ANNEX

to Recommendation No. _____ of
the Eurasian Economic Commission's Board
dated _____ 20___

Amendments to
the Guidelines for the design, exploitation, qualification and maintenance of heating, ventilation and air conditioning systems
for non-sterile medicines

1. The text of the Guidelines shall be amended as follows:

"THE GUIDELINES
for the design, exploitation, qualification and maintenance of heating, ventilation and air conditioning systems for non-sterile medicines

I. General Provisions

1. These Guidelines have been developed to establish unified approaches to the design, operation, qualification and maintenance of heating, ventilation and air conditioning (HVAC) systems in facilities intended for the manufacture of non-sterile medicines. These Guidelines are associated with the Good Manufacturing Practice of the Eurasian Economic Union approved by Decision No. 77 of the Eurasian Economic Commission’s Council dated November 3, 2016 (hereinafter referred to as the Good Manufacturing Practice) and contain recommendations for the design of heating, ventilation and air conditioning systems to prevent contamination and cross-contamination in the manufacturing of non-sterile dosage forms, including tablets, capsules, powders, liquids, creams and ointments. A properly designed heating, ventilation and air conditioning system also provides environmental protection and safe, comfortable working conditions for personnel.

2. The design of heating, ventilation and air conditioning systems affects building architectural and space-planning decisions, including the location of airlocks, doorways, and corridors, which in turn determine room pressures, pressure differentials, pressure cascades, contamination, and cross-contamination monitoring. Consequently, the essential technical decisions on heating, ventilation and air conditioning systems should be adopted at the initial design stage of a pharmaceutical manufacturing plant.

3. Temperature, relative humidity and ventilation must meet the manufacturing requirements and must not adversely affect the quality of medicines during their manufacture and storage, as well as the proper operation of equipment and devices.

4. An approach based on science and risk assessment should be applied to the design, operation and maintenance of heating, ventilation and air conditioning systems. However, this approach does not allow for withdrawing from compliance with the requirements of the Good Manufacturing Practice.

5. The principles established in these Guidelines for heating, ventilation and air conditioning systems are also applicable to facilities producing other dosage forms as well as final processing of active pharmaceutical substances. Additional special requirements may apply to air handling systems for pharmaceutical products containing hazardous substances, sterile products and biological products.

II. Terms and Definitions

6. For the purposes of these Guidelines, the terms below shall have the following meaning:

Validation Master Plan is a document that establishes the overall validation plan as a whole and summarizes the manufacturer's approach and

philosophy that will be used to validate continued compliance. It contains information about the manufacturer's validation program, defines the details and timing of the necessary validation work, including the distribution of liabilities of the participants in the process;

Airlock is a confined space with two or more doors located between two or more rooms (e.g., belonging to different cleanliness grades) used to control the air flow between those rooms when entry is required. Airlocks are designed and used for both personnel transition and material handling;

"recovery" means room recovery or clean-up tests that are performed to determine whether the installation is capable of returning to a specified cleanliness level within a specified period of time, after being exposed briefly to a source of airborne particulate test;

Exhaust Air is an air that leaves the room and can then either be recirculated to an air handling unit or released to the atmosphere (removed air);

Closed System is a system in which the active pharmaceutical substance or medicinal product is not directly affected by the manufacturing environment.

Air Infiltration is air introduction into the controlled room from the outside environment;

Laminar Cabinet is a cabinet or shelter, typically used for the sampling or weighing, that provides for product containment and operator protection.

Pressure Cascade is a technical decision for maintaining the pressure difference between manufacturing rooms (areas), in which the air flow is directed from the manufacturing area with higher pressure to the manufacturing area with lower pressure;

Installation Qualification (IQ) is documented evidence that the installation of facilities, systems, and equipment (installed or modified) is in

accordance with the approved project, manufacturer's recommendations, and/or user requirements;

Design Qualification (DQ) is documented evidence that the proposed project of the manufacturing facilities, equipment, or systems is fit for intended purpose;

Operational Qualification (OQ) is documented evidence that facilities, systems, and equipment (installed or modified) are functioning as required in all intended modes of operation;

Performance Qualification (PQ) is documented evidence that facilities, systems, and equipment, when used jointly, operate efficiently and reproduce performance in accordance with approved requirements and process characteristics;

Critical Process Parameter (CPP) is a manufacturing process parameter whose variability affects critical quality indicators and which should be monitored and controlled to ensure the required product quality;

Controlled Room (Area), Classified Room (Area) is a room (area) at a plant (manufacturing site) for which specific personnel actions and environment parameters, including concentrations of viable and non-viable particles, are defined, controlled and monitored to prevent degradation, contamination or cross-contamination of products;

Controlled Unclassified Room (Area) is a room (area) at a plant (manufacturing site) for which some conditions of the manufacturing environment or other indicators (e.g. temperature) are controlled, but this room (area) does not belong to the category of clean rooms (areas);

Change Control is a formalized system with reference to which appropriate experts review proposed or actual changes that could affect the validation status of rooms, systems, equipment, or processes in such a way as

to determine whether action is needed to ensure and document that the system is maintained in a validated condition;

Air Exchange Rate is the ratio of the volume flow rate of air supplied per unit time to the room (in m^3/h) to the volume of this room (in m^3);

Acceptance Criteria are numerical limits, ranges, or other suitable metrics for test results acceptance;

Critical Parameter or Component is a process parameter (e.g., temperature or relative humidity) that affects product quality or a component that can directly affect product quality;

Containment is the process of restricting products, dust or contaminants movement in one area, preventing their transfer to another area;

Local Exhaust Device is a device for capturing harmful and explosive gases, dust, aerosols, and vapors (umbrella, built-in exhaust device, fume hood, hood-air receiver, etc.) at the places of their formation (machine, apparatus, bath, work table, chamber, cabinet, etc.), connected to the air ducts of local exhaust systems and is, as a rule, a part of the technical equipment;

Good Engineering Practice are established engineering methods and standards that are applied throughout the life cycle of a project to ensure acceptable and cost-effective solutions;

Non-Critical Parameter or Component is a manufacturing parameter or system component, the deviation of which, or the failure of which, would have an indirect effect or no effect on product quality;

Non-Unidirectional Airflow is air distribution in which the air entering the clean area is mixed with the inside air by the supply air jet;

Normal Operating Range is the range of parameter values that the manufacturer selects as acceptable during normal operation. This range must be within the operating range;

Unidirectional Airflow is a controlled air flow passing at a constant velocity and with approximately parallel lines of current across the entire cross-sectional area of the clean area;

Recovery Time Determination is determination of the average time required to restore a given room cleanliness grade after a short-term introduction of a contamination source, by diluting the concentration of aerosol particles;

At-Rest Condition is the room (area) condition when the equipment has been assembled and installed, the equipment is functioning in accordance with the requirements agreed upon by the customer and the supplier, but no personnel is present;

Relative Humidity (RH) is the ratio of the mass fraction of water vapor in the air to the maximum possible at a given temperature. Measured as a percentage. If the air is saturated with water vapor to the highest possible level, the relative humidity of such air is 100%;

Differential Pressure is the difference in pressure between two points, for example, the differential pressure between an enclosed space and an independent reference point, or the differential pressure between two enclosed spaces;

Cross-Over Bench is a transverse or stepped bench in the locker room to differentiate between different garment change procedures;

As-Built Condition is a condition in which the installation of a clean room or clean area is complete, all service systems are connected, but no equipment, furniture, materials, or personnel are present;

Acceptance is a documented procedure for confirming that systems and equipment have been installed in accordance with approved technical documentation, are ready for operation, and are functioning properly.

Acceptance is performed at various stages of the project before validation work begins;

Action Limit is the value of the controlled parameter set by the user, upon reaching which immediate action is required, including investigation and elimination of causes;

Alert Limit is the value of the controlled parameter, exceeding which indicates that the process is close to exceeding the limits of normal operating conditions, indicating that corrective measures may need to be taken to prevent the action limit being reached;

Plant, Manufacturing Site, Facility is a built environment in which clean rooms and controlled areas function jointly with engineering and/or support infrastructure;

Design Condition is a condition relating to the specified range or accuracy (precision) of an adjustable variable used by the designer as the basis for determining the performance requirements of the designed system;

Pass-Through Hatch or Transfer Box is a chamber with two or more doors (or other locking devices) for equipment, materials, or products transfer. Used when maintaining a pressure cascade at the interface separating two controlled areas. The passive pass-through hatch or transfer box does not provide for air supply and removal. The active pass-through hatch or transfer box is equipped with a system for supplying air directly into the airlock or box volume;

Procedures (Standard Operating Procedures) are documents containing requirements for the performance of certain operations;

Parameters Operating Range is the range of validated critical parameters of the manufacturing environment, ensuring the possibility of products manufacturing, the quality indicators of which are within the specified limits;

Separation is a process or device designed to contain a substance (product), dust or contaminants in one area and prevent them from entering another area. A special case of separation is isolation;

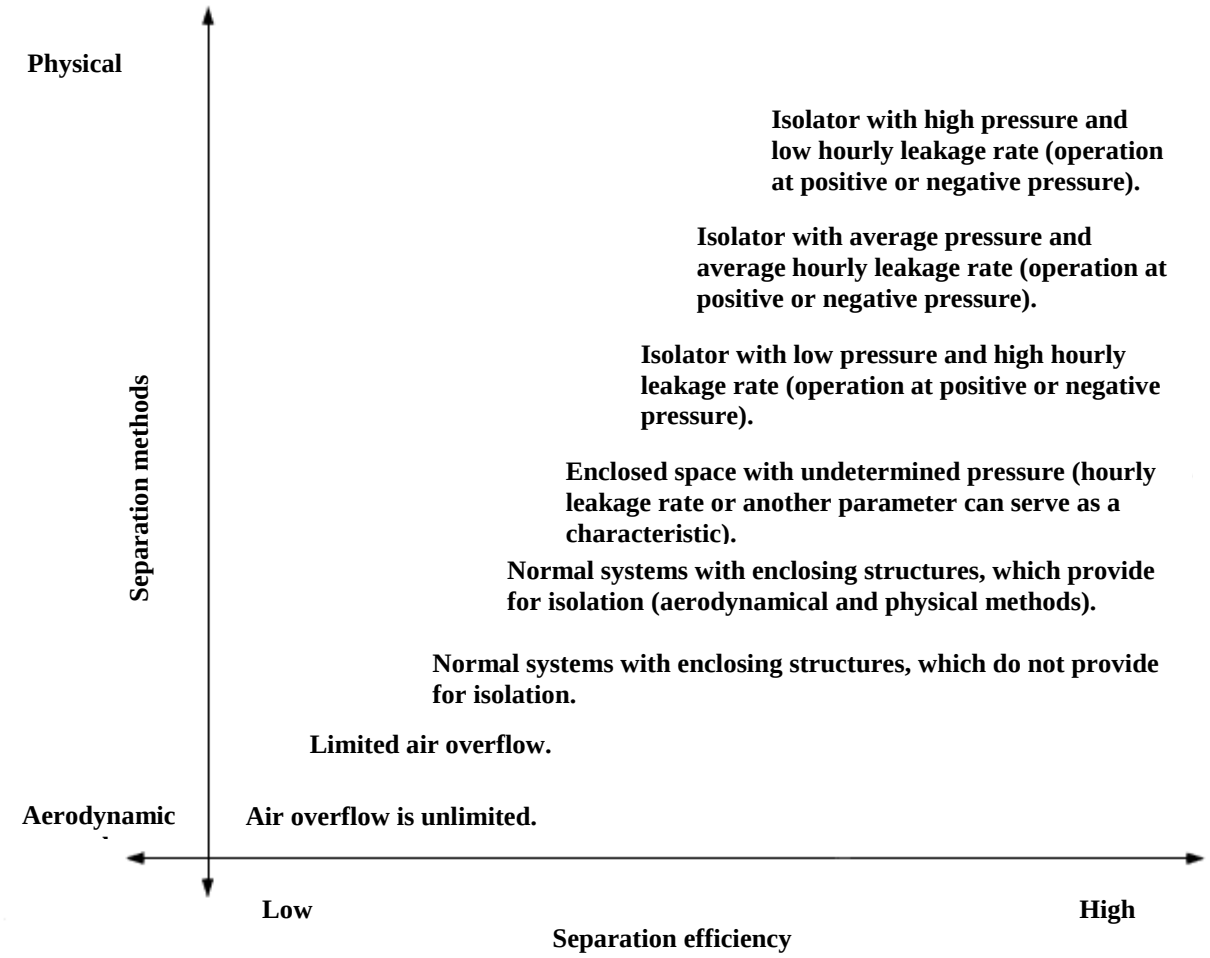


Figure 1. Illustration of separation (isolation) efficiency depending on the methods used (from aerodynamic to physical); the shift in the diagram shows an approximate characterization of efficiency (ISO 14644-7-2007)

Indirect Impact System is a system that is expected to have no direct impact on product quality, but is auxiliary for direct impact systems. These systems shall be designed and accepted in accordance with the Good Engineering Practice;

No-Impact System is a system that has no direct or indirect impact on product quality. These systems shall be designed and accepted in accordance with the Good Engineering Practice;

Direct Impact System is a system that can directly affect product quality. These systems shall be designed and accepted in accordance with the Good Engineering Practice. Direct impact systems are subject to qualification;

Air Handling Unit (AHU) is a component of the heating, ventilation and air conditioning (HVAC) system. A unit designed to bring air parameters to the specified values and provide air supply to the rooms of the facility in the required volume;

Clean Room (Area) is a room (area) in which aerosol particle concentrations and microbial contamination levels are controlled and which is designed, constructed, and operated to minimize the entry, release, and retention of particles and contaminants therein.

Operational Limits are minimum and/or maximum values of operational characteristics ensuring achievement and compliance with the established requirements for the quality and safety of medicines and manufacturing safety;

Operational Condition is the condition of the room (area) assessed during the rooms classification tests, when normal manufacturing process takes place with the use of operating equipment and presence of a given number of personnel in the rooms;

Air Exfiltration is air leakage from the controlled room to the outside environment;

HEPA Filter is a high efficiency air filter.

Other terms used in these Guidelines shall be applied in the meanings defined in the Good Manufacturing Practice, Guidelines on Validation of Manufacturing Processes of Pharmaceuticals for Human Use (Annex to Recommendation No. 19 of the Eurasian Economic Commission's Board dated September 26, 2017) and Guidelines on Manufacturing of Pharmaceuticals

Containing Hazardous Substances (Annex to Recommendation No. 9 of the Eurasian Economic Commission's Board dated May 21, 2020).

III. Rooms for Manufacturing of Non-Sterile Medicines

7. The non-sterile medicines must be manufactured under controlled conditions of the manufacturing environment as defined by the manufacturer. Contamination risks should be controlled, especially for potent contaminants, to ensure protection of materials, products, operators and the environment

8. The heating, ventilation and air conditioning system should be designed in close connection with the architectural design of the building. Both the building architecture and space-planning decision and the heating, ventilation and air conditioning system should be carefully considered when attempting to achieve the overall goals of preventing contamination and cross-contamination, as well as providing an appropriate environment for medicines manufacturing and control. It is important to ensure that the required conditions of manufacturing environment, cleanliness and tightness are achieved and maintained.

9. Infiltration of air into the facility bypassing the filtration system should be prevented as this can lead to contamination.

10. Facilities should, as a rule, maintain a positive pressure relative to external pressure to prevent the introduction of contaminants. Where facilities must maintain negative pressure relative to external pressure, special precautions should be taken to minimize all risks.

11. Medicines manufacturing areas, especially where materials and products are exposed to the manufacturing environment, should have an appropriate level of cleanliness. The air cleanliness levels for the different areas should be determined in accordance with the requirements of the

medicines produced, the manufacturing process, and the medicines susceptibility to degradation. If a cleanliness grade of the rooms (areas) is specified, the manufacturer should indicate whether the grade is for rooms (area) in as-built condition, at-rest condition, or operational condition. Infiltration of contaminants from outside air should be minimized through the use of appropriate filtration systems, room pressure differences, and airlocks. Manufacturers may use different terms when classifying areas, for example: Grade A, B, C, D, or ISO7, ISO8, or Level 1, Level 2, or others (Table 1). When classifying an area, the selected grade must be defined and described.

Table 1

Examples of areas classification

Example of classification	Example of area characterization
Level 1	Common rooms with routine cleaning and maintenance where there is no possibility of product contamination, e.g. storage areas
Level 2	A protected area where measures are taken to protect the pharmaceutical starting material or product from direct or indirect contamination or degradation, e.g. secondary packaging, storage, first-stage garment change rooms
Level 3	A controlled area in which specific conditions of the manufacturing environment are defined, controlled and monitored to prevent contamination or degradation

12. The heating, ventilation and air conditioning system must be able to maintain certain indoor conditions (e.g., by heating, cooling, filtration, distribution, airflow, and air exchange rates).

13. Any area where raw materials, products, primary packaging materials, instruments and equipment are exposed to the manufacturing environment must have the same cleanliness level or classification as the area where the products are manufactured. In addition to the rooms design, the

protection of materials, products and personnel is ensured by the HVAC system. Where specified, temperature, relative humidity, viable and non-viable particle content should be maintained in rooms within specified limits. To ensure that cleanliness is maintained within specified limits, rooms are usually classified. When classifying rooms, the manufacturer should indicate whether the classification refers to as-built, at-rest, or operational condition.

14. To contain dust, achieve the required cleanliness grade and appropriate levels of protection for pharmaceutical products, personnel and the environment, appropriate utilities and controls for the rooms, heating, ventilation and air conditioning systems must be installed. When designing facilities where the highest level of particle containment is required, the guidance in the Guidelines for the Manufacture of Medicines Containing Hazardous Substances should be considered.

15. Particle containment, facility cleanliness and protection of products, personnel and the environment can be achieved by:

а) adequate layout of the building;

б) building proper finishing;

в) use of airlocks for personnel and/or airlocks for materials;

г) use of pass-through hatches;

д) use of garment change rooms and corridors;

е) maintaining sufficient pressure differentials.

16. Detailed schematics should be developed including, but not limited to, the type of system (direct flow or recirculation), air handling units, system network elements, air exchange pattern and room air parameters, room pressure differences and airflow directions.

17. Where possible, the movement of personnel and materials from a high cleanliness area to a low cleanliness area and vice versa should be

prevented. When it cannot be avoided, risks should be identified and controlled.

18. The final garment change room for personnel room should have the same level of cleanliness (in at-rest condition) as the area to which it leads.

19. If simultaneous opening of the airlock doors could lead to a risk of cross-contamination, it should be impossible to simultaneously open the airlock doors to prevent this. Controls such as interlocking systems and/or notification systems and procedures should be implemented for these purposes.

If necessary, airlocks, garment change rooms, and pass-through hatches can be provided, and efficient ventilation and air filtration can be ensured. Particular attention should be paid to door design, as gaps between doors and the floor, doors that open into low-pressure areas, and sliding doors can cause changes in pressure differential between areas. If necessary, a locking system and a visual and/or audible warning system can be used to prevent more than one door from being opened simultaneously.

20. Swing doors must open towards the high-pressure room (area). Such doors shall be equipped with automatic closing devices. Exceptions to the direction of door opening should be provided and justified for emergency fire exits or other health and safety measures. In emergencies, automatic door closing mechanisms should be carefully monitored and other controls applied to prevent any risks from arising.

21. Sampling, weighing and distribution areas should be appropriately designed to provide the required levels of containment, operator and product protection (an example of sampling area design is given in Figure 4 of the Annex to these Guidelines).

22. Starting materials should be sampled and weighted under such conditions of the manufacturing environment, which are created within the boundaries of rooms (areas) for the next stage of product processing.

23. The air flow should not introduce any error in the scales operation.

24. The position of the operator, equipment and containers should not disrupt the airflow model and lead to risks.

25. If an area is qualified with specific locations for operators, equipment, and manufacturing processes, its configuration should be maintained during daily activities.

26. Installed exhaust and recirculation filters and distribution grilles must be fit for purpose and their design must facilitate cleaning and maintenance processes.

27. The impact on the heating, ventilation and air conditioning system and the risks associated with such impacts should be considered when planning for changes to an existing facility (e.g., facility modifications and modernization).

IV. Design of Heating, Ventilation and Air-Conditioning Systems and Components

28. The heating, ventilation and air conditioning system should be designed in accordance with the design of the manufacturing facility with different rooms (areas) for storage of raw materials, materials, intermediate products, bulk products and finished medicines, material and personnel flows. The design should ensure the required cleanliness grades as well as other parameters of the operating environment such as air filtration, air velocity, air exchange rates, pressure differentials, temperature, relative humidity, number of viable and non-viable particles and degree of separation. Manufacturers should determine the limits of the operating environment parameters

depending on the requirements for medicines manufacturing in order to minimize cross-contamination of products. The limit values of the operating environment parameters at the time of designing shall be achievable, suitable and scientifically justified for the at-rest, operational and as-built conditions. When determining these, consideration should be given to relevant factors and risks, including but not limited to: potential malfunctions of air handling units (AHUs), seasonal variations in temperature, relative humidity, natural light, properties and types of materials and products, number of employees, and cross-contamination risks.

The heating, ventilation and air conditioning system should be monitored throughout its life cycle. Heating, ventilation and air conditioning system drawings should be updated regularly to demonstrate changes in said system.

29. The principles of risk management (e.g. appropriate design, operation and monitoring, control of climatic conditions and prevention of contamination and cross-contamination) are applied in accordance with decisions about heating, ventilation and air conditioning systems.

30. The productivity of the heating, ventilation and air conditioning system shall be sufficient to ensure that the stated performance is maintained during normal use (taking into account leakage from the facility and air duct and filter conditions).

31. Materials for the components of the heating, ventilation and air conditioning system should not become a source of contamination.

32. Air ducts, pipes, heating, ventilation and air conditioning equipment, sensors, and other system components should be clearly marked or labeled (if possible) for easy identification, location indication, and flow direction.

33. Air intake and outlet devices should be positioned in relation to each other so as not to cause a risk of cross-contamination.

34. Air handling units should include properly designed drains to remove condensation that may form in them.

35. Conditions and limit values for parameters such as temperature, relative humidity and air purity must be established and achieved during manufacturing.

36. Where applicable, a decontamination rate shall be established and achieved to confirm that the heating, ventilation and air conditioning system is capable of returning the area to a specified level of cleanliness, temperature, relative humidity, room pressure, and microbiological cleanliness within a specified time.

37. The nature and consequences of failures of critical heating, ventilation and air conditioning system components should be analyzed. The analysis should include possible changes in room pressure due to fan malfunction and the possible effect of a partial system shutdown on the degree of ease with which doors can be opened to evacuate personnel.

38. Air distribution and airflow patterns should be suitable and efficient.

39. The air inlet and exhaust grilles should be positioned to ensure efficient ventilation of the room and to prevent stagnant air areas.

40. Heating, ventilation and air conditioning system performance should be monitored and actual performance indicators should be documented regularly to ensure continued compliance. The specified performance limits should be justified.

41. Automated control systems shall be capable of reporting any out of specification values of the air environment parameters using an alarm or other similar system. Where automated control systems are designed as manufacturing room (area) systems in accordance with good practice, they should be validated.

42. Appropriate alarm systems should be used to alert personnel in the event of failure of a critical system component (e.g. fan).

43. The impact of the fan malfunction on the building and heating, ventilation and air conditioning system components should be assessed. A fan lockout matrix should be installed in case of malfunction (if necessary).

44. Periodic shutdowns of the air handling unit (e.g., overnight or weekends) and reduction of air supply when there is no manufacturing activity should be avoided so that materials and/or products are not at risk. To shut down an air treatment unit, appropriate justification and evidence that there is no risk to materials and/or products is required. This procedure and its acceptability should be justified and documented.

45. Standard operating procedures for performing these processes should be available for starting and stopping the air handling unit and records should be kept of the performance of these processes.

V. Full Fresh Air Systems and Recirculation Systems

46. Full fresh air systems or recirculation heating, ventilation and air-conditioning systems can be used. Fresh air should be properly filtered to remove contaminants. When using recirculation systems, there should be no risk of contamination or cross-contamination.

47. HEPA filters can be installed in the supply air system or in the recirculation air system) to remove contaminants and prevent cross-contamination. In this case, the HEPA filter should be classified not lower than class H13 according to the interstate standard EN 1822 (or a filter with similar characteristics according to EN 1822 of the European Committee for Standardization).

48. HEPA filters may not be required for cross-contamination control when cross-contamination is proven to be impossible, when other filters or other reliable engineering software and hardware are used, or when the air handling unit serves a single-product facility.

49. The required amount of fresh air supply should be determined, taking into account:

sufficient fresh air volume to compensate for leakage from the facility and loss through exhaust air systems;

number of operators;

requirements of the legislation of the Eurasian Economic Union Member States.

50. Air that may be contaminated with organic solvents or highly hazardous materials is usually not recirculated.

51. The need for and extent of exhaust air filtration should be considered based on risk assessment, exhaust air contaminants and the environmental legislation of the Member States of the Eurasian Economic Union.

52. When energy recovery units are used in facilities that produce more than one type of medicines, measures (control elements) should be implemented to ensure that the units do not become sources of cross-contamination.

VI. Air Filtration, Airflow Directions and Pressure Differentials

53. When different types of medicines are produced simultaneously in different areas or rooms on the same manufacturing site, measures should be taken to prevent dust from entering from one room to the other. Such measures to reduce the risk of cross-contamination are proper facility design and layout,

appropriate levels of air filtration, organization of airflow directions, and creation of pressure differentials.

54. The selected filters must be suitable for the intended purpose and their classification must be in accordance with the international classification given in the table.

Table 2

International classification of filters and comparison of their test standards (approximate equivalents)*

Classification according to Eurovent 4/5 (superseded)	ASHRAE Standard 52.2	Eurovent 4/5 ASHRAE 52.1 BS6540 Part 1	Eurovent 4/5 ASHRAE 52.1 BS6540 Part 1	EN 779** and EN 1822			ISO 29463	ISO 16890
	Minimum Efficiency Reporting Value (MERV)	Average efficiency, Am (%) (superseded)	Average arrestance, Em (%) (superseded)	Integral overall efficiency for most penetrating particle size (%)	Evaluation according to EN			
				99.999995	U17	EN 1822: 2009	75E	
				99.99995	U16		65E	
EU 14				99.9995	U15		55E	
EU 13				99.995	H14		45E	
EU 12				99.95	H13		35E	
EU 11				99.5	E12		25E	

Classification according to Eurovent 4/5 (superseded)	ASHRAE Standard 52.2	Eurovent 4/5 ASHRAE 52.1 BS6540 Part 1	Eurovent 4/5 ASHRAE 52.1 BS6540 Part 1	EN 779** and EN 1822			ISO 29463	ISO 16890
	Minimum Efficiency Reporting Value (MERV)	Average efficiency, Am (%) (superseded)	Average arrestance, Em (%) (superseded)	Integral overall efficiency for most penetrating particle size (%)	Evaluation according to EN			
EU 10				95	E11		15E	
EU 9	MERV 16		> 95	85	E10			
EU 9	MERV 15		95		F9	EN 779: 2012		$ePM_{1,}$ $ePM_{2.5}$
EU 8	MERV 14		90		F8			
	MERV 13	> 98	85		F7			
EU 7		> 98	80					
	MERV 12	> 95	75			EN 779: 2012		ePM_{10}
EU 6		> 95	70		M6			
	MERV 11	> 95	65					

Classification according to Eurovent 4/5 (superseded)	ASHRAE Standard 52.2	Eurovent 4/5 ASHRAE 52.1 BS6540 Part 1	Eurovent 4/5 ASHRAE 52.1 BS6540 Part 1	EN 779** and EN 1822		ISO 29463	ISO 16890
	Minimum Efficiency Reporting Value (MERV)	Average efficiency, Am (%) (superseded)	Average arrestance, Em (%) (superseded)	Integral overall efficiency for most penetrating particle size (%)	Evaluation according to EN		
		> 95	60				
	MERV 10	> 95	55				ePM$_{10}$
EU 5	MERV 9	> 95	50		M5		
	MERV 8	> 95	45				
		> 95	40				
	MERV 7	> 90	35				Course
EU 4		> 90	30		G4		
	MERV 6	90	25				
EU 3	MERV 5	85	20		G3		

Classification according to Eurovent 4/5 (superseded)	ASHRAE Standard 52.2	Eurovent 4/5 ASHRAE 52.1 BS6540 Part 1	Eurovent 4/5 ASHRAE 52.1 BS6540 Part 1	EN 779** and EN 1822			ISO 29463	ISO 16890
	Minimum Efficiency Reporting Value (MERV)	Average efficiency, Am (%) (superseded)	Average arrestance, Em (%) (superseded)	Integral overall efficiency for most penetrating particle size (%)	Evaluation according to EN			
		80	< 20					Course
	MERV 4	75						
EU 2	MERV 3	70			G2	EN 779: 2012		
	MERV 2	65						
EU 1	MERV 1	< 65			G1			

*Make sure that the filters classification is relevant. The filters classification refers to EN 1822 (EN 1822) and EN 779 (EN 779 standard includes filter classes G1-F9, and EN 1822 and EN 1822 filter classes E10-U17).

**Since December 14, 2016, EN 779 has been replaced by ISO 16890 standards.

55. Airflow direction should be appropriate taking into account the position of the operator and equipment.

56. The differential pressure between the areas at the facility should be evaluated individually in accordance with the products and the required level of protection. The pressure differential and airflow direction must be appropriate for the product and manufacturing process, while protecting the operator and the environment.

57. The pressure differential should be designed so that the airflow is directed away from the clean area (e.g., from the corridor into the room), and resulting in particles containment.

58. The limit values for the differential pressure between adjacent areas should be such that there is no risk of backflow of air in the set dynamic operating ranges.

59. As a general rule, the corridors of the rooms (areas) where the particle source is located should be kept at a higher pressure than the rooms (areas) themselves. The pressure in such rooms (areas) must exceed the atmospheric pressure.

60. A visual indication of the differential pressure in the rooms should be provided. This can be done using pressure gauges or suitable electronic systems (manufacturing environment monitoring systems or building monitoring systems). The range of the pressure to be measured and the range scale divisions of this pressure indicating instruments must allow them to be read with adequate accuracy (precision). The normal operating range, alert and action limits must be set and displayed at the point of indication or in the manufacturing environment monitoring system or building monitoring system.

Room pressure should be monitored to a representative outside pressure (by adding pressures in the rooms) to determine the actual absolute pressure in the room.

The pressure monitoring and tracking devices used should be calibrated. Pressure monitoring and tracking devices should be regularly checked to ensure that they meet specifications and that the results of comparing measured values to specifications are documented.

61. Pressure monitoring devices should, wherever possible, be connected to an alarm system installed in accordance with levels determined by risk analysis and reasonable delay times.

62. Setting of measuring instruments to zero should be protected against any unauthorized access and checked regularly.

63. When using airlocks, the selected differential pressure should be appropriate. When selecting the differential pressure level in the room, temporary changes (e.g. in the operation of the exhaust systems of the equipment) must be taken into account.

VII. Temperature and Relative Humidity of Rooms (Areas)

64. Temperature and relative humidity of rooms (areas) should be controlled, monitored and recorded, where relevant, to ensure compliance with requirements for the materials and products and provide a comfortable environment for the operators.

65. Manufacturers should establish appropriate upper and lower temperature and humidity limits for different rooms (areas). Alert limits (levels) and temperature and humidity action limits (levels) should also be set for critical rooms and areas for the handling of medicines. When determining the limits, the required storage conditions specified for materials and products (packaging materials, raw materials, intermediates, finished product) should be taken into account. The air conditioning system should be designed so that these limits can be met at all seasons of the year.

66. In the event of vapor generation or excessive humidity in a room (area), the heating, ventilation and air conditioning system should be monitored to ensure its persistent efficiency to prevent the spread of moisture that could increase the uncontrolled load on the heating, ventilation and air conditioning system. If necessary, air shall be humidified or dehumidified by appropriate means, which shall not be a source of contamination.

67. Dehumidification or humidification systems require special attention due to the risk of contamination (e.g. condensation, bacterial and fungal contamination, contaminated steam and risks when using mobile systems moved between different areas). Do not add chemicals such as corrosion inhibitors or chelating agents to the boiler system that may have an adverse effect on the product. Humidification systems should be well drained (dried). Condensation must not accumulate in air conditioning systems. Other humidification devices such as evaporative systems, nozzles and water mist sprayers should not be used due to the potential risk of microbial contamination. Air filters should not be installed directly behind humidifiers, as moisture on the filters may cause bacterial growth. Cold surfaces should be insulated to prevent condensation from forming in the clean area or on air conditioning components. Chemical desiccants using silica gel or lithium chloride are acceptable provided they do not become sources of contamination.

VIII. Dust, Vapor and Fume Control

68. Manufacturers should ensure that dust and fumes (vapor) are efficiently removed from manufacturing rooms. Dust extraction systems should be designed and qualified to ensure and validate efficiency. Such systems must maintain sufficient air velocity to ensure the efficient removal of dust and fumes. Dust, vapor and fume emission sites should be carefully selected to prevent contamination and cross-contamination.

69. Dust, vapor, and fumes can be sources of contamination and must be properly controlled. If possible, they should be removed in close proximity to their source. Heating, ventilation and air conditioning systems typically serve as the primary dust control mechanism. A dust extraction system is, as a rule, not used in different rooms where different products may be handled simultaneously, due to risks such as backflow or crossflow from room to room, which can lead to contamination and cross-contamination.

70. Dust collection systems should be properly designed and installed. If a dust collection system component has failed or airflow is disturbed, prevent dust flow in the opposite direction. The velocity of the air mass transfer must be sufficient to ensure the possibility of dust extraction and to prevent it from settling in the air duct. Dust extraction ducts should be designed with sufficient air velocity (determined depending on the processed packaging materials, raw materials, semi-products, finished product) so that dust is carried away (not trapped) and does not settle in the air ducts (recommended value is 15 to 20 m/s). Since vapor can be problematic, unidirectional airflow can be used to remove it.

71. Dust collection points should be located in such a way as to prevent the release of dust, as this leads to contamination and cross-contamination. Consideration should be given to the density of steam (vapors) by locating exhaust grilles at high level or both high and low levels.

72. Air should not pass through a dust extraction duct or recirculation duct from a room with a higher pressure to a room with a lower pressure.

73. Periodic inspections should be made to prevent dust accumulation in the air duct.

74. Provision should be made for mutual interlocking of the dust collection systems and associated air handling systems. This system should

eliminate the risks of contamination and cross-contamination if the pressure cascade fails.

IX. Environmental Protection

75. When the air leaving the equipment (e.g., fluidized bed dryer, dust collection systems and equipment) carries large quantities of dust, proper filtration or other control technologies should be used to prevent environment contamination.

76. Waste from dust collection systems should be disposed of in accordance with the requirements established by the legislation of Member States of the Eurasian Economic Union in the field of environmental protection.

77. Wet dust should be removed in accordance with appropriate means, such as a drainage system or waste disposal system.

X. Acceptance of Heating, Ventilation and Air Conditioning Systems

78. Heating, ventilation and air conditioning system commissioning precedes system qualification and validation and is usually associated with good engineering practices. Manufacturers should clearly document acceptance.

XI. Heating, Ventilation and Air Conditioning Systems Qualification

79. Manufacturers should consider all stages of qualification of their HVAC systems. This includes (where applicable), specification of user requirements, design qualification, factory acceptance testing, customer acceptance testing, installation qualification, function qualification and operation qualification. The qualifications that will be performed throughout

the life cycle of the HVAC system, including changes to the system, should be described and performed. Heating, ventilation and air-conditioning systems, including recirculation systems and full fresh air systems, should be qualified to ensure continuous operation in accordance with specifications and to achieve the required indoor conditions.

80. The scope and extent of heating, ventilation and air conditioning systems qualification should be determined on the basis of the principles of quality risk management.

81. The basis for qualification is: validation master plan, protocols, reports and test source data. The purpose and scope of the qualification is determined on the basis of a risk assessment. Manufacturers should justify the parameters and limits included in the qualification (e.g. temperature test, airflow direction, number of viable and non-viable particles).

82. When applicable, the procedures used for testing heating, ventilation and air conditioning systems shall comply with specific parts of International Standard ISO 14644, and with the relevant acts of the Eurasian Economic Union bodies.

83. Design conditions, operating ranges, alarm and action limits should be established. Alarm levels should be based on the capacity of the heating, ventilation and air conditioning systems.

84. The performance parameters that should be included in the qualifications of the heating, ventilation and air conditioning systems are determined through a quality risk assessment.

85. Allowable deviations for heating, ventilation and air conditioning systems, where applicable, should be determined prior to installation of these systems.

86. If deviations are identified, tests of the applicable parameters of the manufacturing environment and HVAC systems should be carried out:

temperature;

relative humidity;

supply air quantity;

return or exhaust air quantity;

air exchange rate in the room;

room pressure and pressure fluctuations;

airflows visualization;

unidirectional airflow velocity;

air velocity in containment systems;

HEPA filters integrity;

countable concentration of particles in the room;

air duct sealing;

integrity and technical condition of structural elements;

microbiological indicators;

parameters of dedusting and dust removal systems.

Table 3 lists some typical HVAC system parameters that should be included in testing during qualification, and the selection of parameters whose testing should be justified.

Table 3

The rationale for test parameters and procedures

Parameter	**Procedure**	**Note**
Temperature	International Standard ISO 14644	adapt the tests to the ISO international standard in case of longer assessment periods and consider the possibility of temperature mapping
Relative humidity	International Standard ISO 14644 and	adapt the tests to the ISO international standard in case of longer assessment periods and consider the possibility of temperature mapping

Parameter	Procedure	Note
Pressure fluctuations	International Standard ISO 14644	longer periods should be considered to demonstrate consistency in the maintenance of pressure differentials
Air flow rate	International Standard ISO 14644	
Integrity of the filtration system	International Standard ISO 14644	
Countable particle concentration	International Standard ISO 14644	
Airflow directions	ISO 14644 international standard or company procedure (airflow visualization)	Continuous recording of the process should be provided, e.g. video from correct angles to show airflow directions, and appropriate records and markings reflecting date, time, signatures and area names should be provided.
Air flow velocities	International Standard ISO 14644	
Recovery time	internal procedure	
Air exchange rate		

87. The re-validation frequency depends on the risk for quality, the type of facility, the level of product protection required, the operational characteristics of the systems and the scope of the control activities to be performed.

88. Any change in heating, ventilation and air conditioning systems must be monitored. The scope of qualification or re-qualification shall be determined on the basis of the scope of the heating, ventilation and air conditioning systems application and the impact of the change on the operating parameters of said systems.

XII. Maintenance of Heating, Ventilation and Air Conditioning Systems

89. Heating, ventilation and air conditioning systems operation and maintenance records, procedures, and manuals should be available and updated with details of any heating, ventilation and air conditioning system review performed, including all relevant information.

90. Heating, ventilation and air conditioning systems operation and maintenance manuals, drawings, records and reports shall be retained as reference documents for future changes and improvements to said systems.

91. Heating, ventilation and air conditioning systems operation and maintenance manuals include the following information:

system description;

operating Instructions;

troubleshooting processes;

commissioning data;

maintenance instructions;

list of equipment suppliers;

list of spare parts;

equipment data (its capacities description);

supplier literature;

description of the control system;

wiring diagrams;

as-built drawings.

92. The scheduled preventive maintenance program should be developed for the heating, ventilation and air conditioning systems system. Program details must be appropriate to the criticality of the systems and their components.

93. Maintenance activities should not interrupt or adversely affect the manufacturing process and should be scheduled for non-manufacturing time.

94. If the heating, ventilation and air conditioning systems are shut down, the appropriate quality management system procedures should be followed. The underlying causes and consequences of the shutdown should be identified in a timely manner and appropriate corrective and preventive actions should be taken. Consider qualifying or re-qualifying the heating, ventilation and air conditioning system if necessary.

95. HEPA filters should be replaced by a competent person, after which the installed filters should pass penetration tests.

96. Heating, ventilation and air conditioning systems maintenance records should be kept for a sufficient amount of time."

2. Add an annex to read as follows:

"ANNEX

to the Guidelines for the design, exploitation, qualification and maintenance of heating, ventilation and air conditioning systems for non-sterile medicines

E X A M P L E S
of manufacturing rooms (areas) design

1. Design of weighing, dosing, and sampling areas

The weighing room (e.g. materials dosing) must be suitably designed in accordance with the examples given in Figures 1 and 2. A manufacturer should have several rooms designed for weighing. They may include a weighing preparation area, a personnel airlock, a material airlock, a weighing area with safety cabinet, a weighing preparation area, a material accumulation area after weighing, a washing area, and a waste disposal area. The heating, ventilation

and air conditioning system for such areas shall maintain at least the same cleanliness grade as other manufacturing areas where materials and products are exposed to the environment, a logical flow of materials and personnel, an appropriate number of air handling units, and appropriate pressure differentials, insulation, dust propagation control, and air exchange rates. The purpose of installing a cabinet in the weighing room is to limit the spread of dust and provide protection for the operator. For example, dust generated in the weighing area should be removed through a perforated countertop, protecting the operator from inhaling dust while at the same time protecting the material and product from contamination by the operator through vertical airflow. The velocity of the air flow should be such that it does not disturb the sensitivity of the scales.

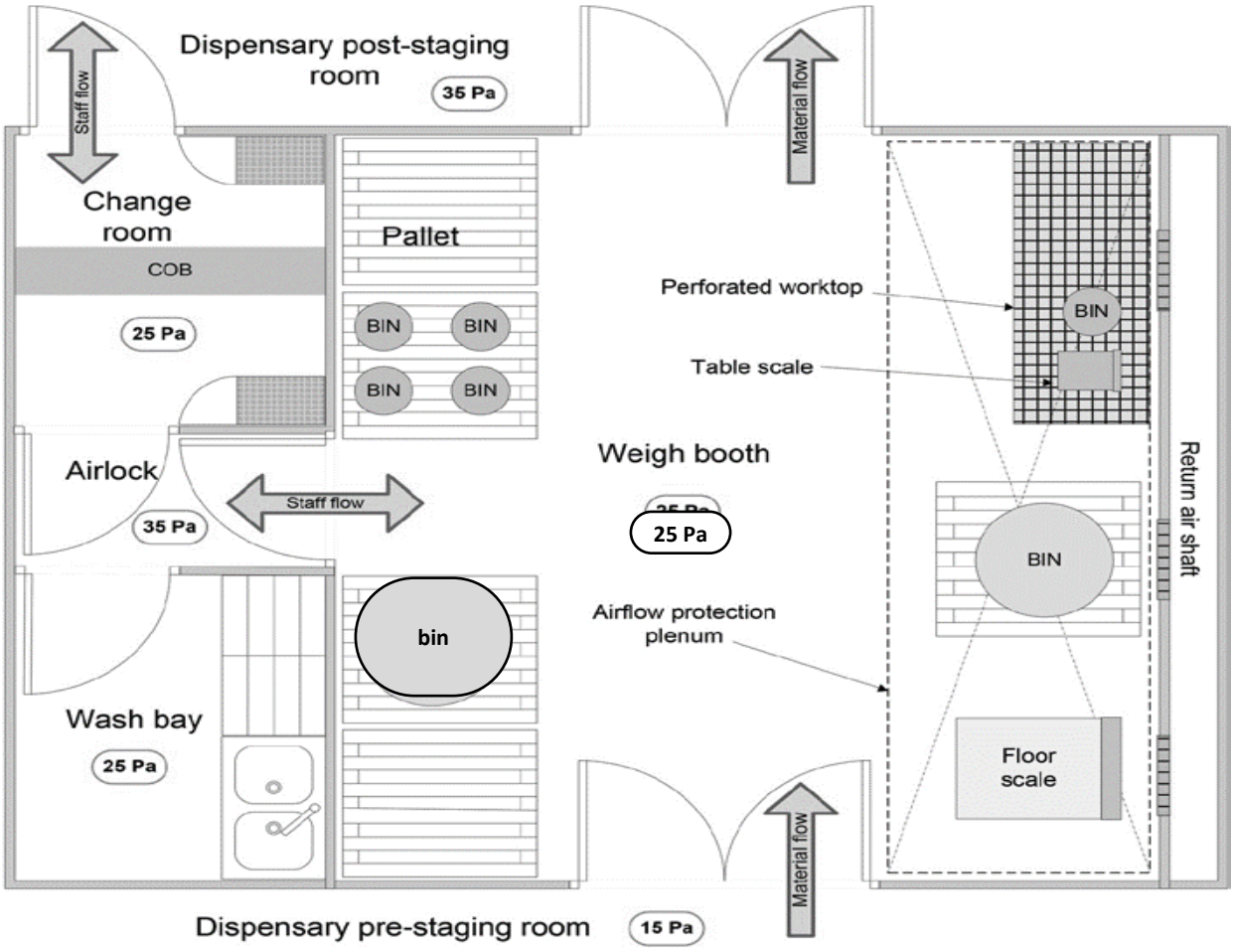
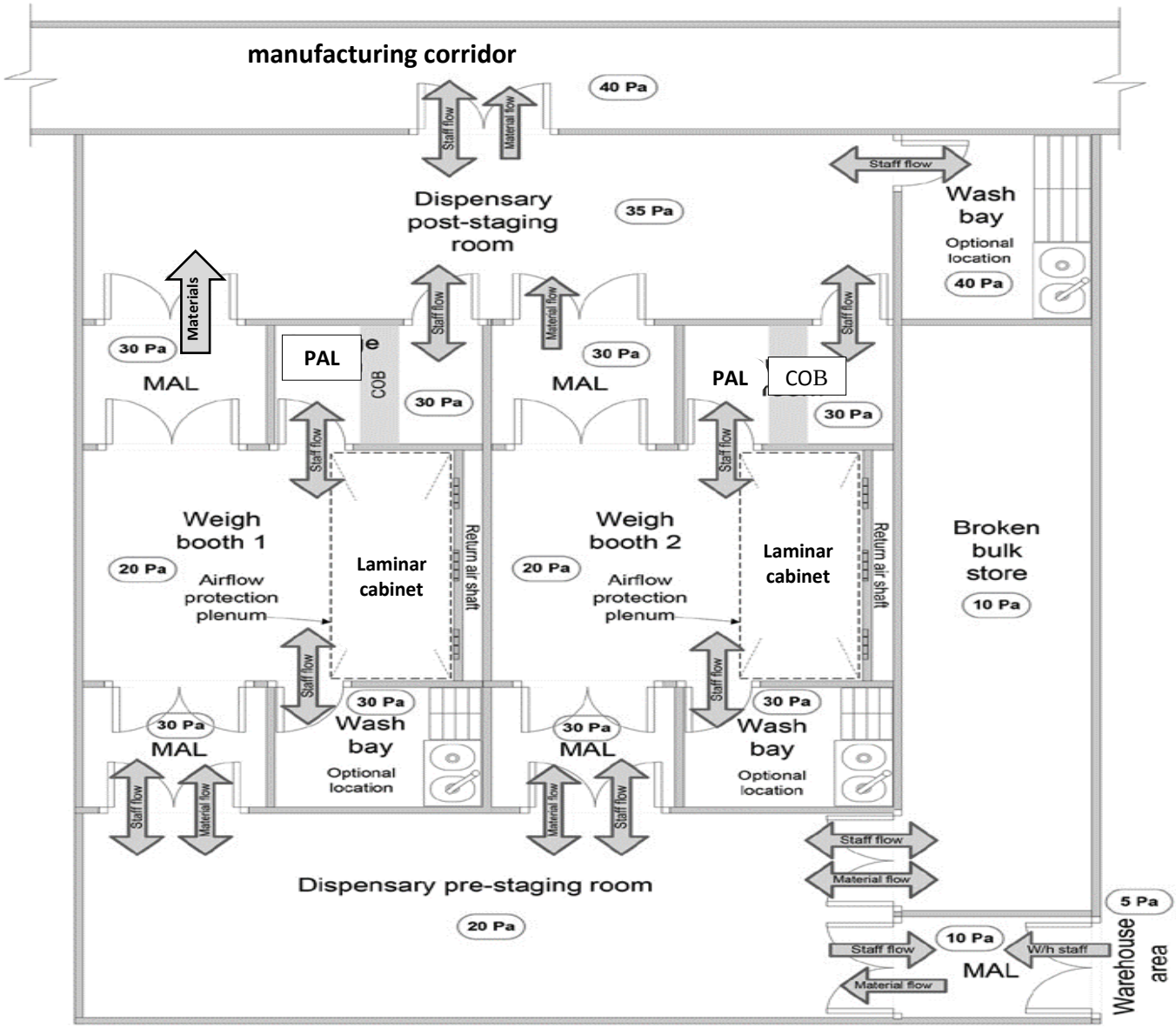


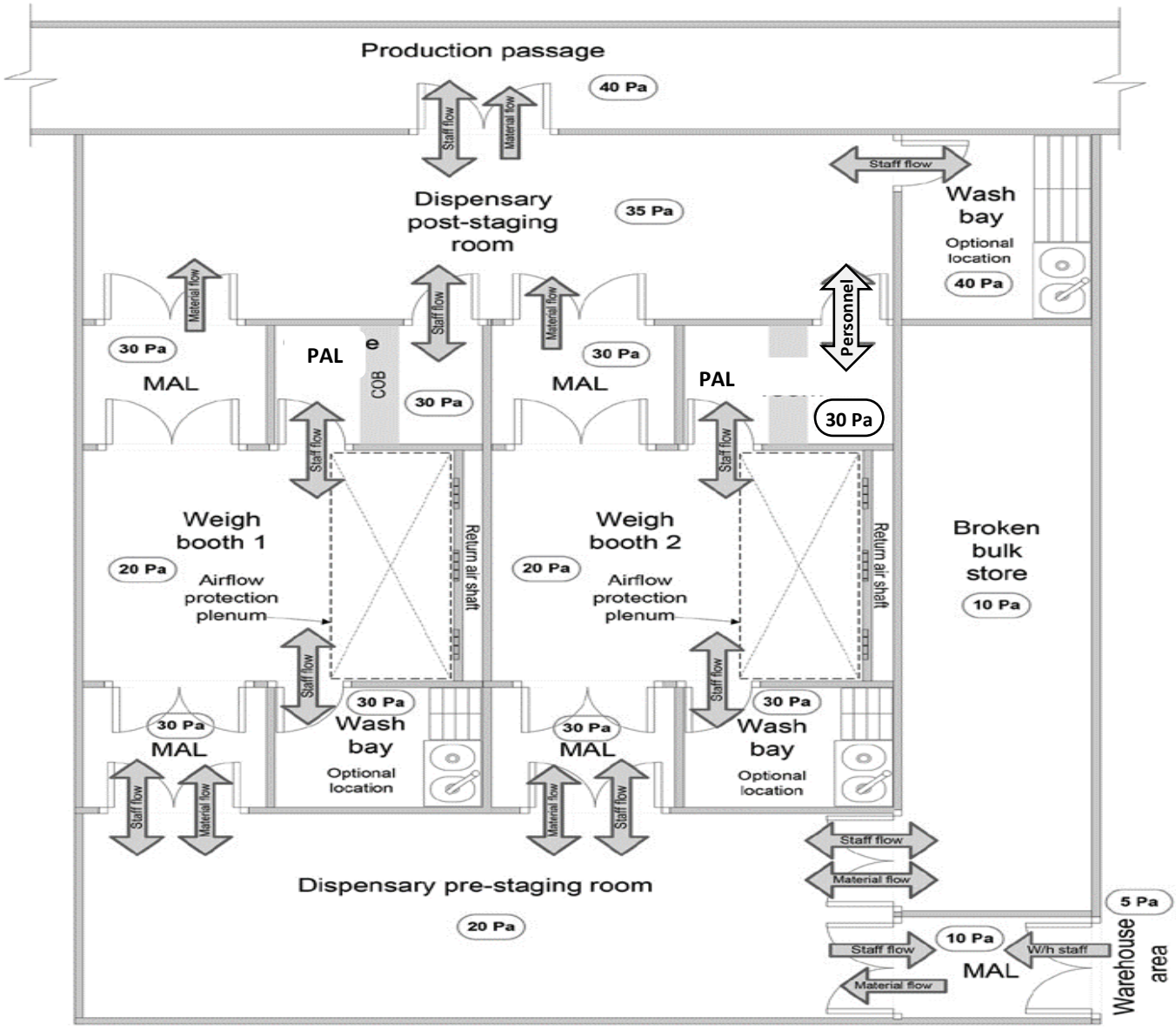
Figure 1. Example of weighing area organizing



PAL: Personnel Airlock
MAL: Material Airlock

Figure 2. Example of a weighing area project (cascade)

Figure 2 shows the complex of rooms with weighing areas, where the cascade of pressure differentials from the manufacturing corridor (40 Pa), through the storage room of weighted amounts (35 Pa) to the airlocks (30 Pa) is realized.



PAL: Personnel Airlock
MAL: Material Airlock

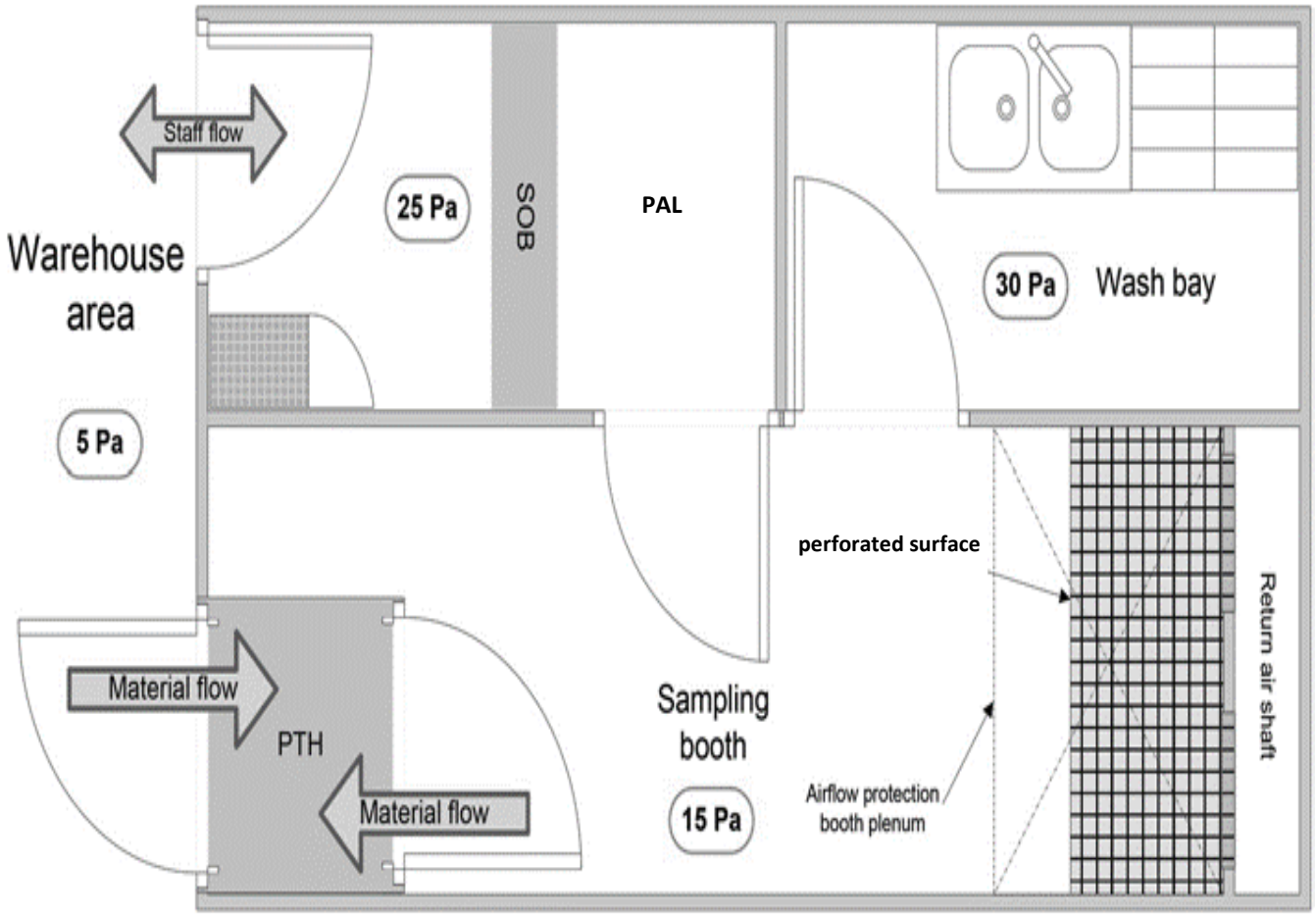
Figure 3. Example of weighing area (shell) organizing

Figure 3 shows the same complex of rooms as in Figure 2 with the realization of pressure differentials in a shell type, where the storage room for the weighted amounts is characterized by the lowest pressure differential (20 Pa), surrounded on all sides by adjacent rooms with high pressure values (30 Pa). In both versions, the weighing rooms themselves are characterized by the lowest pressure differential (20 Pa) relative to the surrounding adjacent rooms. In this case, the main engineering decisions to prevent the spread of exposed

materials from the weighing areas are shelters with unidirectional airflow with a recirculation loop.

Note that the pressure in adjacent rooms affects the determination of the pressure in the weighted amounts storage room.

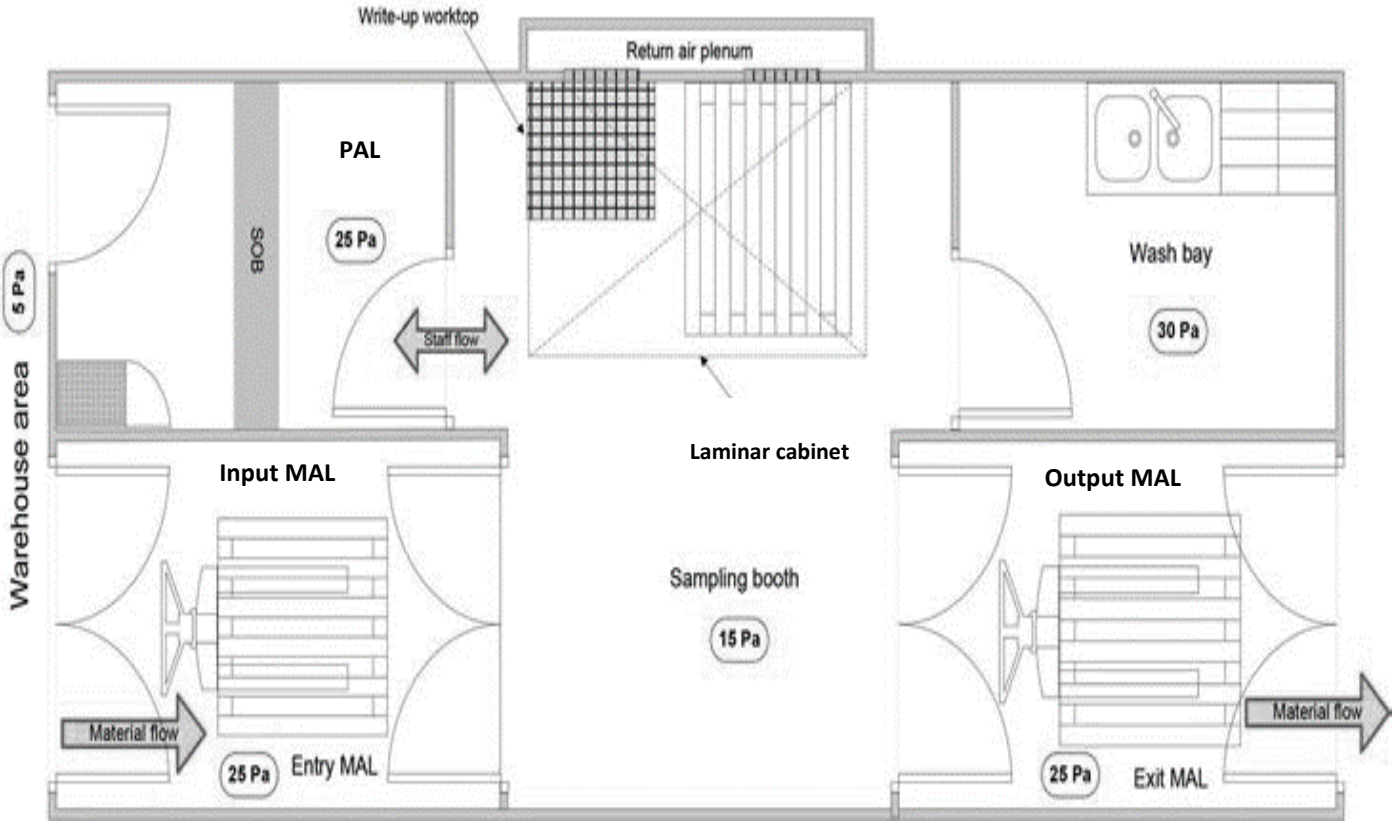
Similar aspects should be considered in the design of the sampling area, as materials and primary components may be exposed to the environment during sampling (see examples in Figures 4 and 5).



PTH: Pass-Through Hatch
PAL: Personnel Airlock

Figure 4. Example of the sampling area (with pass-through hatch)

Figure 4 shows a version of the sampling area with a pass-through hatch (box), usually active, through which materials are transferred both to and from the sampling area.



PAL: Personnel Airlock
MAL: Material Airlock

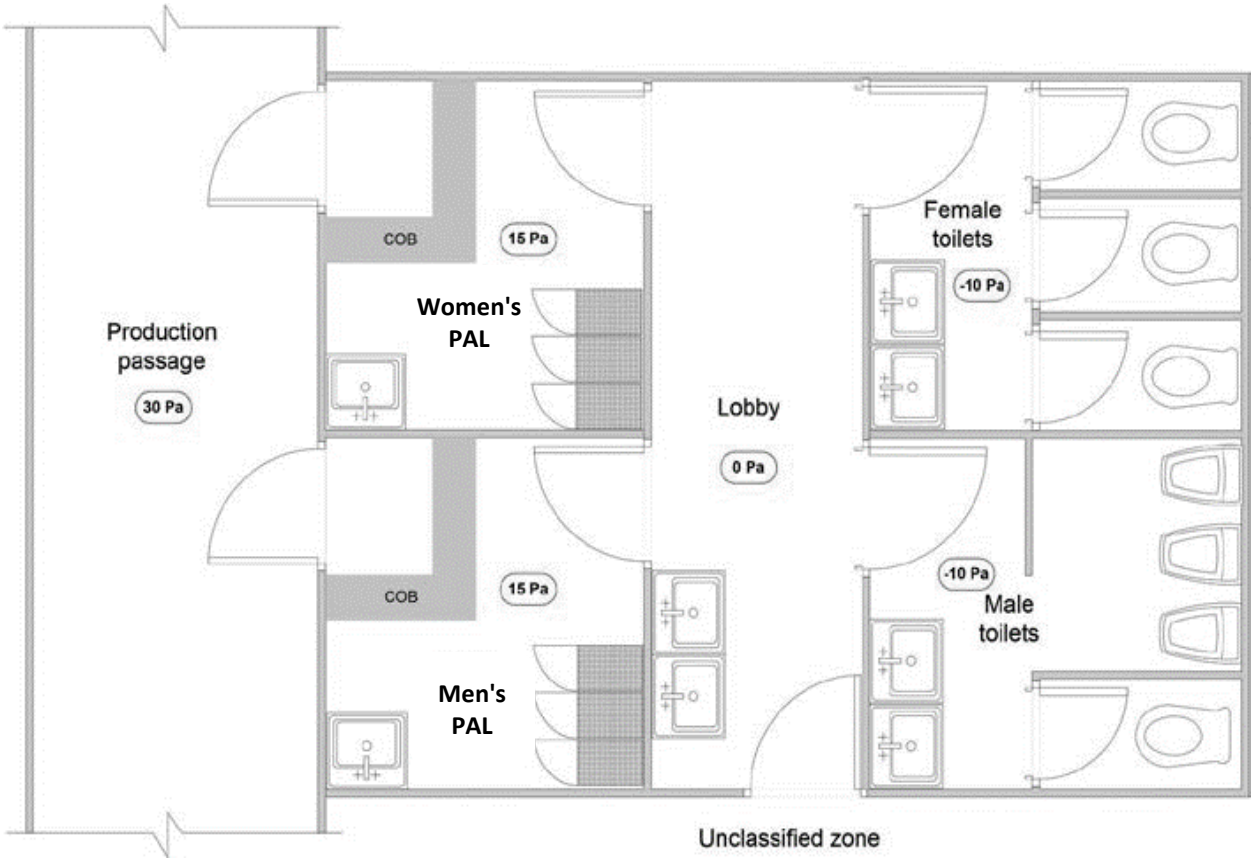
Figure 5. Example of sampling area design with material airlocks

Figure 5 shows a version of a sampling area with two material airlocks, where the first airlock is for transferring materials into the sampling area and the second airlock is for transferring materials out of the sampling area. In both versions shown in Figures 4 and 5, the sampling rooms themselves are characterized by the lowest pressure (15 Pa) relative to the surrounding adjacent rooms. The main engineering decisions to prevent the spread of exposed materials from the sampling areas are unidirectional airflow shelters with a recirculation loop.

2. Design examples for manufacturing rooms

For manufacturing areas for non-sterile oral solid dosage forms, a clean corridor concept is recommended, where the pressure is maintained at a higher pressure than in airlocks or manufacturing rooms opening into the corridor,

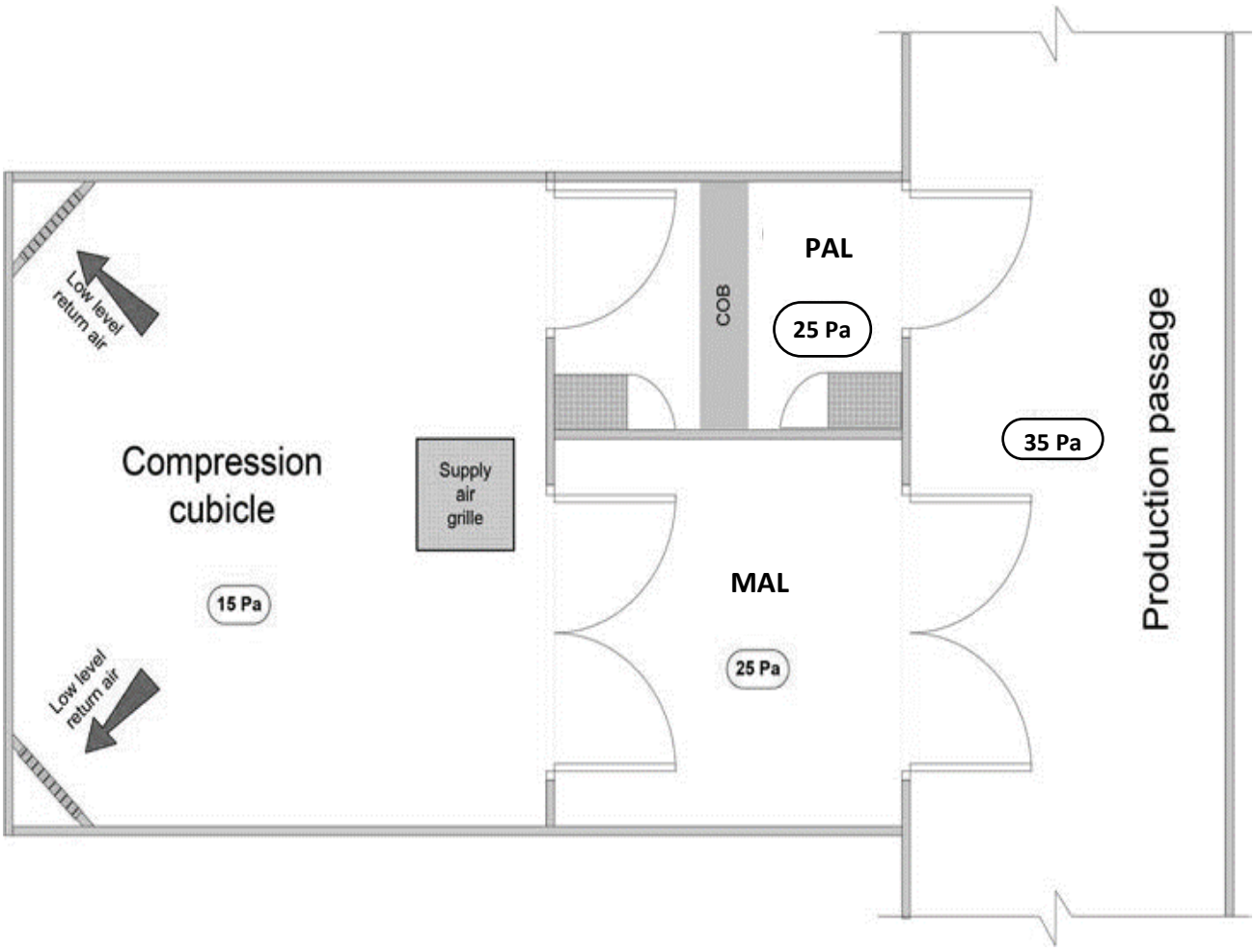
facilitating containment of dust and contaminants that may be generated in the manufacturing rooms (an example of the manufacturing rooms organization is shown in Figure 6).



PAL: Personnel Airlock

Figure 6. Example of organization of a locker room at the entrance to manufacturing rooms

To further support the separation, consideration should additionally be given to having Material Airlocks (MALs) and Personnel Airlocks (PALs), where appropriate, to enter and exit manufacturing areas (see Figure 7 for an example). Appropriately designed airlocks can help ensure separation. Additional controls such as pressure differentials between areas, appropriate air exchange rates and adequate air filtration should be provided. The use of airlocks helps to ensure containment, but other means, such as closed systems and pressure differentials between adjacent areas, are acceptable to achieve this goal.



PAL: Personnel Airlock
MAL: Material Airlock

Figure 7. Example design of a tablet forming room with a material airlock (MAL) and a personnel airlock (PAL)
(also used as a garment changing area)

Washing areas should be designed and utilized so that equipment and components are not re-contaminated after cleaning. The supply and exhaust ventilation system for the area(s) should be designed to achieve this objective. Design principles include (but are not limited to) air filtration, pressure differentials between rooms, air exchange rates, and airflow directions (as an example is given in Figure 8).

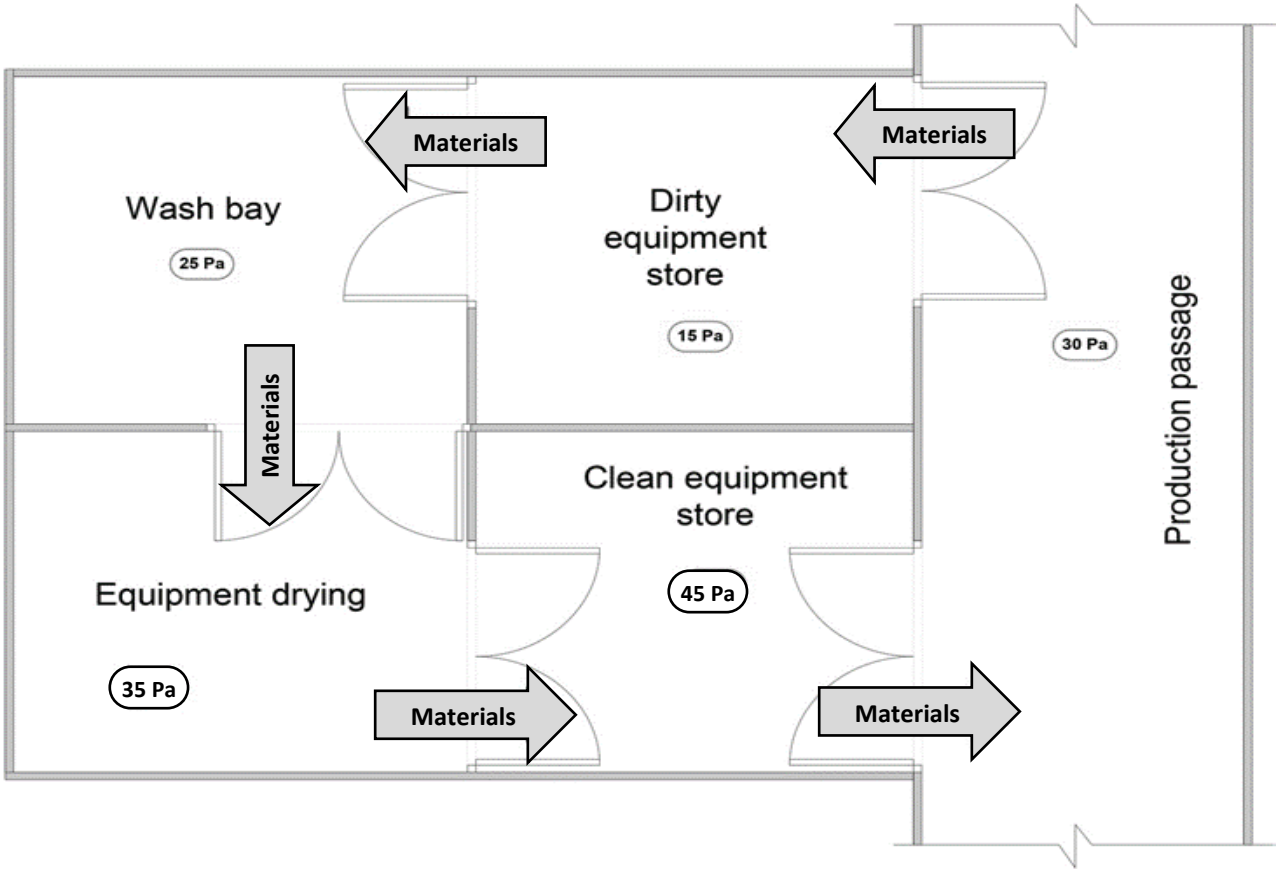


Figure 8. Example of equipment washing area organization

3. Design of HVAC systems and components

The HVAC systems should be designed taking into account the manufacturing rooms, storage areas, materials and semi-products, raw materials and material flows served by them. The required cleanliness grades of rooms (areas) should be provided, as well as other parameters in accordance with air filtration, air velocity, air exchange rates, pressure differentials, temperature, relative humidity, appropriate levels of microbial contamination, aerosol particle counts and separation. The conditions and limits of the system operating parameters (if applicable) should be defined. The manufacturer should define limit values.

The limit values of the parameters to be monitored must be appropriate to the technology and scientifically justified for the at-rest, operational and as-

built conditions. Relevant factors and risks should be considered when determining limit values, including but not limited to:

possible malfunctions of the air handling units (AHU);

seasonal variations such as temperature, humidity and other external conditions;

properties and types of materials and products;

number of employees;

risks of cross-contamination.

At the design stage, the manufacturer should agree on such project parameters as the level of air filtration, the required number of air handling units, the need for local dust extraction systems, and recirculation parameters (percent of fresh air mixing).

The manufacturer should retain schematic drawings of the HVAC system, air handling units (AHUs) and their components that reflect the original design decisions and installation as well as their current status. Changes made during the system life cycle should be reflected in change control records, qualification protocols, and reports.

The components selected for the HVAC system must have sufficient capacity to ensure that the design indicators (e.g. heating, cooling, humidification, dehumidification, airflow volumes) are achieved, taking into account factors such as, for example, air losses due to leakage and seasonal variations. The materials from which the components are made and their arrangement should be such that they do not become a source of contamination. For example, components should not release particulates, and the sequence of components placement should be logical (e.g., filters should be placed so that any possible contaminants generated in the system can be trapped by the filters and not enter the manufacturing area).

To prevent room contamination, access to components such as ventilation dampers, filters and other service components should be provided at outside of the manufacturing areas (e.g. in technical corridors).

The overall design should eliminate the possibility of unwanted, unfiltered air or contaminants entering manufacturing areas.

Separation

Manufacturers should take the necessary measures to contain product dust within the manufacturing area, thereby preventing or minimizing the risk of contamination of other areas and possible cross-contamination. In some cases, airlocks or pass-through chambers between rooms or areas are recommended. Additionally, area separation can be further maintained by sufficient air dilution, pressure differentials and airflow directions (recommended minimum pressure differentials are 5 Pa, but attention should be paid to the technical difficulty of achieving and controlling a 5 Pa differential).

Cleanliness of manufacturing areas

Certain cleanliness grades should be maintained in manufacturing rooms (areas). The HVAC system can support these, for example, through appropriate levels of air filtration, dilution and dust removal. Equipment, containers, personnel, and other related components should be properly located so that they do not interfere with airflow and the efficient operation of the HVAC system.

Re-contamination should be prevented by ensuring the movement of materials and personnel within an area of the same grade (rather than between areas of different cleanliness grades). Where such

movement back and forth is unavoidable, appropriate control measures should be identified and implemented to ensure that movement from a higher grade area to a lower grade area and back to a higher grade area does not result in the contaminants introduction into the higher grade area.

Automatic monitoring systems

The efficiency of the HVAC system in achieving and maintaining the desired results for parameters such as temperature, relative humidity, airflow, and pressure differential should be carefully controlled and monitored. This is to ensure that no deviations from the limits are allowed during manufacturing. Monitoring systems should be available to ensure that the system is operating within design values (manual or automated (computerized) systems).

Automated monitoring systems can provide continuous monitoring capabilities with greater assurance of compliance with limits. Where these automated systems are GXP-critical, they should be validated. The scope and extent of validation of the computerized system should be defined, justified and performed appropriately. This includes, but is not limited to, different levels of software access, limit setting, alarm monitoring and acknowledgement, audit trails, controls and reporting.

Shutdown of air handling units

It is recommended to operate the HVAC system continuously. If the manufacturer decides to use energy saving modes or to shut down certain selected air handling units (AHUs) for specific time periods, such as overnight, weekends or longer, care must be taken to ensure that materials and products are not affected. In such cases, the decision, procedures and records should be sufficiently documented and should include risk assessment, standard

operating procedures, records and validation. This includes procedures and records for the AHU start and stop sequence.

Design of direct flow and recirculation systems

Manufacturers can choose direct flow systems (an example is shown in Figure 9) or systems that recirculate the air supplied to the manufacturing rooms (in direct flow systems, no air is recirculated; in recirculated systems, a certain percent of air is recirculated). In both cases, the air supplied to the manufacturing rooms must be appropriately treated to ensure accordance with the specified conditions of the manufacturing environment and to control the risks of contamination and cross-contamination. Manufacturers using recirculated systems should determine the percentage of fresh air to be supplied to the relevant manufacturing areas, taking into account the requirements of the legislation of the Eurasian Economic Union Member States in the field of occupational health and safety and environmental protection. This volume of air should be checked during qualification. In both cases, appropriate filtration levels are applied in accordance with the need to prevent contamination and cross-contamination. Manufacturers should ensure that when High-Efficiency Particulate Absorbing (HEPA) filters are used, they are properly installed, undamaged and fit for purpose (in accordance with this section of the Guidance).

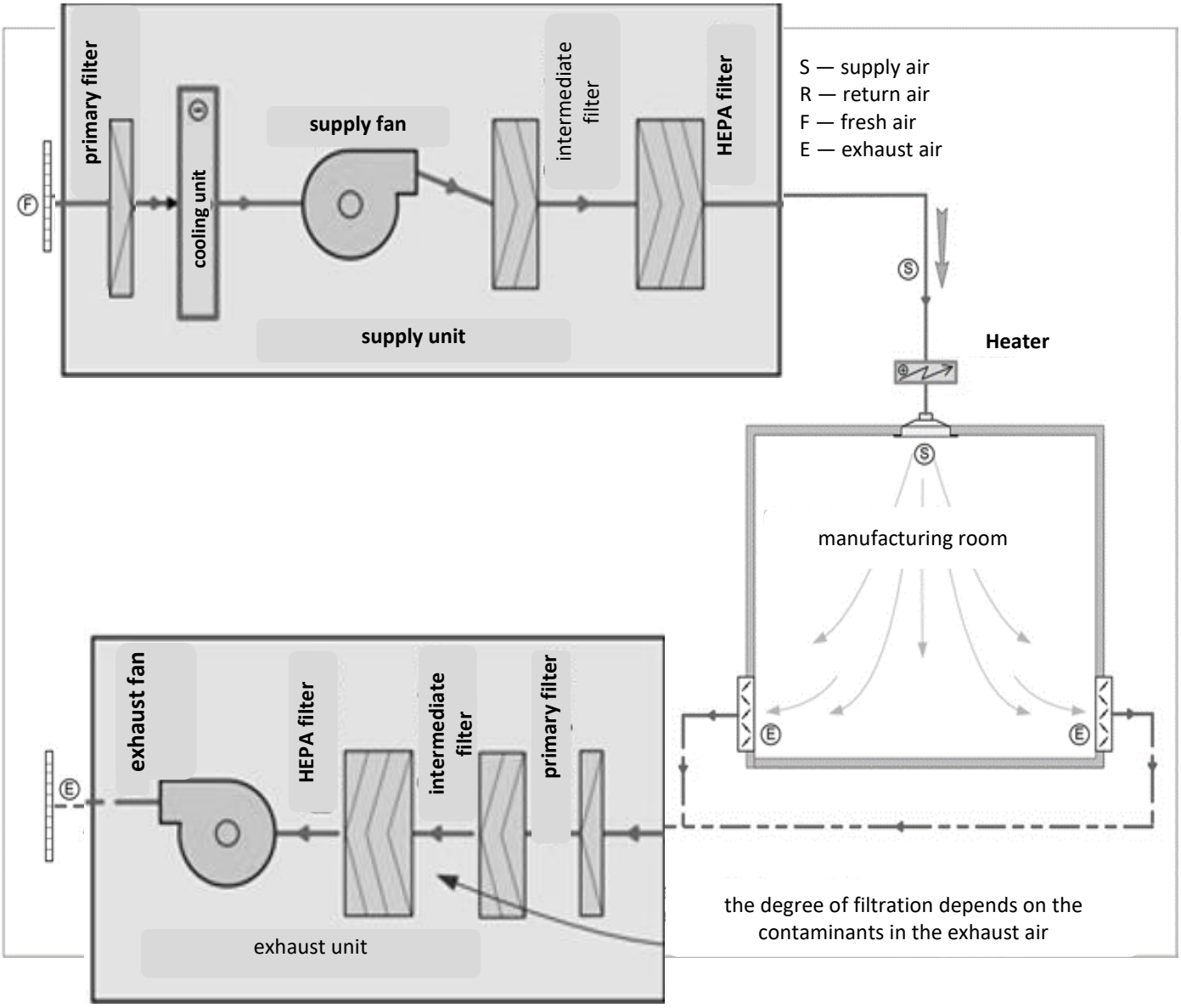


Figure 9. Example of direct flow system organizing

Air filtration, air flow direction and pressure differentials

Effective ventilation and appropriate filtration levels are recommended in the acts of the Union authorities in accordance with the field of medicines manufacturing. Manufacturers should determine which filters grades should be used to ensure that contaminants from the outside do not enter the manufacturing rooms, and if recirculation systems are used, filter the recirculated air with efficiency to eliminate the risk of cross-contamination. If

different products are produced simultaneously in different areas of the same plant, appropriate controls must be in place to contain and prevent contamination and cross-contamination.

The filters selected for air filtration must be identified and specified. If the manufacturer chooses to install HEPA filters to achieve the required degree of air filtration, these filters may be placed in the AHU, or may be installed in close proximity to the supply grille.

Filters affect the clean room grade or level of protection. The different levels of protection and recommended filter brands are shown in Table 1.

Table 1

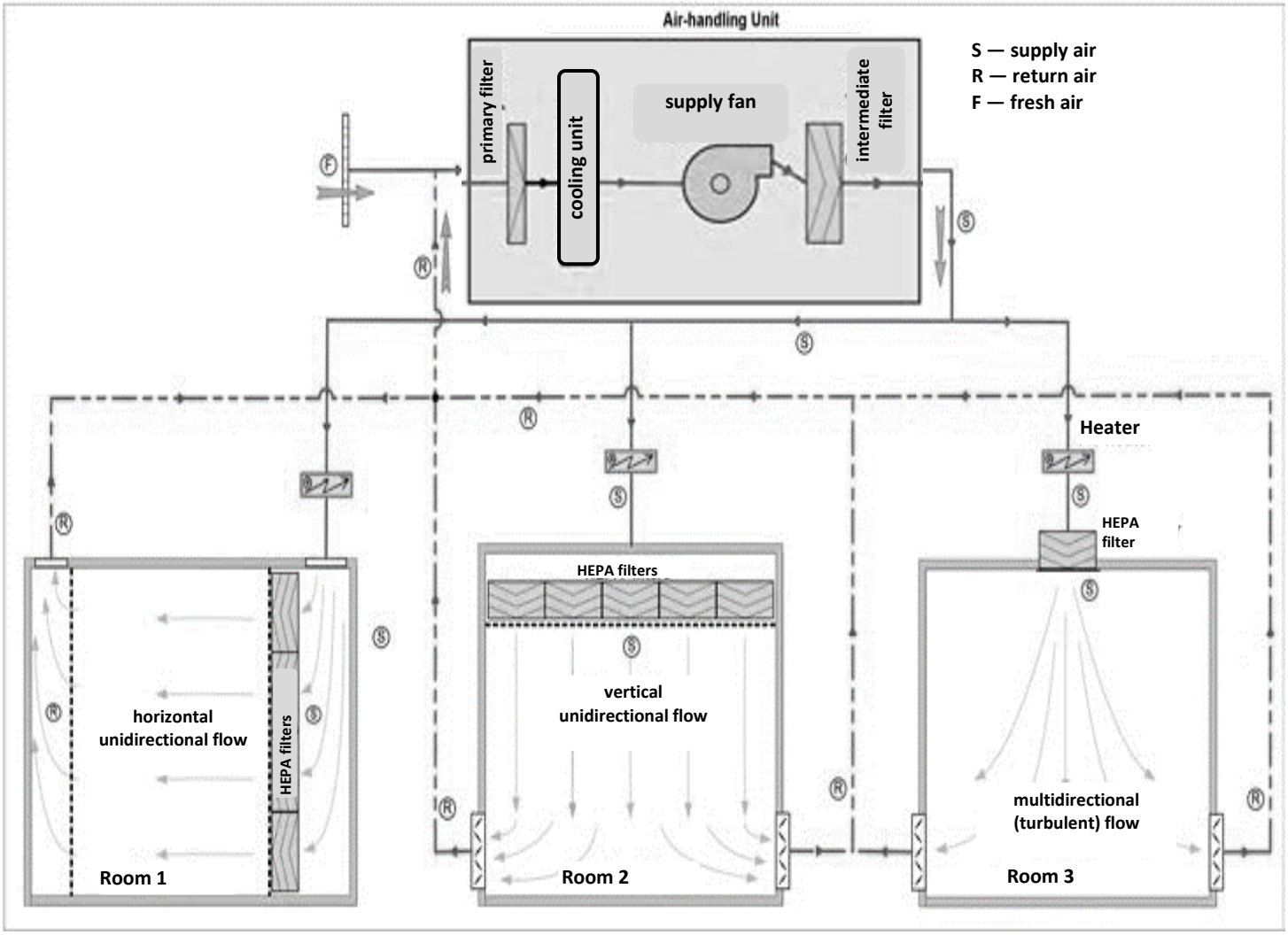
Protection levels and recommended filtration

Protection level	Recommended filtration
Level 1	primary filters only (e.g. EN 779 G4 filters)
Level 2	protected rooms operating at 100% outside air: primary and secondary filters (e.g. EN 779 G4 plus F8 or F9 filters)
Level 3	manufacturing room operating on recirculated and ambient air where there is a possibility of cross-contamination: primary, secondary and tertiary filters (e.g. EN 779 G4 plus F8 plus EN 1822 H13; for a complete fresh air system without recirculation, G4 and F8 or F9 filters are allowed)

The number of air changes or air exchange rate should be sufficient (an approximate value is 6 to 20 air changes per hour). Producers should also determine how long it takes for a room that is out of compliance with its classification to return to the acceptable limits of the specified grade (cleanup or recovery time). The approximate period of time for cleaning or recovery is 15 to 20 minutes.

Airflow directions should be determined and verified to ensure separation. Equipment, utilities, containers, or personnel shall not have a negative impact on the direction of airflow. The direction of air flows is determined by the mutual arrangement of the supply and exhaust air grilles.

An example of a ventilation system serving rooms with horizontal unidirectional flow, vertical unidirectional flow, and turbulent flow for Rooms 3, 4, and 5, respectively, is shown in Figure 11. In these rooms, HEPA filters are installed at the air duct inlet to the rooms (terminal arrangement) rather than in the air handling unit (AHU). The terminal arrangement ensures that cross-contamination between rooms is prevented in the event of a fan failure.



UDAF — unidirectional airflow

Figure 11. Examples of airflow, horizontal (Room 1), vertical (Room 1) and turbulent with exhaust grilles located at low level (Room 3)

The pressure differential should be sufficient to provide containment and prevent backflow, but should not be so large as to create turbulence problems. It is recommended to consider pressure differentials from 5 Pa to 20 Pa. If the design pressure differential is too small and the tolerances are at opposite limits, flow reversal can occur. There must be no risk of overlapping the permissible operating range, e.g. 5 Pa to 15 Pa in one room and 15 Pa to 30 Pa in an adjacent room, resulting in failure of the pressure cascade (examples are given in Figure 12). The upper and lower limits of the pressure difference between the rooms at the facility must be specified by the manufacturer. If there are adjacent rooms, the limit values must be in accordance so that the actual values do not overlap, as this can lead to a loss of pressure difference between the rooms and even a change in airflow direction. The total tolerances of differential pressure measuring devices must not create a situation in which an undetected reversal of air flow is possible. This can be achieved by setting limits so that there is no overlap in the difference between adjacent rooms at the extremes of the tolerances, or by using a common reference point, such as a corridor outside the room complex.

The pressure monitoring and control devices used should be calibrated and, if possible, linked to an alarm system configured in accordance with the levels set.

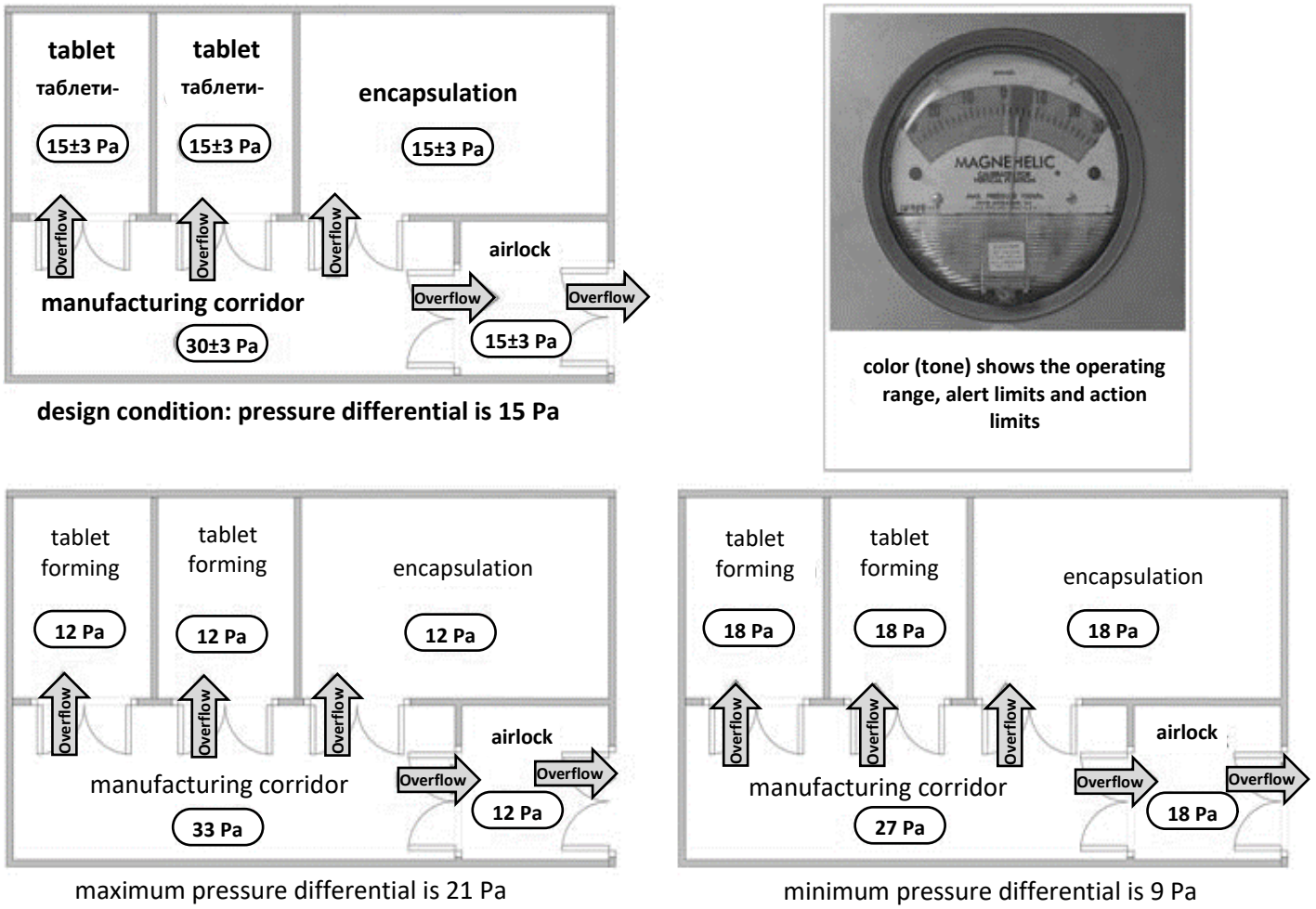


Figure 12. Examples of pressure cascades and example of a differential pressure monitor with operating range, alert limit and action limit

4. Design of airlocks

Airlocks with various pressure cascade modes include cascade airlock, shell-type airlock and bubble-type airlock:

The cascade airlock has higher pressure on one side of the airlock and lower pressure on the other side (an example is given in Figure 13);

shell-type airlock: reduced pressure inside the airlock and increased pressure on both outer sides (an example is given in Figure 14);

Bubble-type airlock: increased pressure inside the airlock and reduced pressure on both outer sides of the airlock (an example is given in Figure 15).

Approaches to the organization of pressure differentials in airlocks can also be applied to the organization of pressure differentials for other rooms with other functional purposes.

In most cases, the internal pressure in the airlock is not critical; the important criterion is the pressure difference between the two outer sides.

The differential pressures relative to the environment shown in Figures 13, 14, and 15 are for illustrative purposes only. The determining factor is the pressure differential between adjacent rooms and the direction of the overflows.

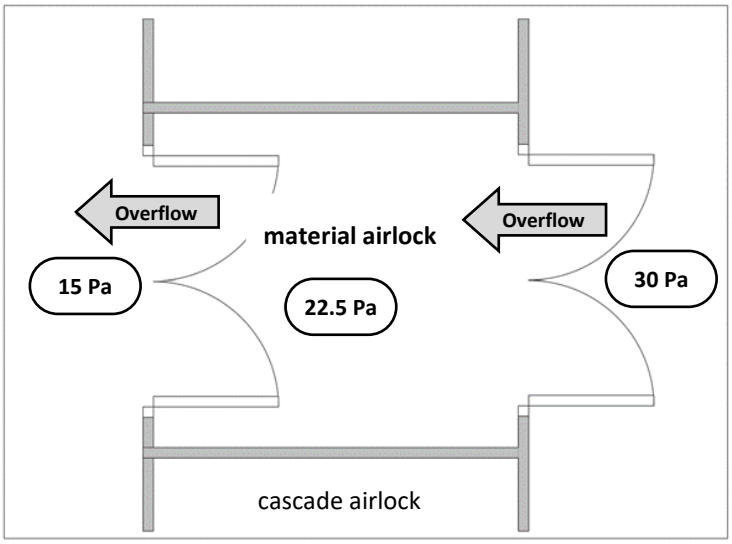


Figure 13. Example of the cascade material airlock

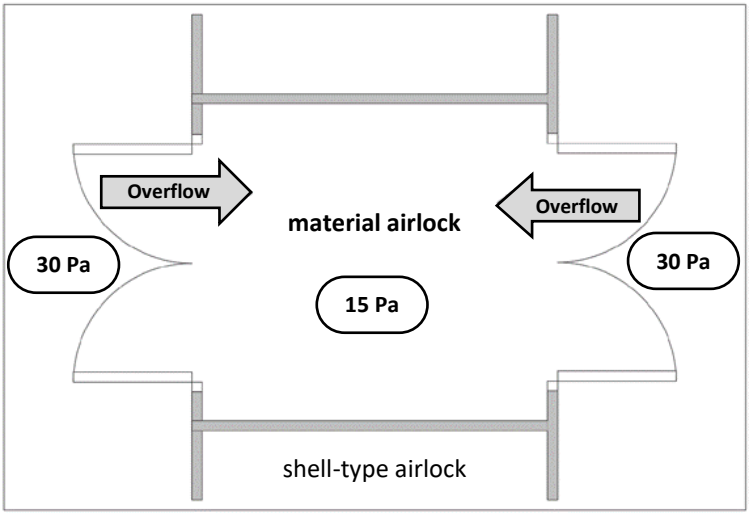


Figure 14. Example of shell-type material airlock

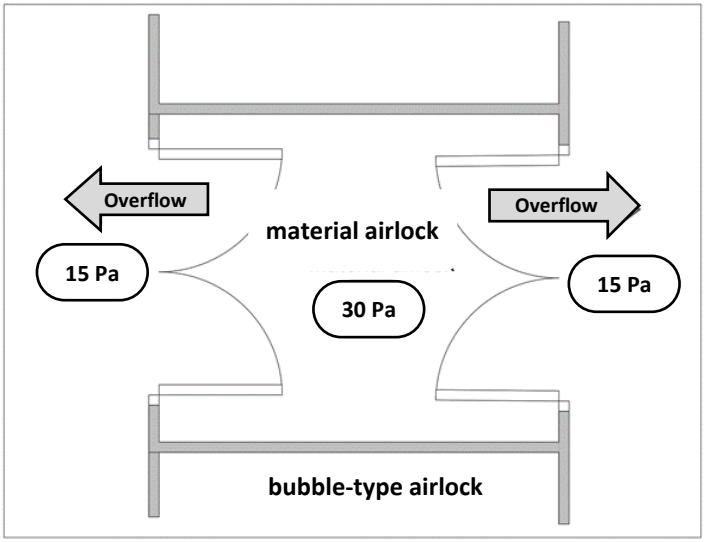


Figure 15 Example of a bubble-type material lock

Additional controls should be identified during the risk identification and assessment. For example, where possible, personnel should not move between different areas during manufacturing (e.g. tablet forming room and in-process quality control room) unless there is no risk of contamination of other areas. Personnel are often a source of contamination because they can carry dust from one area to another. Airlocks or garment change procedures are means of controlling and restricting such transfers.