User Requirement Specification

Ex vivo Facility (EVF) for Stem Cell Treatment, Cellular Therapy and Regenerative Medicine

Bergen Stem Cell and Regenerative Medicine Facility

Haukeland University Hospital

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1 Publication record

All changes to this document are recorded in the Publication Record Table.

PUBLICATION RECORD				
Version	**Change description**	**Initials**	**Section**	**Date (d/m/y)**
01	New document	KJH		27.09.2018

Content

2 Abbreviations and Supporting figures

Table 1. List of Abbreviations

AIT	Department of immunology and transfusion medicine
AHU	Air handling unit
BSC	Biological Safety Cabinet
C	Commissioning
CAV	Constant Air Volume
EurPharm	European Pharmacopoeia
EVF	Ex vivo facility
FAT	Factory Acceptance Test
GEP	Good Engineering Practice
GMP	Good manufacturing practice
HEPA	High Efficiency Particulate Air
HSE	Health, Safety and Environment
HUS	Haukeland University Hospital
HVAC	Heating, Ventilation and Air Conditioning
IQ	Installation Qualification
JACIE	Joint accreditation committee ISCT EMBT
LAF	Laminar Air Flow
LK	Laboratory Clinic
MAL	Material Air Lock (= pass box)
MC	Multiconsult
NA	Not Applicable
PB	Passbox (= MAL)
PQ	Performance qualification
PV	Performance validation
Q	Qualification
QA	Quality assurance
QC	Quality control
QM	Quality management
QMS	Quality management system

QP	Qualified Person
RFQ	Request for Quotation
SAT	Site Acceptance Test
SOP	Standard operating procedure
URS	User Requirement Specification
VAV	Variable Air Volume
VMP	Validation master plan (this document)
VP	Validation plan
VSR	Validation Summary Report

Table 2. List of supporting Figures/Tables in Appendix

Appendix A1	Layout drawing of EVF
Appendix A2	Personnel flow diagram
Appendix A3	Starting material flow diagram
Appendix A4	Product flow diagram
Appendix A5	Ancillary material flow diagram
Appendix A6	Waste flow diagram
Appendix A7	Differential pressure cascade
Appendix A8	List of permanent equipment
Appendix A9	Validation and project life cycle

Additional supporting figures, tables and diagrams can be found in *129995-TVF-Beskrivelse* and *VMP for EVF*.

3 Purpose of URS

This User Requirement Specification (URS) intends to provide the requirements for the Ex Vivo Facility (EVF) at Haukeland University Hospital (HUS) in Bergen, with regard to design, construction, ventilation, utilities and permanent installations in order to manufacture medicinal products in accordance to national authority regulations and EU-GMP guidelines. This URS along with the layout drawing provides the elements of the conceptual design.

This URS as part of the Request for Quotation (RFQ) provides bidders with the necessary guidance to design the Ex Vivo Facility and to achieve mandatory compliance. At the same time, the goal is not to stifle innovation from the design team and Vendor seeking to provide an optimal solution to meet the client's operational objectives and regulatory compliance.

3.1 Deviations

Deviations from the requirements of this specification may only be applied after obtaining a written approval from the Purchaser.

3.2 Conflicting requirements

All conflicts between the requirements of this URS, codes, standards, purchase order and drawings shall be brought to the project engineers' attention for clarification before proceeding with the design, manufacture or procurement of the relevant part.

3.3 Design responsibility

Nothing contained in this specification, purchase order, drawings etc. shall relieve the Vendor of his responsibility for constructing the facility to meet the specified conditions.

3.4 Code compliance

It shall be the Vendor's responsibility to determine and comply with the requirements of applicable mandatory rules (i.e. city, national, codes or ordinances). The costs of the required inspections to comply with code(s) or governmental rules and regulations shall be included in the proposal.

3.5 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).

4 General overview

4.1 Purpose of the EVF

The construction of the ex-vivo facility is supported by funding from the Helse Vest Foundation and was initiated based on two evolving demands. Firstly, this facility aims to meet the interests of the scientific community in need of a GMP compliant clean room facility to manufacture advanced therapy medicinal products (ATMPs) for phase I and phase II clinical studies. Secondly, the facility will include a dedicated clean room area for minimal manipulation of human cells, an activity which is currently being conducted by the Department of immunology and transfusion medicine (AIT), but new facilities are needed to meet the requirements of the Norwegian regulations for processing human cells and tissues (FOR-2016-09-07-1052).

The facility will have a pharmaceutical quality management system (QMS) in line with GMP guidelines, and the entire facility should be built and run according to EU-GMP guidelines and Norwegian regulations, and will be subjected to inspection (and approved) by the Norwegian Medicinal Agency. Areas and activities where minimal manipulation is conducted will be under the inspection of the Norwegian Board of Health Supervision (Statens helsetilsyn).

4.2 Scope

This URS describes specifications for the GMP-compliant clean rooms that are part of the so-called EVF, to be established in the Laboratory Building, floor 1M for manufacturing and/or manipulation of human cells, including supporting clean room corridors/transition spaces, a sluice system for appropriate gowning and material airlocks (MALs) for transfer between classification levels. The URS also includes specifications for quality control areas and storage areas for ancillary material and biological material.

4.3 Site location

The EVF will be located on the 1M floor of the Laboratory Building at Haukeland University Hospital. This mezzanine constitutes around 262 m^2 and will have a ceiling height of 2.40m (roof total height 3.24m). There is not sufficient space for a ventilation system above the roof of the facility, so the

ventilation system and main technical area, including the computer server/IT system, will be situated on floor 1 directly beneath the facility.

4.4 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), including tissue engineered products and somatic cell therapy medicinal products for use in clinical trials. 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 (routine preparation of stem cell products) will be conducted 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 tanks, which is part of the current treatment offered to patients at HUS.

5 Space and layout requirements

5.1 Design strategy and layout

Our layout drawing and URS aim to ensure that the manufacturing process and quality of the product is sufficient according to required EU-GMP standards. It aims to minimalize the risk of cross-contamination or mix-ups that can occur through the circulation of personnel and material. Several requirements are taken into account to ensure the quality of the product and safety of personnel.

- Personnel working in different clean room classes have dedicated gowning rooms leading to rooms authorized for the particular category, minimizing the risk of interference from other classes.
- Flow of ancillary material and personnel is segregated, with separate entrances, and MALs are used to transfer materials into grade C and grade B clean rooms.
- Process segregation is maintained by having a transition space (corridors), with a change in pressurization.

- The layout of the facility is designed in such a way to minimize the generation of dust, particles etc, to avoid contamination and mix-up of products, and support efficient cleaning and maintenance of the facility and permanent installations.
- The pressure differential concept and a specialized HVAC system are used.
- The facility also aims to provide acceptable comfort and good working conditions for personnel, with regard to health, safety and environment.

Our goal is that this modular clean room facility is up-to-date and efficient at start-up and in the forthcoming years, being able to adjust to capacity changes as well as product and technology changes in the next 6-10 years. There is no free area for disposal besides the area shown on the layout, so planning for a potential expansion of the facility in the future is not taken into account.

5.2 Description of layout

A brief description of all rooms is shown in Table 3 and the layout is shown in Appendix A1, and the classification of clean rooms is shown in *129995-RIV-TEG-002*. The facility has two grade B production rooms where the biological safety cabinets (BSCs) provide a grade A manufacturing area for substantial manipulation of cells (ISO-5). There is also one grade C production room (ISO-7), and a grade D production room (ISO-8) for minimal manipulation of human cells. Minimal cell manipulation performed in the grade D production room will be first and foremost dedicated to activities related to hospital routine preparation of stem cell products, such as centrifugation and freezing of cells. There is also a room for conducting controlled-rate freezing of products, where tanks filled with liquid nitrogen are used for cryopreservation of products. Access to manufacturing clean rooms is through supporting corridors and gowning sluices where personnel change into appropriate clothing before accessing the various rooms.

Ancillary materials arrive through the dedicated entrance for incoming goods (Sluice 4), where goods are checked and cleaned before being put in quarantine. All ancillary materials are kept under quarantine after receipt until being inspected for rejection or approval. Then approved materials are moved to the approved material storage area.

Finally, there is a quality control (QC) area which is spatially separated from the production area and divided into several work stations based upon the activities to be executed. All starting/raw materials enter the facility through the main entrance and will be registered after receipt at a dedicated work station in corridor D. The quality control testing of all starting materials, intermediate products and final products will be performed in the QC testing lab, where there is i.a. a BSC and flow cytometer.

Finally, finalized products will be packaged at dedicated work stations (in LN2 room for products manufactured in grade D, or in corridor D for products manufactured in grade B or C). Adjacent to the QC area, there is also a room dedicated for microbiological testing, including storage of settle and contact plates and recording of the results.

Table 3. Cleanroom Overview

Room name	*Area,m^2	**Grade	**Pa	Main activity
Main entrance	7.55	CNC	5	Entrance for personnel and starting material, and for collecting products.
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, QC – incl. receipt and packaging area	31.92	D	30	Transition space, reception of starting material and packaging of product
QC-testing lab	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
Sluice 4 - Incoming materials	14.06	D	15	Main entrance for goods intended for use in the production process.
Quarantine materials	17.31	D	45	Storage of materials until rejected or approved for use
Approved materials	14.41	D	45	Storage of approved materials

*Area according to layout drawing **According to EU-GMP ISO 14644-1 ***Rooms of different clean room grading should always have 10-15 Pa difference independent of the indicated pressure ranges. CNC, controlled not classified; QC, quality control.

5.3 Flow in the 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 have different routes into and out of production cleanrooms for more-than-minimal manipulation. Materials enter grade C and grade B production rooms through material airlocks (MALs) while personnel enter through controlled-access gowning rooms (sluices).

5.3.1 Personnel flow

Personnel will primarily enter the facility through the key-card controlled main entrance. Outdoor shoes and clothing is not brought into the facility. Personnel will gown appropriately in Sluice 1 before entering Corridor D. From Corridor D, the personnel can either enter i) the liquid nitrogen storage room (ii) the grade D production room by bypassing the liquid nitrogen storage room iii) the QC area iv) the grade C production room after gowning in Sluice 2 or v) the grade B production rooms after gowning in Sluice 3 and bypassing Corridor B. A limited number of people should generally be present in the clean rooms. Personnel enter and leave the clean rooms through the same sluices, so-called bidirectional flow. An overview of the personnel flow is shown in Appendix A2 (*129995-RIV-TEG-010*). Detailed description of i.a. gowning procedures and behavior in the clean rooms are described in SOPs.

5.3.2 Starting material and (intermediate/final) product flow

Starting material to be used in manufacturing rooms will enter the facility through the main entrance where outer packaging is cleaned and transferred to corridor D through a MAL (PB01), see Appendix A3 (*129995-RIV-TEG-007*) showing a flow diagram for starting material. The material will be transported by personnel to the receipt desk in corridor D dedicated for inspection, labelling and registration of the material. Here the approved starting material will be double-packed if necessary, and then it will be transferred to either grade D production room (minimal manipulation) by personnel or transferred through MALs to either grade C or grade B production rooms.

During manufacture, intermediate products for quality control testing will be transported through MALs and brought to the QC area for QC analyses. The *final product* will be transported to the dedicated area at QC for correct labelling and packaging of products. The final product is contained adequately before being transported out of the MAL in the LN2 room, to the main entrance (see

Appendix A4, *129995-RIV-TEG-006*). Products to be stored in the gaseous phase of liquid nitrogen tanks are labeled, and either kept in a quarantine tank (before performing relevant tests) or in a normal tank, before their final release.

5.3.3 Ancillary material flow

Ancillary materials will enter the facility through the main entrance for materials (Sluice 4). Ancillary materials include components, solvents, reagents and plastics used during the manufacture of cell therapy products but are not intended to be part of the final products. Ancillary materials intended for use in manufacture are taken into the clean rooms by personnel through a dedicated entrance (Incoming materials – sluice 4). Materials are cleaned and disinfected according to procedures by personnel, registered, labeled and then stored in a clearly marked quarantine area after receipt until they are checked and approved. The materials should first be inspected for damages or other quality impacts and freed from outer packaging if required. Materials which are out of specification or expired are rejected and moved out of the facility. Approved material is labeled and moved to the approved storage area. All items are visibly labeled with colored stickers according to their status (date, quarantine, approved). Materials to be used in manufacturing processes are transferred by personnel through dedicated MALs which allow the transfer of material between rooms. MALs are used to transfer materials to grade B production rooms (PB06) and grade C production room (PB07). Materials to be used in grade D production room are brought into the room by the personnel. Ancillary materials to be used in quality control analyses or for microbiological testing, and equipment as well as parts of equipment, also follow the same route into the facility; and after approval, they can be transferred to their respective rooms for their intended use. An overview of the ancillary material /consumable flow is shown in Appendix A5 (*129995-RIV-TEG-009*).

5.3.4 Waste flow

Waste will be contained in plastic bags and transported out of the facility through MALs according to the flow chart shown in Appendix A6 (*129995-RIV-TEG-008*). Waste bins suitable for clean rooms are present in rooms where necessary. The waste will be collected from the MALs and taken out of the facility before activity closes down for the day, according to standard procedures. A dedicated area is situated in the main entrance for waste disposal. 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.

5.3.5 Gowning rooms and material airlocks

Gowning rooms, also called sluices, are of appropriate size so at least two people can be in the room simultaneously while one person is gowning. All personnel will follow a written procedure on how to enter the respective room to minimize contamination of clean areas and clean-area clothing. Sluices are separate rooms designed such that the last airlock has the same clean room grade as the corridor/room it leads into. Clean protective garments will be provided in each sluice which will be of sufficient size to change clothes. The sluices will be flushed with filtered air to minimize microbial and particulate contamination. Airflow patterns must minimalize contamination risk (avoiding particle flow from particle-generating personnel/equipment to zone of higher risk for the product). In critical areas or contamination risk areas (where trolleys are used), special floor-cover/sticky mats may be used to reduce contamination. Transport of ancillary materials, consumables etc between different rooms is performed using material airlocks (MALs), also called passboxes (PB). These MALs help to control the contamination risk and reduce the level of human intervention.

6 Operational requirements

6.1 Operation time

Normal operation time is between 06 am till 8 pm on working days, but 24/7 operation must be possible in periods. Monitoring of the facility is automated and done continuously, though fan/filter units are programmed to scale back to lower speed, such as “night mode”, to reduce energy consumption when the facility is not in use.

6.2 Access control

All entrance in and out of the facility is logged electronically using access cards. An access control system will assure that only authorized people can enter the classified clean room areas, using a pin code system, thus these areas are access-restricted (see *129995-XX-1M-E-543-20-01*). Personnel must be sufficiently trained in i.a. personnel movement and gowning procedures, before being authorized to work in the facility. Each personnel must also be specifically trained for the appropriate grade of clean room where the personnel will be working. Training is documented and maintained continuously according to GMP guidelines. Under certain circumstances, such as during training of

new personnel and supervisory situations, personnel may enter the facility while being accompanied by trained personnel.

6.3 Microbiological monitoring

The facility will be routinely monitored with regard to microbiological count (viable particles). Sampling of aseptic processing areas is done after each operating shift; details about frequency and location of sampling and monitoring procedures will be described in SOPs. Reading of plates is performed in the Microbiology room which has a lower pressure than the adjacent room, to prevent air leakage.

7 External additional supporting facilities

Floor 1, directly beneath the facility, will be used for technical installations and the computer server system. A small area of 3.5m^2 is available for technical installations on floor 1M.

8 Central monitoring system

Monitoring is performed with a system called Facility Monitoring System (FMS, environmental monitoring) 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 be UPS-powered. Monitors will be placed at convenient places in the facility, so personnel can easily see the status of clean rooms before entering.

The final number and location of critical sensors shall be determined by means of a risk assessment and compliance with ISO 14644 in detail design, performed by the supplier and the users. Continuous monitoring of the facility will be performed and each room will have the necessary integrated sensors to automatically record and store the following parameters for later documentation:

- Number of airborne particles per cubic meter of air
- Pressure and differential pressure (pressure difference between rooms / pressure regime)
- Temperature
- Relative humidity (% RH)

- Air flow
- Airlock status (door open/ajar)
- Equipment alarm systems (including freezer, refrigerator, incubator)

In addition, a warning system should indicate failure to meet the requirements and send alerts via email and telephone. The system should have an analysis and reporting tool and also be fully configurable, user-friendly and maintainable. The alarm system is shown in diagram *129995-XX-1M-E-563-20-01_Rev2*.

In addition, alarms and monitoring of air quality in BSCs shall automatically be monitored continuously and have real-time data collection (particle counters), and this monitoring is integrated into the larger FMS.

9 Lighting and acoustics

9.1 Lighting

Adequate lighting must be present in all areas of the facility, according to the different processes performed in each room and to maintain a good working environment for personnel. Three windows will be placed in the facility to allow natural light into two of the rooms, with two windows in Production-D room and one in QC-testing lab, where it is expected that personnel will spend a lot of their time. Direct sunlight into the facility, which might increase the temperature, is not considered a problem as the building is facing north-west on the first floor.

Artificial lighting should be adjustable, with the possibility of three levels of lighting. There should be between 3500-6500 Kelvin, with tunable white to easily change the color temperature. Long-lived LED lights have a required life cycle of 20 years without maintenance (and clean room reclassification). They should be corrosion-resistant, as well as dust and water-resistant. If maintenance of lighting is not possible from the roof of the facility, then appropriate protocols must be in place when changing lights from the inside (enclosed panels) with appropriate fixtures. Light panels must also tolerate cleaning and disinfection solvents over time. A motion sensor turns light on automatically and light is kept on in Corridor-D as long as someone is inside the facility. Lights can be coupled between certain rooms and turned on as a group in several rooms.

9.2 Acoustics

Walls and material in general should be noise cancelling where possible, to reduce noise from i.a. equipment, ventilation systems and ventilated hoods. Technical regulations refer to Norwegian Standard NS 8175 - "Sound conditions in buildings - Sound classification of different building types".

Class C is the sufficient/minimum requirement. Furthermore, we would like to point out the Regulations for Action and Limit Values (FOR-2011-12-06-1358) where EVF will belong to Group 2 working conditions. For new buildings it's desirable to achieve minimum ten decibels below the limit value.

10 Utilities

10.1 Water

Drains and sinks are prohibited in grade B rooms. Sinks for hand washing are only present in non-classified rooms (NC) or grade D rooms, as well as the first stage of Sluice 2 (Table 4). Water piping has no direct connection with class C or class B rooms and should not pose a risk of contamination of premises. Sinks for hand washing have both cold and warm water. All sinks have hands-free automatic faucets, are made of cleanroom compatible material (corrosion resistant and without seams that collect particles) and prevent splash back. High quality grade water will be purchased when water is required for production or for cleaning purposes.

Table 4. Location of sinks

Room name	Class	Purpose
Main entrance	CNC	General purpose
Sluice 1	D	General purpose
Production-D	D	General purpose
LN2 room	D	General purpose
QC-D	D	General purpose
QC testing lab	D	Dispose of liquid waste
Incoming materials – sluice 4	D	General purpose
Sluice 2	C	General purpose

10.2 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 (CO_2), medical air (compressed air) and nitrogen (N_2). These three gases are required in all production rooms (grade D/C/B) and the QC testing lab. Process gases are provided through hidden piping in the walls. There should be a back-up system in case the main gas supply fails.

10.3 Liquid nitrogen

Liquid nitrogen (LN2) will be used for storage of cells in closed containers, and will be supplied through piping to 1M from the main supply tank for HelseBergen.

11 HVAC requirements

An air handling unit (AHU) controls the air in the facility, with a cooling, heating and (de)humidifying system (see *129995-RIV-TEG-004*). The HVAC system should be appropriate for the activities performed and should not negatively affect the products/ATMPs or functioning of the equipment; and specifications should also be met continuously all year, also with equipment and people present in rooms (in operation and at rest). The HVAC system should be in compliance with ISO 14644. Detailed information of the HVAC system can be found in the *URS for EVF HVAC and Utility* and the HVAC principle drawing (*129995-RIV-TEG-004*) and flowsheet for air distribution (*129995-RIV-TEG-005*).

11.1 Air changes

A dedicated and efficient HVAC system will continuously supply and distribute required volume and quality of air to the facility, with uniform air distribution (avoiding airflow turbulence), in accordance with ISO 14644 (see *129995-RIV-TEG-012*). Air supply to the clean rooms must be sufficient in order to reach and maintain the B, C and D air grades even under stressful conditions with a maximum number of people present per room (see Table 5). 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, without compromising other URS. The AHU redundancy is nominally 1x100%, with separate air supply and discharge “trains” (for flexible installation). However, each train should have 2x100% capacity fan units, with motor frequency converter, all operating normally at 50 % capacity. Speed is increased to 100% capacity (volume and pressure) in case of fan break down, in order to maintain the pressure regime. The AHU and its distribution system are all connected to existing UPS. A description of the HVAC system is shown in detailed diagrams. A separate new extract air ventilation system is to eject sanitizing aerosols outside each MAL (pass box) (SHA related) and evacuate due to a liquid N_2 leakage in an emergency situation. Supply and extract air flowsheets are shown in *129995-RIV-TEG-013* and *129995-RIV-TEG-014*.

The number of air changes (change rates per hours) should be calculated to provide optimal cleanliness as required per the grades and should be related to the size of the room, the equipment

present and the numbers of personnel present (see Table 5). The particle limits given in the table for the “at rest” state should be achieved after a short “clean up” period of 15-20 minutes (guidance value) in an unmanned state after completion of operations.

11.2 Air flow

Air flow will be unidirectional in class B clean rooms (avoiding turbulence), and air flow will also be unidirectional in BSCs where the product is exposed. Airflow should ensure the required airborne particulate cleanliness class and avoid airflow turbulence which can create contamination.

11.3 HEPA filters and other filters

Air filtration should be set to ensure that the defined clean area classification is attained. The air system is HEPA-filtered to obtain the clean room requirements:

- Class B and C clean rooms H13 in line filter and H14 terminal filters
- Class D clean rooms H13 in line filter

HEPA filters shall be in accordance with NS EN1822. Leak test (scanning) shall be in accordance with NS EN 14644-3. See our *URS for EVF HVAC and Utility* and flowsheet for air distribution *129995-RIV-TEG-005*.

11.4 Relative humidity

The relative humidity (% RH) should ensure a good working environment for the personnel and not pose any risk to the quality of the product. The aim is to keep 45+/-5% RH, with a lower limit of 40% RH and a maximum of 60% RH, to minimize the risk of microbial growth and contamination. A detailed description of a technical solution is shown in the HVAC flowsheet showing the air handling unit and dehumidifier unit *129995-RIV-TEG-004*.

11.5 Temperature

The temperature in the facility should meet the specifications even with heavy equipment and maximum number of people in rooms. The temperature can be regulated in each room between 19-25 degrees, and should be within +/-1◦C when a specific temperature is set. The range differs between rooms and should ensure that the personnel have a comfortable working enviroment and

take into consideration the clothing requirements of the personnel in each room (lower temperature in grade B rooms, higher temperature in sluices), and the number of people in each room. The temperature must also be appropriate for the product, i.a. stem cell products require between 19-25 degrees so the room temperature where biological/stem cell products should never be below 19 degrees, and maximum 25 degrees.

11.6 Air tightness

The room will be air-tight as far as possible to minimize the ingress of less clean air from areas of lower grad into areas with higher grade (more clean) due to pressure differentials.

11.7 Pressure and zoning

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. The manufacturing rooms are the cleanest and have the highest pressure. Pressure gradients between rooms in the facility must guaranty air cleanliness, maintain particle requirements and aid to prevent cross contamination. In critical areas, such as between adjacent rooms of different clean room grades, there should be a minimum pressure difference of 10-15 Pa. The pressure in each room should aim to maintain +/-5 Pa from its set point level (specific values will be determined together with the supplier), but must still be able to maintain the minimum pressure difference between rooms of different clean room grades. Thus no major fluctuation should occur in directions that can result in a less differential. There is always ascending pressure towards the cleanest areas; as shown in Appendix A7 with a drawing of the differential pressure cascade, 129995-RIV-TEG-003. A stable reference set point is chosen (0 Pa) nearby, outside the facility.

An overview of cleanroom parameters is shown in Table 5.

Table 5. Cleanroom Parameters

Room name	***GMP grade**	**Particles *at rest,* operational**	**Pa**	**Maximum number of people**	****Air change (h^{-1})**
Main entrance	CNC	NA	5	5	>5

Sluice 1	D	*3.520.000* nd	15	4	>20
Corridor D, including QC – receipt and packaging	D	*3.520.000* nd	30	6	>20
LN2 room	D	*3.520.000* nd	45	6	>20
Production-D	D	*3.520.000* nd	45	6	>20
QC-D	D	*3.520.000* nd	30	6	>20
Microbiology	D	*3.520.000* nd	20	3	>20
Sluice 2	C	*352.000* 3.520.000	45	4	>25
Production-C	C	*352.000* 3.520.000	52	4	>25
Sluice 3	B	*3.520* 352.000	60	3	>30
Corridor B	B	*3.520* 352.000	60	3	>30
Production-B1	B	*3.520* 352.000	75	3	>30
Production-B2	B	*3.520* 352.000	75	3	>30
Sluice 4 -Incoming materials	D	*3.520.000* nd	15	5	>20
Quarantine materials	D	3.520.000 nd	45	4	>20
Approved materials	D	3.520.000 nd	45	4	>20

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

12 Electrical system

Electrical outlets are provided for power to the equipment and are shown in the drawing of the electrical system *129995-XX-1M-E-400-20-01_Rev2*, also showing which equipment has uninterruptible power supply (UPS)-powered. Electrical in general and errors in a room should not affect systems and equipment in other rooms. All material and design must be GMP compliant, with smooth, round surfaces and sealed to secure air. Material can resist cleaning and disinfection.

- 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 lighting is to be of type LED, and required life cycle of 20 years (and clean room reclassification).
- All biosafety cabinets are provided with separate UPS power, to protect product even if clean room ventilation system should break down. The monitoring system for BSCs and facility monitoring, including monitors, are to be UPS powered. BSCs shall maintain laminar air flow in case of power outages until emergency power is available.
- The AHU and MALs are UPS-powered (risk assessment required).
- With regard to the fire alarm system, the AHU is running until smoke is detected in the air inlet duct.
- 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 URS (risk assessment required).
- Monitoring of equipment critical parameters such as temperature should be UPS powered (refrigerator / centrifuges / incubators).

12.1 Interlocking system

An interlocking system must be implemented with a visual warning system to avoid simultaneous door opening. Two doors in the same sluice cannot be opened at the same time, then a visual warning system will show a green light when the sluice is ready and doors can be opened, a red light when the sluice is in use, or due to interlocking. See diagram for illustration of interlocking systems (*129995-RIE129995-05*). Doors should generally open towards higher pressure; with a self-closer

system; though changes are allowed based on emergency exits or HSE requirements. A button at the main entrance is able to override the interlocking system in the facility if neccesary.

13 Permanent furnishing and equipment

Each room should contain the minimum items of furnishing and equipment required to be operationally, and only contain the necessary equipment required for its intended use. A complete table/list of permanent equipment/furnishing to be supplied by the Vendor is shown in Appendix A8, and detailed specifications for each piece of equipment/furnishing can be found in the *URS for permanent equipment*. A layout drawing showing all the equipment and furnishing in the GMP facility is shown in Appendix A1, Layout of EVF. Equipment, as shown on the layout drawing, which is not supplied by the Vendor, should still be taken into account by the Vendor when installing/constructing the facility, systems and other equipment. The equipment should i.a. produce a low level of noise as possible to be in compliance with national regulations.

All equipment must be CE-marked and be documented to be in compliant with GMP requirements, both with regard to construction and the type of materials used. The specified equipment is correctly delivered and installed by the supplier, in accordance with an installation plan. A plan should also be made by the vendor with a time schedule for the delivery, installation and validation of each piece of equipment. In addition the mounting and placement of the equipment and installations should ensure easy cleaning. The equipment should be built to minimize negative effects on the product quality and be corrosion-resistant. 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 adequately.

13.1 Biological safety cabinets and MALs

Biological safety cabinets (also referred to as laminar air flow benches) and MALs (also referred to as pass boxes) are described in more detail in a separate URS (*URS for permanent equipment*). A class II BSC will be situated in each grade B manufacturing room, providing a grade A environment to perform the most critical processes. Other rooms will also contain BSCs, including Production room grade C, Production room grade D, the QC testing lab and the Quarantine materials room, as seen in Appendix A1 (Layout of EVF).

MALs are installed with a defined air change rate and positive pressure for transferring materials between rooms with different pressure. MALs should be at least 500x500x500 mm (HxWxD, interior measurements) for transfer of products and goods, and for waste they should be 1000x600x600 mm (HxWxD, interior measurements). Air change rate should be sufficient to ensure transfer between clean room grades, with >50 air change (h-1). Objects are sprayed with disinfectant before being placed in the MALs, and therefore spot ventilations must be installed beside MALs to protect users when disinfectant sprays are used, with a see-through hood, with an air change of 150 m3/h.

MALs are interfitted with HEPA filters to maintain particle control when situated between rooms with different cleanroom grades. The MALs have an interlocking system, and only one door of the MAL can be opened at a time (thus both doors cannot be opened simultaneously). They are all dynamic (ventilated system inside) to prevent the entrance of contamination into the most clean areas (see Appendix A7, *129995-RIV-TEG-003*), and their efficiency must be validated.

13.2 Communication system

A communication/intercom system allows personnel to easily communicate with anyone else in other rooms in the facility. Telephones suitable for the different grade of cleanliness are also situated where specified to communicate with contacts outside the facility, and also function as a back-up system if intercom should break down. Telephones must have a smooth surface which will not trap particulate matter, with buttons that are easy for gloved hands to use, and should also be easy to clean and resistant to alcohols and cleaning agents. Certain rooms will have a monitor and/or door-opening function. A description is shown in the drawing of the communication system (see *129995-XX-1M-E-535-20-01_Rev2*). In addition, alarm panic buttons will be present in grade B and grade C Production rooms as well as the LN2 room.

13.3 Computer system

Computers must be applicable for clean rooms of different grades (D/C/B), including being waterproof, dustproof and easy to disinfect. Computers must be compatible with the HelseVest IKT system, such as ACL OR-PC slim series, and should be installed together with HelseVest IKT system.

14 Cleaning and sanitizing agents

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. Storage cabinets for cleaning supplies are situated in several areas in the facility.

Ethanol will be used as a detergent, and disinfectants for cleaning may include, biquanide, klercide quat, klercide amine or similar agents appropriate for cleanrooms. 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 the detergent and disinfection agents.

15 Methods of construction

The overall construction 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 minimize the production of particles or other substances that may contaminate or have a negative influence on the product, and should be in accordance with WHO TRS Annex 6, §11.1-11.7. Construction should also support efficient 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. The facility is also designed to facilitate efficient cleaning and disinfection, so pipework, light fittings and ventilation points should be accessible from the outside (WHO TRS Good manufacturing practices for biological products, Annex 3, §12.28-12.29) or a protocol must be in place for maintenance/cleaning from the inside. In addition, construction should be done in such a way as to enhance the life-time of the facility.

15.1 Interior finishes and materials

Interior finishes should have smooth, impervious and unbroken surfaces that are cleanable and resistant to disinfectants. There should be a minimum of projecting cupboards and equipment, and ceilings along with pipes and ducts from utilities should be sealed to prevent contaminations. Wiring and cables are enclosed in conduit where possible to minimalize accumulation of dirt and dust. Flooring should be impervious; it must cover the floor and continue along the walls and corners avoiding dead angles, and should be of material resistant to sanitizing agents such as vinyl, and tolerate regularly cleaning. Silicone sealant of appropriate quality for clean rooms is used where necessary to have smooth surfaces and seal openings. Cleanroom flooring/mats are located at the main entrance and in front of the entrance into Sluice 2 (gowning room). Other important junctures such as where equipment is passed into the cleanroom may also have cleanroom flooring/mats if found necessary. Mats are designed to capture dirt, dust and debris from foot traffic and equipment wheels by allowing particles to adhere to the adhesive coat on the mat. In the grade D room where

liquid nitrogen containers are situated, there should be flooring around the containers such as metal, which can resist liquid nitrogen.

Glass walls are used where possible, to let in light and reduce a feeling of isolation, and also so supervisory personnel may visualize operation of processes ongoing in grade C or B areas while standing in lesser clean areas. Walls and material in general should be noise cancelling where possible (rooms are class C minimum, according to *Forskrift om tiltak og grenseverdier*), to reduce noise from i.a. equipment, ventilation systems and ventilated hoods. Pipes and ducts and other utilities should be installed so that they do not create recesses, unsealed openings and surfaces which are difficult to clean. A more detailed description of interior finishes and materials can be found in the report *129995-TVF-Beskrivelse*.

15.2 Doors

All doors should open into the room with the highest pressure unless documented that power-assisted doors function efficiently in either direction. Doors should be large enough to move equipment in and out of the modular clean room (for maintenance or exchange), and doors as well as corridor D must be wide enough to allow transport of nitrogen tanks (1100mm diameter) out of the facility if necessary. Doors are preferable of glass where possible/applicable. Double-leafed doors are preferable, with a door of at least 900mm and a side panel of at least 200mm which can be opened when needed, though prevention of air leakage should be guaranteed long-term. All doors inside the facility open automatically with a motion sensor and some doors are interlocked. There are also certain doors that can only be opened using a keypad access control system.

16 Regulatory Requirements

The facility, equipment and related activities shall comply with the EU GMP requirements described in the EudraLex, Volume 4, Good Manufacturing Practice (GMP) guidelines. Volume 4 of “the rules governing medicinal products in the European Union” contains guidance for the interpretation of the principles and guidelines of GMP for medicinal products for human and veterinary use laid down in Commission Directives 91/356/EEC, as amended by Directive 2003/94/EC, and 91/412/EEC, respectively. The facility must be built so that the rooms, and equipment, are in accordance with the EU GMP requirements and guidelines and to obtain approval by the obtain approval by the Norwegian Medicines Agency.

16.1 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)

16.2 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
- NS EN 1822 Series for High efficiency air filters(EPA, HEPA og ULPA)
- NS EN 12469 Biotechnology - Performance criteria for microbiological safety cabinets
- NS 8175:2012 Acoustic conditions in buildings - Sound classification of various types of buildings
- European Pharmacopeia.

16.3 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
- Norske legemiddelstandarder (NLS)
- Forskrift om 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.

17 Documentation

The Vendor must comply with good documentation practice and deliver the necessary documentation to prove that the facility, system and equipment is constructed according to GMP guidelines and in line with our URS. Thus, it must be documented that the materials used are compliant with GMP guidelines and the appropriate validation tests have been performed. Checklists should be used to validate that all parts of construction, equipment and systems are in concordance with GMP guidelines. These should include, but not be limited to: the material used, quality specification, certificates, test methods/protocols, responsible test person, number of tests performed, test results, transfer plans and reports, IQ, OQ, PQ, Certificate of Analyses (CoA) /Compliance (CoC), validation and documentation. Guidelines for documentation can also be found in the requirement specifications and the report *129995-TVF-Beskrivelse*.

18 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, according to good engineering practice (GEP). The facility, equipment, 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.

19 Qualification and validation

The Vendor is responsible for preparing a validation program and validation plans. This program/plan should provide an overview of what shall be validated, responsibiites during validation, along with a time table and order of the validation process. 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 project management group has prepared a Validation master plan (*VMP for EVF*), which the Vendor should give input on based upon their Validation program and which afterwards will be finally approved.

Validation procedures should be developed either as separate procedures or integrated into protocols and or tests. All tests performed by IQ, OQ and PQ shall be performed in accordance with approved and detailed protocols and procedures, as described in *VMP for EVF*.

A validation group should be set up with at least one representative from HUS and the representative from HUS will follow the project closely under the whole process (see *VMP for EVF*). Authorized personnel must approve protocols and reports, and any changes in documents should be approved by a validation group. The validation work must be completed as defined in specific approved protocols. All results must be recorded as they are obtained. If changes have to be made to documents that have been approved by the validtion group, the validation group must be informed and approve the new changes before the work can proceed.

Among other, the volume of air and change rates must be documented to be correct and stable over time. The air flow must be shown to not impose a contamination risk. Test should show that valves etc are situated correctly in rooms, also when all equipment is in place in each room. The particle counts should be tested according to ISO 14644-1. The cleanliness of rooms, including viable

particles, shall be according to GMP requirements. The validation will be divided into several different actions, because each one of them will be completed at different times.

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

- VMP Validation Master Plan (this document)
- VP Validation Plans
- FAT Factory acceptance test
- SAT Site acceptance test
- 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 Summary Report (VSR) should sum up all the activities and results and together with the VMP forms the basis upon which the Norwegian Medicines Agency (SLV) can approve the facility. HUS will submit a manufacturing authorization to SLV based upon the VSR. The VSR must be authorized by the Validation Group, and the end-users approval of the VSR creates a foundation for being able to start production.

19.1 Validation elements

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 give a detailed requirement description for the different validation activities, including:

- Validation and Qualification of 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 system validation
- Cleaning validation
- Interval based requalification

19.2 Factory acceptance test

At Vendor's or Manufacturer's premises a Factory Acceptance Test (FAT) will be executed in the presence of representatives of Purchaser. Purpose of the FAT is to assure that the equipment is ready for shipment to the installation location. FAT will be executed according to a protocol that is to be prepared by Vendor. Vendor will provide a FAT protocol for review (by the validation group). During the FAT, certain items belonging to the IQ and OQ will also be checked.

Purchaser may decide to execute IQ/OQ based on IQ/OQ protocols prepared by Vendor. Therefore, Vendor will provide with his quotation the content pages of these protocols and a separate price for these protocols. Purchaser may decide to have Vendor execute the IQ/OQ. Vendor will provide a separate price for this in this quotation. Vendor will give ample opportunity to Purchaser's representatives to execute checks required for IQ and OQ. At successful completion of the FAT, Purchaser's representative will authorise a Release Note thereby indicating that the equipment is ready for shipment to site. Possibly a number of outstanding items is identified that need to be solved before shipment takes place.

19.3 Site acceptance test

After the complete installation and final configuration, the Site Acceptance Test (SAT) will be performed. 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.

19.4 Acceptance criteria

Specific acceptance criteria for the various qualification elements will be included in the respective protocols provided by the Vendor. 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

19.5 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

19.6 EVF in ordinary use

Ordinary use will start when the facility (including personnel) is approved by SLV. 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.

20 Life cycle and revalidation

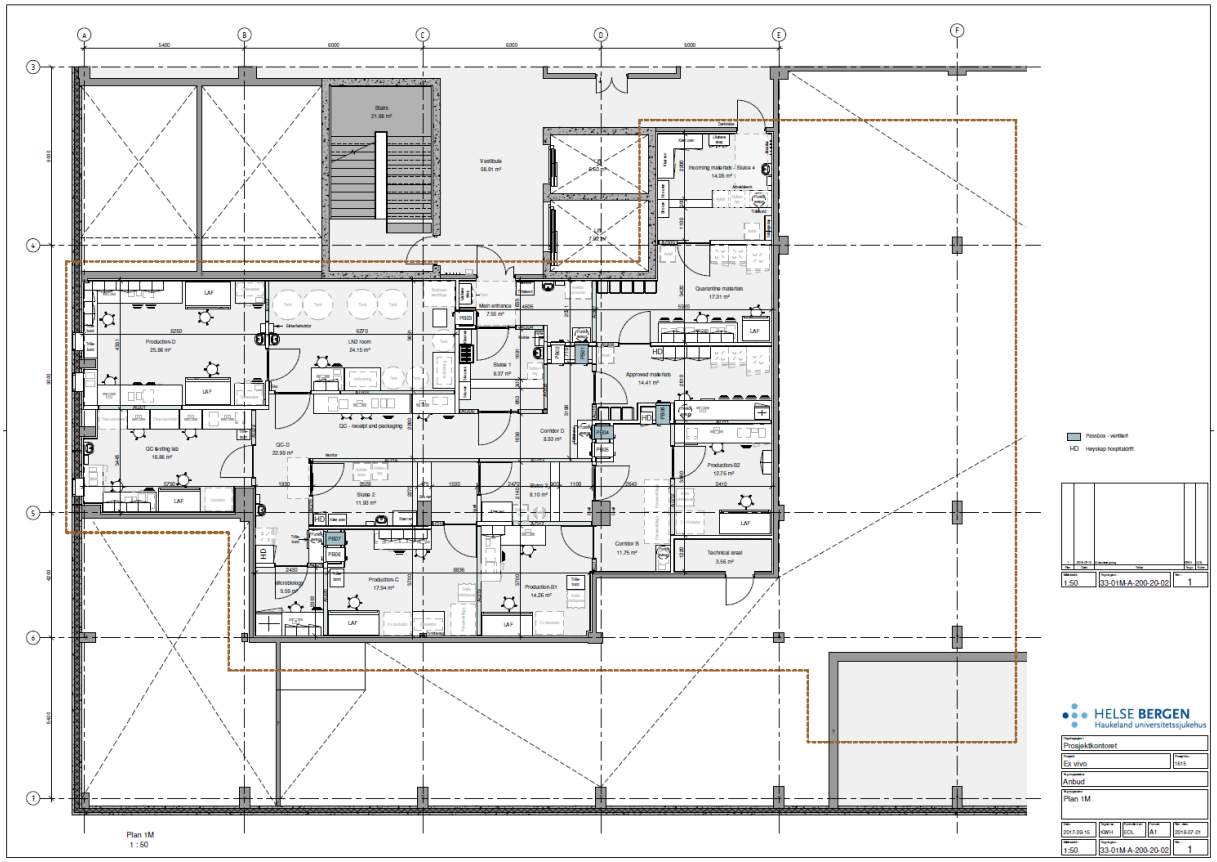
After the cleanroom has been installed, it must be tested to check that it conforms to the stipulated design. Critical systems must be validated. Clean areas should be qualified in accordance with ISO 14644-1 and re-qualified at appropriate intervals in accordance with ISO 14644-2. In particular, periodic classification testing (in accordance with ISO 14664-1) is expected annually, but a risk assessment should be performed to determine the frequency. During the lifetime of the cleanroom, the room must be monitored and revalidated to ensure that it continually achieves the standards required. 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.

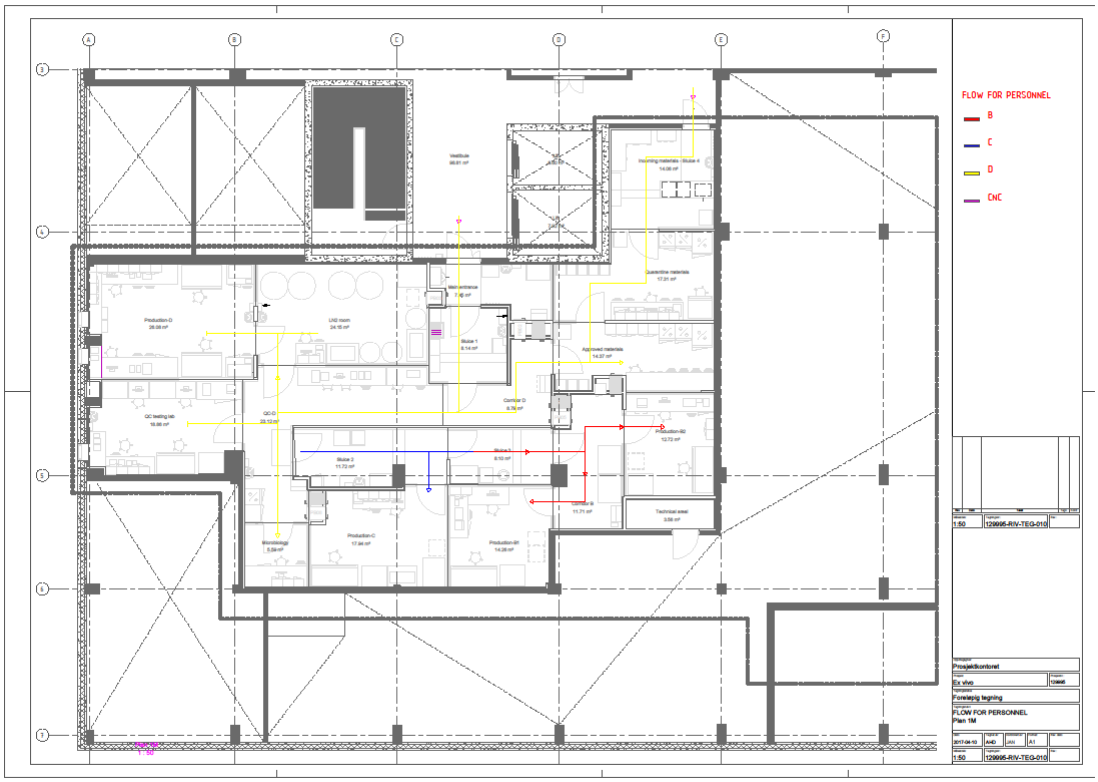
21 Appendix

Appendix A1. Layout drawing of EVF

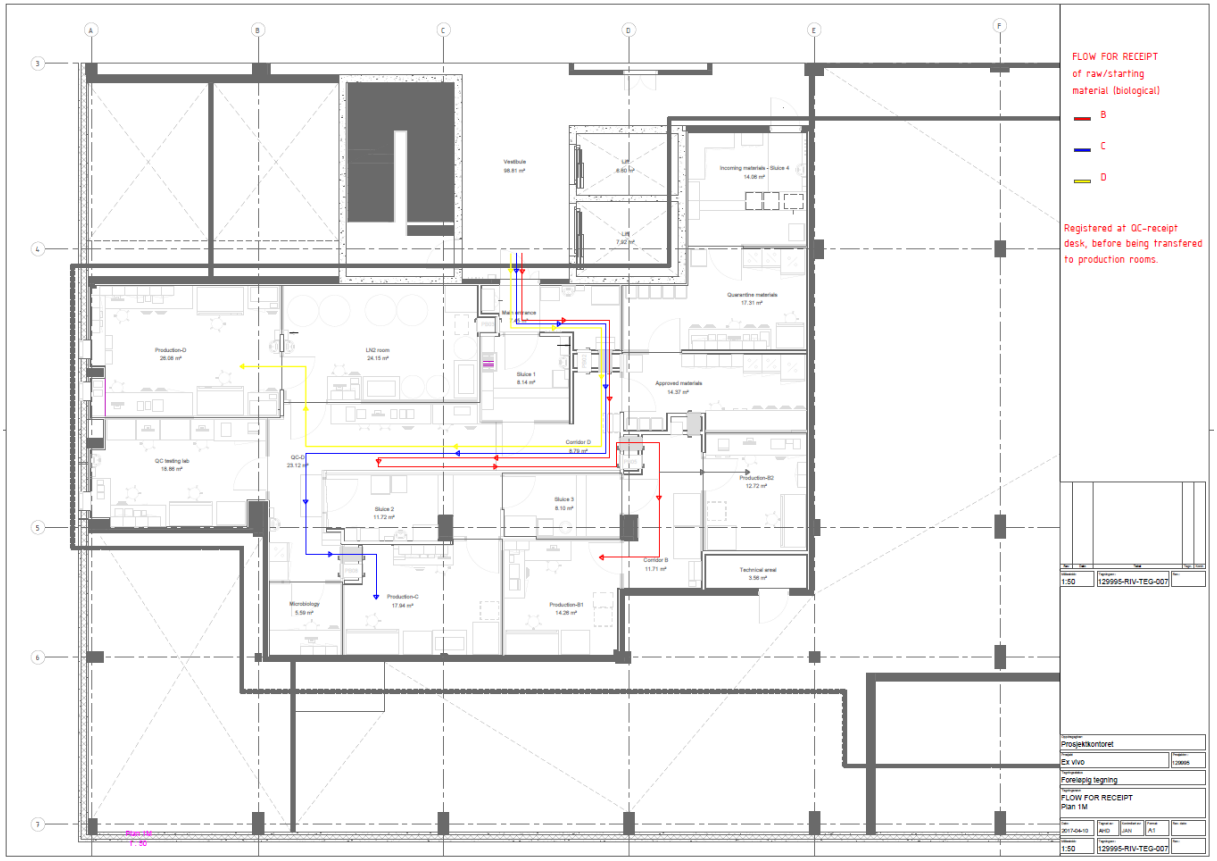
(Drawing: *33-01M-A-200-20-02*)



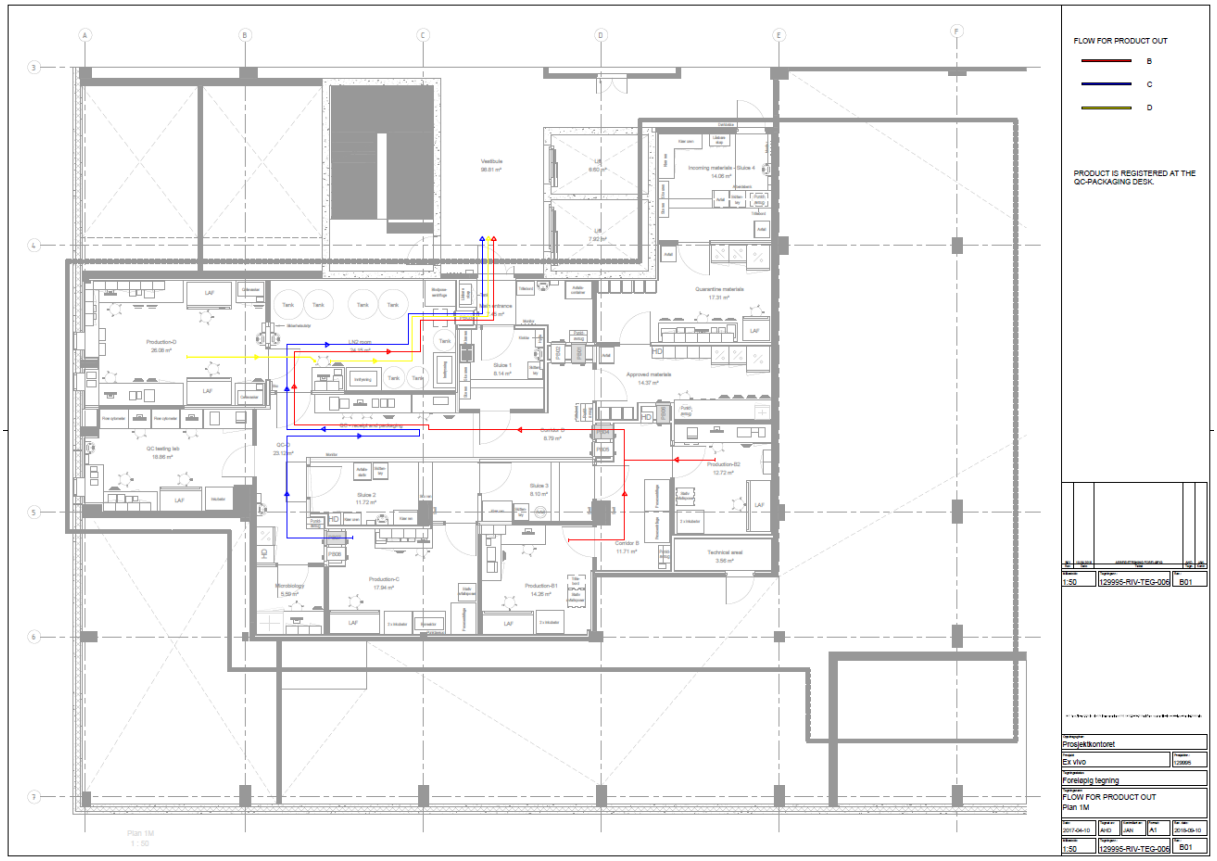
Appendix A2. Personnel flow diagram



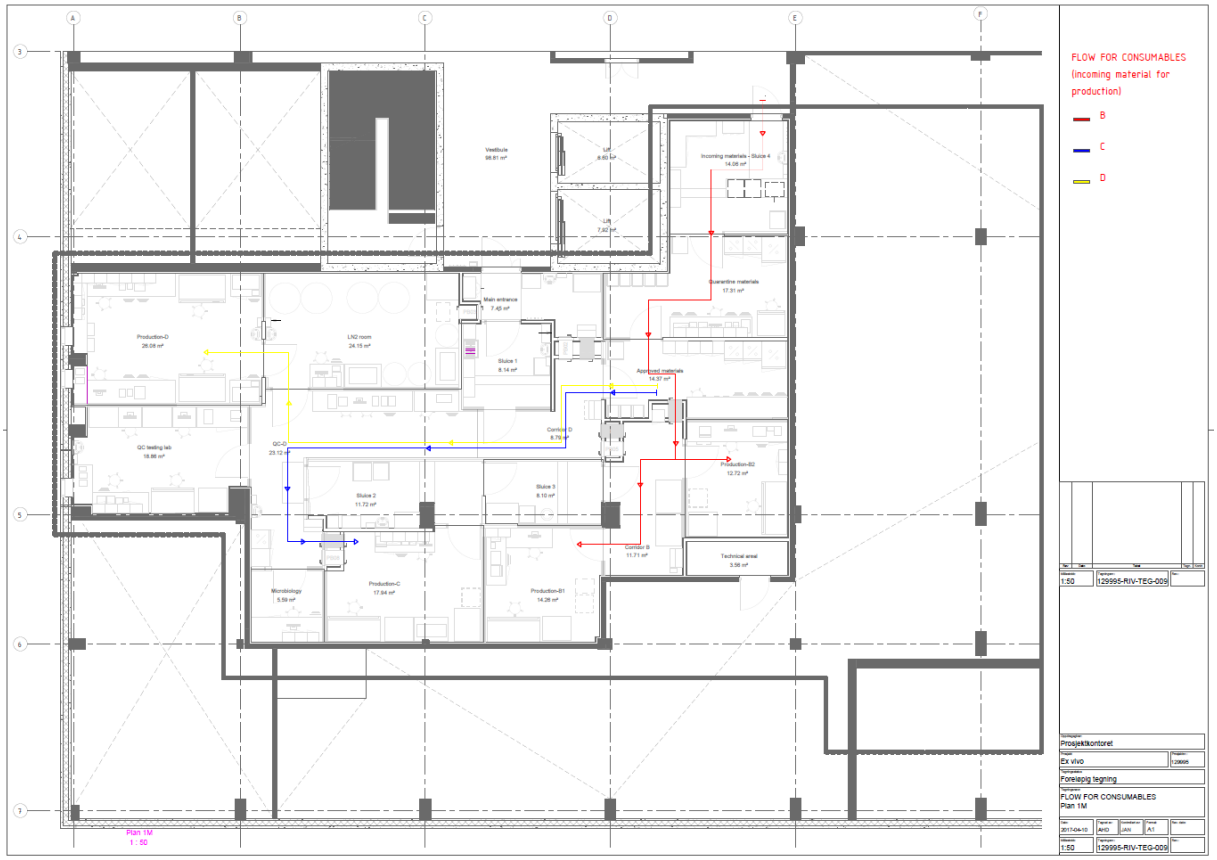
Appendix A3. Starting material flow diagram



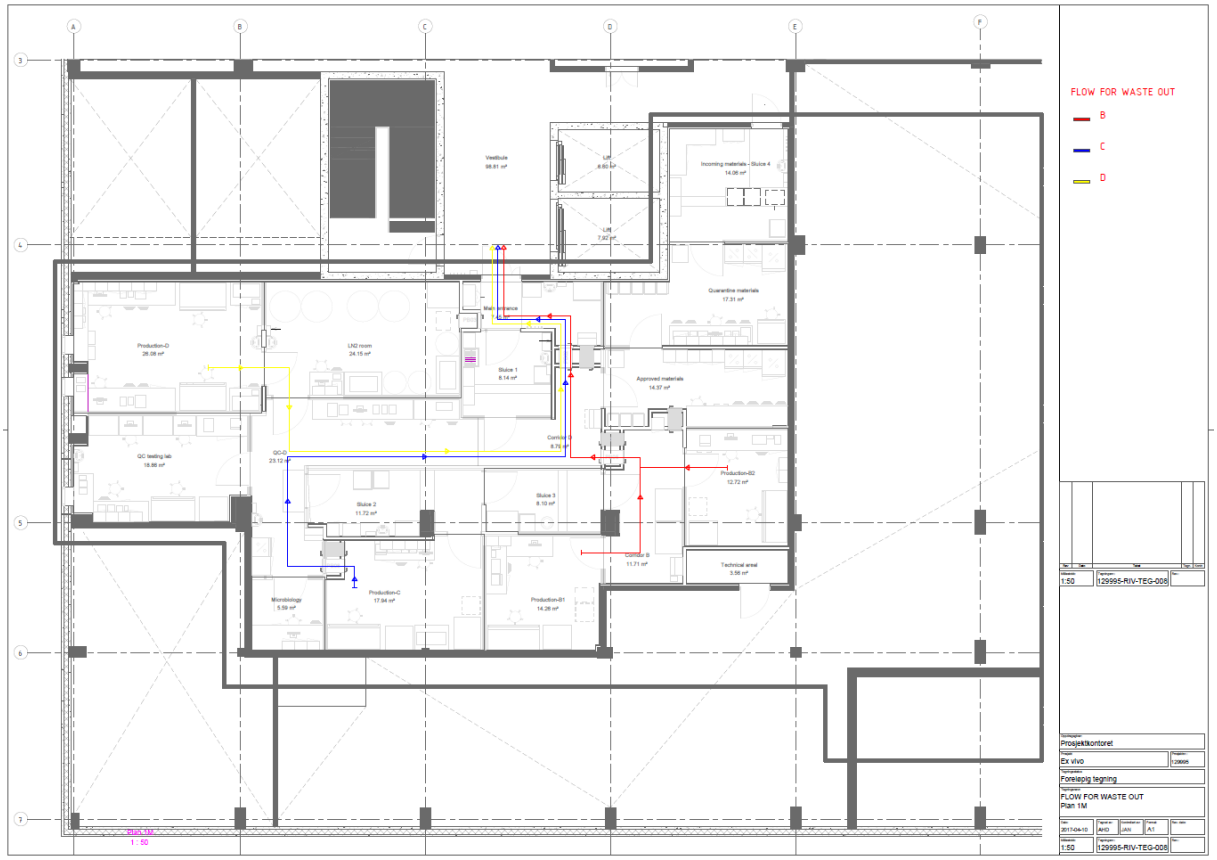
Appendix A4. Product out flow diagram



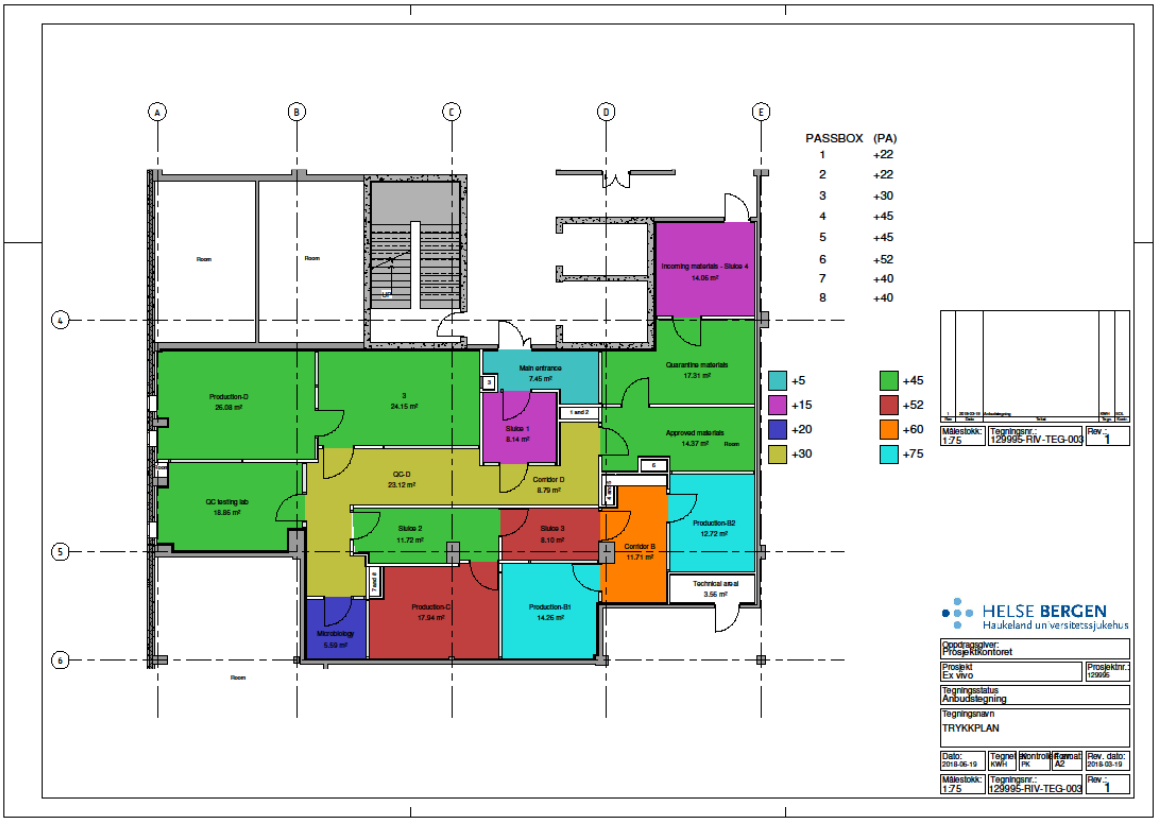
Appendix A5. Ancillary material /consumables flow diagram



Appendix A6 Waste flow diagram



Appendix A7. Differential pressure cascade



Appendix A8 List of permanent equipment

Number	Type	Size, mm (WxDxH)
25	Work desk	Varied, adjust to room size
22	Chair	-
1	Shelf	60(W)x30(D)
8	Shelf system for storage	Adjust to room size, 400x400x2000
6	Shelf system for clothes	Varied sizes, adjust to room size
4	Cupboard for storage	400x400x2000
3	Cupboard for cleaning/mops	400x400x2000
1	Cupboard for cleaning/mops	600x600x2000
8	Sink with dispenser etc	400x330
3	Coat hook (4-10 hooks on a row)	Adjust to room size
2	Valuable lockers	680x400x850
3	Monitor	-
32	Wall cabinets	Adjust to room size
8	Pass box /MALs	500x500x500 / 600x600x1000
7	Spot ventilation system	-
1	Biological safety cabinet (Quarantine room)	1100x800x2000
3	Biological safety cabinet (Production-C and B)	1700x800x2000
2	Biological safety cabinet (Production-D)	1500x900x2150
1	Biological safety cabinet (QC - D)	1400x800x2000
5	Shoerack- wall – both sides of sluice	Varierer, 600 (W)x1200(H)
22	Under desk drawers, on wheels	Fit under desk
3	Mirror	600(W) eller 500(W) x 2100(H)
3	Step over-bench	Adjust to room size
1	Step over-bench w/shoe storage	Adjust to room size
4-7	Telephone	-
15	Cleanroom cart	Varied sizes

Appendix A9. Validation and project life cycle