel Nielsen		JAN	
Project senior consultant (MC)	Ar Groeneweg		AG	
User representative (AIT)	Merete Kallekleiv		MK	
User representative (AIT)	Tilo W. Eichler		TWE	
User representative (AIT)	Ingvill M. C. Curran		IC	
Project technical leader (replaced M.W. Haraldsen)	Geir Egil Pedersen		GEP	
Project technical leader (HUS)	Mona W. Haraldsen		MWH	
Vendor?	xxx		xxx	
Authorised by				
Project Manager (AIT)	Einar K. Kristoffersen		EKK	
Project Owner (HUS)	Alf Henrik Andreassen		AHA	

PUBLICATION RECORD			
Version	Change description	Name	Date
01	New document	KJH	27092018

Innhold

List of Abbreviations

AIT	Department of Immunology and Transfusion Medicine
AHU	Air handling unit
AM	Ancillary materials
BSC	Biological safety cabinet
BSCC	Bergen Stem Cell Consortium
C	Commissioning
DQ	Design Qualification
EK	Electronic quality handbook
EurPharm	European Pharmacopoeia
EVF	Ex Vivo Facility
FAT	Factory acceptance test
GMP	Good Manufacturing Practice
HUS	Haukeland University Hospital
HVAC	Heating, Ventilation and Air Conditioning
HBE	Helse Bergen HF
HEPA	High-efficiency particulate air
HSE	Health, Safety and Environment
HUS	Haukeland University Hospital
IQ	Installation Qualification
JACIE	Joint accreditation committee ISCT EMBT
LAF	Laminar Air Flow
LK	Laboratory Clinic
MAL	Material airlock
MC	Multiconsult
NA	Not Applicable
OQ	Operational Qualification

PB	Passbox (=MAL)
PQ	Performance Qualification
PV	Process Validation
QA	Quality Assurance
QC	Quality control
QM	Quality Management
QMS	Quality Management System
QP	Qualified Person
QS	Quality system
SAT	Site acceptance test
SOP	Standard operating procedure
SLV	The Norwegian Medicines Agency
UPS	Uninterruptible power supply
URS	User Requirement Specification
VMP	Validation Master Plan (this document)
VP	Validation Plan
VSR	Validation Summary Report

1 Purpose

The purpose of this Validation Master Plan (VMP) is to identify the validation and testing requirements necessary to manufacture human biological medicinal products in a controlled environment in the Ex Vivo Facility (EVF) according to EU Good Manufacturing Practice (GMP) guidelines.

1.1 Site location

The EVF will be located on the 1M floor of the Laboratory Building at Haukeland University Hospital, Jonas Lies vei 87, N-5021 Bergen.

1.2 Background

The establishment of the Ex Vivo Facility for Stem Cell Treatment, Cellular Therapy and Regenerative Medicine, hereby referred to as EVF, is supported by funding from the Helse Vest Foundation after initiation by the scientific community in the Western region of Norway in need of a GMP compliant laboratory to manufacture advanced therapy medicinal products (ATMPs) to conduct phase I and phase II clinical studies.

As manufacturers of ATMPs for use in humans, the facility will have a pharmaceutical quality management system (QMS) in line with GMP guidelines, and the entire facility will be built and run according to EU-GMP guidelines and Norwegian regulations. In addition to ATMP manufacturing, the facility will include a dedicated controlled area (grade D) to conduct minimal manipulation of human cells. Minimal manipulation of human cells is currently executed at the Department of immunology and transfusion medicine (AIT), 3rd floor of the Laboratory Building, but new locations are required for this activity to meet the requirements of the Norwegian regulations for processing human cells and tissues (FOR-2016-09-07-1052, “Forskrift om håndtering av humane celler og vev”). The facility will be subject to inspection by the Norwegian Medicinal Agency; while areas where minimal manipulation is conducted will also be under the inspection of the Norwegian Board of

Health Supervision (Statens helsetilsyn). Manufacturing of ATMPs is regulated by the Norwegian Medicines Agency and the facility must achieve manufacturing authorization before starting manufacturing of ATMPs.

1.3 Type of products

The facility will primarily manufacture ATMPs according to Annex 1; Manufacture of Sterile Medicinal Products (as found in Directive 2001/83/EC, amended by Regulation EC 1394/2007) for use in clinical trials. ATMPs manufactured may include both tissue engineered products or somatic cell therapy medicinal products, and future production may also include combined ATMPs where human cells are embedded in a biodegradable matrix or scaffold. Human blood and blood products, as well as (extra)cellular- and tissue-based materials, may also be processed.

In addition to ATMPs, minimal manipulation of human cells will be conducted in the facility in a dedicated area according to Tissue and Cells Directive 2004/23/EC. Minimal manipulation will include, but not be limited to, routine preparation of stem cell products including preparation of stem cell products before cryopreservation and storage of products in liquid nitrogen containers, which is part of the current treatment offered to patients at Haukeland University Hospital (HUS).

1.4 Scope

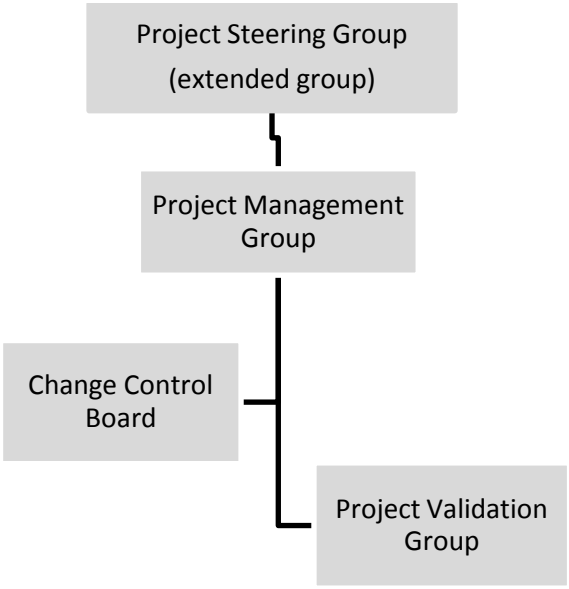
This document provides a description of the clean rooms and addresses activities related to different systems that are critical to ensure sufficient product quality. All relevant aspects of GMP manufacture in the EVF , including equipment, utilities, facility systems (air handling system, electrical systems etc), operating systems (personnel, quality management and environmental monitoring), processes, test methods and cleaning are subject to qualification and/or validation in accordance with this VMP. This VMP will also describe responsibility and roles in the project for constructing a compliant GMP-facility and Helse Bergen`s requirements to establish the EVF; as well as the documentation, qualification and validation

strategy that will be followed during the project until regular operation. Relevant guidelines and standards relevant for establishment of a GMP compliant clean room are listed in a separate section of this document. The responsibilites of personnel, the quality management system (QMS) and the environmental monitoring system will only be described briefly in this document, as they will be described in more detail in separate documents.

2 Organization and responsibilities

Reviewers, approvers and executers of this project are captured in the approval routing tab of this document. The project, to establish a GMP compliant clean room facility, has four main project groups which are described in more detail below. The project and validation life cycle of the EVF is shown in Appendix A9; the planning and design phase takes place in 2018, the construction will be executed during the first quarter of 2019, and the bulk of the validation effort is expected to take place in the last three quarters of 2019, while some recurrent validation and qualification work will be ongoing for the lifetime of the facility.

Diagram 1. Infrastructure of the EVF project



2.1 Project Steering Group

In the initial phase of the project, a steering group was established with members as listed in Table 1. This Project steering group should be informed by the project manager of any changes made that may have major effects on the progress and/or establishment of the project. The project manager should have an overall view of the progress of the project and report to the project owner, who is overall responsible for the project achieving its goals. The steering group should quality assure the project's deliveries, make decisions and ensure that these are implemented in the business the project is affecting.

Table 1. Project steering group members.

PROJECT STEERING GROUP		
Role	**Name**	**Affiliation**
Project owner, Helse Bergen	Alf Henrik Andreassen	Head of Department of Rheumatology
Project manager	Einar Kristoffersen	Head of Dept. for Immunology and Transfusion Medicine
Member	Gunnar Mellgren	Head of the Laboratory Clinic
Member	Kristin Pundsnes	Chief Financial officer
Member	Ida K. J. Linde	Health and safety representative
Member	Askjell Utaaker	Head of Division of Operations and Technical Department
Member	Lars Birger Nesje	Head of the Dept. of Hematology
Member	John-Helge Heimdal	Head of the Surgical Clinic
Member	Eyvind Rødahl (replaced by Marit Bakke)	Vice Dean for research, UiB
Member	Vigdis Fjeld	Union representative, NITO

2.2 Project management group

Einar Kristoffersen is the project manager and also leader of the Project management group until the EVF has been appointed a facility manager. The Project management group was established with members as listed in Table 2. This group has been involved in generating the layout design, user requirement specifications, describing equipment and utility needs, risk assessments and establishing standard operating procedures (SOPs). In addition, members of the Bergen Stem Cell Consortium (BSCC) steering committee and its advisory board have been continuously informed of the progress, and have provided input to the project, concerning requirements

The leader of the Project management group is responsible for organizing meetings as needed until the facility is in operation. This responsibility has been delegated to the project coordinator (Kimberley Hatfield) who has the overall overview of the project and reports back to the Project manager. The Project manager should still be proactive and manage the project progressively to achieve the specified goals. This involves managing Project steering group meetings, informing the project coordinator, distributing and following up tasks, submitting a decision-making basis for the steering group and following up / reporting the status of the project. Weekly meetings, at least once a week, are held by the User representatives at AIT, with contribution from consultants and architects when necessary. The project manager attends these meetings at least once a week when possible, and the Head of the Project office is also invited to these meetings when necessary. The Head of the Project office also invites the Project management group to meetings when necessary.

The Project manager`s responsibilities will include:

- Evaluate organizational structure of facility
- Evaluate roles of personnel working in facility
- Approve and prioritize proposed validation areas (facilities, systems and equipment)
- Approve overall validation plans
- Ensure availability of relevant resources

- Coordinate multiple stakeholder perspectives
- Give strategic direction and advice
- Discuss out-of-tolerance issues (tolerance defined as the flexibility granted to the Project manager for +/- variations from targets)

Table 2. Project management group members.

PROJECT MANAGEMENT GROUP		
Role	**Name**	**Affiliation, HUS**
Project manager	Einar K. Kristoffersen	Head of Dept. for Immunology and Transfusion Medicine
Project technical leader	Mona W. Haraldsen	Project office, Division of Operations and Technical Dept.
Project coordinator, User representative, AIT	Kimberley J. Hatfield	Dept. for Immunology and Transfusion
User representatives, AIT	Tilo W. Eichler	Dept. for Immunology and Transfusion
User representative, AIT	Merete Kallekleiv	Dept. for Immunology and Transfusion
User representative, AIT	Ingvill M. C. Curran	Section leader of Cell therapy, Dept. for Immunology and Transfusion
Architect	Eirik O. Lie (replaced by Katrine Wang Høiem)	Origo Arkitektgruppe AS
Project technical leader	Geir Egil Pedersen (replacement for Mona W.Haraldsen)	Head of Project office, Division of Operations and Technical Department

2.3 Validation group

The validation group will consist of a core team, as listed in Table 3, and will hold meetings as found necessary for the progress of the project. The main tasks are listed below.

- Decide a validation approach and make plans for the implementation according to correct guidelines
- Ensure IQ / OQ / PQ protocols are prepared
- Ensure validation (summary) reports are prepared after completion of validation
- Ensure that validation is in accordance with the project's functional requirements
- Perform sufficient risk assessments
- Create, update and archive necessary templates and documents
- Give strategic direction and advice

The validation group should be strengthened with discipline specialists and/or consultants when needed. Helse Bergen's project organization is a large organization and both Helse Bergen and user representatives will have different tasks, roles and responsibilities in the validation activities as described in the Table 3.

Table 3. Validation Group members.

VALIDATION GROUP	
Name **Role/ Affiliation**	**Task**
Einar K. Kristoffersen Project manager, AIT	Responsible for overall project management. Must have adequate understanding of the operation of facilities and equipment.
Kimberley J. Hatfield, Project coordinator, AIT	Establish a URS document and VMP (this document) for the facility and maintain documents. Review and write validation protocols and SOPs. Provide input to specific test plans and documents.Follow-up validation program and project progress. Provide documents and perform risk

	assessment analysis. Prior to handover, have adequate understanding of the operation of facilities and equipment.
User representatives, AIT	Assist with the generation and review of URS and VMP documents. Identify and write validation protocols, write SOPs and implementation plans and reports, perform risk assessment analysis, review and provide input to specific test plans and documents. Prior to handover, have adequate understanding of the operation of facilities and equipment.
User representatives for minimal manipulation, AIT	Identify validation requirements for all systems related to user activities (related to/relevant for minimal manipulation), risk assessment analysis, and provide input to specific test plans and documents. Prior to handover, have adequate understanding of the operation of facilities and equipment.
Vendor	Responsible for establishing a validation plan/program, performing validation tests and providing documentation for facilities, systems, equipment and utilities. Participate in risk assessment analysis.
Geir Egil Pedersen, Project technical leader (HUS)	Responsible for overall building management, including qualification and validation of premises and primary equipment (in collaboration with Vendor). Participate in risk assessment analysis.
Nina Kleven-Madsen, to be confirmed, Department of Radiology, Center for Nuclear Medicine(PET)	Provide input to planning, design reviews, qualification and validation documents and plans, validation tests, input to protocols and reports. Participate in risk assessment analysis.
Engineering and technical support (HUS)	Contribute to completion of the validation of premises and equipment, and responsible for future maintenance of facility and equipment (re-qualification). Review and approve validation tests and reports, and assist performing with risk assessments. Must have adequate understanding of the operation of the utilities and equipment.
Name to be confirmed, Health and safety representative	Provide input and perform risk assessment analysis.

3. Change Control Processes

Any stakeholder involved with the project may request changes. For example, end-users may realize that their requirements have changed or testing of a product may show that it is inappropriate in some unforeseen way. The project may be affected by changes in legislation, changes in government policy or changes in business strategy. It is also possible that project team members may believe that an emerging technology may offer a better solution to that originally planned, that Vendor`s proposals may be a better option or that a product just might not work the way that it was supposed to. All of these potential changes that might be made need a process to control them and their effect on the project. This process, called change control, should ensure that proposed changes are interpreted and evaluated in terms of their potential effect on project timescales, costs, benefits, quality and personnel.

After it is determined and accepted that a change is required, the change is documented and implemented. After implementation of the change, the changed process must be revalidated and this revalidation is executed on the whole life cycle of the process to review the effects on previously documented IQ, OQ and PQ results.

3.1 Change management system

Although changes may be initiated verbally, they must always be recorded in written form and entered into a change management system as a formal change request. As such, they will be subject to the process specified in the change control system and must be either approved or rejected.

3.2 Change control board

If a change request or document update request is raised, then an impact/risk analysis should be performed. This process looks at the knock-on effects of the change on other

products/systems, and also the effect if the changes are not implemented. This decision is usually taken by the Project manager or a change control board responsible for approving or rejecting change requests. The purpose of the impact analysis is to arrive at a balanced view of the effect of the proposed change on the projects ability to satisfy its mandate. This will enable project management to decide whether to proceed with the change or not. Approved change requests can require new or revised cost estimates, activity sequences, schedule dates, resource requirements, and analysis of risk response alternatives. The change control board members will consist of minimum the project technical leader (HUS) and/or representatives from engineering ("Drift-teknisk avdeling", HUS), HVAC experts/consultants and user representatives who have significant knowledge of the project.

4 Projects document formats and controls

4.1 Document Management System

Project documents that are related to the construction of the facility, including details about permanent equipment, will be published at http://helsebergenprosjekt.com/Ex-vivo/ITBase/. Personnel from Multiconsult use LiveLink – ECM (OpenText) as a document management system. User representatives from AIT will publish documents related to quality management in the Helse Bergen`s Electronic Quality handbook (Elektronisk Kvalitetshåndbok (EK)). All relevant documents for the project will be uploaded to ITBase for distribution to all involved in the project. The project steering group utilize Sharepoint website https://prosjekt.ihelse.net/Pro/Prosjekt/exvivo/ to share information about the project.

4.2 Format

Documents should be entered with the letter codes as listed in the table below:

Table 4. Document format

Prefix	Type of document
DQP / DQR	Design Qualification Protocol / Design Qualification Report
IQP / IQR	Installation Qualification Report / Installation Qualification Report
OQP / OQR	Operational Qualification Protocol / Operational Qualification Report
PQP / PQR	Performance Qualification Protocol / Performance Qualification Report
PVP / PVR	Process Validation Protocol / Process Validation Report
QAD	Quality Approved Document (General Code for Controlled Document)
QRA	Quality Risk Assessment
TP / TR	Test Protocol / Test report (FAT, SAT, commissioning etc)
URS	User Requirement Specification
VMP	Validation Master Plan
VP	Validation Plan
VSR	Validation Summary Report

4.3 Approval and signing

All documents must be signed by the responsible person and dated.

5 Description and design of facility

The facility, constituting modular clean rooms, will be situated on the 1M floor of the Laboratory Building, with its own dedicated ventilation system placed on floor 1 directly beneath the facility. The total area of the EVF on floor 1M is around 262 m^2, with a ceiling height of about 2400mm.

The facility is designed to ensure that the manufacturing process and quality of the product is sufficient according to required EU-GMP standards. The layout and design of the facility aims to minimalize the risk of cross-contamination or mix-ups that can occur through the circulation of personnel and material. In addition, relevant parameters in the facility will be controlled as necessary to comply with EU-GMP standards, including particles, temperature, humidity and pressure.

5.1 Facility layout and description of rooms

The current layout drawing of the facility is visualized in Appendix A1. The overall construction, design and layout of the facility should aim to minimalize the introduction, generation and retention of viable and non-viable particles inside the rooms, including dust, lubricants and microbes, to avoid any negative influence on the products, and also to minimize cross-contamination.

A general description of the main activities in all clean rooms is given in Table 5. There are two grade B production rooms where the biological safety cabinets (BSCs) provide a grade A manufacturing area, one grade C production room and one grade D production room. Manufacturing of ATMPs will be performed in the grade B and C production rooms, while the grade D production room will be dedicated to conduct minimal cell manipulation activity. In addition, the facility will have dedicated rooms to perform quality control analysis, microbiological monitoring, approval and storage of consumables and storage of products in liquid nitrogen containers.

Access to all production areas is done through supporting corridors and gowning sluices where personnel will change into appropriate clothing before accessing the various rooms. There are material airlocks (MALs, also called pass boxes) between rooms for transport of materials between rooms of different clean room classification, which also help to separate the flow of personnel from the flow of material into the clean rooms.

The main entrance is not classified as a clean room, but it is defined as a clean environment, where there is limited access, defined room pressure, air filtration, specified airflow, regular cleaning. The room will be monitored, but not qualified according to viable or non-viable particle levels, such as to have an adequate barrier before entering grade D gowning room.

The construction and design of the facility should also support efficient cleaning, operation and maintenance of the facility and permanent installations, e.g. rooms must have smooth surfaces that are easy to clean and that don`t create surfaces where microorganisms will thrive. Non-shedding material should be used which is both easy to clean and is resistant to cleaning and disinfecting solutions.

The pressure differential concept is used with a pressure differential towards the cleanest rooms. The air pressure in all rooms of the facility are controlled, with the highest pressure in the cleanest room to ensure that any airflow is pushed outwards from the room, and dirty air cannot enter by default; thus the manufacturing rooms are the cleanest and have the highest pressure. The facility also has its own specialized HVAC system that maintains the airflow and air change rates needed to comply to GMP standards.

Table 5. General description of clean rooms

Room name	*Area,m^2	**GMP grade	***Pa	Main activity
Main entrance	7.55	CNC	+5	Entrance for personnel and starting material
Sluice 1	8.37	D	+15	Gowning for grade D
LN2 room	24.15	D	+45	Freezing and storage of products in liquid N_2 storage tanks
Production-D	25.86	D	+45	Production room for minimal manipulation of biological material
Corridor D, including QC – receipt and packaging	31.92	D	+30	Transition space, reception of starting material and packaging of product
QC-D	18.86	D	+30	Quality control area
Microbiology	5.59	D	+20	Microbial testing
Sluice 2	11.93	C	+45	Gowning for grade C
Production-C	17.94	C	+52	Production room for more-than-minimal activity
Sluice 3	8.10	B	+60	Gowning for grade B
Corridor B	11.75	B	+60	Transition space, access to grade B production rooms
Production-B1	14.26	B	+75	Production room for more-than-minimal activity
Production-B2	12.76	B	+75	Production room for more-than-minimal activity
Sluice 4 - Incoming materials	14.06	D	+15	Main entrance for consumables intended for use in the production process.
Quarantine materials	17.31	D	+45	Storage of consumables until rejected or approved for use
Approved materials	14.41	D	+45	Storage of approved consumables

*Area per room according to layout drawing (Appendix A1)**According to ISO 14644-1

***There should always be 10-15 Pa difference between rooms with different clean room grading independent of the indicated pressure values. CNC, controlled not classified; QC, quality control.

5.2 External non-controlled associated areas

5.2.1 Toilet facilities

Toilets are easily accessible and close to the facility (but have no direct connection with production or storage areas). Existing sanitary pipes on the roof must be sufficiently secured to prevent any leaking into the facility.

5.2.2 Lunch room

A lunch room is accessible on the 3rd floor of the Laboratory building and the nearby Haukeland University Hospital (Sentralblokken).

5.2.3 Changing room and personal valuables lockers

Outdoor clothing and shoes can be removed, and replaced with indoor shoes and garments, in the changing room situated on the 1st floor of the Laboratory building. Small personal item lockers are also situated in both entrances of the clean room facility.

5.2.4 Storage and office area

On floor 1M, non-controlled storage areas will be made available to be used to store materials and larger boxes that are not temperature-dependent (e.g. containing garment), until being ready to be taken into the facility and checked for approval. The storage area must be clean and dry, and of sufficient size to provide sufficient separation of different categories of material and allow orderly storage. Storage conditions are monitored and documented to achieve GMP compliance when required. On floor 1, beneath the facility, there will also be room from necessary utilities, including the computer server system. Offices for writing reports and protocols are placed outside the facility.

5.2.5 Technical area

A small area of 3.5m^2 on floor 1M (shown on layout) is dedicated to technical installations.

6 Flow in Facility

The facility will assure a logical flow of material and personnel within the facility to assure the manufacturing of products according to GMP guidelines. Material and personnel primarily have different routes into and out of the facility. The following sections give a general description of the flow of personnel, ancillary material, starting material, product and waste in the facility. On layout drawings, MALs are referred to as pass boxes (PB01-PB08) and are ventilated systems to minimize contamination (Appendix A7, *129995-RIV-TEG-003*), and their efficiency must be validated.

6.1 Personnel flow

Personnel working in the production rooms or quality control testing laboratory primarily enter the facility through the key-card controlled main entrance, and then they enter the controlled-access sluice 1 (gowning room). Personnel working in different clean room classes have dedicated gowning rooms which lead to rooms authorized for the particular category, minimizing the risk of interference from other classes. The flow of personnel is bidirectional, meaning personnel leave and enter the clean rooms through the same sluices. An overview of the personnel flow is shown in Appendix A2. A limited number of people should generally be present in the clean rooms, and also a maximum allowed number of people is defined per room. Detailed description of i.a. gowning procedures and behavior in the clean rooms are described in SOPs.

6.2 Starting material in and product flow out

Starting material to be used in manufacturing will be transported into the clean room through a MAL (PB01 in layout drawing) in the main entrance. The material will then be transported by personnel to the dedicated desk for receipt of starting material where it is inspected and registered. Approved starting material will be transported through MALs into the grade C and grade B clean rooms for manufacturing. Materials to be manipulated in the

grade D production room (minimal manipulation) are taken into the room by personnel. During manufacture, intermediate products for quality control testing will be transported to the QC room using MALs situated in each production room. The final product is taken to the LN2 room for cryopreservation and storage, or transported out of the facility through the MAL (PB03). The flow of starting material into the production rooms and flow of final product out is shown in Appendix A3 and A4.

6.3 Ancillary material flow

Ancillary materials (AMs) are components or reagents used during the manufacture of cell therapy products but are not intended to be part of the final products. Materials, reagents and solvents intended for use in manufacture are taken into the clean rooms by personnel through a dedicated entrance (Incoming materials – Sluice 4). All consumables are cleaned appropriately upon receipt and then transferred to the Quarantine material room, where they are inspected, registered and labeled. If specifications are met and documentation of a certificate of analysis is present, then the item can be approved for use in the manufacturing process. Consumables are then re-labeled, moved and stored in the Approved material room. Consumables to be used in manufacturing processes are transported into the clean rooms through ventilated MALs. Equipment parts can also be transferred through MALs. The MALs have an interlocking system, where only one door of the MAL can be opened at a time, thus both doors cannot be opened simultaneously. They are all dynamic, with a ventilated cascade system inside to prevent the entrance of contamination into the cleanest areas. Efficiency of MALs should be verified by validation tests. Consumables to be used in quality control analyses or for microbiological testing, or equipment as well as parts of equipment, also follow the same route into the facility, and after approval, they can be transported by personnel to their respective rooms for their intended use. An overview of the ancillary material flow is shown in Appendix A5.

6.4 Waste handling

Waste will be contained in plastic bags and transported out of the facility through MALs according to the flow chart shown in Appendix A6. Waste bins suitable for clean rooms are present in rooms where necessary. Items designated as “sharps” are collected in biohazard sharps containers Liquid waste that poses no risk to the environment or health can be emptied in the sink situated in the QC testing lab or else it can be packaged in a sealed box and transported out of the facility with other solid wastes.

7 Quality management system

Quality assurance and quality control systems provides support to ensure that products are manufactured, processed and tested in compliance with the minimum requirements of EU-GMP. The facility and its activities will have a pharmaceutical quality system, including having self-audits, a change control system and deviation handling system etc. All procedures in the facility are conducted according to SOPs that comply with EU-GMP guidelines, with quality control and quality assurance oversight. The accuracy of the manufacturing process will be ensured by following SOPs developed for use of the facility and equipment, as well as for the production of cell therapy products.

7.1 Microbial monitoring

Premises will be monitored for viable contaminants using contact plates. Personnel, air and area surface will be monitored for microbial contamination, including monitoring after validation of systems and cleaning. Viable/microbiological monitoring of clean rooms will be performed according to a monitoring program (SOP) to identify any contaminants present that might influence the product. Based upon a risk assessment, a sampling plan will determine the location of sampling (including personnel, air and area surfaces) and the frequency of sampling to be performed, and may depend upon changes in equipment and processes, number of personnel and trending analysis. Monitoring will also show that the

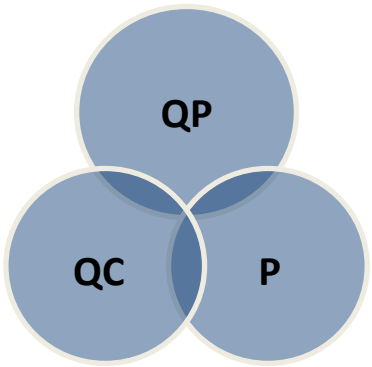
clean room is functioning as designed and is properly maintained. Reading of plates is performed in the Microbiology room which has a lower pressure than the adjacent room, to prevent air leakage.

8 Employees

There will be sufficient personnel with the necessary qualifications and practical experience to carry out all tasks which are the responsibility of the manufacturer.

8.1 Responsibilities

The facility in operation with have a minimum of at least three key personnel in permanent positions which are currently being established: a qualified person (QP), head of production (P) and head of quality control (QC). Individual responsibilities will be stated clearly in written job descriptions (filed in EK), and are not so extensive that they present any risk to quality of the product. The relationships between the personnel should also be clearly stated in the job descriptions with no overlaps in main responsibilities. The need for more employees will be evaluated periodically.



8.2 Training and qualification

Training will occur for all personnel who work in the facility (both in production and supporting areas). Also personnel who are responsible for operation and maintenance of utility systems and equipment, facility cleaning and maintenance will receive proper training and should be aware of the principles of GMP. Training is the responsibility of qualified trainers, and should be done according to a written training program, and records of employee training/re-training must be filed, maintained and documented. Employees will

receive training before executing their tasks according to the standard training procedure. There must be continuous training of training of personnel, to update the skills and knowledge of the employee in accordance to current GMP, and training should be periodically assessed.

9 Utilites

All critical utilities must be EU-GMP compliant.

9.1 Water system

The facility will not need a water production system. High quality grade water will be purchased when water is required for production or for cleaning purposes. Water piping and plumbing systems should not pose a risk of contamination of premises.

9.1.1. Sinks

The sinks situated in grade D rooms are for hand washing, and there is also one sink in the QC laboratory for disposal of liquid waste. In addition, there is a sink for hand washing at the first stage of Sluice 2 (gowning room). Sinks will meet strict cleanroom standards. Sinks and drains are prohibited in grade A/B areas.

9.2 Process gases

Compressed process gases which are in contact with the product (or direct impact on product quality) are critical systems and should be of suitable quality (compliant with EurPharm). Three types of medical gases are included: carbon dioxide (CO2), medical air (compressed air) and nitrogen (N2). These three gases are required in all production rooms (grade D/C/B) and the QC testing lab. There should be a back-up system in case the main gas supply fails.

9.3 Electrical

Electrical outlets are provided for power to the equipment. Electrical in general and errors in a room should not affect systems and equipment in other clean rooms.

- MALs are uninterruptible power supply (UPS)-powered.
- Sluice door automation and interlocking between doors are UPS powered to maintain the barrier in case of power outages until emergency power is available. The same applies to evacuation in an emergency situation.
- All LAF cabinets are provided with separate UPS power, to protect product even if clean room ventilation system should break down. The monitoring system for LAF cabinets (LIS) and facility monitoring, including monitors, are to be UPS powered. LAF benches shall maintain laminar air flow in case of power outages until emergency power is available. AHU is provided with emergency power.
- Supply and extract fans are to be emergency powered, but may partly be UPS powered to maintain clean room pressure regime. Typical scenario is in case of power outages until emergency power is available (to be risk assessed in detail design).
- The extract air system is supplied with UPS.
- Monitoring of equipment critical parameters such as temperature should be UPS powered (refrigerator / centrifuges / incubators).
- All lighting is to be of type LED, and required life cycle of 20 years (and clean room reclassification).
- With regard to the fire alarm system, the AHU is running until smoke is detected in the air inlet duct.

9.4 Units

All measurements and units used in design, fabrication and documents shall be in SI units.

An exception may be pressure in bar(a) or bar(g).

10 Heating, Ventilation and Air Conditioning (HVAC) system

The facility with have its own dedicated ventilation system, and this air handling unit (AHU) controls the air in the facility, with a cooling, heating and (de)humidifying system. Air flow will be unidirectional for grade B clean rooms (and air flow will be unidirectional for class A LAF cabinets, where the product is exposed), avoiding airflow turbulence. Airflow should ensure the required airborne particulate cleanliness class. The air system is HEPA-filtered air to obtain the clean room requirements (see *URS for GMP facility* for details).

A dedicated and efficient HVAC system will supply and distribute required volume and quality of air to the facility. The air handling unit (AHU) conditions 100% outside air normally once, but may recirculate clean room air, up to 75%, in order to save energy (see *URS for GMP facility* for detailed description). The AHU and its distribution system are all connected to existing UPS. A separate new extract air ventilation system is to eject sanitizing aerosols outside each pass box (SHA related) and evacuate a N_2 leakage in an emergency situation.

Air supply to the clean rooms must be sufficient in order to reach the B, C and D air grades. As described in the *URS for the GMP facility*, the number of air changes (change rates per hours) should be related to the size of the room, the equipment present and the numbers of personnel present, to maintain cleanliness, as required per the grades (see Table 6).

10.1 Temperature and humidity

The range differs between rooms and should ensure that the personnel have a comfortable working site and take into consideration the clothing requirements of the personnel in each room (lower temperature in grade B rooms), and the number of people in each room. The temperature in the facility should meet the specifications throughout the whole year even with heavy equipment and maximum number of people in rooms. The temperature must be appropriate for the product, i.a. biological / stem cell products should not be exposed to temperatures below 19 degrees and maximum 25 degrees. The temperature can be regulated in each room and should be within +/-1◦C when a specific temperature is set.

The relative humidity (% RH) should aim to keep 45+/-5% RH, with a lower limit of 40% RH and a maximum of 60% RH, to reduce the risk of microbial growth and contamination.

Table 6. Clean room parameters

*Cleanroom grade	Room name	**Particles ≥0.5µm Air change (h-1)
Grade B	Production-B1, Production-B2 Corridor-B, Sluice 3	at rest: 3.520 in operation: 352.000 Air change rate: >30
Grade C	Production-C, Sluice 2	at rest: 352.000 in operation: 3.520.000 Air change rate: >25
Grade D	Sluice 1, Corridor D, QC-D, LN2 room, Production-D, Microbiology Sluice 4 – Incoming materials Quarantine materials, Approved materials	at rest: 3.520.000 in operation: nd Air change rate: >20
Main entrance	CNC	at rest: nd in operation: nd Air change rate: > 5

*Grading according to EU-GMP. Grade B rooms corresponds to ISO 5, grade D rooms to ISO 7, grade D rooms to ISO 8 **Optimal air exchange rates need to be calculated; nd, not defined, CNC, defined as controlled-non-classified.

11 Facility Monitoring System

Monitoring is performed with a system called Facility Monitoring System (FMS) while control and regulation are performed by a Building Management System (BMS). The FMS will be provided by the Vendor and used to test that the clean rooms are performing as required, both at rest and in operation. The FMS should at minimum meet the requirements specified by EU-GMP, and will continuously monitor the following parameters:

- Number of airborne particles per cubic meter of air
- Room pressure (and thus pressure difference between room / pressure regime)

- Temperature
- Relative humidity (% RH)
- Airlock status

The final number and location of critical sensors shall be determined by means of a risk assessment in detail design. Alarms and monitoring of air quality in BSCs (grade A) shall be monitored continuously and have real-time data collection. Monitoring of BSCs is integrated into the larger facility monitoring system.

12 Equipment

Each clean room will contain only the necessary equipment required for its intended use, and personnel will be trained sufficiently to use equipment and training will be documented. Equipment should be correctly installed in accordance with the installation plan, as per supplier and purchaser requirements. All equipment will be used, calibrated, validated and cleaned according to written procedures (SOPs).

12.1 Primary equipment

This class of equipment has a direct effect on the quality of the product or verifies (by testing or measurement) the quality of the product being manufactured. This equipment may require IQ, OQ and PQ validations. This critical equipment will be monitored and alarms systems will be connected (freezers, refrigerator, incubators etc).

12.2 Support and non-critical equipment

This class of equipment assists the personnel and primary equipment in support of the manufacturing process. This equipment may be regularly calibrated, though may not need further validations. This equipment may not be essential to keep the production ongoing, such as shelves and bins.

12.3 Qualification and validation of equipment

All equipment within the facility will be assessed to determine the extent of qualification required, and also criticality according to its designated impact and risk priority. Equipment will be assessed and categorized as having a direct impact, indirect impact, safety impact or no impact on product. The Vendor will supply and validate the permanent furnishing and equipment described in the *URS for permanent equipment*.

All equipment should be evaluated, reviewed and assessed for validation requirements. Specific validation requirements will be supplied for critical equipment. The need for validation, maintenance and monitoring of equipment will be specified in SOPs. Protocols and tests must be established and conducted to assure that equipment is working correctly under normal and worst case scenarios. During the validation process, protocols, procedures, specifications, and acceptance criteria for test results to validate equipment must be reviewed, checked and authorized by qualified personnel.

Applicable equipment should be verified for proper function in the facility through IQs. Detailed calibration procedures, cleaning procedures and maintenance procedures should be written for each specific piece of equipment as necessary, and PQs will be performed after the equipment is successfully installed. Risk management should be performed to identify any potential risks to this VMP that may occur related to equipment, e.g. identify possible causes / risks and how to act if equipment does not pass validation. IQ and OQ will be attached to the Validation plan for each piece of equipment. PQ will be performed to satisfy requirements.

12.4 Cleaning and maintenance of equipment

Cleaning of GMP equipment or parts of equipment must be proceduralized to ensure consistency over time and from operator to operator. Equipment may be contaminated by products, cleaning agents, microorganisms or other materials. During manual cleaning, a cleaning validation plan must be set up to identify critical parameters for each type of equipment, such as rinse/scrub time, temperature and volume of water, cleaning agent

concentration and type. In addition, acceptance limits for cleaning agents and sanitizers must be set, to make sure residuals do not exist on the surfaces of equipment or pose any major risk to the performance of the equipment. This will provide documented evidence of a robust and repeatable cleaning process to reduce contaminates. A log of cleaning, preparation and usage of equipment must be recorded and continuously monitored during production.

Equipment fittings and services should be designed and installed, so that maintenance and repairs can be done outside the clean room if possible. When maintenance is carried out within a clean area, clean instruments and tools should be used and the area must be cleaned and disinfected again.

13 Cleaning and sanitizing agents

Cleaning of the facility is performed by authorized and trained personnel according to defined procedures to provide aseptic conditions. Wipes/sponges/mops must be of material and designed to minimize shedding of particles (such as polyester) and have each wedge sealed to minimalize contamination. Disinfectants and detergents are of such a character that they are tolerable for materials of the equipment and facility surrounding, and also fulfill their purpose to adequately kill microbial contaminants. Cleaning is performed by moving from the cleanest areas to the less clean areas according to the specified SOPs, with appropriate storage areas for cleaning supplies. Clean room flooring/mats are situated at critical areas to reduce and prevent contamination. Materials in building construction, flooring, walls, equipment material and surfaces, and steering panels (for light or electricity etc) must all tolerate disinfection agents.

14 Qualification and validation approach

14.1 Overview

A validation program, with validation plans, will be established by the Vendor, based upon the document *URS for GMP Facility*. The validation program/plans will be approved by the project validation group. The premises, technical installations, and equipment must be qualified and validated by the Vendor to establish that all is adequate for the intended operations, according to EU GMP annex 15 and WHO guide to GMP requirements, part 2: Validation. The validation work must be completed as defined in specific approved protocols, and all results must be recorded as they are obtained. Validation procedures are developed either as separate written procedures (SOPs) or integrated into protocols and or tests.

All tests performed by IQ, OQ and PQ shall be performed in accordance with approved protocols and procedures and summarized in corresponding final reports. A document hierarchy will be made showing validation plans, test, protocols and finished reports. Each protocol and report is uniquely identified as described in a SOP, and authorized personnel must approve the protocols and reports.

14.2 Validation and qualification elements

The flow chart for validation activities in Appendix A8 details relationships between the different parts of the project and validation activities.

Validation elements to be identified include, but are not limited to:

- VMP Validation Master Plan (this document)
- VP Validation Plans
- URS User Requirement Specification
- DQ Design Qualification
- IQ Installation Qualification
- OQ Operational Qualification

- PQ Performance Qualification
- PV Process Validation
- VSR Validation Summary Report

The validation activities will be divided into several different areas, because each one of them will be completed at different times. Separate validation plans will be established by the Vendor and give a detailed requirement description for the different validation activities, including minimum:

- Validation and Qualification of premises/facilities and utilities, including HVAC system
- Validation and Qualification of equipment, in production and QC laboratory
- Process validation of manufacturing processes
- Validation of QC methods and test methods
- Computer and/or environmental monitoring system validation
- Cleaning validation
- Interval based requalification

Facility qualification will verify that construction and utility installation is according to design and that the process requirements are met.
Equipment verification will verify and document that installation is according to design (IQ) and meets functional requirements (OQ) and user requirements (PQ).
Validation of manufacturing processes will be conducted using defined SOPs. Process validation should show that the process can produce efficiently and repeatable, while complying with the requirements of the predefined product specifications and quality requirements. The manufacturing process is validated after OQ and PQ are completed and the validation plan may be carried out with a normal or upgraded level of sampling, analysis, process control etc.
All computer systems, including the environmental monitoring system, employed in the facility will also be subject to computer validation as required by annex 11, vol 4.

Test instruments must be qualified and validated, and all the different steps in the manufacturing process from raw material supply, batch record, product storage, and testing must be evaluated to document that manufacturing processes are capable of consistently yielding product that meets predetermined quality attributes.

Cleaning validation is a documented verification that the cleaning methods used in the facility are consistent and sufficient to prevent cross contamination from one area to another. Cleaning validation will assure a clean environment for manufacturing product and that cleaning agent residues are kept at predetermined acceptable limits. The validated state of the critical processes will be requalified periodically.

For each validation plan a risk assessment will be done in advance to define which procedures are to be validated.

14.3 User Requirement Specification (URS)

The URS should define the requirements of a system or equipment in relation to what the system will produce, the capacity and under what conditions the system shall operate. The URS should describe what a system should do, not how, and should be prepared before equipment or a system is to be procured, or before existing ones are used for other purposes. For further details see *URS for GMP facility*.

An URS may contain the following types of requirements:

- Requirements for process conditions
- Requirements for functions
- Instrumentation requirements
- Requirements for automation / connection to operating systems
- Design and construction requirements
- Material quality requirements
- Requirements for hygiene / cleaning-friendly
- Requirements for maintenance and technical support

- Requirements for security
- Requirements for testing (e.g., FAT, SAT, Commissioning, Qualification)
- Training requirements
- Requirements for compliance with regulatory requirements and guidelines (GMP, GAMP, HSE, other)
- Requirements for compliance with internal requirements, guidelines, procedures.

14.4 Qualification elements (DQ, IQ, OQ, PQ)

14.4.1 Design Review and Design Qualification

Design review will be ongoing throughout the project until the design is frozen. Design qualification is the first element in the validation of a new facility, system or equipment and is based on the generated URS. It is a documented verification that the proposed design of the facility, system or equipment fits the purpose. DQ is often a more or less continuous process under development of design and leads to approved drawings and substrates for construction and assembly.

14.4.2 Installation Qualification

Installation Qualification (IQ) is a documented verification that the facility, system or equipment, as installed, is in accordance with approved (and qualified) design and to the supplier's recommendations. An IQ protocol is prepared that describes what to check and what the acceptance criteria should be for these checkpoints. It is the detailed design of clean rooms, systems and equipment that is the starting point for the protocol. The implementation of the IQ test, based on the IQ protocol, is documented by an IQ report. This is signed and approved as properly executed and confirms that OQ can begin. Deviations that occur during the activity will be recorded and processed. National and local regulatory guidelines must be followed.

The qualification shall include, but not limited to:

- Clean rooms must meet the classification requirements and materials must meet the design intent
- A check of installed equipment, pipes, utility systems, instrumentation vs. drawings and specifications. Conformance to design specifications and construction drawings, as-built drawings are used in the process
- A check and compilation of documentation from supplier with regard to operation and maintenance
- Calibration
- Pressure testing
- Verification of material qualities and materials of construction
- Initial sanitization of each room shall have been performed in accordance with appropriate SOPs.

14.4.3 Operational Qualification

Operational Qualification (OQ) is a documented verification that the facility, system or equipment, as installed and modified (after IQ), works as provided for all planned operating conditions. OQ is performed after approved IQ and will normally involve:

- Tests that verify function, based on previous operating experience and knowledge of the facility, system or equipment.
- Tests that challenge the entire operating area of the facility (stress tests), system or equipment and also a worst case situation.
- The following operational parameters should conform with the design criteria: air distribution such as air changes per hour, air flow pattern and air velocities, airborne particles (at different conditions), pressure differentials between rooms and recovery tests

- Several components should be tested: lighting, electrical systems, acoustics/noise, vibration, process equipment and systems, compressed medical gases, HEPA filters, HVAC systems, and the cleanroom enclosure
- The distribution gas system to be sanitized/cleaned in accordance with appropriate SOPs, and the in/out (I/O) signal test of user point valves
- Microbial monitoring at rest shall demonstrate compliance with GMP requirements
- Verification that procedures for use are available
- Verification that training plans exist
- Verification that instrumentation is calibrated and that calibration certificates exist.

An OQ protocol is created that describes what to check and what acceptance criteria should be for these checkpoints. It is the operating requirements /functional specifications that are the starting point for the protocol. The implementation of the OQ test, based on the OQ protocol, is documented by an OQ report. This is signed and approved as properly executed and confirms that PQ can begin. Deviations that occur during the activity will be recorded and processed.

OQ is performed during three different installation phases, as-built, at-rest and operational. There should also be maintenance of staff training to perform operational qualification.

14.4.4 Performance Qualification

Performance Qualification (PQ) can start after OQ is approved by the validation group. PQ is a documented verification that the facility, system or equipment, as it has been installed, optionally modified and connected (after IQ and OQ), can perform in an efficient and repeatable manner. Tests shall be based on relevant and well-known processes and product specifications.

PQ will involve, but not be limited to:

- Tests according to what is defined in User Requirements (URS)
- Under operational conditions, pressure stability and airborne particle levels, as well as microbial levels, in clean rooms must conform to design criteria (GMP standards)
- That the results achieved meet the relevant quality criteria
- Verification that training plans exist
- Verification that instrumentation is calibrated and that calibration certificates exist.

A PQ protocol is written that describes what to check and what the acceptance criteria should be for these checkpoints. The Vendor shall conduct the tests, measurements and prepare documentation/reports. It is the user requirements (URS) that is the starting point for the protocol. The implementation of the PQ tests, based on the PQ protocol, is documented by a PQ report. The PQ report is signed and approved as properly executed by the validation group and confirms that PV can begin - if applicable. Deviations that occur during the activity will be recorded and processed. Finally, after approved PQ, overall qualification can be summarized in the VSR.

15 Impact and risk assessments

15.1 Risk Assessment (RA)

In addition to design reviews, impact assessments and criticality assessments, technical solutions will undergo a risk assessment process performed with relevant analytical methods. The purpose of risk assessments is to identify major GMP risks embedded in equipment, systems and processes that can affect features, performance and safe operation. Risk assessments will be conducted as part of qualification / validation exercises through development and construction processes and will be reviewed in connection with major design or process changes.

15.2 Impact Assessment (IA)

In order to determine the impact of each device or system on the quality of the product, an impact assessment is performed (in accordance with the ISPE Baseline Guide Volume 5 Commissioning and Qualification). In the assessment, commissioning and qualification activities are determined for each system according to the following categories:

- Direct impact. A system or equipment that is directly in product contact and may affect product quality. These are systems/ equipment that will be commissioned in accordance with Good engineering practice (GEP) and additionally subject to IQ, OQ, PQ and PV.
- Indirect impact system. A system or equipment which is not in contact with product, but which can affect the performance or operation of a direct impact system/equipment. These are systems / equipment that are designed and commissioned in accordance with GEP. If they affect the performance of a direct impact system they will additionally be subject to requirements for IQ and / or OQ.
- Safety impact system. A system that does not work directly on product, and whose primary function is a safety requirement for operators during GMP manufacture.
- No impact system. A system that does not work directly or indirectly on the product.

15.3 Criticality assessment at component level

Following an impact assessment, a component-level assessment is made for direct impact, indirect impact, safety impact and no impact systems, in accordance with the ISPE Baseline Guide Volume 5 Commissioning and Qualification. The assessment determines the criticality of components in the categories “critical” and “not critical”. Components considered not critical can be controlled by GEP alone, while critical components will be subject to qualification requirements. Indirect and no impact systems consist only of non-critical components. Direct impact systems consist of both critical and non-critical components. If, in an indirect and no impact system, one or more critical components are included, then the system is incorrectly classified or the component is misjudged. The outcome of the impact

assessment and the criticality assessment process is a validation matrix detailing the protocols that will be produced and implemented in the project.

16 Commissioning

Commissioning is performed by the Vendor and is defined as the process by which the facility, systems and equipment are tested to ensure/verify that the design of the facility is fit for its intended use. The facility, equipment, systems, utilities and environment must meet both the URS and regulatory requirements. The commissioning process starts at the pre-design phase and continues through construction until the final qualification is performed; it can be divided into phases of pre-design, design, construction and operation.

After goals and requirements are identified in the design phase, the construction phase will start, where all systems are manufactured, inspected, tested and installed in accordance with specified documents.

Suppliers must provide furnishing, systems and equipment as specified in the URS and the systems must meet the design intent. At Vendor's or Manufacturer's premises a Factory Acceptance Test (FAT) will be executed in the presence of representatives of Purchaser. FAT will be executed according to a protocol that is to be prepared by Vendor. Vendor will provide a FAT protocol for review which is approved by the project validation group. During the FAT, certain items belonging to the IQ and OQ will also be checked. FAT will be executed using protocols to inspect and test functional operation of materials, systems and equipment at the supplier`s factory before it arrives on-site. Testing should include all critical components identified in the impact assessment and criticality assessment at component level.

After the complete installation and final configuration, the Site Acceptance Test (SAT) will be performed. Site-acceptance test protocols will be used to verify that equipment, systems and material have not been damaged during transport and work as properly installed. Tests will be executed that are required to complete FAT/SAT by repeating FAT or an acceptable subset of the test to verify that no damage has occurred during shipment and installation. All

outstanding items from FAT shall be solved. FATs and SATs will be performed using test procedures and checklists.

17 Acceptance criteria

Relevant acceptance criteria must be established and approved prior to each qualification and validation protocol. General guidelines for specifying acceptance criteria shall be described in Helse Bergen's procedures and specific ones are described in specifications and requirements (URS and detailed design). Results that differ from the approved acceptance criteria shall be documented in accordance with non-compliance procedures and shall be classified as “major” or “minor”. Significant deviations must be solved and closed before the next phase of qualification and validation can continue and/or before a report can be approved.

The validation is aiming for design, execution and validation in accordance with:

- EU GMP requirements described in the EudraLex - Volume 4 - Good Manufacturing Practice (GMP) guidelines
- Helse Bergen requirements (HSE)
- Implement SOP where necessary.

18 Validation report

After all qualifications are summarized and approved via a documented process, a summary report to this VMP will be created to list and document all necessary qualifications and actions required by this VMP.

18.1 Handover to end-users

- Knowledge transfer from supplier to end-users in the building hand-over phase
- Allowing an agreed period of time after completion to “guide” and support the end user
- Support the customer/end user through the commissioning process
- Recommendations for ordinary use

18.2 EVF in ordinary use

The chosen supplier will provide

- Recommendations for ordinary use
- Set up regular training sessions with potential users and facility/maintenance teams responsible for the asset after occupation/use so they understand the systems.
- Operational and Maintenance (O&M) manuals and the Health and Safety File.
- Use a building user guide, if appropriate, to draw attention to the important items from the technical manuals in a pictorial, easy to follow, format for the management team.

19 Revalidation

The clean room must continue to perform efficiently and according to requirements throughout its lifespan (Appendix A9). A monitoring plan and risk assessments must be performed to determine the frequency of testing and validation of facility and individual processes. Certain requirements are continuously monitored (such as pressure differentials) while others are tested at specified maximum time intervals between tests depending on the grading of the room (cleanliness). At specified time intervals testing will include, but not be limited to, testing of airborne particle concentrations, air flow velocities, filter leak tests, airflow volume supply, recovery time and additional tests may include i.a. containment leak testing and flow visualization tests, according to ISO 14644-2 and ISO 14644-3.

20 References

20.1 GMP and relevant guidelines

The facility shall comply with the EU GMP guidelines as described in the EudraLex - Volume 4 - Good Manufacturing Practice (GMP) guidelines, Part I and Part IV.

Other relevant international guidelines and codes are as followed:

- The Pharmaceutical Inspection Convention and Pharmaceutical Inspection Co-operation Scheme (PIC/S), Guide to good manufacturing practice for medicinal products, part 1; latest version
- International Conference of Harmonization, ICH Q7A
- International Society for Pharmaceutical Engineering (ISPE), latest editions
- FACT-JACIE International Standards for Hematopoietic Cellular Therapy Product Collection, Processing, and Administration (FACT – JACIE Joint Accreditation Committee ISCT-Europe & EBMT)
- US FDA Guidance for Industry, Sterile drug products produced by aseptic processing - current good manufacturing practice, by U.S. Department of Health and Human Services, FDA, CDER, CBER, ORA
- WHO Technical Report Series (TRS). (incl Annex 3, 4 and 5).

20.2 International standards and codes

- NS EN ISO 14644 Series Cleanroom Standards
    - 14644-1, Title: Classification of air cleanliness by particle concentration
    - 14644-2, Title: Monitoring to provide evidence of cleanroom performance related to air cleanliness by particle concentration
    - 14644-3, Title: Test methods
    - 14644-4, Title: Design, construction, and start-up

- European Pharmacopeia (Ph. Eur.)
- PIC/S Guide to good manufacturing practice for medicinal products
- NS EN ISO 1822 Series for High efficiency air filters(EPA, HEPA og ULPA)
- NS EN 12469:2000 Biotechnology - Performance criteria for microbiological safety cabinets
- NS 8175:2012 Acoustic conditions in buildings - Sound classification of various types of buildings.

20.3 Norwegian regulatory requirements

- Lov om legemidler (legemiddelloven)
- Forskrift om legemidler (legemiddelforskriften)
- Forskrift om tilvirkning og import av legemidler (tilvirkningsforskriften)
- Forskrift om legemidlers kvalitet, standarder m.m.
- Forskrift om håndtering av humane celler og vev
- https://lovdata.no/dokument/SF/forskrift/2015-12-07-1430
- Norske legemiddelstandarder (NLS)
- Forskrift om Systematisk helse-, miljø og sikkerhetsarbeid i virksomheter (Internkontrollforskriften)
- Lov om planlegging og byggesaksbehandling (plan- og bygningsloven)
- Lov om arbeidsmiljø, arbeidstid og stillingsvern mv. (Arbeidsmiljøloven).
- Forskrift om utforming og innretning av arbeidsplasser og arbeidslokaler (Arbeidsplassforskriften)
- Forskrift om tiltaksverdier og grenseverdier for fysiske og kjemiske faktorer i arbeidsmiljøet samt smitterisikogrupper for biologiske faktorer (forskrift om tiltaks- og grenseverdier)
- Veiledning om klima og luftkvalitet, best. nr. 444 fra Arbeidstilsynet.

21 Appendix

List of Appendices

Appendix A1 Layout drawing of ex vivo facility

Appendix A2 Personnel flow diagram

Appendix A3 Starting material flow diagram

Appendix A4 Product flow diagram

Appendix A5 Ancillary material /consumables flow diagram

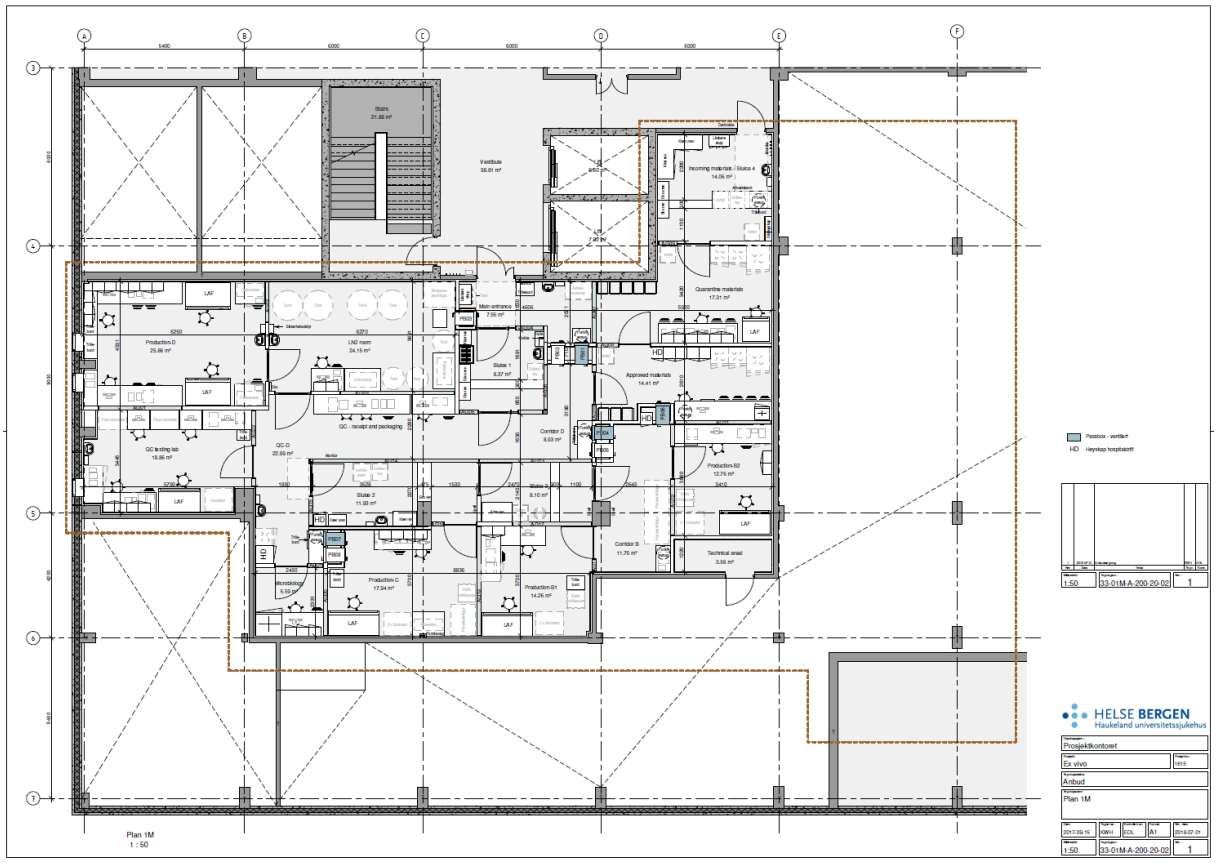
Appendix A6 Waste flow diagram

Appendix A7 Pressure cascade concept

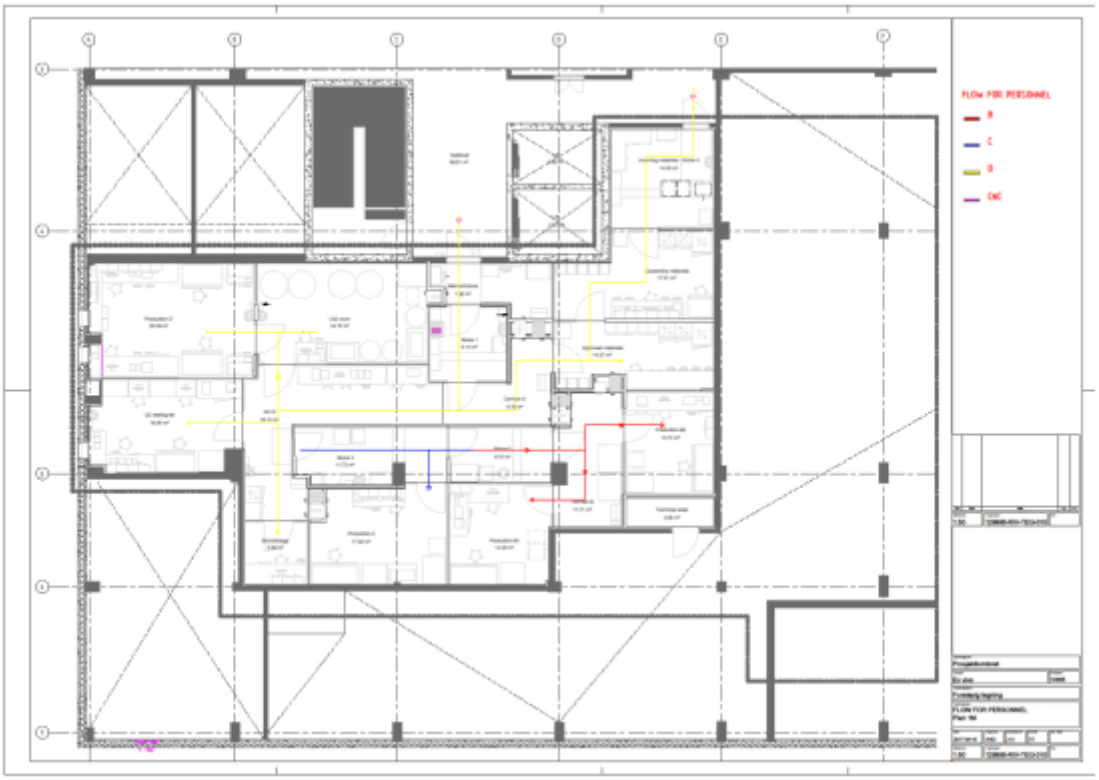
Appendix A8 Validation Model

Appendix A9 Validation and project life cycle

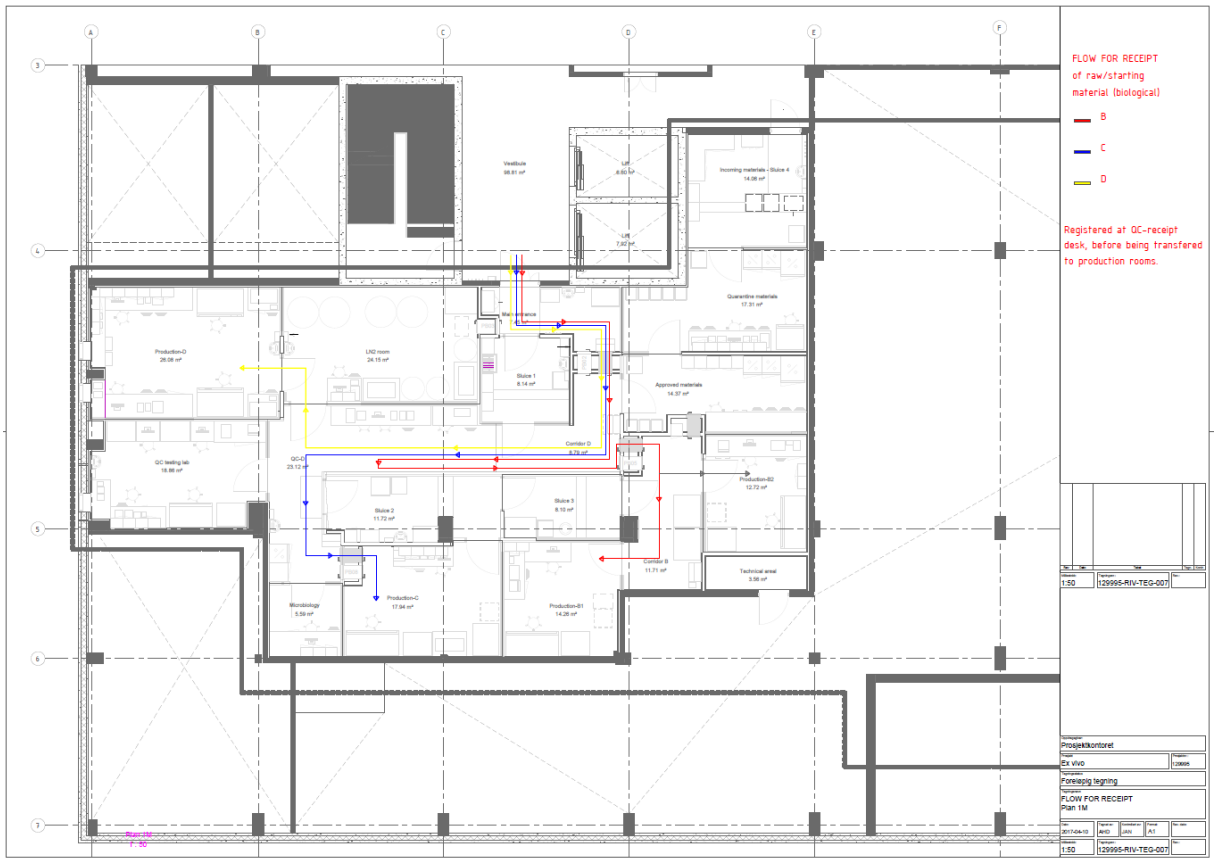
Appendix A1. Layout drawing of ex vivo facility



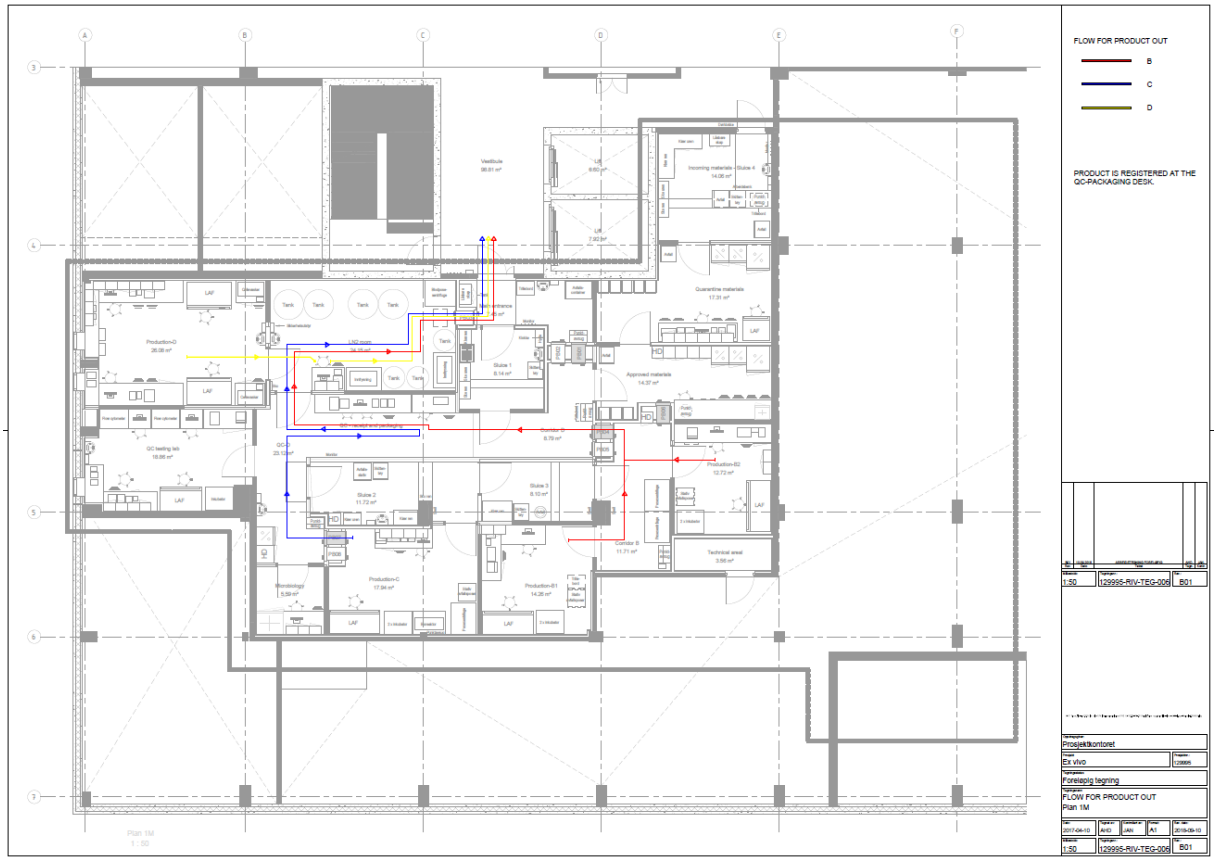
Appendix A2. Personnel flow diagram



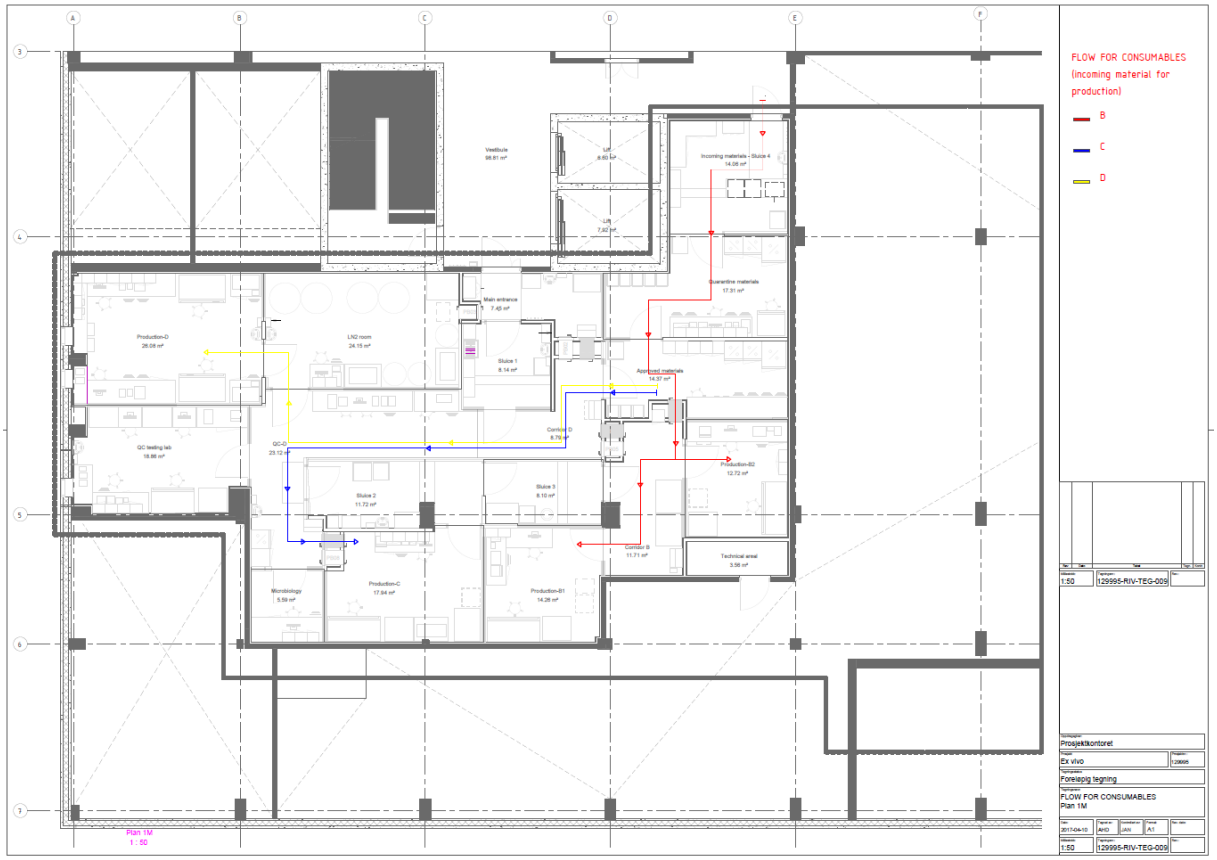
Appendix A3. Starting material flow diagram



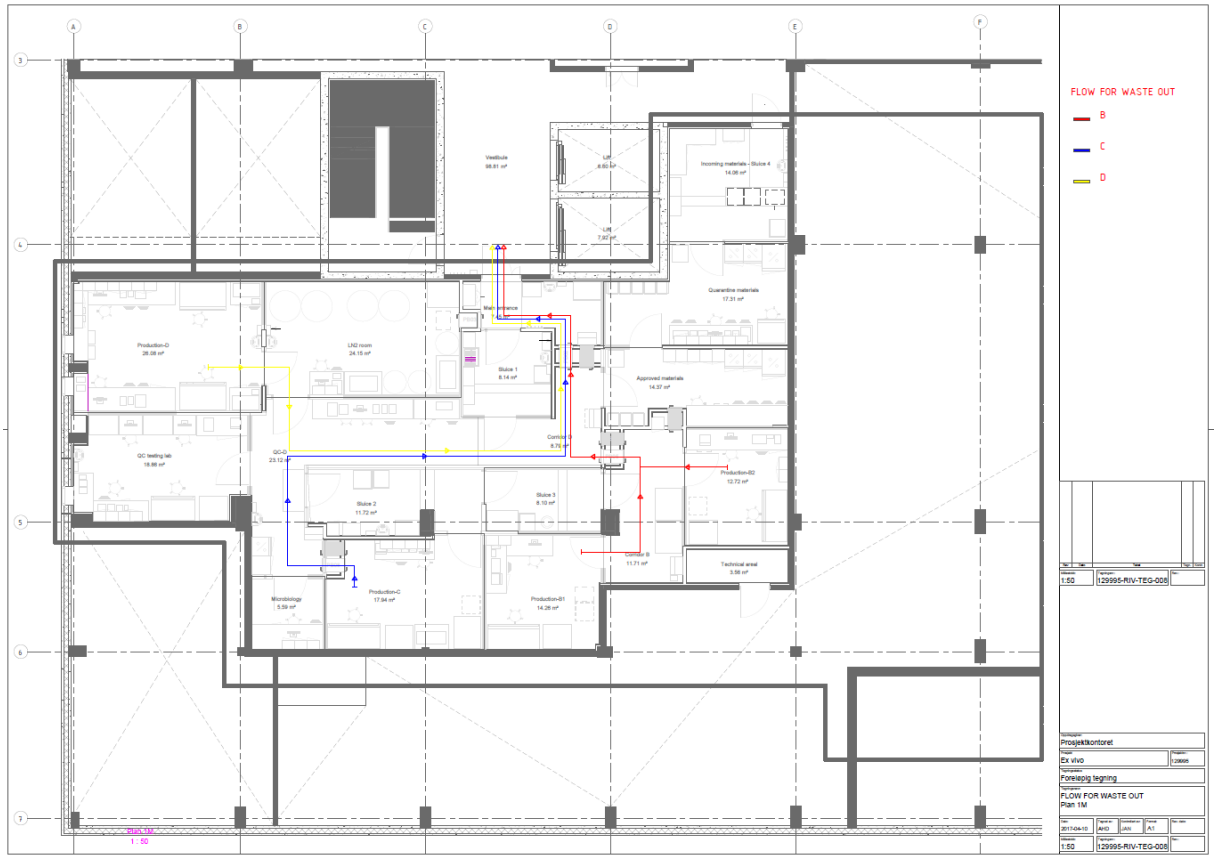
Appendix A4. Product flow diagram



Appendix A5. Ancillary material / consumables flow diagram



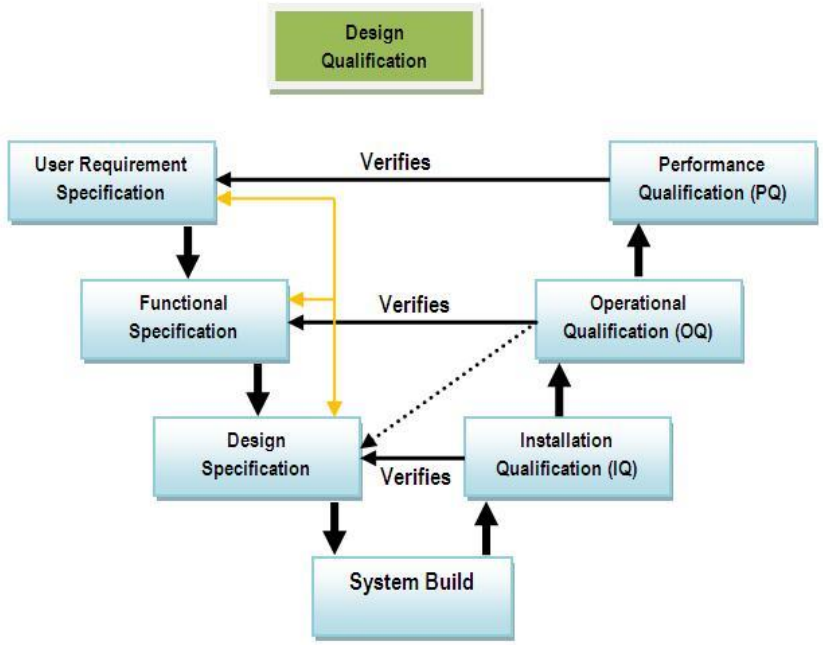
Appendix A6. Waste flow diagram

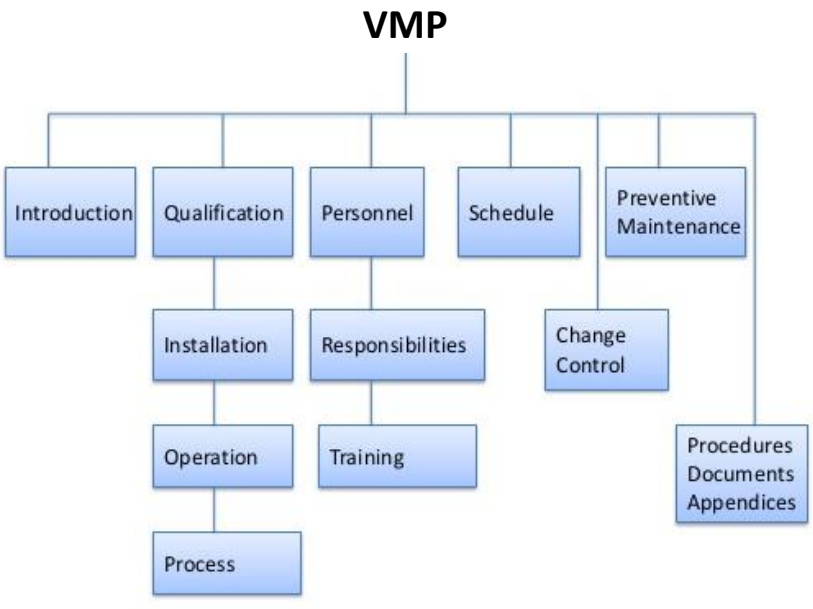


Appendix A7. Pressure cascade concept

Appendix A8. Validation Model

This project follows the "V-model" for critical systems (top figure), where relevant. It visualizes the relationship between user requirements, design and the specifications designed to meet them. Also part of the validation process is further testing performed as part of the startup and qualification of installed and operated systems and clean rooms.





Appendix A9. Validation and project life cycle

The various activities in the qualification and validation are schematically described in the flow chart below. It does not show the correct time period of implementation.