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CLEANROOMS IN PHARMACEUTICAL PRODUCTION

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DESCRIPTION

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Abstract

The subject of this thesis was studying how cleanrooms are designed, controlled and maintained. During process of studying cleanroom technology I firstly met different requirements and regulations for a certain industry. Each of them has their definite property and purpose. So every cleanroom for every industrial field should be designed according to their own manufacturing characteristics. In this thesis was shown detailed rules of designing cleanrooms for pharmaceutical production. Here was also described a proper behavior of personnel, their clothing that protect both a product and a human.

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CONTENTS

1. INTRODUCTION

Nowadays cleanrooms are used in many industries such as defense industry, biotechnology, microelectronics, pharmaceuticals and nanotechnology. Cleanrooms may be different size from small to complex multilevel structures with large serviced equipment and utilities.

Cleanroom is a controlled placement where different products are manufactured. And concentration of airborne particles is controlled to specified limits. So we need to control process of killing ultrafines airborne contaminants. The contaminations are generated by people, processes, facilities, and equipment. They must be continually removed from the air. The level of air cleanliness in the room must be regulated by standards. The most frequently used standard is the ISO 14644. It is a document that establishes standard classes of air cleanliness in terms of airborne particulate levels in cleanrooms and clean zones.

> ” A room which the concentration of airborne particles is controlled, and which is constructed and used in a manner to minimize the introduction, generation, and retention of particles inside the room and in which other relevant parameters, e.g. temperature, humidity, and pressure, are controlled as necessary. ” /1/

The basic function of a cleanroom is to protect the manufactured product from contamination. In the pharmaceutical production economical survival of the manufacturer depends on the safety of the finished product. So, it is needed to know a potential source of contamination, which could include the working environment itself.

Requirements of the quality of supply air have increased due to development of new high technologies in different sectors of human activities. Main operation factors which characterize air quality are temperature, humidity, pressure, and cleanness. Settings are chosen on conditions to support every individual technological process.

Maximum requirements for air quality are concentration of suspension particles per unit of air capacity and maximum permissible quantity of viable microorganisms per unit of air capacity

Therefore, we can not use general ventilation systems in pharmaceutical cleanrooms for the permanent maintaining of these parameters. In this case we need systematic methods to create special engineering constructions. Cleanroom means a complex of technological tools for supporting set-up parameters of air quality.

In this thesis I would like to analyze main applications and rules of cleanrooms in pharmaceutical industry. My purpose is study how cleanrooms should be designed and how cleanrooms can be controlled. I also will compare Russian and International requirements of similar spaces.

2. CONTAMINATION SOURCES AND REGULATING STANDARDS

2.1 Contamination sources

There are several sources of contamination such as process equipment, personnel and surfaces.

Bacteria are the most important contaminant in a pharmaceutical cleanroom. Almost all of these come from the people in the room. So we need to know the number of people who are working in the rooms. As this will have a direct behavior on the quantity of air required to dilute and remove the airborne dispersion of contamination from their bodies. The efficiency of their cleanroom clothing will have an influence to the contamination dispersed by the people in the room and air quantity. Cooling load also depends on the type of clothing. The more effective the clothing is in preventing dispersion, the less exchange of air there is through the clothing fabric. Staff will feel discomfort due to high temperature and likely to require lower room temperatures.

Temperature level of cleanroom ordinary is 20°C with an RH of 40% ± 5%. For moisture sensitive materials it is required lower RH 25% ± 5%. Also these levels depend on geographical location, production and clothing worn. So dry bulb temperatures can vary in the range of 18°C to 22°C. /6/

Another significant source of particulate contamination is process equipment. Prevention by removal of particles at source should be the first objective before a

limitation is made for removing it once it has entered the cleanroom space. This will ensure a more cost-effective design.

Coming into the cleanroom an airborne contamination from outside is an ordinary problem. That can happen if outside airborne contamination produced by badly detailed material into the cleanroom. So holes in construction should be minimized. And the room became sealed to prevent this problem.

The entering of contamination can also be provided when personnel, equipment or material are distributed through badly designed airlocks and changing areas. There can be surface or air contamination.

Pharmaceutical cleanroom suites consist of different cleanrooms, where are made several steps of production. Standards of environmental control increase step by step when product materials and packaging components are carried out processes into different rooms. It is continued until one reaches the moment of product filling, closing and sealing. There is required the highest quality condition. Less environmental conditions are required when a sealed product coming for labeling and inspection. Different standards of environmental control are reached by various air supply rates and the usage of unidirectional flow units or isolators at the critical areas.

2.2 International Standards

Cleanrooms are classified by the cleanliness of air. Standards are very important in designing process. Their using increase levels of safety, reliability, quality and efficiency.

The history of cleanroom standards started in the USA. By order of American Air Force first standard was made in 1961. It was called Technical Manual 00-25-203. There was description of entering, designing and cleaning. Also it involves airborne particle requirements. Two years later was published Federal Standard 209. It is the first document that regulates cleanroom facilities. It was entitled "Clean Room and Work Station Requirements, Controlled Environments". There was determined measured size of particle more than 0.5μm. It was so, because there was not better equipment to measure smaller particles at those days. In 1966 Federal Standard 209

was fixed and named 209A. Afterwards every following revising was given letters in alphabetical order: 1973 (B), 1987(C), 1988 (D) and 1992 (E). /2/

ISO – The International Organization for Standards published in 1999 ISO-14644-1 standard which officially replaced Federal Standard 209. This ISO was named "Cleanrooms and Associated Controlled Environments". It is used in all European Union and also some other countries. IEST – The Institute of Environmental Sciences and Technology works out the standard to connect all cleanroom requirements all over the world and published other parts which are: 14644-2 (2000), 14644-4 (2001), 14644- 5 (2004), 14644-7 (2004), 14644- 8 (2006), 14644- 9 (Draft International Standard). /2/

Today there are standards:

- ISO 14644 - standard for Airborne Particulate Cleanliness Classes in Cleanrooms and Clean Zones
- ISO 14698, Cleanrooms and associated controlled environments – Biocontamination control

As applied to Russia an expression "clean room" are given in the standards such as:

- GOST R ISO 14644-1-2002 "Clean rooms and controlled media conditions there"
- Part 1 Classification of air purity. (Translated equivalent of international one)
- GOST R 52249-2004 "Rules of manufacturing and quality inspection of medical agents"
- GOST R 51251-99 "Air cleaner filters. Classifications. Labeling"
- SanPiN 2.1.3.1375-03 " Sanitary requirements for placing, arrangement, equipment, and exploitation hospitals and other health care centers"
- OST 42-510-98 "Rules of factory management and quality inspection of medical agents (GMP)"

Cleanroom technology is used in building and renovating objects of pharmaceutical industry over long period of time. Pharmaceutical cleanrooms provide purity of products. First of all it is a microbiological protection from environmental influence

and protection against mixing products. There are requirements which support sterilized aseptic industry for certain products like injection, vaccine, and some types of ointments.

Special progress of cleanroom technology is connected with industrial Good Manufacturing Practice (GMP) standards distribution. GMP - is a collection of rules, standards, and guidelines which describe manufacturing of medicines, medical apparatus, foodstuff, and food supplements. For the first time GMP rules appears in pharmaceutical industry in the USA in 1960s, then in Western Europe, Southeastern Asia and other regions. There are international equivalents such as GOST P 52249-2004 in Russia. It is identical translation of EU GMP. Previous Russian regulation LD 64-125-91 was first GMP issued in Eastern Europe, but then this standard was replaced with OST 42-510-98.

2.3 General conditions

There are several special requirements in sterile pharmaceutical products production which minimize risk of microorganisms contamination. Implementations of these rules depend on the personnel operational experience, training, and attitude to work. Especially high claims lay to quality supporting, preparations and fulfillment of manufacturing process, their careful development and validation. Backend of production or finished product controlling cannot consider as unique supportive sterility tool or other quality characteristics of product.

Sterilized medications manufacturing must be organized in cleanroom (clean zones) equipped with air chambers for personnel access or moving equipment and materials. Cleanrooms must support purity level according to the standards. Air should supply through relevant efficiency filters.

Original package and product preparation, filling must be done in the detached cleanrooms. Cleanrooms for manufacturing sterilized products classified according to environmental requirements to minimize risk of product contamination. Every working operation needs certain purity level of environment in exploited condition. /3/

2.4 Cleanroom zoning

There are four types of clean zones in manufacturing sterilized pharmaceutical products. The grade is defined by the type of product and a part of process which needs to be protected from contamination.

- A – local zone. For operations that affords high risk for product quality, e.g. filling, closing, ampoule and bottle opening zones. Usually in such zones is used laminar air flow which provides similar velocity 0.36-0.54 m/s.
- B – zone, which is circled A-zone, is used for an aseptic preparation and fulfill
- C and D – is a clean zones for less responsible stages of manufacturing sterilized products. /6/

2.5 Cleanroom classification

Cleanrooms are divided into different classes in standards. The equivalence of classes form different international standards is shown in table 1. For the manufacturing sterile products there is certain classification (table 2) with grades A to D which are characterized to activity category (tables 3 and 4).

Table 1. Class limits for Federal 209D and ISO Standards. /1/

Class		Measured particle size (micrometers)					
Federal 209D	ISO	0.1	0.2	0.3	0.5 (a)	1.0	5.0
1	3	1 000	237	102	(1)	8	
10	4	10 000	2 370	1 020	(10)	83	
100	5	100 000	23 370	10 200	(100)	832	29
1 000	6	1 000 000	237 000	102 000	(1 000)	8 320	293
10 000	7				(10 000)	832 000	2 930
100 000	8				(100 000)	8 320 000	293 000

Remarks: (a) - particle count for this particular size is per ft^3 (for illustration purposes) while all others are per m^3.

Table 2. Air particle classification system for the manufacturing of sterile products. /3/

Grade	Maximum permitted number of particles per m^3 equal to or above			
	At rest (b)		In operation (b)	
	0,5 μm (d)	5 μm	0,5 μm (d)	5 μm
A	3 500	0	3 500	0
B (a)	3 500	0	350 000	2 000
C (a)	350 000	2000	3 500 000	20 000
D (a)	3 500 000	20 000	Not defined (c)	Not defined (c)

Remarks: (a) In order to reach the B, C, and D air grades, the number of air changes should be related to the size of the room and the equipment and personnel present in the room. The air system should be provided with appropriate filters such as HEPA for grades A, B, and C.
(b) At rest should be received unmanned state after the 15-20 min “clean up” period.
(c) Appropriate alert and action limits should be set for the results of particulate and microbiological monitoring. If these limits are exceeded, operating procedures should prescribe corrective action.

Demands for other parameters like temperature, relative humidity, etc. depend on product and manufacturing operation nature. These parameters have no connections to purifying classes.

Table 3. Terminally sterilized products. /3/

Grade	Examples of operation
A	Filling of products, when unusually at risk
C	Preparation of solutions, when unusually at risk. Filling of product.
D	Preparation of solutions and components for subsequent filling

Remarks: Preparation of most products should be done in at least a grade D environment. If there is an unusual risk, grade C environment should be used.

Table 4. Aseptic parameters. /3/

Grade	Examples of operation
A	Aseptic preparation and filling
C	Preparation of solutions to be filtered
D	Handling of components after washing

Remarks: After washing, components should be handled in at least a grade D environment. Handling of sterile starting material should normally be done in a grade A environment with a grade B background. The preparation of solutions which are to be sterile filtered during the process should be done in a grade C environment; if not filtered, the preparation of materials and products should be done in a grade A environment with a grade B background. The handling and filling of aseptically prepared products should be done in a grade A environment with a grade B background. The preparation and filling of sterile ointments, creams, suspensions and emulsions should be done in a grade A environment, with a grade B background, when the product is exposed and is not subsequently filtered.

It is needed to control purity of zones by particles in operation state. And it is necessary to make microbial control often at an aseptic production. Recommended levels are shown is table 5.

Table 5. Recommended limits for microbial contamination in the operation state (average values). /3/

Grade	Air sample, cfu/m^3	Settle plates (diameter 90mm), cfu/4 hours (a)	Contact plates (diameter 55mm), cfu/plate	Glove print, 5 fingers cfu/glove
A	< 1	< 1	< 1	< 1
B	10	5	5	5
C	100	50	25	-
D	200	100	50	-

Remarks: (a) Individual settle plates may be exposed for less than 4 hours.
Cfu – colony-forming unit.

Limitation of warning and action for contamination by particles and microorganisms depends on results of controlling. Also you should provide for corrective action in case of exceeding these limits. /3/

2.5 Prevention of contamination

Cleanroom standards and GMP guidelines require that rooms are maintained at different pressures to guarantee different conditions that held in each cleanroom. It is possible to reduce contamination transfer to prevent an unacceptable flow of air from a lower area to a higher area. Using a complex pharmaceutical processing suites including several rooms, show us that reaching of a sensible relative room pressure level and its later support offers main design, commissioning and operational problems.

The standards said that the room pressure difference between cleanrooms should be 10-15 Pa. These values can be quickly reached, easy to control and appears to prevent contamination transfer. It is good to understand that cleanroom requirements may define a pressure difference of 10 or 15 Pa but this guideline is only a means to an end. The pressure difference is not important when there is no adverse air flow between the rooms in the suite. But, this statement can not be clear, and not accepted. The same situation may happen with isolators. But, in this case due to controlled environment is small, the displacement effect of gloves is important and must be taken into account when selecting and finding pressure differences. Ordinary pressure differences for isolators are 15-60 Pa.

The exhaust of the cleanroom can be in an outside neighboring corridor coming through an airlock or changing area and can be in area where pressure is in two levels lower than the room. Surplus of pressure difference of over 30 Pa can cause “whistling” through the door cracks and it can be difficult to open and close swing doors.

Another thing that can be a problem is manufacturing equipment that crosses room-pressure boundaries. It can be presented by examining a tunnel process where a component is washed, sterilized, and filled as it passes from a component preparation area into an aseptic filling room. The pressure difference will cause air to flow

between the two areas connected by the tunnel. This air flow can change the heating descriptions of the hot air oven and can bring hot spots and damage the tunnel. Fluctuation of pressure difference will cause changes in the volume of air flow. This can bring changes in efficiency and difficulty in validating the system. Due to crossing between areas of tunnel boundaries of different pressure it is needed to constrain the flow through the tunnel by some type of masking. But if it is not happen, surplus of air will be ordered to be supplied to the area of highest pressure. Or with a well-masked tunnel should be added to the supply air. This can be calculated from Equation 1.

Two ways by which cleanrooms in a suite may be sealed are available and known as the “closed door” and “open door” solutions. The “open door” solution has been developed and is of particular value where airlocks are inconvenient or unpractical to provide, for example hospital operating room. An example of a ‘closed door’ solution as applied to a cleanroom suite is shown in Figure 1. /6/

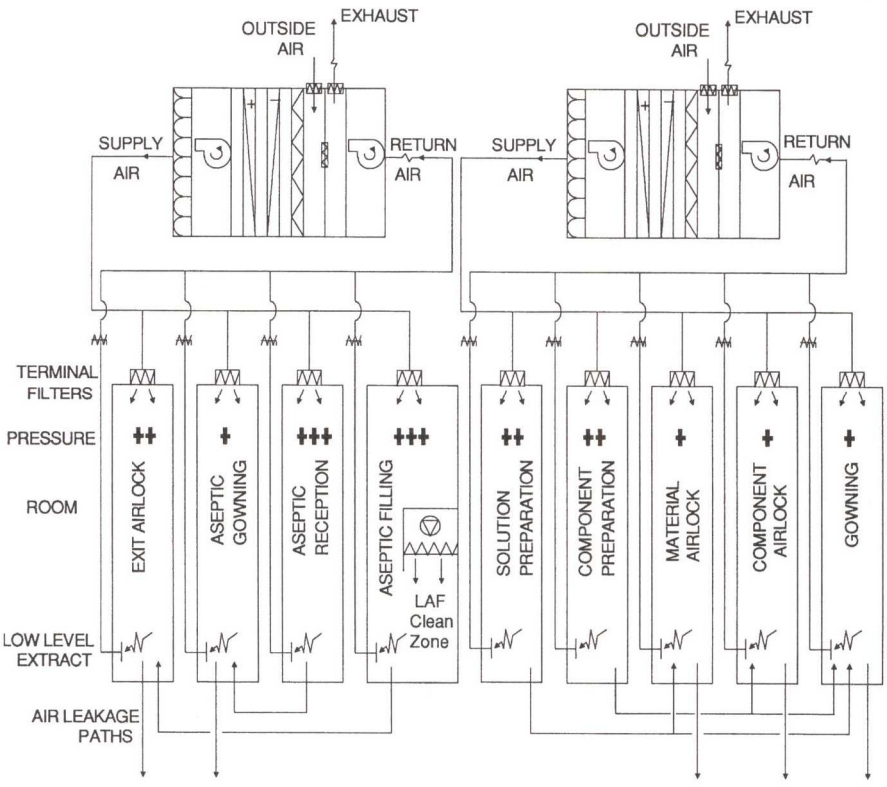

Figure 1. Air supply and extract in cleanroom suite using the “closed door” solution /6/

Amount of air supplied to each room is amount that is needed according to the standards for dilution of contamination or for cooling requirements. To give the correct pressure difference exhausts of rooms are adjusted. Extract air can be adjusted

manually or it is possible to install automatic dampers that are regulated by the room pressure. Benefit of “closed door” solution is simplicity and probability that it will work with few problems. It will minimize the air transfer between areas if the air supply and extract in each room are balanced.

One of the most important things, that have been written earlier, is guarantee that the rooms are built in an air-tight way to minimize the air flow out of the room's envelope. But, it is impossible to prevent air flow through the door cracks from an area of high pressure to one of low pressure. Using the following formula 1 we can calculate the amount of air leakage through small gaps and holes.

$$Q = A \cdot \alpha \sqrt{\Delta p}\,, \qquad (1)$$

where Q – air volume (m^3/s),

A – area of air leakage (m^2),

Δp – pressure difference (Pa), and

α – coefficient of discharge (0.85).

An estimation of door leakage can be calculated if the detailed sizes of the door are given but the total leakage will depend on the quality of building detailing. And this data can not be known until the commissioning of the room is made. So it is necessary to guarantee that the air handling system has enough capacity to accommodate more leakage than is expected.

In Figure 2(a)-(c) are layouts of the “open door” solution. The calculations show us that the air flow in the suite should be in the correct direction, for example from cleaner to less clean areas. This solution to the air distribution control requirements has been calculated by Peter Robertson, formerly of Building Services Research Unit, University of Glasgow. It is needed to guarantee that the air distribution will be in the correct direction throughout the suite is about $0{,}69 m^3/s$ to the filling room and about $0{,}63 m^3/s$ to the solution preparation room. These volumes refer to air movement control and take no consideration of the air requirement for the cooling load or that required to dilute the airborne contamination. Additional air can increase the door protection, or can be extracted in the room. /6/

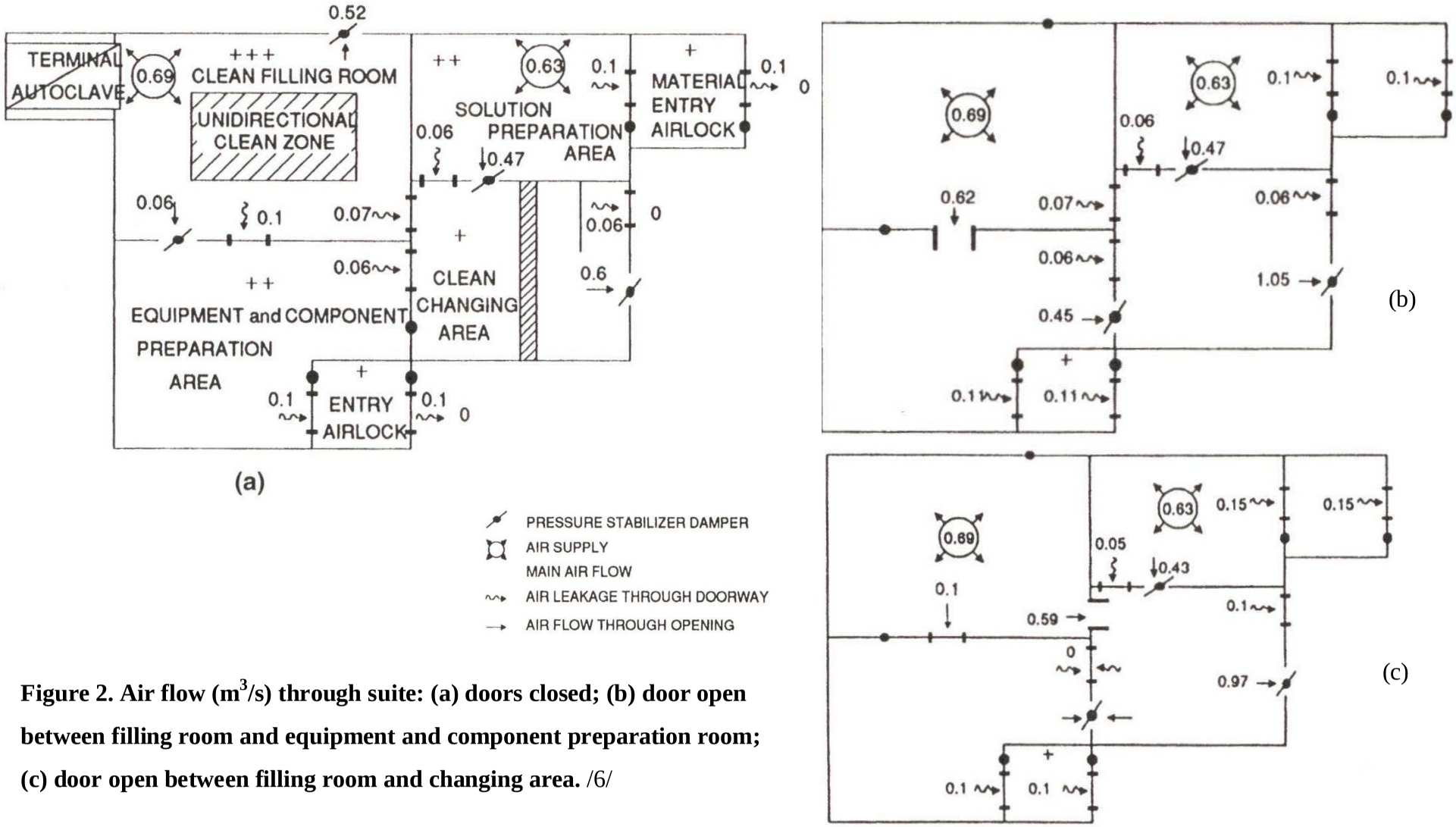

Figure 2. Air flow (m^3/s) through suite: (a) doors closed; (b) door open between filling room and equipment and component preparation room; (c) door open between filling room and changing area. /6/

2.5.1 Isolating technology

The using isolating technology minimizes human influence on processing zones. In aseptic manufacturing it can considerably decrease the risk of microbial contamination of product from environment.

In the isolators and all types of transfer units must hold fixed air quality requirements. Also it is necessary to consider, what are the possible leaks or damages caused by features of a design or materials of an insulator. Transfer devices can be different: from designs with a single or double door to completely sealed systems providing carrying out of sterilization.

Transferring materials inside and outside of an insulator is the main potential source of pollution. The space in an insulator is intended for carrying out of the operations representing high risk for quality of production. At the same time the organization of working zones in an insulator without laminar flow of air is supposed. Requirements to cleanliness of air in the environment surrounding an insulator depend on a design of an insulator and its appointment. This environment should be controlled and corresponds to aseptic manufacture, at least, to zone D.

Insulators can be placed in operation only after validation which should consider all critical factors of isolating technology, for example quality of air inside and outside of an insulator, an order of processing of an insulator, technology of transfer and integrity of an insulator.

It is necessary to establish the order of the current control including frequent carrying out of tests for presence of leaks in an insulator.

2.5.2 Blowing-filling-hermetic sealing technology

The device "blowing - filling - hermetic sealing" - is an equipment of a special design. Packages which are filled with a product and sealed are formed during one continuous work cycle. All these operations are spent within one automatic complex. The equipment "blowing - filling - hermetic sealing", used in aseptic manufacture zone A

with an effective air flow, can be established in a zone C if personnel will wear clothes applied in zones A and B. Environment in the equipped condition should correspond to the fixed requirements of particles and microorganisms, and in a maintained condition - only of microorganisms. The "blowing - filling - hermetic sealing" equipment, which is used in manufacturing of the products which sterilized, should be established, at least, in zone D.

Special attention must be paid to the following aspects:

- A design and certification of equipment;
- Certification and reproducibility of processes "clearing on a place" and "sterilization on a place";
- Parameters of a cleanroom in which the equipment is located;
- Training of operators and their clothes;
- Actions in a critical zone of the equipment, including performance of connections and building up in aseptic conditions before the filling begins. /4/

2.6 Personnel

Cleanrooms should remain minimum amount of the personnel. It is especially important for an aseptic manufactures. Inspections and controlling should be done, being outside of clean zones.

All personnel (including the personnel occupied with clearing and maintenance service), working in such zones, should have regular training concerning manufacture of sterile products, including the bases of hygiene and microbiology. It is necessary to pay special attention to instructing and the control over the workers who have not taken such training but it is necessary for them to enter into a cleanroom (for example, to the persons occupied in building or maintenance service).

3. DESIGNING & IMPLEMENTING PHARMACEUTICAL CLEANROOMS

The main role of the clean room is the protection of the product from contamination. In the pharmaceutical industry the lives of patients and reputation of the manufacturer depend on the purity of the product. It is important because of determination the potential sources of contamination. These may contain the working facilities, the raw materials, process equipment, and manufacturing personnel.

So, you should take into account that control of the operating procedures in the room, means that the raw materials, process equipment, and manufacturing personnel, is a condition of successful cleanroom operation—good housekeeping. Possibly the clearest statement of these factors when looking for a definition of the expression "cleanroom" is found in the IES Recommended Practice, which states that:

> "A cleanroom is a room in which the:
>
> - air supply
> - air distribution
> - filtration of air supply
> - materials of construction and
> - operating procedures
>
> are regulated to control airborne particle concentrates to meet appropriate cleanliness levels as defined by Federal Standard 209B or latest issue". /5/

Cleanrooms in the pharmaceutical facility cannot be designed in isolation. The solution to use clean spaces cannot be taken easily. They are expensive places to build and to work. Actually, the term cleanroom can be use to a wide range of areas from those with minimal environmental and housekeeping controls to aseptic areas using laminar flow air distribution, total change of working garments and the most active cleaning and sterilizing conditions.

The design department needs to solve most difficult problems: minimum risk against optimum cost. It means, what level of cleanliness is required to minimize the risk of product being contaminated while at the same time producing a facility which is both economical to design and run without adding restrictions to the product unit cost.

3.1 Purpose and strategy of design

The design purposes of a pharmaceutical cleanroom suite, in a manufacturing facility, can be summarized as follows:

- Exclusion of the environment external to the suite of cleanrooms
- Removal or dilution of contamination arising from the manufacturing process
- Removal or dilution of contamination arising from personnel working in the area
- Containment of hazards arising from the product
- Control of product-to-product cross-contamination
- Protection of personnel
- Control and management of the flow of material through the process steps by means of layout and configuration
- Control and management of personnel movement by optimizing the arrangement and connection of individual rooms
- Overall security of the operation by control of the entry and egress of personnel and materials
- Optimum comfort conditions for personnel
- Special environmental conditions for products, e.g. low RH for powder filling
- Accommodation of process plant and equipment to ensure safe and easy use, as well as good access for maintenance
- Effective monitoring of the conditions of the room

All these statements are important, and cleanrooms should be designed so that they overlap and function well. That is why it is necessary to explore all the requirements and develop the solution in an organized manner. An easy phased plan can be summarized as follows:

- Analyze production stages
- Prepare process flow diagrams
- Define activities associated with rooms
- Define environmental quality requirements
- Quantify production, process and space requirements
- Prepare room association diagrams

- Define the accommodation needs
- Develop layouts and schemes
- Prepare designs and specification
- Undertake the detailed design and construction process

These steps can be carried out at different levels of detail due to the physical size, scale and complexity of a facility. It is always important to define the responsibilities of all the parts that involved, and provide that experience is appropriate in those responsible. /6/

3.2 Layout of cleanroom suite

In pharmaceutical manufacturing cleanrooms are built as a suite of rooms that have definite functions. These are illustrated in Figures 3 and 4.

In the figure 3 we can see a typical suite of cleanrooms designed to meet the requirements of producing an injectable product that can be terminally sterilized. The staff who works in this manufacture would enter the suite of cleanrooms through the 'clean changing area'. In this room factory clothes are removed, hands washed, and appropriate cleanroom clothes put on. Raw materials and components, such as containers, would enter through their corresponding entry airlocks. In these airlocks procedures are used to decrease the contamination which may come from outside to the cleanrooms. Solutions are prepared in the “solution preparation” room for transfer, directly or indirectly, by pipes or mobile containers, to the filling operation in the “clean filling” room. Primary containers and closures would be prepared and washed in the “component preparation” room and manually transferred to the filling stage or by using a conveyor system. Containers are filled and packed under the unidirectional flow clean zone in the “clean filling” room. Filled and packed, containers of product leave the cleanroom suite through the terminal sterilization autoclave. At the ending of a work period, personnel would leave the suite through the changing room where cleanroom protective suite would be removed.

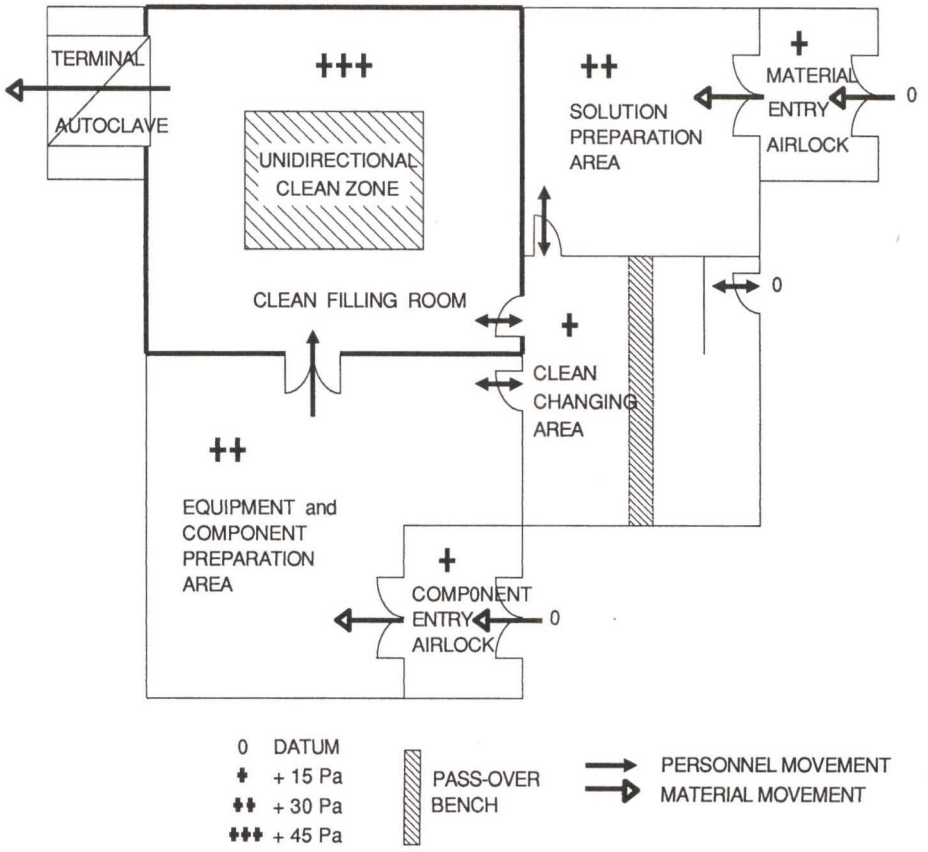

Figure 3. Typical suite of rooms for terminally sterilized injectables. /6/

Figure 4 shows a typical suite of cleanrooms configured for the production of a product employing an aseptic filling technique. The differences in the process requirements refer to the following key variations: the rooms are separated into clean and aseptic rooms. The barriers between them are created by the oven, autoclave and transfer hatch for items entering the aseptic suite, and through the separation of the “solution preparation” and “aseptic filling” rooms. Separate and more exact changing room control is provided for the aseptic suite, due to the differences between environmental control of the clean and aseptic suites. Also the isolator can be used in place of the unidirectional flow workstation.

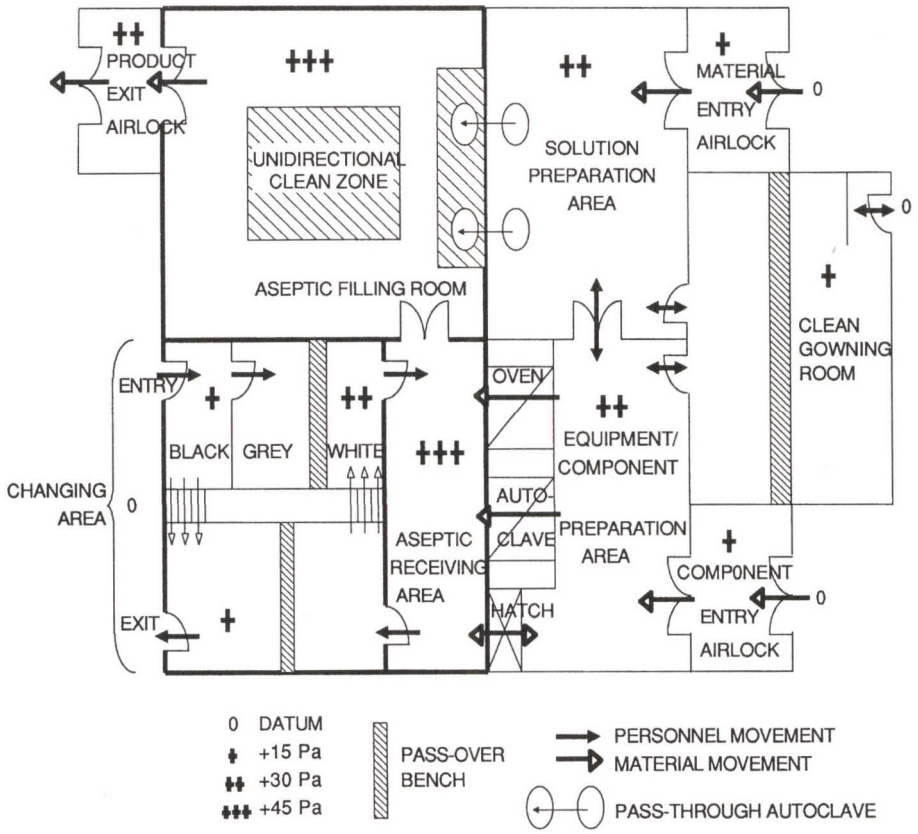

Figure 4. Typical suite of rooms for aseptic filling. /6/

The most difficult requirement to achieve correct level of cleanliness of the internal environment usually is caused by:

- The amount of contamination released in the room.
- The quality of the air supplied to the room.
- The quantity and method of supply of room air, i.e. conventional/turbulent ventilation or unidirectional flow, or a combination of both.
- The amount of incoming contamination from areas adjacent to the room. When isolators are used, many of the same considerations are required, but generally the ingress of contamination from outside the isolated volume is minimized. /6/

3.3 Changing room

The modern cleanroom requires that management should tell what staff should do. So the discipline in staff and operators by which the complete contamination control activity is maximized should be strict enough. Personnel influence starts in the

changing areas when movements should rise from “black” through “grey” to “white” zones.

Personnel change and store outer clothing in the “black” zone. These rooms are normally equipped with individual lockers. There should be storage of wet and heavy outdoor clothing and footwear. Floor should be cleaned often and quick. Entrances should be protected by contamination control. The “black” zone change room may be located away from the cleanrooms. They could be close to the employee's entrance to the building.

The “grey” area is where specialist may be held when applicable. If personal domestic clothing is changed for uniform undersuits it is required separate male and female sections. A personal secure locker will be required where a total garment change is implemented. The flow progresses to storage and use of cleanroom clothing proper, where the installation will depend on the clothing selection and change frequency. In the “grey” area should be available facilities for staff to “scrub-up” and to remove make-up. The reality of distributing cleanroom clothes may be different. It can be vertical laminar flow control cabinets or simple rails with hangers. Flooring should be contamination controlled and lead to the “white” area.

The “white” area is a room where staff changes into their cleanroom footwear. Ideally, the complete changing environment would include an air flow moving from “clean air” at the “white” zone through “grey” to the “black” zone. The changing room must also contain facilities for distributing cleaned sterile clothing, masks, gloves, and equipment for the collection of dirty items to be prepared for cleaning. Showers may be provided for emergency use or for routine use. They are situated in areas where there is risk of personnel contamination by toxic substances. /7/

3.4 Material distribution technology

Material movements throughout the pharmaceutical technological process are important, but their entrance and transfer from cleanrooms must be controlled if they are not to bring contamination.

Raw materials must be manufactured and packed in clean conditions. Polythene and similar envelope materials should be used more than paper. Where paper is necessary it must be removed and the contents decontaminated well before materials enter the cleanroom.

Materials must be transferred through airlocks. And special vehicles or trolleys should be used if it is possible. Not to use truck to pass from “grey” to “white” areas. Pallets, when used, should always be of plastic construction.

Materials that have smaller sizes can be transferred through air lock hatches, using special trays. It may be necessary to introduce separate conveyors with dead plate transfers at the cleanroom entry point to avoid transferring contamination from “grey” area to “white”. Fluid materials may require filtration at the point of use to support the absence of particles once in the manufacturing process.

It must be recognized that certain powder based processes such as tabletting and vial filling are used when handling a particulate material. Prevention the entrance of foreign particulate substance can be solution in these situations. It is important to decrease the risks to personnel and to the environment by explosion.

The following text examines key points of construction against the skeleton of the cleanroom definition mentioned in the beginning of this section 3.

3.4.1 Air supply

Due to clean air technology is directly related to airborne particulate contamination, the number of particles of a defined size measured in a given amount of air at a defined point.

So, first three aspects of the cleanroom definition — air supply, air distribution, and filtration — are very closely connected. Decisions on cleanliness influence the filtration requirements. And the filtration requirements influence supply air quantities. Studying these items separately, it should be noticed that decisions made on one aspect will influence the others.

The size of air handling plant, the number of utilities such as power, steam, and chilled water influence the air volume in each area. And they will also determine the size of services zones necessary to accommodate ductwork and plant rooms to accommodate generating equipment.

At the beginning of the HVAC design we have to decide the quantity of air to be supplied to any room. So we should know if the air volume significant to dissipate the heat load in the room or not. Engineers trained to calculate their designs with accuracy are usually disappointed due to indefinite character of cleanroom design. The validation demands to meet needed class limits are exact enough. But there is no equation that is able to connect air change rates to level of cleanliness. In this situation designer will help his experience to accumulate exact data about the character of the operations in the room, the number of participated people, the nature of the equipment, and the condition of room where it is to be tested. Then he should decide required air quantity. Earlier standards had given minimum number of air changes, without recommendation to the level of cleanliness. For instance it was 20 changes per hour. Unfortunately, this was because of misunderstanding and has often been taken in detailed specifications as a complete requirement. /7/

A considerable factor in the prevention of particulate accumulation in cleanrooms is the use of overpressure. In suites of rooms with different levels of cleanliness, pressure gradients can be designed. Usually pressure difference between adjoining rooms is about 12 Pa. Bigger overpressure can provide noise in the gaps and difficulties in opening doors. It is necessary to support pressure difference between adjoining rooms 5 Pa in the blocks of cleanrooms with different classes of cleanroom. So in the rooms with higher level of cleanliness is supported more pressure. So the most sensitive areas come to the highest overpressure where distribution of contamination from room to room is supported and minimized. Gradients can be achieved in different ways. For example, by careful calculation of air flow rates each room can be designed to a fixed overpressure, independently of the others or by distributing of air from room to room, by flowing air through transfer grilles and pressure relief dampers.

The first method minimizes risk of cross-contamination but is not easy to balance in the beginning and to support in balance if HEPA filters blocked at differing rates. Due to the second method is interactive it becomes autonomous once achieved. The system characteristics are rapidly supported by growing the supply air flow rate as filters blocked through a constant volume damper or by a manually operated damper in the main supply duct. Negative pressure cascades operate in an equal and opposite way with areas of highest sensitivity protected by the lowest negative pressure. Order of coming to a containment suite should be defended by a positive pressure zone to prevent a net inflow of dirty air. /7/

3.4.2 Air distribution

There are two known types of air distribution in the cleanroom. First, turbulent flow (Figure 5) is a traditional design. It is used in cleanrooms where terminal outlets form only a part of the total area of ceiling placed to suit the individual process requirements or general room transfer. Extracts may be located at the ceiling or at low level of walls. Air flows are predictable but impossible to guarantee. Cleanliness levels as high as Class 1000 can be achieved when HEPA filters are installed in terminal housings.

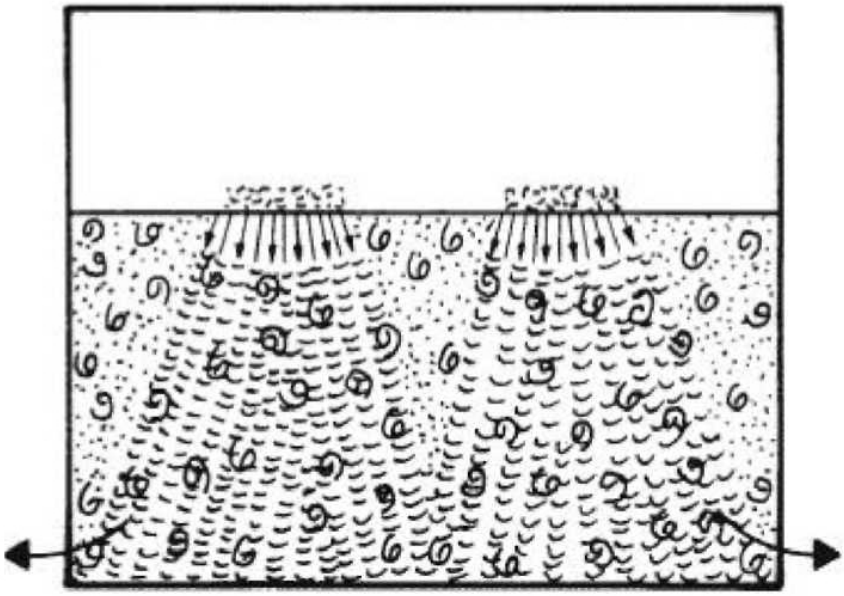

Figure 5. Turbulent flow air distribution. /7/

Secondly a unidirectional downflow (laminar flow) air distribution is necessary for facilities which need Class 100 and better conditions (Figure 6), particularly when “in use” testing is required. With a vertical air flow of available velocity 0.45 m/s from a

fully filtered ceiling, particle transfer is easier to predict, there being no dead areas for increase of contamination. /7/

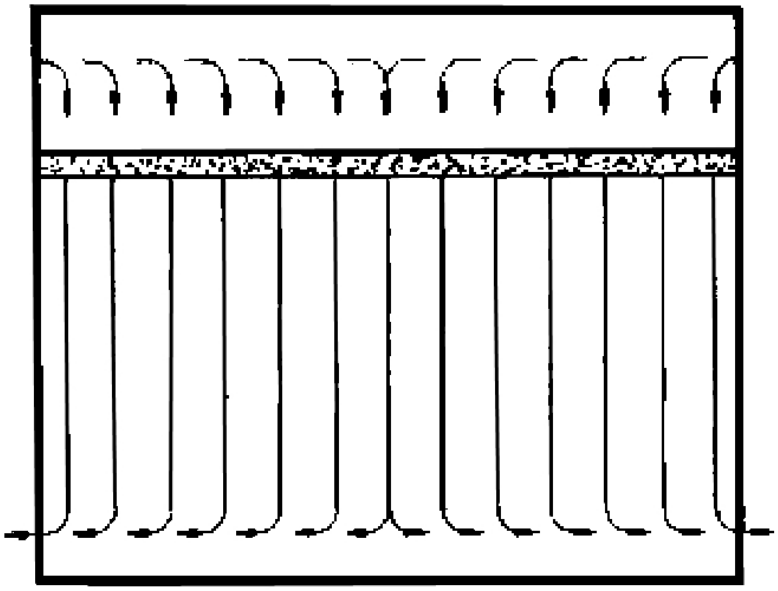

Figure 6. Unidirectional downflow air distribution. /7/

We know that air change rate depends on air flow rate and size of the cleanroom. Cleanrooms with high level of contamination will need a higher air change rate, and vice versa. In the Table 6 is given numbers of air changes that are allowed in the cleanroom classification.

Table 6. Air change rates for cleanrooms. /6/

Class of cleanroom	Air change rate per hour
ISO 8	2 – 10
ISO 7	10 – 100
ISO 6	> 100
≤ ISO 5	use unidirectional airflow

Because of growing levels of cleanliness, location of air exhaust becomes more significant. Cleanliness levels of Class 100 000 can be supported reasonably with exhaust air grilles located in the ceiling or at high-level in walls. As higher would be cleanliness levels, so low-level extraction becomes essential. This demand of using double-skin walls or ductwork located in service chases if ugly implementations in the cleanroom are to be avoided.

Predictability of airflow is the final requirement. In this case systems can be designed to protect the product and the operator from the contamination. But, it must be noticed that even in laminar downflow areas the introduction of people, equipment, and the ceiling construction itself into the airstream will affect the areas of turbulence which must be minimized (Figure 7).

Unidirectional airflow can also be provided horizontally. Its use much less popular at the present time, because air quality destroys quickly the further away from the filter bank one moves. Each operation ends the airflow through the room, reducing predictability of direction and introducing contamination which is continued to following operations. Horizontal laminar flow is still used widely in rooms where product safety is the only solution. /7/

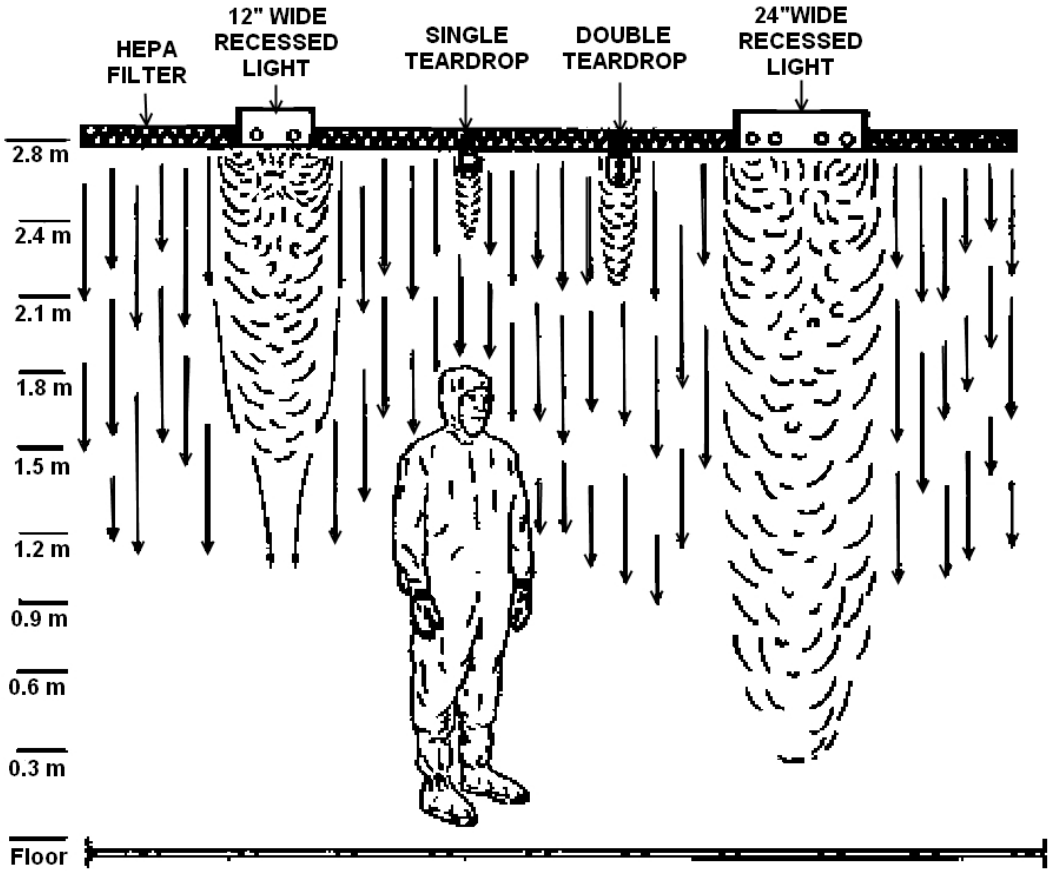

Figure 7. Obstruction cased turbulence in a laminar flow cleanroom. /7/

3.4.3 Filtration and supply air

The use of high-efficiency particle stopper (HEPA) filters including pleated packs of high-density glass fibre paper with aluminium or craft paper separators, sealed into a timber or metal frame with urethane, influenced by cleanroom technology. In pharmaceutical industry it is required to install HEPA and ULPA filters of H14 – U17 classes. The most penetrable particle size in below classification (Table 7) is more than 0.1µm but less than 0.3µm.

Table. 7 Classification of high-efficiency filters according to the EN 1822. /9/

	Integral value		Local value	
Filter class	Collection Efficiency %	Penetration %	Collection Efficiency %	Penetration %
H10	85	12	–	–
H11	95	5	–	–
H12	99.5	0.5	–	–
H13	99.95	0.05	99.75	0.25
H14	99.995	0.005	99.975	0.025
U15	99.9995	0.0005	99.9975	0.0025
U16	99.99995	0.00005	99.99975	0.00025
U17	99.999995	0.000005	99.9999	0.0001

Better production methods depend on the availability of a range of minipleat filters with a nominal depth of five centimeters. These may be up to twice as much paper as ordinary fifteen centimeters filters, achieved by changing separators with more densely pleated, independent media. The principal advantages are:

- Lower pressure drop, producing decreased system resistance.
- Higher loading capacity, resulting in longer service life.
- Minimizing risk of friction, small leaks, and off-gassing, connected with separators.

It is very important to know the relative efficiency of HEPA fillers. All filters will be tested at least once during the production process. There are some regulations that present efficiency and testing of leak for filters. Efficiency tests may approve overall efficiency but cannot identify possible harmful pinholes. Until delivering an overall instruction that the specified efficiency has been obtained, they can not maintenance during transportation or adjustment. Because of that qualifier will constantly order to install leak test to implement as part of the system validation.

Better production is not limited to the filter medium. Until it always placing filters into constant housings as part of the room ductwork system using a “fluid” seal, factory sealed cassette filters including filter and housing have been broadly fabricated in lately. One of the greatest benefits of factory control over the difficult filter seal and lower initial cost are, objected by a higher replacement cost and a separation of room integrity during filter changing. The cassette filters are not usually used in pharmaceutical areas.

Filters must be placed as close as possible to the point of extract from the room to be more effective. So decreasing ductwork runs sensitively to minimize contamination. Filters must be changed without breaking the integrity of the ductwork system. Filters need special frame and bagging techniques to avoid replacing and distributing any contaminants collected on the media. It is called “safe change”. A standard method of filter changing is shown in Figure 8. /7/

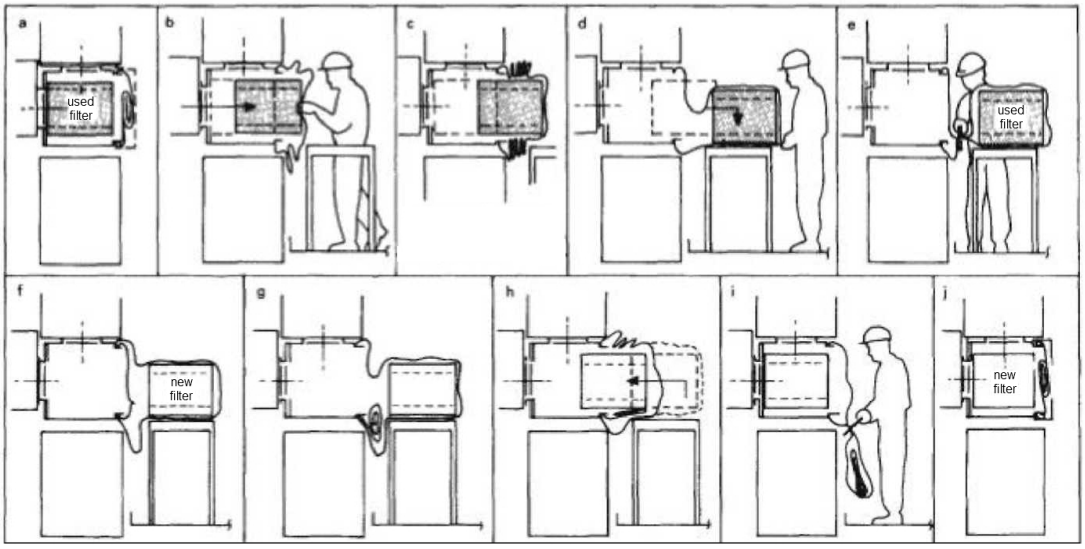

Figure 8. Safe procedure of changing a filter. /7/

a- Remove the cover.

b- Plastic bag extended, unlock filter from outside of canister, grasp filter handle through center of end of bag, and pull filter almost half out.

c- Feed bag over end of filter in concertina fashion.

d- Hold filter by supports clear of concertinered bag and slide out rest on table.

e- Heat seal 3 continuous lines across bag and cut the back on the middle line. Encased dirty filter can now be safely disposed of. Move bag back to first swage.

f- Insert a new filter. Feed beaded edge of new bag containing new filter over existing bag and second swage.

g- Removal of old bag must be carried out without disturbing position of new bag over second swage.

h- Lift filter to top of bag and manoeuvre old bag underneath slide filter into unit. Observe that old bag is not trapped between underside of filter and clamping frame.

i- Clamp up filter. Manoeuvre old bag to extreme end of new bag hot seal as before and cut off.

j- Fold up bag in flat roll. Replace cover and secure. /7/

3.4.4 Materials of construction

The success of any pharmaceutical construction project does not depend on the process and services maintenance but on the “quality” of the facility based on an

individual estimation. Due to selection of materials and the detail of the installation or application must accept a high priority for the designer.

It is also important in considering structural solutions for a project that in addition to the obvious requirement for suitability, allowance is made for the significant services loads often imposed in a pharmaceutical application. The structure accepts regularly penetration for holes and slots. Engineers should be careful in design of floor especially in places of movement connections to guarantee that they do not compromise the integrity of applied floor.

Some external factors depend on the choice of construction technology. The key factors are: facility location, flexibility, cost effective solutions.

First of all construction materials depend on the location of a facility, not only in terms of availability of raw materials and installation skills, but also by strict explanation of building codes.

Flexibility is the principle demand of facility managers. It is very difficult to solve different problems together. Such as designing of facility which meets current performance requirements, adjusting and accommodating of rapid equipment changes, upgrading without requiring total renovation.

In spite of many different requirements to be satisfied, you should pay attention for a cost effective solutions. A final engineering exercise is required at the detail design stage to guarantee that the offered solutions perform best price per unit.

Production areas must be “fit for purpose”. The selection of a proper materials and construction technologies orders the designer to keep balance between cost and risk. Risk that materials may break down and contaminate the technological process and control of project cost.

Cleanrooms are built using traditional building construction techniques. Every system must give an effective and adequate compromise between something which is ideal everywhere and something which is buildable due to cost and timescale.

The quality of construction of the cleanroom suite has a direct influence on the amount of air leakage out, or into, the room and such leakage should be prevented. It is needed to avoid dirt traps during windows and doors selection. The air conditioning system, services and technological equipment must be integrated into the building envelope. Air ducts should be air tight and cleanable too.

Pharmaceutical cleanrooms and technological equipment often ordered to renovate when changes are made to production activities. The supply of vertical service ducts in walls and service access over the cleanroom will allow changes to the services to be more easily adapted. Replacement of things is more difficult but the use of prefabricated walls may help. /7/

3.4.5 Operating procedures

The last phase of the expression quoted earlier in the beginning of the section 4 relates operational procedures in cleanroom facility. It is very important as an overview of all questions about contamination control, due to impossibility of designer to have an influence and completely the responsibility of the user. There are several aspects of cleanroom operation that can effect to manufacturing process like sanitization, validation and simply clothing.

4. CONTROL AND MAINTENANCE OF CLEANROOM AREAS

Raw materials entering the cleanroom must be controlled by careful primary selection, preliminary treatment to clean materials by removing packing and good housekeeping practices as the materials are processed through the room.
Technological equipment can be designed to minimize contamination by using of non-shedding materials such as stainless steel. Moving elements such as motors and drives can be packed, or removed from the clean room altogether.

Manufacturing staff is the biggest source of contamination in the manufacturing process. It is represented in figure 9. It displays the relative contamination levels during whole period of working day. Also it shows the effects of people movements in the room during manufacturing and cleaning processes. According to the standards there are three states in which the room may be validated:

- ”As built”, a test principally used to establish that the cleanroom constructor has met his contractual obligations
- “At rest”, a test taken with the room fully equipped ready for production but with no equipment running and personnel absent.
- “In use”, a test taken with the room fully operational. /6/

From Figure 9 it can be quickly evaluated that there is a main difference in the amount of particulates in the room between testing “at rest” at 6.00 am and testing “In use” at noon or at 8.00 pm when the cleaners are at work. It is very important to understand that the guidelines and technology of construction must be required if the cleanliness levels are achieved. Also engineers should understand how the room will be used and how the room will be implemented before the design is started.

But in the same time there are some cases in where it is necessary to protect the personnel from the product. Cleanroom technology has developed to provide this protection in a different ways. Negative pressure rooms may be used for secondary containment of enclosed manufacturing processes, or controlling work may be held in safety cabinets or isolators to guarantee needed level of protection. /7/

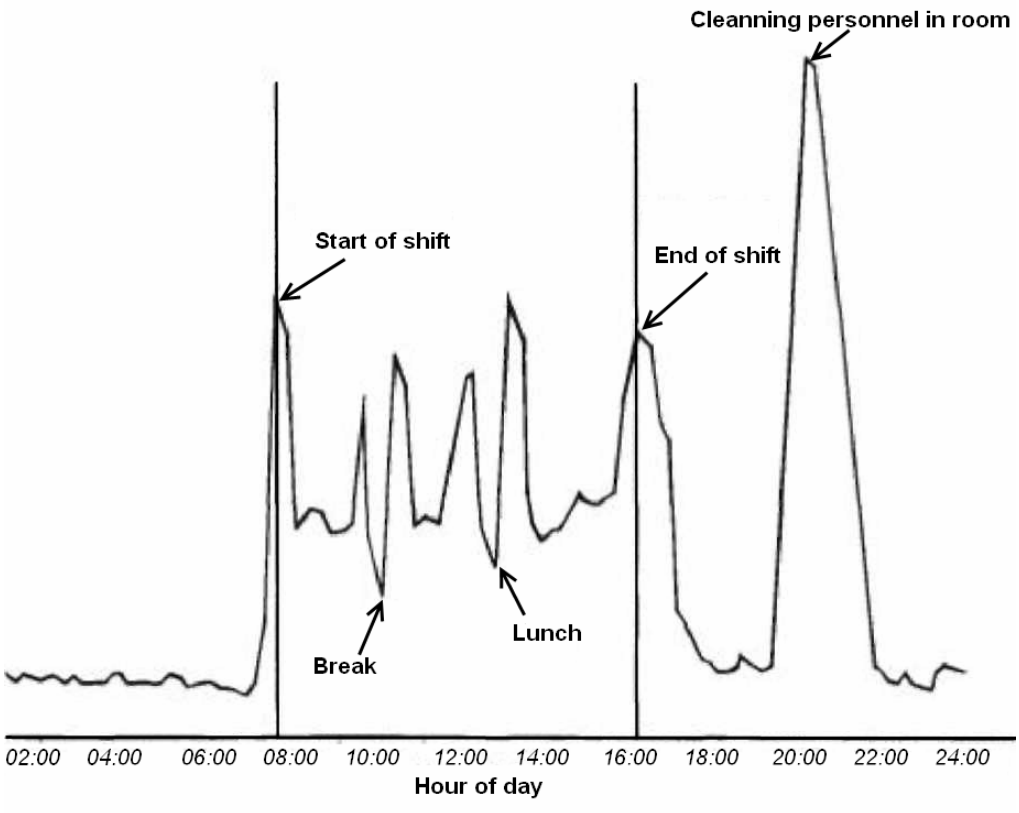

Figure 9. People effect in the cleanroom. /7/

4.1 Cleanroom Clothing

As it was mentioned earlier the biggest source of contamination in the cleanroorm is personnel. But, this problem is not very important nowadays. Because there are wide range of garments today, which offer enough protection to the product.

The proper usage of cleanroom clothing in the pharmaceutical industry is becoming more significant, as cleanrooms themselves operate at high levels of performance for both product integrity and operator safely. Cleanroom clothing must protect the environment from the personnel and should be designed and manufactured according to the highest requirements.

Table 5. Cleanroom clothing applications

Cleanroom class	Coveralls	Headgear	Footwear	Coats/ frocks	Hands
1	Yes	Full hood and mask	Long overboots	No	Powder and lint free
10	Yes	Full hood and mask	Long overboots	No	Powder and lint free
100	Yes	Full hood mask as required	Long overboots	No	Powder and lint free
1000	Yes or coat	Hood or snood	Overboots or overshoes	Yes or coverall	Powder and lint free
10 000	Yes or coat	Hat or tap	Overshoes	Yes or coverall	As required
100 000	Not required	Hat or cap	Overshoes	Yes	As required

It may be noted that the above recommendations are based on a density of one person per 9 m^2 of floor space. /7/

Now facilities order to use one-piece, working suits, normally with integral hoods, knee-length overboots, and gloves. Cleanroom operators should store their street clothes and outdoor footwear in change rooms. They must use face coverings also. Clothes must be made from 100% synthetic.

Take care to estimate the actual antistatic performance of the garment if antistatic material is used as well as its basic ability to keep particulates. Garments should be designed and economically engineered to fit correctly with openings scaled to reduce emission, and the whole garment being loose enough to decrease internal friction and increase pressure.

4.2 Cleaning instructions

First of all it is necessary to clean the floor with a wet and dry vacuum cleaner. In the beginning it is needed to use the dry vacuum cleaner to remove visible dust or dirt. Second step is usage of wet mops on the floor of the cleanroom. A tacky roller is a good tool in cleaning surfaces and removing microbes. Then it is recommended to use a special floor scrubbing machine with rotary brushes that clean the floor. Cleaning solution should not be toxic or flammable, it should dry rapid and it should not affect the cleanroom surfaces.

4.3 General cleanroom regulations

There is a list of requirements that are a minimum rules for the successful operation of a cleanroom. Everyone who is connected to cleanroom should accept following regulations.

All personal items such as keys, watches, rings, matches, lighters and cigarettes should be stored in the personal locker outside the gowning room. Valuables such as wallets may be allowed in the cleanroom if they are never removed from the cleanroom garments. It is forbidden to eat, smoke, chew a gum, wear cosmetics.

In the cleanrooms you are allowed to use only ball point pens and approved cleanroom paper. It is suggested to use hand dryers equipped with HEPA filters. All tools and

containers that are used in the cleaning process should be cleaned to the same degree as the cleanroom surfaces. /8/

You are not allowed to touch any item or surface that has not been fully cleaned wearing gloves or finger cots (medical supply used to cover one or more fingers). Every tool should be placed on a cleanroom towel which is approved for the Class of cleanroom. It is forbidden to enter the cleanroom people who is physically ill, especially with respiratory or stomach disorders. Also it is forbidden to run, walk fast, sitting on equipment or work surfaces, remove items from the cleanroom garments, wearing the cleanroom garment outside the cleanroom, and wearing a dirty or broken suits.

4.4 Measurement of the airborne particles

There are special instruments to estimate the amount of particles in the cleanrooms. Particle detector or counter is a such tool. In pharmaceutical cleanrooms are used aerosol particle counters. They are implemented to evaluate the air quality and sizing the amount of particles in the air. As it was mentioned earlier cleanrooms have strict limitations about number of particles per cubic meter. So an aerosol particle counter is used to evaluate cleanroom to the classification standard.

Many particle counters are equipped with the alarm to prevent following contamination of manufacturing process. Also this monitoring system can be integrated in the building automation. It can record the moments of contamination to help personnel to support air quality in cleanroom.

Most popular way to prevent contamination is to catch a moment of it formation. It is necessary to have a serial selection system, or one dedicated remote particle counter to monitor different cleanroom environments. A highly sensitive handheld particle counter can find a place where particle emitted. /10/

5. CONCLUSION

The pharmaceutical production must effectively control the contamination from people, raw materials, finished products as well as accommodating-services, process plant and equipment. The requirements that are available involved in the overall design and a complex construction process.

The main purpose of building a cleanroom suite is to provide a vital element in the assurance of product quality according to whole concept of good pharmaceutical manufacturing operation. The resultant facility should prevent contamination of the product, and should be seen to be doing so by the incorporation of effective monitoring devices.

During process of studying cleanroom technology I firstly met different requirements and regulations for certain industry. Each of them has their definite property and purpose. So every cleanrooms in different industry should be designed according to their own manufacturing characteristics. In this thesis was shown detailed rules of designing cleanrooms by example of pharmaceutical production.

Here was also described proper behavior of personnel. Staff is also main component of cleanroom environment. People should be trained and well qualified to work and maintain in the cleanroom. They need to wear special clothing that can protect both a product and a human.

Another task which was set in the beginning was comparing of international and Russian standards. In spite of big number of different standards both Russian and international, where term cleanroom is mentioned, the main idea is expressed in ISO 14644. It was real surprise that cleanrooms in Russia are designed according to the same identical standard, which is translated equivalent of the international one. For example GMP was translated in Russian with some additions that are indicated in special appendix. Adjustments are generally applied to the standards and requirements that are mentioned there. They are substituted for Russian equivalents. So there is no principal difference in designing cleanrooms in various countries.

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